Improving Clinical, Endoscopic and Histological Outcomes in Inflammatory Bowel Disease

Britt Christensen

BSc, MB BS (Hons), FRACP, MPH

A thesis submitted for the degree of *Doctor of Philosophy* at

Monash University in 2020

Department of Gastroenterology

Alfred Hospital, Melbourne, Australia

and

Inflammatory Bowel Disease Center,

Department of Gastroenterology, Hepatology and Nutrition

University of Chicago Medicine, Chicago, Illinois, USA

Copyright notice

I certify that I have made all reasonable efforts to secure copyright permissions for third-party content included in this thesis and have not knowingly added copyright content to my work without the owner's permission.

This work is dedicated to my loving husband Jason, my delightful, intelligent and wonderful daughters Saskia and Sage and my sweet and determined son Micah.

Abstract

Inflammatory bowel disease (IBD) is a chronic relapsing remitting inflammatory condition of the bowel. Persistent inflammation leads to structural bowel damage and its associated complications (stricturing and penetrating phenotype in Crohn's disease, uncontrolled disease and colorectal cancer in ulcerative colitis) and clinical outcomes (reduced response to therapy, hospitalisation and surgery). The adoption of endoscopic mucosal healing as the primary target of therapy, as opposed to clinical remission only, has improved outcomes and represents a new era of treatment strategies.

This thesis has addressed two important questions in the light of this new era. First, is mucosal healing the ideal target or can we do better by assessing for histologic normalisation or histologic healing? Second, how does the new, gut-selective anti-integrin approach with vedolizumab perform in reaching those targets in real-world practice and in the challenging setting of primary sclerosing cholangitis (PSC)?

In addressing question one, it was found that complete histologic normalisation is possible in ulcerative colitis and occurs in ten percent of patients. Complete histologic normalisation is associated with less extensive disease and predicts improved clinical outcomes above that of endoscopic healing or histologic quiescence. Additionally, disease regression, as defined by segmental normalisation of histology, occurs in approximately one third of ulcerative colitis patients and is associated with younger age of diagnosis and current cigarette smoking. Normalisation can occur in any direction but is most likely to occur in a proximal to distal fashion. Unlike complete histologic normalisation, segmental disease regression does not signal improved clinical outcomes. Finally, histologic healing is possible in patients with ileal

Crohn's disease. Histologic healing was found to be a stronger predictor of clinical outcomes, clinical relapse and medication escalation compared to endoscopic mucosal healing.

In regard to the second question, this thesis explores the role of a new medication, vedolizumab, on outcomes in patients with IBD. The utility of vedolizumab in both anti-tumour necrosis factor (TNF) naïve and refractory patients in clinical practice was confirmed, and vedolizumab was found to be durable and safe in patients with complex and treatment-resistant Crohn's disease and ulcerative colitis. Evidence for the benefit of dose intensification and the utility of vedolizumab in achieving mucosal and endoscopic healing has also been provided. Furthermore, a novel treatment regimen for patients with moderate or severe IBD utilising combination therapy of vedolizumab with either cyclosporin or tacrolimus is described and was found to be effective and safe at inducing clinical remission in patients with either ulcerative colitis or Crohn's disease. This provides an alternative treatment regimen for patients who are steroid-refractory or who have already failed anti-TNF treatment. Finally, despite biological plausibility, this thesis demonstrates that vedolizumab does not improve liver biochemistry in patients with PSC and IBD but is associated with improvements in bowel disease and has a favourable safety profile.

This series of studies on the importance of histology on disease outcomes and the use of a novel medication to improve clinical, endoscopic and histological outcomes in IBD hold the prospect of changing both future clinical care and clinical trial design.

Publications during candidature

Publications included in this thesis:

Background concepts

- **Christensen B**, Rubin DT. Recurrent CD: Medical Prophylaxis. In. Fichera A, Krane MK, editors. Crohn's Disease: Basic Principles. New York: Springer International Publishing; 2015. p. 219-227
- **Christensen** B, Rubin D. Understanding Endoscopic Disease Activity in IBD: How to incorporate it into clinical practice. *Curr Gastroenterol Rep.* 2016;18(1):5. doi. 10. 1007/s11894-015-0477-6
- **Christensen B**, Rubin DT. Objective assessment of endoscopic disease activity and mucosal healing In. Baumgart D, editor. Crohn's Disease and Ulcerative Colitis: From Epidemiology and Immunobiology to a Rational Diagnostic and Therapeutic Approach. 2nd ed. New York: Springer International Publishing; 2017. p. 267-277

Improving the target of therapy

- **Christensen B**, Hanauer S, Ehlrich J, Kassim O, Gibson PR, Turner JR, Hart J, Rubin DT. Histologic normalisation occurs in UC and is associated with improved clinical outcomes. *Clin Gastro and Hepatol.* 2017;15(10):1557-1564. doi. 10.1016/j.cgh.2017.02.016
- **Christensen B,** Hanauer SB, Gibson PR, Turner JR, Hart J, Rubin DT. Segmental histologic normalisation occurs in ulcerative colitis but does not improve clinical outcomes. *J Crohn's Colitis*. 2020;14(10):1345-1354 doi. 10.1093/ecco-jcc/jjaa068

- **Christensen B**, Ehrlich J, Gibson PR, Turner JR, Hart J, Rubin DT. Histologic Healing is More Strongly Associated with Clinical Outcomes in Ileal Crohn's Disease than Endoscopic Healing. *Clin Gastro Hepatol.* 2020;18(11):2518-2525. doi. 10.1016/j.cgh.2019.11.056

Reaching targets of therapy with vedolizumab in the real word.

- **Christensen** B, Colman R, Micic D, Gibson PR, Goeppinger SR, Yarur A, Weber CR, Cohen RD, Rubin DT. Vedolizumab as induction and maintenance for inflammatory bowel disease: 12-month effectiveness and safety. *Inflamm Bowel Dis.* 2017;24(4):849-860. doi. 10.1093/ibd/izx067
- **Christensen** B, Gibson PR, Micic D, Colman RJ, Goeppinger SR, Kassim O, Yarur A, Weber CR, Cohen RD, Rubin DT. Safety and efficacy of combination treatment with calcineurin inhibitors and vedolizumab in patients with refractory inflammatory bowel disease. *Clin Gastro Hepatol.* 2019; 17(3):486-493. doi. 10.1016/j.cgh.2018.04.060
- **Christensen** B, Micic D, Gibson PR, Yarur A, Bellaguarda E, Corsello P, Gaetano JN, Kinnucan J, Rao VL, Reddy S, Singh S, Pekow J, Rubin DT. Vedolizumab in patients with concurrent primary sclerosing cholangitis and inflammatory bowel disease does not improve liver biochemistry but is safe and effective for the bowel disease. *Aliment Pharmacol Ther*. 2019; 47(6):753-762. doi. 10.1111/apt.14525

Publications during candidature included as supplementary material:

- Israel A, Christensen B, Jurdi KE, Rai V, Ollech JE, Cohen RD, Sakuraba A, Dalal SR, Rubin DT. Follow-Up of Ulcerative Colitis Patients Who Have Achieved Histological Normalization. *Clin Gastro Hepatol*. 2020;18(4):987-099. doi. 10.1016/j.cgh.2019.06.025
- Ollech JE, Dwadasi S, Rai V, Peleg N, Normatov I, Israel A, Sossenheimer PH, Christensen B, Pekow J, Dalal SR, Sakuraba A, Cohen RD, Rubin DT. Efficacy and Safety of induction therapy with calcineurin inhibitors followed by vedolizumab maintenance in 71 patients with severe steroid-refractory ulcerative colitis. *Aliment Pharmacol Ther.* 2020; 51(6):637-643. doi. 10.1111/apt.15616
- Christensen B, Gibson PR, Rubin DT. Vedolizumab for autoimmune liver disease associated inflammatory bowel disease – Authors Reply. *Aliment Pharmacol Ther.* 2018;47(10):1423-1424. doi. 10.1111/apt.14638

Publications on IBD during candidature not included in this thesis:

- **Christensen B**, Sparrow M. Editorial: international consensus in clinical trial end-points in ulcerative colitis – clarity or just a step clearing the fog? *Aliment Pharmacol Ther.* 2017; 45(9):1274-75 doi. 10.1111/apt.14007
- **Christensen B,** Sparrow M. Editorial: adalimumab or infliximab as monotherapy, or in combination with an immunomodulator, in the treatment of Crohn's disease. *Aliment Pharmacol Ther*. 2017;45(1):178-9. doi. 10.1111/apt.13842
- Yarur A, Gondal B, Hirsch A, **Christensen** B Cohen RD, Rubin DT. Higher thioguanine nucleotide metabolite levels are associated with better long-term outcomes in patients with inflammatory bowel disease. *J Clin Gastro.* 2017; 52(6):537-44 doi. 10.1097/MCG.0000000000000889

- Shedda S, **Christensen B**, Tjandra J. Chapter 26: Inflammatory Bowel Disease In. Tjandra J, editor. Textbook of Surgery. 4th ed. Chester UK: John Wiley & Sons Ltd; 2018. 255-266
- Vaughan R, **Christensen B**, Rubin DT. Chronic Active UC In. De Cruz P, Ding N, editors Biomarkers in Inflammatory Bowel Disease. New York: Springer International Publishing, 2018. 131-140
- Al-Ani AH, Prentice RE, Rentsch CA, Johnson D, Ardalan Z, Heerasing N, Garg M, Campbell S, Sasadeusz J, Macrae FA, Ng SC, Rubin DT, **Christensen B.** Review article: prevention, diagnosis and management of COVID-19 in the IBD patient. Aliment Pharmacol Ther. 2020 Jul;52(1):54-72. doi. 10.1111/apt.15779.
- Al-Ani AH, Rentsch CA, Azim S, Bidgood E, Onasseril P, **Christensen B**. Letter: IBD nurse-pivotal role in the time of the pandemic. Authors' reply. *Aliment Pharmacol Ther*. 2020;52(4):746-747. doi. 10.1111/apt.1595
- Al-Ani AH, Johnson D, **Christensen B.** Letter: is pneumococcal vaccination safe during the COVID-19 pandemic? Authors' reply. *Aliment Pharmacol Ther*. 2020;52(5):921-922. doi. 10.1111/apt.15940
- Aysha AA, Rentsch C, Prentice R, Johnson D, Bryant RV, Ward MG, Costello SP, Lewindon P, Ghaly S, Connor SJ, Begun J**, Christensen B**. Practical management of inflammatory bowel disease patients during the COVID-19 pandemic: expert commentary from the Gastroenterological Society of Australia Inflammatory Bowel Disease faculty. Intern Med J. 2020 Jul;50(7):798-804. doi. 10.1111/imj.14889.
- Garg M, **Christensen B,** Lubel JS. Letter: Gastrointestinal ACE2, COVID-19 and IBD - opportunity in the face of tragedy? [published online ahead of print, 2020 Apr 27]. *Gastroenterology*. 2020;S0016-5085(20)30570-9. doi. 10.1053/j.gastro.2020.04.051

- Garg M, Al-Ani A, Mitchell H, Hendy P, **Christensen B.** Editorial: low population mortality from COVID-19 in countries south of latitude 35 degrees North-supports vitamin D as a factor determining severity. Authors' reply. *Aliment Pharmacol Ther*. 2020;51(12):1438-1439. doi. 10.1111/apt.15796
- Prentice RE, Al-Ani AH, Bond K, Johnson D, **Christensen B.** Letter to the Editor: Asymptomatic Screening for SARS CoV-2 prior to commencement of biologic therapies in patients with Inflammatory Bowel Disease-a potentially harmful practice. Dig Liver Dis. In Press. 2020. doi. 10.1016/j.dld.2020.08.035
- Prentice RE, Tjandra D, Garg M, Lubel JS, Fourlanos S, Johnson D, Al-Ani A, **Christensen B**. Letter: ACE2, IBD and COVID-19—why IBD patients may be at reduced risk of COVID-19. *Aliment Pharmacol Ther*. 2020;52(8):1422–1423. doi. 10.1111/apt.15804
- Prentice RE, Al-Ani AA, **Christensen B**. Letter: Covid-19—re-initiating clinical services for chronic gastrointestinal diseases. How and when? Authors' reply. *Aliment Pharmacol Ther*. 2020;52(8):1416. doi. 10.1111/apt.16065
- Al-Ani AA, Pretice RE, **Christensen B**. Letter to the editor: Care of the Patient With IBD Requiring Hospitalisation During the COVID-19 Pandemic. 2020. In Press. doi. 10.1093/ecco-jcc/jjaa183
- Rubin DT, Abreu MT, Rai V (on behalf of the COVID-19 IOIBD Taskforce). Management of patients with Crohn's disease and ulcerative colitis during the coronavirus disease-2019 pandemic: results of an international meeting. *Gastroenterology*. 2020;159(1):6-13. doi. 10.1053/j.gastro.2020.04.002
- Prentice R, **Christensen B**. What is the evolving role of calcineurin inhibitors in inflammatory bowel disease? Curbside Consultation in inflammatory bowel disease. 2020. In Press.

- Flanagan E, Gibson PR, Wright EK, Moore GT, Sparrow MP, Connell W, Kamm MA, Begun J, **Christensen B**, De Cruz P, Shelton E, Dowling D, Andrews JM, Brown SJ, Niewiadomski O, Ward MG, Rosella O, Rosella G, Kiburg KV, Ross AL, Bell SJ. Infliximab, adalimumab and vedolizumab concentrations across pregnancy and vedolizumab concentrations in infants following intrauterine exposure. *Aliment Pharmacol Ther.* 2020;52(10):1551-1562 doi. 10.1111/apt.16102
- Narula N, Aruljothy A, Alshahrani AA, Fadida M, Al-Saedi M, Marshall JK, Rubin DT, **Christensen B**. Histologic remission does not offer additional benefit for ulcerative colitis patients in endoscopic remission. *Aliment Pharmacol Ther.* 2020. In Press. doi. 10.1111/apt.16147
- Novak KL, Nylund K, Maaser C, Petersen F, Kucharzik T, Lu C, Allocca M, Maconi G, Voogd F, **Christensen B**, Vaughan R, Palmela C, Carter F, Wilkens R. Expert consensus on optimal acquisition and development of the International Bowel Ultrasound Segmental Activity Score (IBUS-SAS): a reliability and inter-rater variability study on intestinal ultrasonography in Crohn's Disease. *J Crohn's Colitis* 2020 In Press. doi. 10.1093/ecco-jcc/jjaa216
- Siegel CA, **Christensen B,** Kornbluth A, Rosh JR, Kappelman MD, Ungaro RC, Johnson DF, Chapman S, Wohl DA, Mantzaris GJ. Guidance for Restarting Inflammatory Bowel Disease Therapy in Patients Who Withheld Immunosuppressant Medications During COVID-19. *J Crohn's Colitis.* 2020;14(S3):S769-S773. doi. 10.1093/ecco-jcc/jjaa135
- Buckle AD, **Christensen B**. Editorial: The microscope holds the key to predict need for biologic therapy in immunotherapy-checkpoint inhibitor colitis. *Aliment Pharmacol Ther.* 2020. Accepted: In Press

- **Christensen B**, Rubin DT. Letter: Treat-to Target in Patients with Ileo-colonic Crohn's Disease- Endoscopic Remission or Histologic Healing? Authors' reply. 2020 Accepted: In Press

Abstracts and conference presentations on IBD during candidature:

- **Christensen** B, Ehrlich J, Hanauer S, Rubin DT. 964 Agreement Between Deep Histologic Remission and Mucosal Healing in Ulcerative Colitis and Predictors of Each Outcome. *Gastroenterology*. 2014: 146(5):S-172
- **Christensen** B, Ehrlich J, Hanauer S, Rubin DT. 997 Histological Normalization in Ulcerative Colitis: A New Treatment Outcome. *Gastroenterology. 2014:*146(5);S-174
- Nannegari V, Colwall J, **Christensen** B, Rubin DT. Su1321 Risk Factors of Disease Recurrence After Total Proctocolectomy With End Ileostomy in Patients with Inflammatory Bowel Disease. *Gastroenterology.* 2014: 146(5):2-436
- **Christensen** B, Goeppinger S, Rubin DT. Addressing Sexual Function in Patients with IBD: Results of a National Survey of US GI Physicians: 1720. *Am J Gastroenterol.* 2014:109:S509
- **Christensen** B, Kassim O, Ehrlich J, Hanauer SB, Rubin DT. DOP006 Histological Normalization Is Associated With Superior Relapse Free Survival Compared to Histological Activity and Histological Quiescence in Ulcerative Colitis. *J Crohns Colitis.* 2015: 9: S20-21
- **Christensen** B, Goeppinger S, Colman R Siddiqui D, Yarur A, Bochenek AA, Wichmann A, Hirsch A, Kinnucan J, Sakuraba A, Cohem A, Cohem R, Rubin DT. P615 Post-marketing experience of vedolizumab for IBD: The University of Chicago experience. *J Crohns Colitis.* 2015: 9; S388-89

- **Christensen** B, Goeppinger S, Colman R, Siddiqui D, Yarur A, Hirsch A, Bochenek AA, Wichmann A, Sakuraba A, Cohen R, Rubin DT. Calcineurin Inhibitors are safe and effective for induction of remission in patients commencing vedolizumab for IBD. *J Crohns Colitis*. 2015: 9; S281
- Yarur A, Gondal B, Syed N, **Christensen** B, Hirsch A, Hyman N, Abreu M, Rubin DT. P161 Validation of a Risk Score Predicting Post-Surgical Complications in Patients With Inflammatory Bowel Diseases. *J Crohns Colitis*. 2015: 9;S156-7.
- **Christensen** B, Kassim O, Ehrlich J, Hanauer SB, Rubin DT. 592 Histological Normalization Is Associated With Superior Relapse Free Survival Compared to Histological Activity and Histological Quiescence in Ulcerative Colitis. *Gastroenterology.* 2015: 148(4):S-115
- **Christensen** B, Goeppinger S, Colman , Siddiqui D, Yarur A, Hirsch A, Wichmann A, Bochenek AA, Sakuraba A, Cohen RD, Rubin DT. Crohn's Disease Patients Currently or Previously on Natalizumab Can Be Safely and Effectively Switched to Vedolizumab. Gastroenterology. 2015: 148(4):S-866-S867
- **Christensen** B, Goeppinger S, Colman R, Siddiqui D, Yarur A, Bochenek AA, Wichmann A, Hirsch A, Kinnucam J, Sakuraba A, Cohen RD, Rubin DT. Tu1350 Vedolizumab in the Treatment of IBD: The University of Chicago Experience. *Gastroenterology.* 2015; 148(4):S-866 **(Poster of Distinction, DDW 2015)**
- **Christensen** B, Goeppinger S, Colman R, Siddiqui D, Yarur Am Hirsch Am Bochenek AA, Wichmann AA, Sakuraba A, Cohen RD, Rubin DT. Tu1349 The Efficacy and Safety of Calcineurin Inhibitors in inducing and Maintaining Clinical Remission in IBD Patients Commencing Vedolizumab. *Gastroenterology.* 2015; 148(4):S-866

- Yarur A, Gondal B, Syed N, **Christensen** B, Hirsch A, Hyman N, Abreu MT. Tu1240 Validation of a Risk Score Predicting Post-Surgical Complications in Patients With Inflammatory Bowel Disease. *Gastroenterology.* 2015;148(4)-S-832-S-833
- **Christensen** B, Goeppinger S, Colman R, Yarur A, Hirsch A, Bocheneck A, Wichmann A, Sakuraba A, Cohen R, Siddiqui D, Rubin DT. Endoscopic and Histologic Response and Remission in Inflammatory Bowel Disease Patients Initiating Vedolizumab. 1843. *Am J Gastroenterol.* 2015; 110(S1):S783
- Yarur A, Gondal B, Syed N, Hirsch A, **Christensen B,** Cohen R, Rubin DT. Higher Thioguinine Metabolite Levels Improve Long-Term Outcomes In Patients With Inflammatory Bowel Diseases. *Am J Gastroenterol.* 2015;110(S1):S1920
- Mei S, Thompson A, **Christensen** B, Cunningham G, McDonald L, Bell S, Nguyen T, Iser D, Desmond P. Sustained virological response to HCV halts fibrosis progression: a decade long follow-up. *J Gastroenterol Hepatol.* 2016: 31(S2): 67
- **Christensen B**, Micic D, Gibson P, Singh S, Bellaguarda E, Corsello P, Gaetano JN, Kinnucan J, Rao VL, Reddy S, Yarur A, Rubin DT, Pekow J. P410 Vedolizumab is safe and effective for IBD, but has no effect on liver biochemistry in patients with concurrent PSC. *J Crohn's Colitis.* 2017;11(Suppl_1):S285-S286
- Kassim O, Micic D, **Christensen B**, Pekow J, Sakuraba A, Dalal S, Rubin D, Cohen R. P454 Can calcineurin inhibitors induce a durable remission that is maintained with vedolizumab in IBD? *J Crohn's Colitis* 2017;11 (Suppll_1):S309-S309
- **Christensen B**, Micic D, Gibson PR, Singh S, Bellaguarda E, Corsello P, Gaetao JN, Kinnucan JA, Rao VL, Reddy S, Yarur AJ, Rubin DT, Pekow K. Vedolizumab is safe and effective for IBD, but has no effect on liver biochemistry in patients with concurrent PSC. *Gastroenterology*. 2017;152(5);S405

- Kassim O, Micic D, **Christensen B**, Pekow JR, Sakuraba A, Dalal S, Kahn SA, Rubin DT, Cohen RD. Efficacy of calcineurin inhibitors during induction and maintenance of remission with vedolizumab in IBD. *Gastroenterology.* 2017;152(5):S405
- Kassim O, Micic D, **Christensen B**, Lissoos T, Luo M, Null K, Cohen R. Vedolizumab decreases utilization of healthcare resources in biologic-naïve inflammatory bowel disease (IBD) patients: 615. *Gastroenterology* 2017;112:S334-S335
- **Christensen B,** Ehrlich J, Gibson P, Rubin DT. Histological healing is associated with decreased clinical relapse in patients with ileal Crohn's Disease (A-2293). *J Crohn's Colitis.* 2018;12 (Supp_1):S184-S185
- **Christensen B,** Ehrlich J, Gibson PR, Rubin DT. 603-Histological healing is associated with decreased clinical relapse in patients with ileal Crohn's Disease. *Gastroenterology* 2018;154(6):S128-129
- **Christensen B,** Erlich J, Gibson P, Rubin DT. Histological activity is associated with worse clinical outcomes in patients with ileal Crohn's disease. *J Gastroenterol Hepatol.* 2018;33:88-88
- Prentice R, Vaughan R, Azim S, Ardalan Z, Neerasing N, Sivanesan S, Iyngkaran G, Macrae F, **Christensen B.** Pregnancy counseling and obstetric management of patients with inflammatory bowel disease: Patients and partners perspectives. *J Gastroenterol Hepatol.* 2018:33:110-110.
- Israel A, Jurdi KE, **Christensen B**, Rai V, Ollech JE, Cohen RD, Sakuraba A, Dalal SR, Rubin DT. Sa1845 Follow-Up of Ulcerative Colitis Patients Who Have Achieved Histological Normalization. *Gastroenterology.* 2019;156(6):S424-S425
- Ollech J, Dwadasi S, Normatov I, Israel A, Rai V, Sossenheimer P, **Christensen B**, Dalal S, Pekow J, Sakuraba A, Cohen R, Rubin DT. Efficacy and safety of induction therapy with calcineurin inhibitors followed by maintenance therapy with vedolizumab in severe

ulcerative colitis: a large patient cohort with long-term follow-up. *J Crohn's Colitis*. 2020;14(S1):S401-S401

- Wilkens RK, Nylund K, Petersen P, De Voogd F, Maaser C, Kucharzik T, Maconi G, Allocca M, C Lu C, Palmela C, Vaughan R, **Christensen B**, Novak KL. P175 Fatty liver disease as a complication of immune-mediated inflammatory diseases: prevalence and risk factors in inflammatory bowel disease. *J Crohn's Colitis.* 2020;14(S1): S225
- Shaffer S, Rai V, Traboulsi C, Cleveland NK, Singer J, Akiyama S, **Christensen B**, Rubin DT. Sa1169 Achieving Histologic Normalization In Long-Standing Ulcerative Colitis May Be Protective Against Developing Dysplasia In The Future. *Gastroenterology*. 2020;158(6): S-298
- Kaul A, Denholm JT, Kashkooli S, Garg M, Winter C, McCall S, **Christensen B**. Su1856 Seroconversion For Latent Tuberculosis In Travellers With Inflammatory Bowel Disease. *Gastroenterology* 2020;158(6):S-677
- Vaughan R, Murphy E, Nalder M, **Christensen B**. Su1892 A Single Centre Cross Sectional Cohort Study Examining The Relationship Between Serum Infliximab Levels And Intestinal Utlrasound Findings In Inflammatory Bowel Disease. *Gastroenterology*. 2020;158(6);S-691

Thesis including published works declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes 7 original papers published in peer reviewed journals and 2 published book chapters. The core theme of this thesis is improving outcomes in inflammatory bowel disease.

The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the Inflammatory Bowel Disease Center at The University of Chicago and The Gastroenterology Department, Alfred Hospital, under the supervision of Professor David T. Rubin and Professor Peter Gibson.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of chapter 2-10 my contribution to the work involved the following:

Thesis Chapter	Publication Title	Status	Nature and % of student contribution	Co-author name(s) Nature and % of Co-author's contribution*	Co-author(s), Monash student
1.3	Understanding Endoscopic Disease Activity in IBD: How to incorporate it into clinical practice.	Published	80%. Concept, literature review and writing first draft and review	David T Rubin: Concept and review of manuscript 20%	No
1.4	Objective assessment of endoscopic disease activity and mucosal healing	Published	80%. Concept, literature review and writing first draft and review	David T Rubin: Concept and review of manuscript 20%	No
1.9	Recurrent CD: Medical Prophylaxis.	Published	80%. Concept, literature review and writing first draft and review	David T Rubin: Concept, review of manuscript and development of algorithm 20%	No
2.2	Histologic normalization occurs in UC and is associated with improved clinical outcomes.	Published	70%. Concept, data collection, statistical analysis and writing first draft and review of subsequent drafts	S Hanauer: Concept, review of manuscript 2.5% J Ehrlich: Data collection 2.5% O Kassim: Data collection 2.5% P Gibson: Review of manuscript and drafts 7.5% J Turner: Histology review and manuscript review 2.5% J Hart: Histology review and review of manuscript 2.5% D Rubin: Concept, development and manuscript review 10%	No
2.3	Segmental histologic normalisation occurs in ulcerative colitis but does not improve clinical outcomes.	Published	70%. Concept, data collection, statistical analysis and writing first draft and review of subsequent drafts	S Hanauer: Concept, review of manuscript 2.5% P Gibson: Review of manuscript and subsequent drafts 10% J Turner: Histology review and review of manuscript 2.5% J Hart: Histology review and review of manuscript 2.5% D Rubin: Concept, development and review of manuscript 12.5%	No
2.4	Histologic Healing is More Strongly Associated with Clinical Outcomes in Ileal Crohn's Disease than Endoscopic Healing.	Published	70% Concept, data collection, statistical analysis and writing first draft and review of subsequent drafts	J Ehrlich: Data collection 2.5% P Gibson: Review of manuscript and subsequent drafts 10% J Turner: Histology review and review of manuscript 2.5% J Hart: Histology review and review of manuscript 2.5% D Rubin: Concept, development and review of manuscript 12.5%	No

Thesis Chapter	Publication Title	Status	Nature and % of student contribution	Co-author name(s) Nature and % of Co-author's contribution*	Co-author(s), Monash student
3.2	Vedolizumab as induction and maintenance for inflammatory bowel disease: 12-month effectiveness and safety.	Published	70%. Concept, data collection, statistical analysis and writing first draft and review of subsequent drafts	R Colman: Patient recruitment, data collection and manuscript review 2.5% D Micic: Patient recruitment, data collection and manuscript review: 2.5% P Gibson: review of manuscript 7.5% S Goeppinger: patient recruitment and data collection 2.5% A Yarur: Patient recruitment and data collection 2.5% R Cohen: Manuscript review 2.5% D Rubin: Concept, guidance and manuscript review 10%	No
3.3	Safety and Efficacy of Combination Treatment With Calcineurin Inhibitors and Vedolizumab in Patients With Refractory Inflammatory Bowel Disease.	Published	65%. Concept, data collection, statistical analysis and writing first draft and review of subsequent drafts	P Gibson: Guidance and review of manuscript 7.5% D Micic: Data collection and manuscript review 2.5% R Colman: Data collection 2.5% S Goeppinger: Patient recruitment and data collection 2.5% O Kassim: Patient recruitment and data collection 2.5% A Yarur: Patient recruitment and data collection 2.5% C Weber: Patient recruitment and data collection 2.5% R Cohen: Concept and manuscript review 2.5% D Rubin: Concept and manuscript review 10%	No
3.4	Vedolizumab in patients with concurrent primary sclerosing cholangitis and inflammatory bowel disease does not improve liver biochemistry but is safe and effective for the bowel disease.	Published	67%. Concept, data collection, statistical analysis and writing first draft and review of subsequent drafts	D Micic: Data collection 2% P Gibson: Guidance and manuscript review 5% A Yarur: Data collection 2% E Bellaguarda: Data collection 2% P Corsello:Data collection 2% J Gaetano: Data collection 2% J Kinnucan: Data collection 2% VL Rao: Data collection 2% S Reddy: Data collection: 2% S Singh: Data collection 2% J Pekow: Concept, guidance and manuscript review 5% D Rubin: Concept and manuscript review 5%	No

I have not renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student name: Dr Britt Christensen **Date**: 28th November, 2020

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor Name: Professor Peter R Gibson **Date:** 28th November, 2020

Acknowledgements

This research was supported by an Australian Government Research Training Program (RTP) Scholarship.

I would like to thank my primary supervisor's Dr David Rubin and Professor Peter Gibson.

First to Dr David Rubin who welcomed me to the University of Chicago, fostered my ideas and encouraged me in all my pursuits. He has mentored me over the last five years, has been a key driver in the development of my writing and presentation skills and has helped me grow into a leader and researcher within the field of inflammatory bowel disease. I will always be grateful for the support he offered during not only one but two pregnancies and deliveries during my two and a half years in Chicago despite my bursting into tears at having to tell him the news. Along the journey of research, thesis writing and babies he has also become a lifelong collaborator and friend.

I am also deeply indebted to Peter who mentored me through my final registrar year and these last five years of thesis development and writing. He was the first to encourage me to pursue research and clinical experience overseas and despite his busy schedule has always made time to read and edit manuscripts and talk about research ideas and life decision. He encouraged me to take the leap into a leadership role that I was not entirely sure I was ready for which has hence led me to the position of now running an inflammatory bowel disease unit at a major tertiary hospital in Melbourne. To top it off, he has demonstrated great patience whilst these work duties and family life have slowed the pace of my PhD completion. Again, he has become a life-long friend along the way.

I would like to thank both my parents. To my mother thank-you for instilling in me a love of learning, always believing in me and consistently encouraging me to ask questions even when people tried to silence me. To my father, who is no longer here to see this completed, I love you and miss you greatly. To my sisters and brother thank-you for listening to me, supporting me and always being there throughout this process. Your friendship has meant the world. You are all my best-friends and each day I pinch myself at how lucky I am to have such an amazing,

intelligent and crazy family. To my parents-in-law thank-you for your encouragement whilst working and studying, and particularly for the many hours of babysitting that you have provided, without which I could not have completed these studies. I would also like to thank my gastroenterology colleagues and friends, Georgie, Ilana and Emily who have shared many a night over a glass of wine whilst philosophizing over our life choices and decisions around family, life and work.

Finally, to my family who are my inspiration. To my husband, Jason, the love of my life, I will always be thankful for the support you have offered throughout this process and all the processes I have dragged you along over the last 20 years. You travelled across the world with me, have supported me through life's ups and downs, picked up the duties of primary carer throughout all my work travels and have been my best friend along the way with the ability to always makes me laugh. You have also grown into a mature and thoughtful man, who has embraced co-parenting and who is an inspirational role-model for our children. To my two amazingly strong, intelligent and funny daughters, Saskia and Sage, and my sweet, determined and patient son, Micah, you have been the best part of this process. You bring light to every day, your laughter is infectious and your cuddles make my chest want to burst open. I love seeing you grow and develop and thank-you for all the smiles, cuddles and kisses you endow on me constantly. You inspire me to be a better person and to want to make the world a better place. I wish you all a fun and happy life full of learning, love and laughter.

Table of Contents

Part 1: Introduction, Literature Review and Research Aims

1.1 GENERAL INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are the two main disorders that make up the collective term, inflammatory bowel disease (IBD). IBD is a chronic, progressive, inflammatory disease of the gastrointestinal tract.(1) UC is a disease of the mucosal layer and is associated with an increased risk of colorectal cancer and other serious structural and functional consequences in the long term including the development of colonic strictures, dysmotility, anorectal dysfunction and impaired permeability.(1) CD involves all the tissue layers of the gastrointestinal lining resulting in transmural inflammation, and can involve the mesenteric lymphatic system. Thus, in addition to the above-mentioned complications, CD can result in deep ulcers with fistula formation, abscesses and bowel perforation. In both conditions, endoscopic mucosal healing has emerged as a new therapeutic goal with the aim of preventing these long-term complications of the disease.(2-5) This is despite the fact that endoscopy only surveys the mucosal surface of the colon and terminal ileum.

The main goal of therapy in IBD is to achieve and maintain disease remission. However, what constitutes this remission has changed in recent years. In the past, clinical remission, often defined as cessation of rectal bleeding, urgency and achievement of formed stool in UC and amelioration of abdominal pain and normalisation of stool frequency in CD was the accepted target of therapy when treating IBD. By achieving this goal, we had hoped to improve our patient's health related quality of life and avoid disease related complications including hospitalisations and surgeries.

However while clinical remission may represent the functional improvement most recognizable to the patient, it focuses on the short-term goal of symptom relief and fails to recognise the importance of active inflammation at the transmural level in regards to long-term outcomes.(6, 7) Hence, despite access to many new therapies over the years, the majority of CD patients still undergo surgery and we have not successfully modified the course of IBD in the modern era.(8, 9) The recognition of this fact has recently led to a paradigmatic change in therapeutic approach in IBD. Frequent evaluation of objective markers of intestinal inflammation are being increasingly incorporated into treatment strategies to allow for timely changes of therapy. One such objective maker is that of mucosal healing. Although mucosal healing does not have a standardized or validated definition in IBD, it is most often defined as the absence of friability, blood, erosions and ulcers in all visual segments of the gut in UC (10) and the absence of ulceration in CD.(53) Mucosal healing has increasingly been demonstrated to improve patient clinical outcomes in IBD and has been associated with prolonged remission, fewer hospitalizations and surgical procedures, a lower risk of colorectal cancer, and improved quality of life.(6, 11-14)

Despite the benefits of achieving mucosal healing, mucosal healing is not always an accurate indicator of histologic healing as microscopic evidence of inflammation is common even in patients with clinically and endoscopically quiescent disease.(2) Histologic healing is considered as the ultimate marker of quiescent disease activity and, at least in UC patients, the presence of persistent microscopic inflammation may predict a higher risk of clinical flares, colectomy, colorectal neoplasia and hospitalisation in patients.(15-17). Despite this, up to 63% of patients in clinical and endoscopic remission will have ongoing histologic inflammation and it is still not clearly defined whether normalisation of histology in IBD is possible, what degree of histological healing is required to improve clinical outcomes in IBD and whether persistent

histologic inflammation is associated independently with a worse prognosis in Crohn's disease.(18-20) Furthermore, new therapies are constantly emerging in IBD and how these therapies impact on the clinical, endoscopic and histological outcomes needs to be constantly explored.

Part 1 of this PhD initially outlines the current literature on the topics of: 1) The importance of objective markers of disease activity to guide treatment management in IBD; 2) Endoscopic disease activity in IBD, how to assess for mucosal healing and the prognostic value of a healed bowel; 3) Histology as an endpoint in IBD; 4) Emerging endpoints and surrogate markers of remission in IBD; and 5) Medications used for induction and maintenance of mucosal and histologic remission in IBD. It concludes with a synopsis of the thesis and summary of the studies included.

1.2 OBJECTIVE ASSESSMENT OF DISEASE ACTIVITY IN IBD: THE PROBLEM WITH RELYING ON CLINICAL INDICES TO GUIDE TREATMENT MANAGEMENT

Historically, we have relied on a patient's reports of disease activity to guide our therapy in IBD, with a "step-up" approach based on re-evaluation of response and according to these clinical symptoms. However, this approach to treatment is flawed for several reasons. First, less than half of patients believe that being in remission could mean living without symptoms entirely and 74% believe it is normal to have clinical disease flares.(21) Therefore, if it is patient's perception that clinical symptoms can be a normal part of the disease course, patients may underreport their clinical disease activity. Second, it has been found that, despite feeling well, inflammation is often present in asymptomatic patients with up to 40% of patients in clinical remission being found to have endoscopic disease activity.(13, 18, 22-24) Conversely, despite feeling unwell, patients may have no endoscopic findings of disease activity.(23) This can lead to both under and over treatment if one relies solely on clinical indices to guide treatment strategy. Third, many patients do not have stable disease control, with over 37% of patients having frequent intermittent symptoms over time(25) and only 10% of patients experiencing prolonged clinical remission.(25, 26)

Relying on these historical indices has thus resulted in many patients having ongoing inflammation despite feeling well. Allowing symptoms to direct decision-making is a flawed strategy that is both reactive and not disease modifying. It may be associated with immediate improved quality of life, but it is not until mucosal healing is achieved that patients may avoid future disability from their disease.

1.3 UNDERSTANDING ENDOSCOPIC DISEASE ACTIVITY IN IBD: HOW TO INCORPORATE IT INTO PRACTICE

Increasingly, it has been determined that healing, as ascertained by endoscopic assessment, is the goal of treatment in patients with IBD. The following paper reviews the different endoscopic scoring systems available to document disease activity and mucosal healing in IBD and gives recommendations about the scoring systems to use in both clinical trials and clinical practice.

Curr Gastroenterol Rep (2016) 18: 5
DOI 10.1007/s11894-015-0477-6

Understanding Endoscopic Disease Activity in IBD: How to Incorporate It into Practice

Britt Christensen[1,2] · **David T. Rubin**[1]

Published online: 12 January 2016

Abstract Endoscopic assessment of disease activity is an essential part of clinical practice in inflammatory bowel disease (IBD) and is used for diagnosis, prognosis, monitoring for dysplasia and increasingly for the evaluation of mucosal or endoscopic response to therapy. Recently, mucosal or endoscopic healing has emerged as a key goal of therapy as it has been found that patients who achieve endoscopic remission have improved outcomes compared to those who do not, and this may be independent of their clinical disease activity. However, there is currently no validated definition of mucosal healing and there are numerous endoscopic scoring systems proposed to define endoscopic activity and response to therapy in both ulcerative colitis and Crohn's disease. This article will discuss the most common endoscopic scores used to measure endoscopic disease activity in IBD, the pros and cons of each of these scoring systems and proposed definitions for endoscopic response or remission that exist for each. In addition, the role of endoscopy in prognosticating the disease course is discussed and how endoscopy can be utilized as part of a "treat-to-target" treatment strategy where endoscopy results direct decisions regarding medical strategies in clinical practice is highlighted.

Keywords Crohn's disease · Colonoscopy · Disease activity indices · Endoscopic disease activity · Inflammatory bowel disease · Mucosal activity · Mucosal healing · Ulcerative colitis

Topical Collection on *Inflammatory Bowel Disease*

✉ David T. Rubin
drubin@medicine.bsd.uchicago.edu

[1] University of Chicago Medicine Inflammatory Bowel Disease Center, 5841 S. Maryland Ave., MC4076, Room M410, Chicago, IL 60637, USA

[2] Department of Gastroenterology, Alfred Hospital and Monash University, Melbourne, Australia

Introduction

Endoscopy in IBD is used to diagnose ulcerative colitis (UC) and Crohn's disease (CD), prognosticate disease severity, obtain biopsies of intestinal mucosa for histological examination, monitor for dysplasia and risk of colorectal cancer and more recently to evaluate mucosal or endoscopic response to therapy. Historically, the aim of treatment for patients with inflammatory bowel disease (IBD) has been to induce and maintain clinical (symptomatic) remission. However, increasingly, there has been a paradigmatic shift in therapeutic approach with a push toward aiming for endoscopic remission or mucosal healing as a primary treatment goal. This is in recognition of the fact that treating to induce clinical remission is unreliable as IBD symptoms are subjective, with patients in clinical remission having significant endoscopic disease activity [1–5] and patients who feel unwell having no endoscopic findings of disease activity [3]. This puts a significant proportion of patients at risk of either disease progression due to inadequate treatment or at risk of over treatment with unnecessary medications if we rely on clinical symptoms alone to determine our anti-inflammatory treatment strategy. Furthermore, patients who do achieve endoscopic remission have improved outcomes compared to those who do not, with patients who achieve mucosal healing being found to have a decreased risk of clinical relapse, hospitalizations, surgery and colorectal neoplasia [1, 3, 6••, 7–14].

Therefore, in order to accurately assess disease activity and determine and quantify response to therapy, endoscopic assessment is required and is increasingly becoming the standard of care. This article will discuss the most common endoscopic scores used to measure endoscopic disease activity in IBD and their role in predicting the course of these diseases and their impact on decisions regarding medical strategies. We also provide a brief review of emerging non-invasive markers

of mucosal healing that are increasingly being incorporated into the real world setting and discuss how the assessment of endoscopic disease activity should be incorporated into routine clinical practice.

Endoscopic Disease Activity Indices for Ulcerative Colitis

Endoscopic findings of mucosal inflammation in UC typically include erythema, edema with vascular congestion or loss of fine vascular pattern, and granularity [15]. As the disease progresses in severity, friability, spontaneous bleeding and macroscopic ulceration can also occur [15]. Truelove and Witts developed the initial mucosal scoring system for UC in 1955 [16]. They reported endoscopic lesions as normal or near normal, improved or no change/worse on sigmoidoscopy during a placebo-controlled trial of cortisone for the treatment of active disease. Since then, many endoscopic scoring systems for UC have been developed to measure endoscopic disease activity (Table 1).

As there are many scoring systems available, this review will focus on the most common scoring system used in clinical trials of UC, the Mayo Clinic endoscopy subscore, and the newest scoring system that is currently undergoing validation and is likely to be increasingly adopted in the future, the ulcerative colitis endoscopic index of severity (UCEIS).

The most common endoscopic score used in clinical trials to measure endoscopic disease activity in UC is the Mayo Clinic endoscopy sub-score [26]. This score has four components: erythema, friability, vascular pattern and erosions/ulceration with a maximum total score of 3 (Fig. 1). Although not formally validated, mucosal healing has generally been defined as a Mayo score of either 0 or 1 [29]. This definition has since been found to be fitting with a post hoc analysis of the active ulcerative colitis trials (ACT)-1 establishing that patients who achieve a post-treatment Mayo endoscopic score of 0 or 1 have equivalent rates of colectomy on follow-up and are significantly less likely to undergo colectomy over the subsequent year than those with higher Mayo endoscopic sub-scores [30]. However, of note, patients who achieved a score of 0 were found to have higher rates of steroid-free remission at 1 year compared to those who only achieved a score of 1 [30]. The strengths of the Mayo endoscopic sub-score lie in the frequency of its use in clinical trials and its ease of use. Its weakness lies in its lack of validation, the fact that it does not distinguish between deep and superficial ulceration [31•] and that the score only reflects the most severely affected segment of the bowel visualized without giving any indication of the extent or distribution of mucosal inflammation and setting no minimal insertion length. In addition, the original score includes variable degrees of friability in the score of 1 and 2, which results in high inter-observer discrepancy and inconsistent results [32]. In fact, because of this concern, some studies have used a modified Mayo scoring system that classifies the presence of any degree of friability as an automatic Mayo endoscopic sub-score of 2 [33–35]. This modified Mayo Clinic Endoscopic Score (MMCS) has been found on initial review to have excellent intra-observer and inter-observer reliability (intra and inter-class correlation coefficient and 95 % confident interval [95 % CI] 0.89 [0.85–0.92] and 0.79 [0.72–0.95], respectively) and is responsive to change [36].

Due to the need for a prospectively validated endoscopic assessment tool that can assess mucosal healing in UC and be applied to clinical practice, the ulcerative colitis endoscopic index of severity (UCEIS) [37] and the ulcerative colitis colonoscopic index of severity (UCCIS) [27] have recently been developed and undergone initial validation. The UCEIS (Table 2) is the most cited of these tools and was prospectively developed using multiple validated steps with the final tool evaluating vascular pattern, bleeding and erosions and ulcers with the worst segment of the colon scored for each variable on a 0–2 or 0–3 scale giving a total score of 0–8 [37]. The final scoring system is easy to use and has a high intra and inter-observer agreement with an intra-observer kappa value of 0.82, 0.72 and 0.78 and inter-observer kappa values of 0.83, 0.56 and 0.77, respectively, for three main descriptor domains of vascular pattern, bleeding and erosion/ulcers [28•]. The correlation coefficient (r^2) between the UCEIS and overall severity evaluation was 0.94 ($p < 0.0001$), meaning it accounts for 88 % of the variance in overall assessment of severity between observers [28•]. The main limitation of this score currently is that there is still no threshold set for remission, mild, moderate and severe disease although these are anticipated in the near future. A preliminary study has shown that in patients admitted with acute severe colitis, a score of 7 or 8 out of 8 at the time of admission predicts inadequate response to intravenous steroids and need for rescue therapy with cyclosporine or infliximab [38]. This scoring system is currently being adopted in clinical trials and will likely be adapted for clinical practice in the future.

Endoscopic Disease Activity Indices for Crohn's Disease

Endoscopic findings in CD consist of edema, erythema, apthoid ulceration, cobblestone appearance and strictures [15]. There are currently three major endoscopic indices for evaluating CD disease activity (Table 3). The two validated endoscopic activity scores for CD are the Crohn's disease endoscopic index of severity (CDEIS) [39] and the simple

Table 1 Endoscopic disease activity scoring systems in ulcerative colitis

Endoscopic scores	Variables	Score range	Definition of remission and response	Strengths	Weaknesses
Truelove and Witts sigmoidoscopic assessment [16]	Hyperemia, granularity and change in overall appearance of the mucosa	No description	Not defined	Able to stratify patients by their disease severity	Not validated High inter-observer variability No definition of mucosal healing
Baron score [17]	Severity of mucosal bleeding and friability	0–3	Remission: 0–1 (NV) Response: Not defined	Easy to use Good inter-observer correlation	Not validated No assessment of ulcers No definition of mucosal healing
Modified Baron score [18]	Friability, vascular pattern, granularity, bleeding and ulceration	0–4	Remission: 0–1 (NV) Response: Not defined	Easy to use Good inter-observer correlation	Not validated No definition of mucosal healing
Powell-Tuck sigmoidoscopic assessment [19, 20]	Severity of mucosal bleeding and friability	0–2	Not defined	Easy to use	Not validated No definition of mucosal healing Ulceration not included
Rachmilewitz endoscopic index [20]	Granulation, vascular pattern, vulnerability of mucosa, mucosal damage	4 items rated 0–3. Total of 0–12 points	Remission: 0–4 (NV) Response: Not defined		Not validated Complex and subjective descriptive terms
Sigmoidoscopic index [21]	Erythema, friability, ulceration, mucous, vascular pattern	5 items rated 0–3. Total 0–16 points	Remission: 0–4 (NV) Response: Not defined		Not validated Complex
Sigmoidoscopic inflammation grade score [22]	Edema, vascular pattern Granularity, friability, bleeding, ulcers	0–4	Not defined		Not validated No definition of mucosal healing
Sutherland mucosal appearance assessment [23]	Friability, exudation, bleeding	0–3	Not defined		Not validated Subjective No definition of mucosal healing Easy to use
Endoscopic activity index [24]	Ulcers (size and depth), erythema, bleeding, mucosal edema, mucosal exudate	0–3	Not defined		Complex Not validated No definition of mucosal healing Closely correlated with clinical activity
Matts Index [25]	Granularity, bleeding, edema Ulceration	1–4	Not defined		Not validated No definition of mucosal healing Easy to use Good inter and intra-observer agreement
Mayo endoscopic sub-score [26]	Erythema, vascular pattern, friability, bleeding, erosions, ulcerations	0–3	Remission: 0 or 0–1 (PV) Response: Not defined		Not validated Extensive use in clinical trials and RCTs
Ulcerative colitis colonoscopy index of severity (UCCIS) [27]	Vascular pattern, granularity, ulceration, bleeding/friability	4 items rated 0–2 for vascular pattern, granularity, bleeding/ friability and 0–4 for ulcerations. To total 0–10 points	Not defined	Preliminary validation Based on rigorous methodology Provides pan-colonic assessment	Includes subjective parameters and complex scale No definition of mucosal healing Requires post-procedure time to be scored

Table 1 (continued)

Endoscopic scores	Variables	Score range	Definition of remission and response	Strengths	Weaknesses
Ulcerative colitis endoscopic index of severity (UCEIS) [28•]	Vascular pattern, bleeding, erosions/ulceration	3 items rated 0–3 for vascular pattern and 0–4 for bleeding and ulceration. Total of 0–11 points	Not defined	Preliminary validation Easy to use Based on rigorous methodology Accounts for 94 % of variance between endoscopists for the overall assessment of severity Independent of clinical symptoms	Limited to rectosigmoid Low agreement for normal appearing mucosa Sensitivity to change and mucosal healing remain undefined

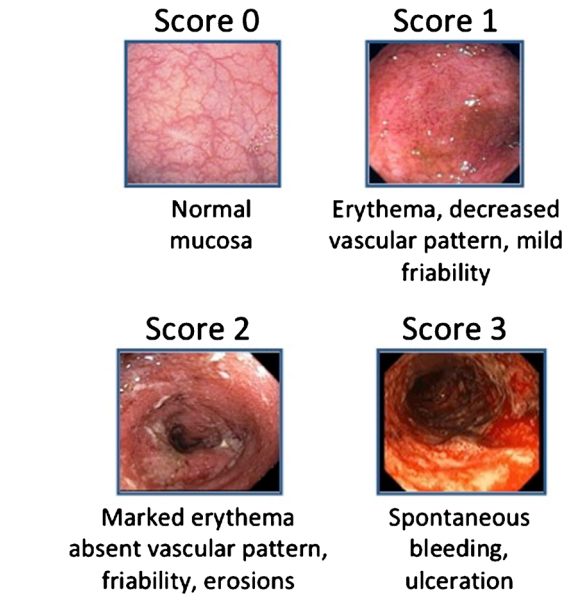


Fig. 1 Mayo endoscopic sub-score

endoscopic score for Crohn's disease (SES-CD) [40]. Both tools have been prospectively validated and shown to be reproducible and have good inter-observer agreement [42–44].

The CDEIS is often considered the gold standard for classifying endoscopic disease activity in CD. The endoscopic parameters of (1) presence or absence of ulcers, distinguished as superficial or deep, (2) percentage of surface ulcerated and/or affected, and (3) presence of stenosis, classified as ulcerated or non-ulcerated stenosis in the five bowel segments (terminal ileum, right colon, transverse colon and sigmoid, and rectum) are evaluated to give a total score of 0–44 [39]. It has good correlation with the Crohn's disease activity index (CDAI), is highly reproducible and is sensitive to changes in endoscopic mucosal appearance and healing [30]. The CDEIS is the most commonly used endoscopic tool to assess disease activity in clinical trials although there is no agreement or formal validation regarding cut-off values for defining endoscopic response to treatment, endoscopic remission or mucosal healing and no data available on long-term clinical outcomes. In the available trials, endoscopic response has previously been defined as a decrease from the baseline score of at least 3 or 5 points [43, 45] although more recently, a post hoc analysis of the SONIC trial by Ferrante et al. [46], showed that defining endoscopic response as a decrease from baseline of the CDEIS score of at least 50 %, was most predictive of corticosteroid-free clinical remission by week 50, including that of a decrease in score of 3 or 5 points. In trials utilizing the CDEIS, endoscopic remission has been defined as "partial" using a cut-off of <6 [40, 45, 47], and "complete" using a cut-off of <3 [40, 45], <4 [48], ≤4 [49] or 0 [50]. The main limitation of the CDEIS is the fact that it is a

Table 2 The ulcerative colitis endoscopic index of severity (UCEIS) [28•]

Descriptor	Score	Definition
Vascular pattern	Normal (0)	Normal vascular pattern with arborization of capillaries clearly defined, or with blurring or patchy loss of capillary margins
	Patchy obliteration (1)	Patchy obliteration of vascular pattern
	Obliterated (2)	Complete obliteration of vascular pattern
Bleeding	None (0)	No visible blood
	Mucosal (1)	Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope, which can be washed away
	Luminal mild (2)	Some free liquid blood in the lumen
	Luminal moderate or severe (3)	Frank blood in the lumen ahead of endoscope or visible oozing from mucosa after washing intraluminal blood, or visible oozing from a hemorrhagic mucosa
Erosions and ulcers	None (0)	Normal mucosa no visible erosions or ulcers
	Erosions (1)	Tiny defects in the mucosa, of a white or yellow colour with a flat edge
	Superficial ulcer (2)	Larger (>5 mm) defects in the mucosa which are discrete fibrin-covered ulcers when compared with erosion, but remain superficial
	Deep ulcer (3)	Deeper excavated defects in the mucosa with a slightly raised edge

The three descriptors are scored for the worst affected area of the colon to give a score of 0–8

[Adapted from. Travis S et al. Reliability and Initial Validation of the Ulcerative Colitis Endoscopic Index of Severity. Gastroenterology. 2013; 145:987–995] [28•]

complex tool that requires training and experience to utilize, resulting in a 2002 expert consensus statement that the CDEIS should be reserved for use in clinical trials only due to its complexity [51].

To overcome these limitations, a simplified index, the simple endoscopic score for CD (SES-CD) was developed. The SES-CD is reliable and correlates well with the CDEIS (correlation coefficient $r^2 = 0.920$) [40]. The endoscopic parameters of (1) ulcer size, (2) ulcerated and affected surfaces, and (3) stenosis are scored from 0 to 3 in each of the five bowel segments (terminal ileum, right colon, transverse colon and sigmoid, and rectum) to give a total score of 0–60 [40]. However, despite it being much simpler than the CDEIS, the SES-CD is still a complex index with limited use in clinical practice. In addition, as with the CDEIS, there is a lack of consensus on the definition of endoscopic response and remission. In previous clinical trials, a SES-CD score of <3 [49, 52–54] or equal to 0 [13, 50, 55–57] has been used to define endoscopic remission or minimal endoscopic activity and, more recently, Moskovitz et al. [58] validated the cut-off values for the SES-CD as 0–2 for endoscopic remission, 3–6 for mild endoscopic disease, 7–15 for moderate endoscopic disease activity and ≥16 for severe endoscopic disease activity. In regard to defining endoscopic response to treatment, as with the CDEIS, Ferrante et al. [46] demonstrated that a decrease from baseline of the SES-CD score of at least 50 % was most predictive of improved outcomes. With this evidence in mind, the International Organization for the Study of Inflammatory Bowel Disease is preparing an expert opinion publication stating that endoscopic response to therapy should be defined as a >50 % decrease in the SES-CD and that remission should be defined as an SES-CD of 0–2 [59].

The final endoscopic activity scoring system commonly used in CD is the Rutgeert's score [41] (Fig. 2). The Rutgeert's score assesses and quantifies endoscopic disease recurrence in the neo-terminal ileum after ileal or ileocolonic resection [41, 60] and is the most commonly used tool used to assess recurrence in postoperative CD trials. The numerical score ranges from 0 to 4; (0) normal mucosa; (1) <5 apthous lesions; (2) >5 apthous ulcers with normal intervening tissue; (3) diffuse inflammation with diffuse ulcers; (4) nodules and/or narrowing. Although it has not been fully prospectively validated, the severity of the Rutgeert's score on endoscopy in an asymptomatic patient within 12 months of the ileocolonic resection has been shown to predict the risk of clinical recurrence with Rutgeert's score of grade 0 or 1 being associated with a very low risk of clinical recurrence (80–85 % asymptomatic at 3 years follow-up) compared to those who have a score of 3 or 4 (<10 % asymptomatic

Table 3 Crohn's disease endoscopic disease activity scoring systems

Score	Variables	Score range	Definition response/remission	Strengths	Weakness
Crohn's disease endoscopic index of severity (CDEIS) [39]	Deep ulceration, superficial ulceration, inflammation, ulcerated stenosis, non-ulcerated stenosis	0–44	Complete remission 0, <3, <4, or <6 (NV) Response: decrease from baseline of 50 % (PV) to 75 % or decrease from baseline of 3–5 points (NV)	Validated Reproducible Extensive use in clinical trials	Complex Many variables Requires training and experience No validated definition of mucosal healing or response
Simple endoscopic score for Crohn's disease (SES-CD) [40]	Ulcer size, ulcerated surface, inflammation, stenosis	0–60	Remission 0 or <3 points (NV) Response: decrease from baseline of 50 % (PV) or decrease from baseline of ≥5 points (NV)	Validated Score correlates well with CDEIS Reproducible	Complex Not practical for clinical setting Validated against CDEIS in only one study No validated definition of mucosal healing or response
Rutgeerts score [41]	Aphtoid lesions, ulcers, inflammation, nodules and stenosis	i0–i4	Score of i0–i1 low risk of clinical recurrence Score of i2 = intermediate risk of clinical recurrence Score of i3 = high risk of clinical recurrence (PV)	Gold Standard for assessment of postoperative recurrence Extensive use in clinical trials Validated cut-off values for clinical recurrence	No formal validation Only useful for ileal or ileal-colonic surgery

NV not validated, *PV* partially validated

at 3 years follow-up) [41]. Therefore, ileocolonoscopy is recommended within 1 year following surgical resection to determine if postoperative treatment is effective or if additional treatment is required.

Endoscopic Assessment Can Predict Disease Severity

Endoscopic severity may predict the future clinical course of IBD. In both UC and CD, severe endoscopic lesions predict an increased risk of colectomy. In CD, severe endoscopic ulceration increases the risk of colectomy to 31 % from a baseline of 6 % at 12 months in those without severe endoscopic lesions [61] and in UC, the odds ratio of colectomy when a patient is admitted for a severe attack is 41 in those with severe lesions on endoscopy compared to those without severe lesions [62]. In addition, it has been shown that only 34 % of patients who respond to medical therapy in severe colitis have severe endoscopic lesions compared to 91 % in those who do not respond to medical therapy (OR >20) [40].

Importance of Achieving Mucosal Healing in IBD

In recent years, mucosal healing has increasingly emerged as a major aim of therapeutic interventions in IBD. This is secondary to the growing evidence that demonstrates improved clinical outcomes in those achieving mucosal healing compared to those who do not.

Improved clinical outcomes in patients who achieve mucosal healing compared to clinical remission alone was first reported back in 1966 by Wright et al. [63] who found that UC patients not achieving mucosal healing when treated with steroids relapsed more frequently during a follow-up period of 1 year compared to patients who did (40 vs. 18 %, respectively). Since then, a plethora of studies have confirmed this finding and demonstrated that in both UC and CD, mucosal healing is associated with prolonged remission, fewer hospitalizations and surgical procedures, less bowel damage (fistulas) in CD, less immunosuppression therapy, a lower risk of colorectal cancer, and improved quality of life [1, 3, 6••, 7–14, 30, 62, 64–66].

Recently, it has also been demonstrated that the severity and chronicity of inflammation in the colon is associated with the risk of colorectal neoplasia [67–70]. The degree of endoscopic and histologic inflammation has been found to correlate with the risk of developing colorectal neoplasia on univariate analysis with more severe disease being associated with higher cancer risk [67, 68]. Despite the fact that on multivariate analysis only histological inflammation was an independent predictor of risk, a follow-up study of colorectal surveillance did find that UC patients who have mucosal healing

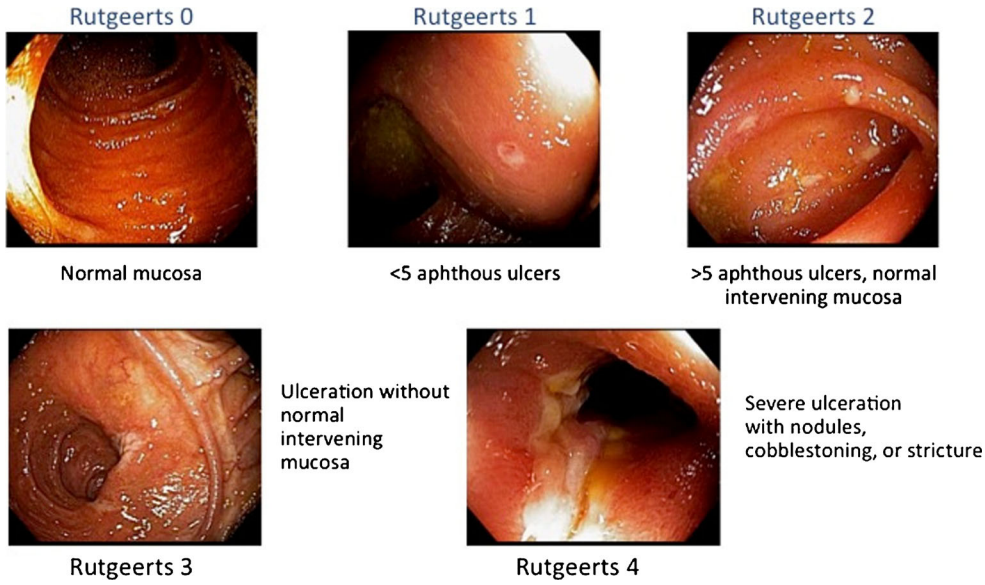


Fig. 2 Rutgeerts' score for postoperative endoscopic recurrence

or a macroscopically normal colon have a colorectal cancer risk similar to that of the general population on 5-year follow-up [68].

Endoscopic Assessment in Clinical Practice

Clinical disease activity is subjective and not a reliable indicator of endoscopic disease activity. It has been found that up to half of patients who are in clinical remission will still have endoscopic evidence of active disease [71]. In addition, a high prevalence of clinical symptoms has been noted in patients who actually have achieved mucosal healing [3, 72]. This leads to a situation in which patients may be either under- or over-treated in relation to their symptoms and disease activity if endoscopic assessment does not occur, and is the reason that assessment of endoscopic disease activity is increasingly being applied to treatment algorithms.

When to Look

In regard to timing of endoscopic assessment, due to the prognostic value of endoscopy in regard to long-term outcomes, patients who have a significant increase in clinical symptoms or are first presenting with symptoms should undergo a baseline endoscopy. This allows an appropriate treatment plan to be initiated that is titrated to the patient's disease severity. Once therapy has commenced, it is now increasingly accepted that a follow-up colonoscopy should occur to assess for mucosal healing or endoscopic response to therapy. The timing of this is still controversial but should likely occur between 3 and 6 months (earlier if the faster acting anti-TNF therapies are utilized and later if the slower acting anti-metabolite or anti-integrin medications are used).

How to Document Endoscopic Activity and Mucosal Healing

The routine use of endoscopic scoring systems is currently limited to trial settings. The reason for this is secondary to the fact that currently there is no one accepted tool that has been standardized for this setting in either CD or UC, often the scoring systems are too complex and time-consuming to be used in clinical practice and many suffer from high inter-observer variability. In addition, the existing scoring systems do not have well-defined and validated thresholds for mucosal response or healing and there is no consensus on degree of mucosal healing that is required to limit future disability or change the natural history of the disease.

However, despite their limitations, the use of an endoscopic scoring system can aid in the reporting of endoscopic findings and allow easy comparison between a patient's current and previous colonoscopy result. If it is feasible, we recommend the use of the Mayo subscore for UC and the SES-CD score for CD. However, in clinical practice, generally documentation of endoscopic disease activity remains subjective. If the endoscopic scoring systems are not used, it is important to report in each segment of the bowel on the following:

- The extent and location of inflammation
- If the bowel involvement is continuous or involves skip areas
- The presence of erythema, loss of vascular pattern, bleeding (contact or spontaneous), presence of erosions or ulceration (superficial or deep) and the presence of strictures or fistulas.

We also recommend specific language in the impressions to distinguish "clinical remission" from "endoscopic remission" from other end points (like histologic remission). Such examples include the following:

> IMPRESSION: Endoscopically moderately active left-sided ulcerative colitis.
> IMPRESSION: Endoscopically quiescent panulcerative colitis and clinical remission (deep remission).
> IMPRESSION: Endoscopically mildly active patchy Crohn's ileitis and proximal colitis.

In addition, on follow-up, ileocolonoscopy is important to note if the endoscopic disease activity has improved, worsened or is stable.

Although not yet suitable for adoption in the clinical setting, currently newer endoscopic scoring systems are being developed and future studies are likely to validate these scoring systems in the clinical setting and demonstrate their role in the day-to-day management of IBD patients. This will help with the comparison between drug efficacies and optimize a treat-to-target treatment algorithm in our patients.

How to Achieve Mucosal Healing

If a patient is symptomatic and has not achieved mucosal healing, then escalation of medical therapies should occur. If a patient who is in clinical remission is found to have unexpected mucosal inflammation, an open dialogue should occur about the goals of treatment. Symptom control and the side effects of therapy should be acknowledged but a discussion about the risks of uncontrolled inflammation and resulting progressive disease should also occur and short and long-term goals recognized. It is now thought that achieving mucosal healing will improve the long-term outcomes of inducing sustained clinical remission and reducing hospitalizations and surgery in patients with IBD and reduce or prevent progressive disease and disability. Therefore, adopting a "treat-to-target" approach is increasingly being accepted with the target being that of mucosal healing. After discussing the pros and cons of escalation of therapy with the patient, techniques to treat to mucosal healing include confirming adherence to medication and overcoming barriers to adherence, optimization of current medical therapies including assessment of medication metabolites or therapeutic monitoring of anti-TNF therapy and adjusting therapy as needed and if required consideration given to switching therapy to another drug within the same class or outside the class depending on the clinical context [73].

Preliminary retrospective data suggest that repeated assessment of endoscopic disease activity with adjustment of medical therapy to the target of mucosal healing is feasible in clinical practice and seems to be of benefit [74••, 75••]. However, although it is thought that mucosal healing will improve long-term outcomes, there are still many unresolved challenges in regard to incorporating endoscopic assessment and the target of mucosal healing into routine clinical practice (Table 4). It is still unclear just how much healing is required and it is yet to be demonstrated prospectively that mucosal healing can prevent disease progression or change the natural history of IBD [73]. Therefore, before any medication adjustment takes place, the risks of medical escalation must be weighed against the benefits of achieving mucosal healing as this escalation of therapy is likely to increase the associated risks of the medication [73, 76••]. For targets of healing, a recent expert statement from the International Organization for the study of Inflammatory Bowel Diseases (IOIBD) has recommended selecting a Mayo endoscopic sub-score of 0–1 to define endoscopic remission in UC and the resolution of ulceration at ileocolonoscopy in CD [77••].

Conclusion

Ileocolonoscopy is now considered the gold standard to assess disease severity, prognosticate a patient's future disease course and quantify mucosal response and healing following treatment in inflammatory bowel disease and is more reliable in determining disease activity than relying on clinical symptoms alone. Numerous endoscopic scoring systems exist however most are limited due to their complexity and a lack of formal validation. In addition, there is currently limited consensus on the value or percentage improvement in these scores that should be used to define mucosal improvement and healing and there is limited data on how these scores can be utilized to predict long term improved clinical outcomes and therapeutic management strategies in regard to continuing or stopping therapy or changing the type of therapy completely. Despite these limitations, the assessment of disease activity and mucosal healing by endoscopy is increasingly becoming standard of care and should now be routinely implemented into clinical practice as part of a treat-to-target strategy.

Table 4 Unresolved challenges to the incorporation of routine endoscopic assessment and mucosal healing in IBD management

How much healing is really needed to impact outcomes?
Can mucosal healing be achieved in most patients?
What is the incremental benefit achieved by dose escalation or switching therapies?
What is the optimal time interval between changes in therapy and subsequent endoscopic re-assessment?
How accurate are the existing less invasive measures of mucosal injury?
Can de-escalation occur after deep remission is sustained for some time?
Will patients agree to therapy changes based only on endoscopic findings?
Will insurers pay for these tests?

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Colombel JF et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology. 2011;141(4):1194–201.
2. Modigliani R et al. Clinical, biological, and endoscopic picture of attacks of Crohn's disease. Evolution on prednisolone. Groupe d'Etude Therapeutique des affections Inflammatoires digestives. Gastroenterology. 1990;98(4):811–8.
3. Rutgeerts P et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353(23):2462–76.
4. Baars JE et al. Majority of patients with inflammatory bowel disease in clinical remission have mucosal inflammation. Inflamm Bowel Dis. 2012;18(9):1634–40.
5. Gomes P et al. Relationship between disease activity indices and colonoscopic findings in patients with colonic inflammatory bowel disease. Gut. 1986;27(1):92–5.
6. •• Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. Gut. 2012;61(11):1619–35. **Excellent review on role of mucosal healing in IBD and how this involves incorportating endoscopy into clinical practice**.
7. Sandborn WJ et al. Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. Gastroenterology. 2009;137(4):1250–60.
8. Froslie KF et al. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. Gastroenterology. 2007;133(2):412–22.
9. Feagan BG et al. The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients. Am J Gastroenterol. 2007;102(4):794–802.
10. Meucci G et al. Prognostic significance of endoscopic remission in patients with active ulcerative colitis treated with oral and topical mesalazine: a prospective, multicenter study. Inflamm Bowel Dis. 2012;18(6):1006–10.
11. Ardizzone S et al. Mucosal healing predicts late outcomes after the first course of corticosteroids for newly diagnosed ulcerative colitis. Clin Gastroenterol Hepatol. 2011;9(6):483–9. e3.
12. Solem CA et al. Correlation of C-reactive protein with clinical, endoscopic, histologic, and radiographic activity in inflammatory bowel disease. Inflamm Bowel Dis. 2005;11(8):707–12.
13. Baert F et al. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. Gastroenterology. 2010;138(2):463–8. quiz e10-1.
14. D'Haens G et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet. 2008;371(9613):660–7.
15. Fefferman DS, Farrell RJ. Endoscopy in inflammatory bowel disease: indications, surveillance, and use in clinical practice. Clin Gastroenterol Hepatol. 2005;3(1):11–24.
16. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J. 1955;2(4947):1041–8.
17. Baron JH et al. Variation between observers in describing mucosal appearances in proctocolitis. Br Med J. 1964;1(5375):89–92.
18. Feagan BG et al. Treatment of ulcerative colitis with a humanized antibody to the alpha4beta7 integrin. N Engl J Med. 2005;352(24):2499–507.
19. Powell-Tuck J et al. A comparison of oral prednisolone given as single or multiple daily doses for active proctocolitis. Scand J Gastroenterol. 1978;13(7):833–7.
20. Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. BMJ. 1989;298(6666):82–6.
21. Hanauer S et al. Mesalamine capsules for treatment of active ulcerative colitis: results of a controlled trial Pentasa study group. Am J Gastroenterol. 1993;88(8):1188–97.
22. Hanauer SB et al. Budesonide enema for the treatment of active, distal ulcerative colitis and proctitis: a dose-ranging study. U.S. Budesonide enema study group. Gastroenterology. 1998;115(3):525–32.
23. Sutherland LR et al. 5-Aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. Gastroenterology. 1987;92(6):1894–8.
24. Naganuma M et al. Novel endoscopic activity index is useful for choosing treatment in severe active ulcerative colitis patients. J Gastroenterol. 2010;45(9):936–43.
25. Matts SG. The value of rectal biopsy in the diagnosis of ulcerative colitis. Q J Med. 1961;30:393–407.
26. Schroeder KW et al. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987;317(26):1625–9.
27. Samuel S et al. Validation of the ulcerative colitis colonoscopic index of severity and its correlation with disease activity measures. Clin Gastroenterol Hepatol. 2013;11(1):49–54.
28. • Travis SP et al. Reliability and initial validation of the ulcerative colitis endoscopic index of severity. Gastroenterology. 2013;145(5):987–95. **Validation study of the newest and validated endoscopy score for UC that is likely to be increasingly incorporated into clinical practice and trials in the future**.
29. D'Haens G et al. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. Gastroenterology. 2007;132(2):763–86.
30. Rutgeerts P et al. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. Gastrointest Endosc. 2006;63(3):433–42. quiz 64.
31. • Mazzuoli S et al. Definition and evaluation of mucosal healing in clinical practice. Dig Liver Dis. 2013;45(12):969–77. **Good review article on mucosal healing and endoscopic outcomes in IBD**.
32. Walsh A et al. Mucosal healing as a target of therapy for colonic inflammatory bowel disease and methods to score disease activity. Gastrointest Endosc Clin N Am. 2014;24(3):367–78. **Good review article on endoscopic indices to quanitfy mcuosal healing**.
33. D'Haens G et al. Challenges to the design, execution, and analysis of randomized controlled trials for inflammatory bowel disease. Gastroenterology. 2012;143(6):1461–9.
34. Kamm MA et al. Once-daily, high-concentration MMX mesalamine in active ulcerative colitis. Gastroenterology. 2007;132(1):66–75. quiz 432–3.
35. Feagan BG et al. The role of centralized reading of endoscopy in a randomized controlled trial of mesalamine for ulcerative colitis. Gastroenterology. 2013;145(1):149–57. e2.

36. Levesque B et al. Responsiveness of central endoscopic assessment of disease activity using the modified mayo clinic score in ulcerative colitis. Gastroenterology. 2014;144(5):S-767.
37. Travis SP et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the ulcerative colitis endoscopic index of severity (UCEIS). Gut. 2012;61(4):535–42.
38. Corte C et al. Association between the ulcerative colitis endoscopic index of severity (UCEIS) and outcomes in acute severe ulcerative colitis. J Crohns Colitis. 2015;9(5):376–81.
39. Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Therapeutiques des affections Inflammatoires du tube Digestif (GETAID). Gut. 1989;30(7):983–9.
40. Daperno M et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc. 2004;60(4):505–12.
41. Rutgeerts P et al. Predictability of the postoperative course of Crohn's disease. Gastroenterology. 1990;99(4):956–63.
42. Annese V et al. European evidence based consensus for endoscopy in inflammatory bowel disease. J Crohns Colitis. 2013;7(12):982–1018.
43. Daperno M et al. Results of the 2nd part scientific workshop of the ECCO. II: measures and markers of prediction to achieve, detect, and monitor intestinal healing in inflammatory bowel disease. J Crohns Colitis. 2011;5(5):484–98.
44. Tontini GE et al. Endoscopic scoring systems for inflammatory bowel disease: pros and cons. Expert Rev Gastroenterol Hepatol. 2014;8(5):543–54.
45. Hebuterne X et al. Endoscopic improvement of mucosal lesions in patients with moderate to severe ileocolonic Crohn's disease following treatment with certolizumab pegol. Gut. 2013;62(2):201–8.
46. Ferrante M et al. Validation of endoscopic activity scores in patients with Crohn's disease based on a post hoc analysis of data from SONIC. Gastroenterology. 2013;145(5):978–86. e5.
47. Colombel JF et al. Association between plasma concentrations of certolizumab pegol and endoscopic outcomes of patients with Crohn's disease. Clin Gastroenterol Hepatol. 2014;12(3):423–31. e1.
48. Laharie D et al. Mucosal healing with methotrexate in Crohn's disease: a prospective comparative study with azathioprine and infliximab. Aliment Pharmacol Ther. 2011;33(6):714–21.
49. Rutgeerts P et al. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. Gastroenterology. 2012;142(5):1102–11. e2.
50. Lemann M et al. A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. Gastroenterology. 2005;128(7):1812–8.
51. Sandborn WJ et al. A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease. Gastroenterology. 2002;122(2):512–30.
52. Colombel JF et al. Adalimumab induces deep remission in patients with Crohn's disease. Clin Gastroenterol Hepatol. 2014;12(3):414–22. e5.
53. Sipponen T et al. Faecal calprotectin and lactoferrin are reliable surrogate markers of endoscopic response during Crohn's disease treatment. Scand J Gastroenterol. 2010;45(3):325–31.
54. Sipponen T et al. Correlation of faecal calprotectin and lactoferrin with an endoscopic score for Crohn's disease and histological findings. Aliment Pharmacol Ther. 2008;28(10):1221–9.
55. Louis E et al. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. Gastroenterology. 2012;142(1):63–70. e5; quiz e31.
56. Aomatsu T et al. Fecal calprotectin is a useful marker for disease activity in pediatric patients with inflammatory bowel disease. Dig Dis Sci. 2011;56(8):2372–7.
57. Dignass A et al. Once versus three times daily dosing of oral budesonide for active Crohn's disease: a double-blind, double-dummy, randomised trial. J Crohns Colitis. 2014;8(9):970–80.
58. Moskovitz D et al. Defining and validating cut-offs for the simple endosocpic score for Crohn's disease. Gastroenterology. 2007;132(4):A173–S1097.
59. Columbel JF. Measuring severity of disease and defining treatment benefit using the simple endoscopic activity score (SES-CD). US Food and Drug Administration's gastroenterology regulatory endpoints and the advancement of therapeutics (GREAT) 3 workshop; Silver Spring, MD 2015.
60. Rutgeerts P et al. Natural history of recurrent Crohn's disease at the ileocolonic anastomosis after curative surgery. Gut. 1984;25(6):665–72.
61. Allez M et al. Long term outcome of patients with active Crohn's disease exhibiting extensive and deep ulcerations at colonoscopy. Am J Gastroenterol. 2002;97(4):947–53.
62. Carbonnel F et al. Colonoscopy of acute colitis. A safe and reliable tool for assessment of severity. Dig Dis Sci. 1994;39(7):1550–7.
63. Wright R, Truelove SR. Serial rectal biopsy in ulcerative colitis during the course of a controlled therapeutic trial of various diets. Am J Dig Dis. 1966;11(11):847–57.
64. Schnitzler F et al. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. Inflamm Bowel Dis. 2009;15(9):1295–301.
65. Rutgeerts P et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. Gastroenterology. 2004;126(2):402–13.
66. Solberg IC et al. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). Scand J Gastroenterol. 2009;44(4):431–40.
67. Rutter M et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology. 2004;126(2):451–9.
68. Rutter MD et al. Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. Gastroenterology. 2006;130(4):1030–8.
69. Gupta RB et al. Histologic inflammation is a risk factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. Gastroenterology. 2007;133(4):1099–105.
70. Rubin DT et al. Inflammation is an independent risk factor for colonic neoplasia in patients with ulcerative colitis: a case–control study. Clin Gastroenterol Hepatol. 2013;11(12):1601–8 e1-4.
71. Peyrin-Biroulet L et al. Clinical disease activity, C-reactive protein normalisation and mucosal healing in Crohn's disease in the SONIC trial. Gut. 2014;63(1):88–95.
72. Halpin SJ, Ford AC. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol. 2012;107(10):1474–82.
73. Bouguen G, et al. Treat to target: a proposed new paradigm for the management of Crohn's disease. Clin Gastroenterol Hepatol. 2015;13(6):1042–1050.
74.•• Bouguen G et al. Feasibility of endoscopic assessment and treating to target to achieve mucosal healing in ulcerative colitis. Inflamm Bowel Dis. 2014;20(2):231–9. **Nice retrospective study that looks at the use of endoscopic assessment and treating to mucosal healing to improve outcomes in UC**.
75.•• Bouguen G et al. Endoscopic assessment and treating to target increase the likelihood of mucosal healing in patients with Crohn's disease. Clin Gastroenterol Hepatol. 2014;12(6):978–85. **Nice retrospective study that demonstrates improved outcomes in CD with the use of routine endoscopic assesment and treating to mucosal healing**.
76.•• De Cruz P et al. Mucosal healing in Crohn's disease: a systematic review. Inflamm Bowel Dis. 2013;19(2):429–44. **Nice review**

article looking at how mucosal healing improves outcomes and markers of mucosal healing in CD.

77.•• Peyrin-Biroulet L et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. Am J Gastroenterol. 2015;110:1324–28. **Expert opinion on new therapeutic goals in IBD that incorporates endoscopic assessment and healing**.

1.4 TREATMENT TARGETS IN IBD: OBJECTIVE ASSESSMENT OF ENDOSCOPIC DISEASE ACTIVTY AND MUCOSAL HEALING

This book chapter reviews the role of endoscopic disease activity and mucosal healing on outcomes in IBD and evaluates the importance of achieving mucosal healing in IBD. It again reviews the available endoscopic scoring systems and gives recommendations on when and how to assess for endoscopic mucosal healing. The chapter concludes with a summary of surrogate markers of endoscopic healing and gives recommendations on how to incorporate assessment of mucosal healing into a treat-to-target protocol.

Objective Assessment of Endoscopic Disease Activity and Mucosal Healing

24

Britt Christensen and David T. Rubin

Introduction

Historically the goal of therapy when treating patients with inflammatory bowel disease (IBD) has been to achieve and maintain symptomatic remission. This has been accomplished using a step-up approach, in which therapies were commenced and their efficacy evaluated based on symptom-based metrics, followed by adjustments of therapy occurring until the patient achieved clinical remission. Clinical remission usually was defined as normal stool frequency, no abdominal pain and no rectal bleeding. By achieving this goal short-term respite was provided to patients with the hope of improving their quality of life and avoiding disease-related complications such as hospitalizations and surgeries. However, recently it has been demonstrated that despite frequently achieving symptomatic remission in our patients and despite access to many new therapies over the years, the course of IBD has not been successfully or substantially modified in the modern era [1, 2].

It is now known that relying on a patient's clinical symptoms to assess the inflammatory response to treatment is unreliable. Up to 40 % of patients in clinical remission will have endoscopic disease activity [3–8] and patients who feel unwell often have no endoscopic findings of disease activity [5]. In addition, although a patient may present in symptomatic (clinical) remission, many patients do not have stable disease control, with over 37 % of patients having frequent intermittent symptom over time [9] and only 10 % of patients experiencing prolonged clinical remission [9, 10] making a single time point assessment of clinical response unreliable. Therefore, this puts a significant proportion of patients at risk of either disease progression due to inadequate treatment, or at risk of overtreatment with unnecessary medications if one only relies on symptoms to choose treatments.

The recognition of these facts has led to a paradigmatic change in the therapeutic approach of IBD. Frequent evaluation of objective markers of disease activity are increasingly being incorporated into treatment algorithms to allow for timely changes of therapy. Thus, achievement of mucosal healing has emerged as a major treatment goal in IBD. Although mucosal healing does not have a standardized or validated definition in IBD, it is most often defined as the absence of friability, blood, erosions, and ulcers in all visual segments of the gut in UC [11] and the absence of ulceration in CD [12]. Therefore assessment of mucosal healing continues to require endoscopic assessment.

This chapter discusses the importance and prognostic role of endoscopic assessment of disease activity and mucosal healing in IBD, summarizes the major endoscopic indices of activity in CD and UC including their strengths, limitations, and application to both clinical trials and clinical practice, and finally, highlights the integration of endoscopic disease activity utilizing a "treat-to-target" algorithm that incorporates endoscopic mucosal healing as a target.

Prognostic Role of Endoscopic Disease Activity and Mucosal Healing in IBD

Historically, clinical evaluation and treating to clinical remission was the objective of treatment in IBD. However it was found that despite advances in medical therapies that improved symptoms, patients still required hospitalization and surgery and the natural history of the disease was unchanged [1, 2]. Therefore increasingly there has been a move to objective assessment of disease activity, and endoscopic assessment has been the gold standard. Endoscopy can be used both at diagnosis to prognosticate the disease course and to determine response to therapy.

B. Christensen, M.B.B.S., F.R.A.C.P., M.P.H.
Department of Medicine, University of Chicago Medicine
Inflammatory Bowel Disease Center, 5841 S. Maryland Avenue, MC4076, Chicago, IL 60637, USA

Department of Gastroenterology, Alfred Hospital and Monash University, Melbourne, Australia

D.T. Rubin, M.D. (✉)
Department of Medicine, University of Chicago Medicine
Inflammatory Bowel Disease Center, 5841 S. Maryland Avenue, MC4076, Chicago, IL 60637, USA
e-mail: drubin@uchicago.edu

D.C. Baumgart (ed.), *Crohn's Disease and Ulcerative Colitis*, DOI 10.1007/978-3-319-33703-6_24

Table 24.1 Benefits of mucosal healing and unresolved challenges to the incorporation of routine endoscopic assessment of mucosal healing into clinical practice

Benefits of mucosal healing	Unresolved issues of mucosal healing
Decreased clinical relapse	How much mucosal healing is required to impact outcomes?
Decreased hospitalizations	Can mucosal healing be achieved in most patients?
Decreased rate of surgery	What is the incremental benefit achieved from dose escalation or switching therapies?
Increased quality of life	What is the time interval between changes in therapy and subsequent endoscopic reassessment?
Less incidence of neoplasia	Can de-escalation occur after deep remission is sustained for some time?
Decreased incidence of fistula's	Will patients agree to therapy changes based only on endoscopic findings even if they are in clinical remission?

Endoscopic severity has been shown to predict the future clinical aggressiveness of IBD, specifically non-response to medical therapy and need for surgery. In UC severe lesions increase the odds ratio of colectomy by 41 compared to those without severe lesions [13] and severe endoscopic lesions predict non-response to therapy, with only 34 % of patients with severe endoscopic lesions responding to medical therapy, compared to 91 % of those who have less severe endoscopic disease (OR > 20) [14]. Therefore, an endoscopic assessment is indicated in a newly symptomatic patient or in severe flares of disease to guide appropriate medical or surgical intervention required. In CD, severe endoscopic ulcerations are associated with a 31 % risk of colectomy, compared to a 6 % risk in those without severe endoscopic lesions [15]. In addition, endoscopic assessment within 12 months of ileocolonic resection in Crohn's disease can be used to predict the postoperative clinical disease course [16].

Once a patient has had a baseline colonoscopy to prognosticate their disease course and commence an appropriate therapeutic regimen, there is increasing evidence that assessing for mucosal healing provides further prognostic information regarding future disease course. This is because once a patient is on treatment, achievement of mucosal healing in both UC and CD has been found to be independently associated with improved outcomes including prolonged remission, fewer hospitalizations, reduced surgical procedures, fewer fistulas, less immunosuppression therapy, a lower risk of colorectal cancer, and improved quality of life (Table 24.1) [3, 5, 9, 13, 17–32].

It is now known that whilst treating to clinical symptoms in IBD is important to aid a patient's immediate quality of life, adjustments to therapy frequently are delayed and long-term disability is not prevented [33]. Although no prospective study has demonstrated that treating to achieve mucosal healing rather than clinical symptoms alone changes outcomes, preliminary retrospective studies have demonstrated that repeated endoscopic assessment of disease activity with adjustment of medical therapy to the target of mucosal healing is feasible in clinical practice and is of benefit [34, 35]. In addition one can extrapolate the experience from other chronic diseases, where reaching an objective target does improve long-term outcomes. This is the case for lowered blood pressure in hypertension [36], lowered glycosylated hemoglobin in diabetes [37–39], and most relevant, reduced joint inflammation in rheumatoid arthritis [40–42]. If we take this experience and apply it to IBD, strict disease control with an assessment of the mucosa and an aim to achieve mucosal healing should lead to improved outcomes.

Endoscopic Assessment of Disease Activity in Ulcerative Colitis

Ulcerative colitis involves inflammation of only the large intestine, starting in the rectum and extending proximally, with clear demarcation of normal and abnormal mucosa. At endoscopy, the mucosa is edematous, granular and has a change in vascular pattern [43]. In more severe disease easy friability and bleeding, ulceration, and pseudopolyps can occur [43]. Despite the fact that it has been more than 50 years since the first report on endoscopic lesions and mucosal healing by Truelove and Witts [44], it is not until recently that attempts have been made to validate any of the many subsequent systems (Table 24.2). As there are many scoring systems available, this chapter focuses specifically on the most common endoscopic scoring system used in clinical trials, the Mayo Clinic endoscopy sub-score, and the newer scoring systems currently undergoing validation, the ulcerative colitis endoscopic index of severity (UCEIS) and the ulcerative colitis colonoscopic index of severity (UCCIS).

Currently the most widely used endoscopic scoring system to quantify mucosal disease activity in UC in clinical trials is the Mayo Clinic endoscopy sub-score (Fig. 24.1) [54]. This score assesses vascular pattern, erythema, friability, bleeding, erosions, and ulceration. It is a four-point scale ranging from 0 to 3, with 0 being inactive disease and 3 being severe disease. It is a simple score that is easy to calculate. In most trials, mucosal healing is defined as a Mayo score of either 0 or 1 [11]. Evidence for the appropriateness of this definition was found in a post hoc analysis of the Active Ulcerative Colitis Trials (ACT)-1 that demonstrated that patients with an 8-week post-treatment Mayo score of 0 or 1 had a lower risk of undergoing colectomy and had better clinical outcomes at 1 year compared to those with higher

Table 24.2 Endoscopic disease activity scoring systems in ulcerative colitis

Endoscopic scores	Variables	Score range	Definition of remission and response	Strengths	Weaknesses
Truelove and Witts sigmoidoscopic assessment [44]	Hyperemia, granularity and change in overall appearance of the mucosa	No description	Not defined	Possibility to stratify patients by their disease severity	Not validated High inter-observer variability No definition of mucosal healing
Baron score [45]	Severity of mucosal bleeding and friability	0–3	Remission: 0–1 (NV) Response: Not defined	Easy to use Good inter-observer correlation	Not validated No assessment of ulcers No definition of mucosal healing
Modified Baron score [46]	Friability, vascular pattern, granularity, bleeding and ulceration	0–4	Remission: 0–1 (NV) Response: Not defined	Easy to use Good inter-observer correlation	Not validated No definition of mucosal healing
Powell-Tuck sigmoidoscopic assessment [47, 48]	Severity of mucosal bleeding and friability	0–2	Not defined	Easy to use	Not validated No definition of mucosal healing Ulceration not included
Rachmilewitz endoscopic index [48]	Granulation, vascular pattern, vulnerability of mucosa, mucosal damage	Four items rated 0–3. Total of 0–12 points	Remission: 0–4 (NV) Response: Not defined		Not validated Complex and subjective descriptive terms
Sigmoidoscopic index [49]	Erythema, friability, ulceration, mucous, vascular pattern	Five items rated 0–3. Total 0–16 points	Remission: 0–4 (NV) Response: Not defined		Not validated Complex
Sigmoidoscopic inflammation grade score [50]	Edema, vascular pattern Granularity, friability, bleeding, ulcers	0–4	Not defined		Not validated No definition of mucosal healing
Sutherland mucosal appearance assessment [51]	Friability, exudation, bleeding	0–3	Not defined		Not validated Subjective No definition of mucosal healing Easy to use
Endoscopic activity index [52]	Ulcers (size and depth), erythema, bleeding, mucosal edema, mucosal exudate	0–3	Not defined		Complex Not validated No definition of mucosal healing Closely correlated with clinical activity
Matts Index [53]	Granularity, bleeding, edema, ulceration	1–4	Not defined		Not validated No definition of mucosal healing Easy to use Good inter- and intra-observer agreement
Mayo endoscopic sub-score [54]	Erythema, vascular pattern, friability, bleeding, erosions, ulcerations	0–3	Remission: 0 or 0–1 (PV) Response: Not defined		Not validated Extensive use in clinical trials and RCT's
Ulcerative colitis colonoscopy index of severity (UCCIS) [55, 56]	Vascular pattern, granularity, ulceration, bleeding/friability	Four items rated 0–2 for vascular pattern, granularity, bleeding/friability and 0–4 for ulcerations. To total 0–10 points	Not defined	Preliminary validation Based on rigorous methodology Provides pan-colonic assessment	Includes subjective parameters and complex scale No definition of mucosal healing Requires post-procedure time to be scored

(continued)

Table 24.2 (continued)

Endoscopic scores	Variables	Score range	Definition of remission and response	Strengths	Weaknesses
Ulcerative colitis endoscopic index of severity (UCEIS) [57]	Vascular pattern, bleeding, erosions/ulceration	Three items rated 0–3 for vascular pattern and 0–4 for bleeding and ulceration. Total of 0–11 points	Not defined	Preliminary validation Easy to use Based on rigorous methodology Accounts for 94 % of variance between endoscopists for the overall assessment of severity Independent of clinical symptoms	Limited to rectosigmoid Low agreement for normal appearing mucosa Sensitivity to change and mucosal healing remain undefined

NV not validated
PV partially validated
This table was adapted from Current Gastroenterology Reports. Christensen B et al. Understanding Endoscopic Disease Activity in IBD: How to Incorporate It into Practice. 2016; 8:5; with permission from Springer

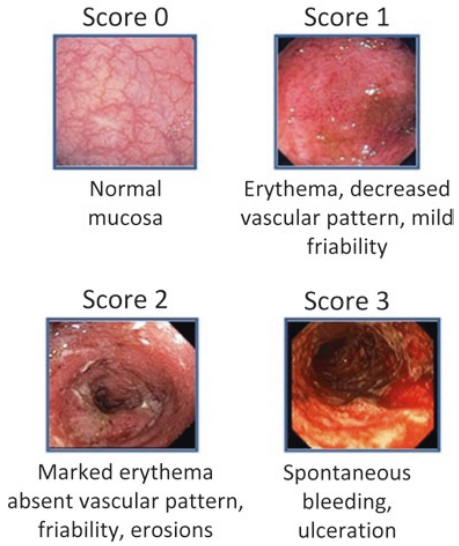


Fig. 24.1 Mayo endoscopic sub-score [54]. This figure was adapted from Current Gastroenterology Reports. Christensen B et al. Understanding Endoscopic Disease Activity in IBD: How to Incorporate It into Practice. 2016; 8:5; with permission

scores [3]. Of note, however, is that patients achieving a Mayo score of 0 also had higher rates of symptomatic remission, corticosteroid-free remission and subsequent mucosal healing at weeks 30 and 54 compared to those with a score of 1 but did not have lower rates of colectomy [3]. Despite its ease of use and frequent uptake in clinical trials, the Mayo endoscopic sub-score is hampered by a lack of validation and a high inter-observer discrepancy, particularly in regard to the inclusion of friability in the score of 1, which has been found to be so subjective as to lead to inconsistent results [58]. To overcome this, some studies have adapted the index and made the presence of friability an automatic Mayo sub-score of 2 [59–61].

Until recently, no endoscopic score to assess disease activity in UC was prospectively or completely validated. To overcome these limitations the ulcerative colitis endoscopic index of severity (UCEIS) [57, 62] and the ulcerative colitis colonoscopic index of severity (UCCIS) [55, 56] have recently been developed as the first prospectively validated scoring systems for UC. The UCEIS was a collaborative effort between 40 IBD specialists from 13 counties and evaluates three variables that were determined to be the most discriminating; vascular pattern, bleeding and erosions and ulcers (Table 24.3) [62]. The worst segment of the colon is given a score of 0–2 or 0–3 for each variable to give a total score of 0–8 and the scoring system has demonstrated excellent intra and inter-observer agreement [57, 58]. Limiting its use currently is the fact that cutoff scores to define disease severity or mucosal healing have not yet been determined and the sensitivity of the scoring system to change in disease activity and mucosal improvement remains unknown. However, validation of thresholds for defining mucosal healing and response are anticipated in the near future. With this in mind, this scoring system is likely to be increasingly adopted in clinical trials and applied to clinical practice.

Unlike the previously mentioned scores, which assess only the recto-sigmoid area of the colon, the UCCIS grades mucosal changes throughout the entire colon, which may provide further important prognostic data. The score examines vascular pattern, granularity, ulceration, bleeding/friability, and severity of damage in each colon segment and overall using a four-point scale and a 10-cm visual analogue scale [55]. As with the UCEIS, the UCCIS has excellent inter-observer agreement apart from the included variable of friability and has been found to have moderate correlation

Table 24.3 The ulcerative colitis endoscopic index of severity (UCEIS)

Descriptor	Score	Definition
Vascular pattern	Normal (0)	Normal vascular pattern with arborization of capillaries clearly defined, or with blurring or patchy loss of capillary margins
	Patchy obliteration (1)	Patchy obliteration of vascular pattern
	Obliterated (2)	Complete obliteration of vascular pattern
Bleeding	None (0)	No visible blood
	Mucosal (1)	Some spots or streaks of coagulated blood on the surface of the mucusa ahead of the scope, which can be washed away
	Luminal mild (2)	Some free liquid blood in the lumen
	Luminal moderate or severe (3)	Frank blood in the lumen ahead of endoscope or visible oozing from mucosa after washing intraluminal blood, or visible oozing from a hemorrhagic mucosa
Erosions and ulcers	None (0)	Normal mucosa no visible erosions or ulcers
	Erosions (1)	Tiny defects in the mucosa, of a white or yellow color with a flat edge
	Superficial ulcer (2)	Larger (>5 mm) defects in the mucosa which are discrete fibrin-covered ulcers when compared with erosion, but remain superficial
	Deep ulcer (3)	Deeper excavated defects in the mucosa with a slightly raised edge

The three descriptors are scored for the worst affected area of the colon to give a score of 0–8
[This table was adapted from Travis S et al. Reliability and initial validation of the Ulcerative Colitis Endscopic Index of Severity. Gastroenterology. 2013; 145:987–95; with permission.]

with laboratory markers of disease activity including CRP and albumin and patient-defined remission [55, 56]. However, as with the UCEIS, there is no validation or definition of response or remission and its future use may be limited due to the need for full colonoscopy limiting its practical application [59].

Endoscopic Disease Activity Assessment in Crohn's Disease

Crohn's disease can affect any part of the gastrointestinal tract from the mouth through to the anorectum and inflammation occurs in a patchy pattern. On endoscopy, findings in CD typically consist of segmental erythema, strictures and apthoid ulceration that can progress to stellate, longitudinal, tortuous, or serpiginous ulcers and a cobblestone appearance [43]. The terminal ileum can be involved and anal or perianal disease is suggestive of CD over UC. There are two validated endoscopic indices for evaluating CD disease activity and a further index that is routinely used to assess postoperative recurrence in CD (Table 24.4).

The Crohn's disease endoscopic index of severity (CDEIS) [12] and the simple endoscopic score for Crohn's disease (SES-CD) [63] have been prospectively validated and been shown to be reproducible, have good inter-observer agreement, have good correlation with the Crohn's disease activity index (CDAI) and are sensitive to changes in endoscopic mucosal appearance and healing [26, 64–66]. The CDEIS was the first endoscopic scoring system developed for CD (Table 24.5) and is the most commonly used endoscopic tool to assess disease activity in clinical trials. The score ranges from 0–44 and examines superficial ulcers, deep ulcers, ulcerated stenosis, and non-ulcerated stenosis in addition to the percentage of ulcerated and affected colonic surface in all five bowel segments (terminal ileum, right colon, transverse colon and rectum). Despite the CDEIS score being reliable and reproducible, its use is limited due to the fact that it is a complex scoring system that is time-consuming and not practical for routine clinical use [58]. To overcome these shortcomings, a simplified index, the simple endoscopic score for CD (SES-CD) was developed and consists of measuring ulcer size, ulcerated and affected surfaces and stenosis in each of the five intestinal segments to give a total score range of 0–56 (Table 24.6). The SES-CD correlates highly with the CDEIS and is a faster and more practical tool [63].

As with the UC endoscopic scoring systems, the CDEIS and the SES-CD do not have validated thresholds for mucosal disease severity, remission or response. In trials utilizing the CDEIS, a score <6 [67] has been used to define partial endoscopic healing or endoscopic remission and <3 [67], 4 [68], ≤ 4 [69] or 0 [70] to define complete mucosal healing. In trials utilizing the SES-CD a score of <3 [69, 71, 72, 73] or equal to 0 [24, 70, 74–76] has previously been used to define endoscopic remission or minimal endoscopic activity although a study by Moskovitz et al. [77] validated the cut-off values as 0–2 for endoscopic remission, 3–6 for mild endoscopic disease, 7–15 for moderate endoscopic disease activity and ≥ 16 for severe endoscopic disease activity. In regard to defining endoscopic response to treatment, Ferrante et al. [78] demonstrated that a decrease from baseline of both the CDEIS and the SES-CD score of at least 50 % was most predictive of corticosteroid free remission by week 50.

Table 24.4 Crohn's disease endoscopic disease activity scoring systems

Score	Variables	Score range	Definition response/ Remission	Strengths	Weakness
Crohn's disease endoscopic index of severity (CDEIS) [12]	Deep ulceration, superficial ulceration, inflammation	0–44	Complete remission: 0, <3, <4 or <6 Response: Decrease from baseline of 50–75 % or decrease from baseline of 3–5 points	Validated Reproducible Extensive use in clinical trials	Complex Many variables Requires training and experience No validated definition of mucosal healing or response
Simple endoscopic score for Crohn's disease (SES-CD) [63]	Ulcers, inflammation, stenosis	0–60	Remission: 0 or <3 points. Response: Decrease from baseline of 50 % or decrease from baseline of ≥5 points	Validated Score correlates well with CDEIS Reproducible	Complex Not practical for clinical setting Validated against CDEIS in only one study No validated definition of mucosal healing or response
Rutgeerts score [16]	Apthoid lesions, ulcers, inflammation, nodules and stenosis	i0–i4	Score of i0–i1 low risk of clinical recurrence Score of i2 = intermediate risk of clinical recurrence Score of i3 = high risk of clinical recurrence	Gold Standard for assessment of postoperative recurrence Extensive use in clinical trials Validated cutoff values for clinical recurrence	No formal validation Only useful for ileal or ileal-colonic surgery

Table 24.5 The Crohn's disease endoscopic index of severity (CDEIS)

Endoscopic variable	Score (range 0–44)
Deep ulcerations	0 if absent or 12 if present
Superficial ulcerations	0 if absent or 6 if present
Length of ulcerated mucosa (0–10 cm)	0–10 according to length in cm
Length of diseased mucosa (0–10 cm)	0–10 according to length in cm

Four variables are scored for each of the following locations: rectum; sigmoid and left colon; transverse colon; right colon; and ileum. Total score is divided by the number of locations explored (1–5). An additional three points are given if ulcerated stenosis is present and a further three points are given if non-ulcerated stenosis is present

[This table was adapted from Mary JY et al. Development and validation of an endoscopic index of severity for Crohn's disease: a prospective multicenter study. Groupe d'Etude Therapeutique des Affections Inflammatoires du Tube Digestif (GETAID). Gut 1989;30:983–9; with permission]

Table 24.6 The simple endoscopic score for Crohn's disease (SES-CD)

Variable	Score 0	Score 1	Score 2	Score 3
Size of ulcers (cm)	None	Apthous ulcers (diameter 0.1–0.5 cm)	Large ulcers (diameter 0.5–2 cm)	Very large ulcers (diameter > 2 cm)
Ulcerated surface (%)	None	<10	10–30	>30
Affected surface (%)	Unaffected segment	<50	50–75	>75
Presence of narrowing	None	Single, can be passed	Multiple, can be passed	Cannot be passed

The SES-CD: sum of the values of the four variables for the five bowel segments. Values are given to each variable and for every examined bowel segment (rectum, left colon, transverse colon, right colon and ileum)

[This table was adapted from Daperno M et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc 2004;60:505–12; with permission from Elsevier]

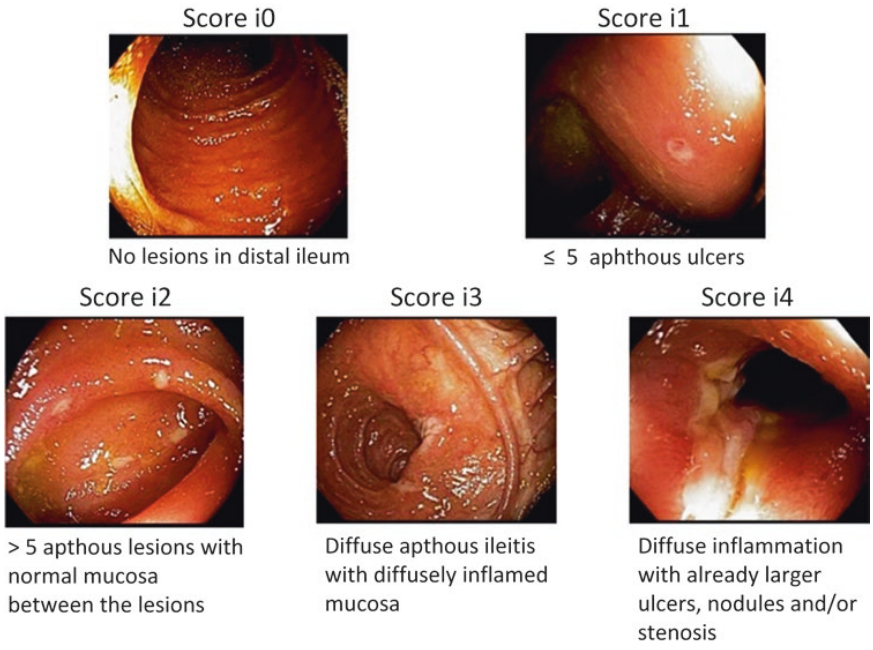


Fig. 24.2 Rutgeerts' score for postoperative endoscopic recurrence [16]. This figure was adapted from Current Gastroenterology Reports. Christensen B et al. Understanding Endoscopic Disease Activity in IBD: How to Incorporate It into Practice. 2016; 8:5; with permission

Many CD patients undergo surgical resection and endoscopic disease recurrence may be as high as 90 % by 1 year [16]. To assess and score this recurrence in the neo-terminal ileum after ileal or ileocolonic resection in CD the so-called "Rutgeert's score" is commonly used (Fig. 24.2) [16, 79]. The score ranges from i0–i4 (where "i" stands for "ileum") and is a quick and easy score to calculate but has not been fully validated. A score of i0 or i1 is commonly classified as endoscopic postoperative remission due to the finding that grade i0 or i1 recurrence is associated with a low risk of clinical recurrence (20 % at 3 years follow-up) compared to those who have a score of i3 or i4 (92 % at 3 years follow-up) [16]. Those with a Rutgeert's score of i2 have an intermediate risk of symptomatic recurrence.

Central Reading of Endoscopic Scoring

The currently available endoscopic disease activity scoring systems are subject to error and bias. To address this, in 2009, a study of delayed-release mesalamine in moderately active UC (as determined using the Mayo scoring system) [80] utilized a central endoscopy reader to determine endoscopic severity and response to therapy with many further studies now following suit. The advantages of a central reader of endoscopy are clearly evident with Feagan et al. [61] demonstrating on a post hoc analysis of a placebo controlled trial of delayed release mesalamine for the treatment of mild to moderate UC that 31 % of participants who had met the inclusion criteria of a Ulcerative Colitis Disease Activity Index (UCDAI) sigmoidoscopy score of ≥2 per a site-investigator were considered ineligible when the images were reviewed by a central-reader of endoscopy. In addition, by comparing the results including all patients originally entered into the trial by the site investigators and just those that met the inclusion criteria per the central reader, the authors demonstrated a greater treatment effect in the mesalamine group and reduced placebo rates when analyzing patients only included by the central reader. In part because of this proof-of-concept analysis, central reading of endoscopy is playing an increasing role in the trial setting and may eventually gain regulatory support in both Europe and the US as a measure for endpoint assessment as well as assessing baseline disease severity as a means to decrease placebo response rates and increase the reliability of trial end-points [81].

Surrogate Markers of Endoscopic Healing

Currently, endoscopic evaluation of the mucosa is the gold standard to determine endoscopic disease activity and mucosal healing. However endoscopy is an invasive test, is not popular with patients and entails a risk to the patient. Therefore several surrogate markers are emerging that may be useful in assessing for smoldering endoscopic inflammation in the setting of minimal clinical symptoms, most of which have been discussed in more detail in other chapters.

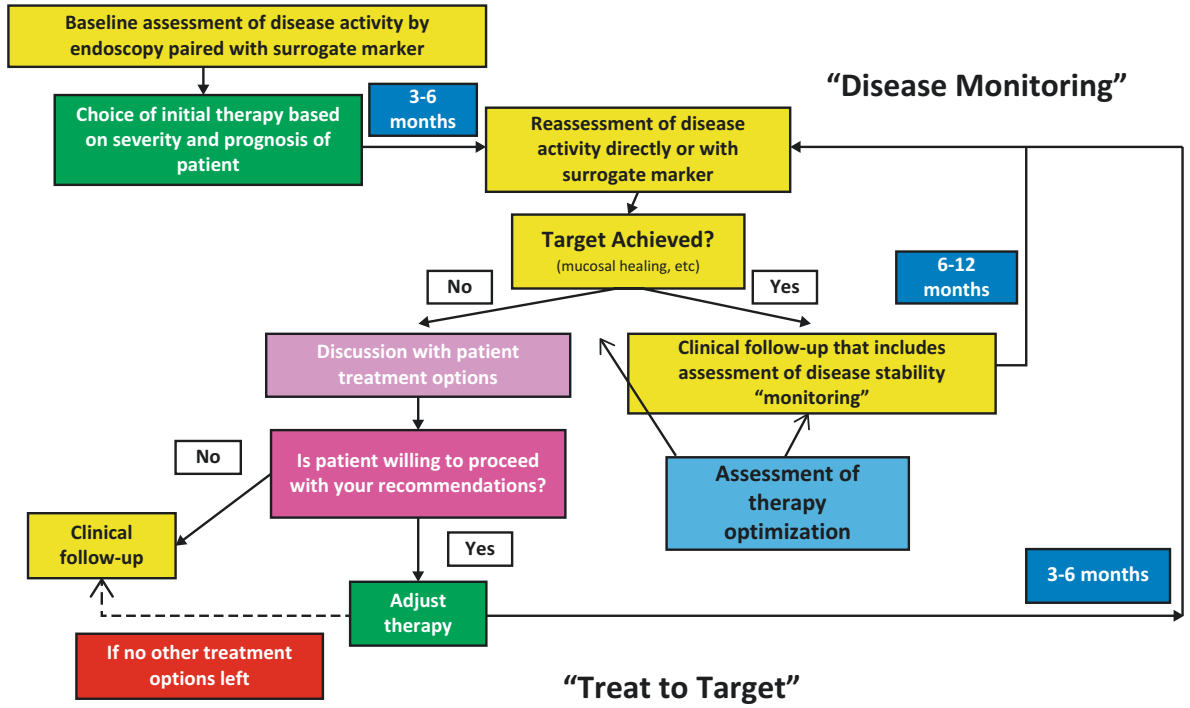


Fig. 24.3 Proposed "Treat to target" algorithm in IBD

Surrogate markers that may have some use in monitoring mucosal activity include the laboratory markers C-reactive protein and albumin, imaging studies including small bowel ultrasound and MRI and the most promising, fecal biomarkers including calprotectin and lactoferrin. All these modalities have their strengths and weaknesses to help in the assessment of mucosal healing however thus far none of these markers have been able to completely replace endoscopic assessment of disease activity in regard to predicting clinical course and response to therapy with complete certainty. Therefore, until further evidence is available, these tools should only be used in conjunction with endoscopic assessment of disease activity.

Incorporation of Endoscopic Assessment of Disease Activity and a "Treat to Target" Algorithm into Clinical Practice

To conclude the chapter, we propose an endoscopic assessment and "treat to target" algorithm incorporating endoscopic mucosal healing as an outcome acknowledging the fact that evidence for this approach in IBD is currently limited (Fig. 24.3). There are still many unresolved challenges in regard to incorporating mucosal healing into the treatment algorithm (Table 24.1); however, recently a group of IBD experts published a consensus summary of which targets should be used in UC and CD. They concluded that the endoscopic therapeutic target when treating patients with UC should be a Mayo endoscopic sub-score of 0–1 and in CD it should be resolution of all ulceration at ileocolonoscopy [82].

The incorporation of a "treat to target" approach to patient care first requires baseline disease assessment by endoscopy to assess disease activity and prognosticate the disease course. Initial therapy should be based on this prognosis and the severity of the findings with the aim to achieve early disease remission and limit bowel damage. Pairing this baseline assessment with a surrogate marker (C-reactive protein or fecal markers) may enable future assessments with the same marker. To quantify response to therapy, this should be followed by an endoscopy or use of surrogates between 3 to 6 months following treatment initiation depending on the type and speed of action of the treatment commenced (earlier if the faster acting anti-TNF therapies are utilized and later if the slower acting antimetabolite medications are used). If, on reassessment, the patient is symptomatic and has endoscopic inflammation, then escalation of medical therapies should occur. If, however, the patient is found to have mucosal activity and is in clinical remission, then the goals of treatment that occur when mucosal healing is achieved including prolonged remission and decreased disability and the risks of treatment escalation including possible higher rates of

malignancy and infection should be discussed. If the patient is agreeable, medication intensification should occur and following this up-titration reassessment should occur every 3–6 months with medical therapies further optimized until the mucosal healing target is reached. Once mucosal healing is achieved then frequent clinical and objective monitoring with surrogate markers of mucosal healing should occur to assess for disease drift or early relapse every 6–12 months and endoscopic evaluation of the mucosa should be considered every 1–2 years [83]. Finally it is important to have an "exit strategy" if treatment escalation is unsuccessful and to maintain clear and open communication with the patient to maximize patient safety and satisfaction and increase the likelihood that the patient will adhere to the agreed on treatment strategy [70].

Conclusion

Endoscopic assessment in IBD is used as a diagnostic tool, to aid in the initial evaluation of disease severity and to prognosticate the disease course and for ongoing assessment of mucosal response and healing once treatment has been initiated. Repeat endoscopic assessment of disease activity with a target to achieve mucosal healing following treatment is increasingly being incorporated into both trial and clinical settings due to the fact that patients who achieve mucosal healing have longer periods of clinical remission, reduced hospitalizations and surgery and are less likely to develop colorectal neoplasia. With modern therapies, mucosal healing is obtainable and as physicians we should increasingly embrace a "treat to target" strategy to decrease the risk of future disability in our patients. Currently restricting this is a lack of consensus on the definition of mucosal healing in IBD and the lack of a single accepted and validated endoscopic scoring system for either CD or UC. Studies are currently underway to overcome these limitations. It is our hope that treating to achieve mucosal healing will help prevent permanent bowel damage in our patients and that utilizing this strategy that we will change the natural history of this disease.

References

1. Bouguen G, Peyrin-Biroulet L. Surgery for adult Crohn's disease: what is the actual risk? Gut. 2011;60(9):1178–81.
2. Filippi J, Allen PB, Hebuterne X, Peyrin-Biroulet L. Does anti-TNF therapy reduce the requirement for surgery in ulcerative colitis? A systematic review. Curr Drug Targets. 2011;12(10):1440–7.
3. Colombel JF, Rutgeerts P, Reinisch W, Esser D, Wang Y, Lang Y, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology. 2011;141(4):1194–201.
4. Modigliani R, Mary JY, Simon JF, Cortot A, Soule JC, Gendre JP, et al. Clinical, biological, and endoscopic picture of attacks of Crohn's disease. Evolution on prednisolone. Groupe d'Etude Therapeutique des Affections Inflammatoires Digestives. Gastroenterology. 1990;98(4):811–8.
5. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353(23):2462–76.
6. Baars JE, Nuij VJ, Oldenburg B, Kuipers EJ, van der Woude CJ. Majority of patients with inflammatory bowel disease in clinical remission have mucosal inflammation. Inflamm Bowel Dis. 2012;18(9):1634–40.
7. Gomes P, du Boulay C, Smith CL, Holdstock G. Relationship between disease activity indices and colonoscopic findings in patients with colonic inflammatory bowel disease. Gut. 1986;27(1):92–5.
8. Rubin DT, Pramoda K, Bonnie LS, Ningqi H. Frequency of subclinical disease activity in ulcerative colitis patients. Gastroenterology. 2011;140(5):S-423.
9. Solberg IC, Lygren I, Jahnsen J, Aadland E, Høie O, Cvancarova M, et al. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). Scand J Gastroenterol. 2009;44(4):431–40.
10. Munkholm P, Langholz E, Davidsen M. Binder V.l. Disease activity courses in a regional cohort of Crohn's disease patients. Scand J Gastroenterol. 1995;30(7):699–706.
11. D'Haens G, Sandborn WJ, Feagan BG, Geboes K, Hanauer SB, Irvine EJ, et al. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. Gastroenterology. 2007;132(2):763–86.
12. Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Therapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). Gut. 1989;30(7):983–9.
13. Carbonnel F, Lavergne A, Lemann M, Bitoun A, Valleur P, Hautefeuille P, et al. Colonoscopy of acute colitis. A safe and reliable tool for assessment of severity. Dig Dis Sci. 1994;39(7):1550–7.
14. Daperno M, Sostegni R, Scaglione N, Ercole E, Rigazio C, Rocca R, et al. Outcome of a conservative approach in severe ulcerative colitis. Dig Liver Dis. 2004;36(1):21–8.
15. Allez M, Lemann M, Bonnet J, Cattan P, Jian R, Modigliani R. Long term outcome of patients with active Crohn's disease exhibiting extensive and deep ulcerations at colonoscopy. Am J Gastroenterol. 2002;97(4):947–53.
16. Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. Gastroenterology. 1990;99(4):956–63.
17. Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. Gut. 2012;61(11):1619–35.
18. Sandborn WJ, Rutgeerts P, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. Gastroenterology. 2009;137(4):1250–60.
19. Froslie KF, Jahnsen J, Moum BA, Vatn MH, Group I. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. Gastroenterology. 2007;133(2):412–22.
20. Feagan BG, Reinisch W, Rutgeerts P, Sandborn WJ, Yan S, Eisenberg D, et al. The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients. Am J Gastroenterol. 2007;102(4):794–802.
21. Meucci G, Fasoli R, Saibeni S, Valpiani D, Gullotta R, Colombo E, et al. Prognostic significance of endoscopic remission in patients with active ulcerative colitis treated with oral and topical mesalazine: a prospective, multicenter study. Inflamm Bowel Dis. 2012;18(6):1006–10.
22. Ardizzone S, Cassinotti A, Duca P, Mazzali C, Penati C, Manes G, et al. Mucosal healing predicts late outcomes after the first course

of corticosteroids for newly diagnosed ulcerative colitis. Clin Gastroenterol Hepatol. 2011;9(6):483–9.e3.
23. Solem CA, Loftus Jr EV, Tremaine WJ, Harmsen WS, Zinsmeister AR, Sandborn WJ. Correlation of C-reactive protein with clinical, endoscopic, histologic, and radiographic activity in inflammatory bowel disease. Inflamm Bowel Dis. 2005;11(8):707–12.
24. Baert F, Moortgat L, Van Assche G, Caenepeel P, Vergauwe P, De Vos M, et al. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. Gastroenterology. 2010;138(2):463–8. quiz e10–1.
25. D'Haens G, Baert F, van Assche G, Caenepeel P, Vergauwe P, Tuynman H, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet. 2008;371(9613):660–7.
26. Rutgeerts P, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. Gastrointest Endosc. 2006;63(3):433–42. quiz 64.
27. Schnitzler F, Fidder H, Ferrante M, Noman M, Arijs I, Van Assche G, et al. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. Inflamm Bowel Dis. 2009;15(9):1295–301.
28. Rutgeerts P, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. Gastroenterology. 2004;126(2):402–13.
29. Rutter M, Saunders B, Wilkinson K, Rumbles S, Schofield G, Kamm M, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology. 2004;126(2):451–9.
30. Rutter MD, Saunders BP, Wilkinson KH, Rumbles S, Schofield G, Kamm MA, et al. Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. Gastroenterology. 2006;130(4):1030–8.
31. Gupta RB, Harpaz N, Itzkowitz S, Hossain S, Matula S, Kornbluth A, et al. Histologic inflammation is a risk factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. Gastroenterology. 2007;133(4):1099–105.
32. Rubin DT, Huo D, Kinnucan JA, Sedrak MS, McCullom NE, Bunnag AP, et al. Inflammation is an independent risk factor for colonic neoplasia in patients with ulcerative colitis: a case-control study. Clin Gastroenterol Hepatol. 2013;11(12):1601–8.e1–4.
33. Jess T, Riis L, Vind I, Winther KV, Borg S, Binder V, et al. Changes in clinical characteristics, course, and prognosis of inflammatory bowel disease during the last 5 decades: a population-based study from Copenhagen. Denmark Inflamm Bowel Dis. 2007;13(4):481–9.
34. Bouguen G, Levesque BG, Pola S, Evans E, Sandborn WJ. Feasibility of endoscopic assessment and treating to target to achieve mucosal healing in ulcerative colitis. Inflamm Bowel Dis. 2014;20(2):231–9.
35. Bouguen G, Levesque BG, Pola S, Evans E, Sandborn WJ. Endoscopic assessment and treating to target increase the likelihood of mucosal healing in patients with Crohn's disease. Clin Gastroenterol Hepatol. 2014;12(6):978–85.
36. Weber MA, Julius S, Kjeldsen SE, Brunner HR, Ekman S, Hansson L, et al. Blood pressure dependent and independent effects of antihypertensive treatment on clinical events in the VALUE Trial. Lancet. 2004;363(9426):2049–51.
37. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352(9131):837–53.
38. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352(9131):854–65.
39. Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. N Engl J Med. 1993;329(5):304–9.
40. Fransen J, Moens HB, Speyer I, van Riel PL. Effectiveness of systematic monitoring of rheumatoid arthritis disease activity in daily practice: a multicentre, cluster randomised controlled trial. Ann Rheum Dis. 2005;64(9):1294–8.
41. Stenger AA, Van Leeuwen MA, Houtman PM, Bruyn GA, Speerstra F, Barendsen BC, et al. Early effective suppression of inflammation in rheumatoid arthritis reduces radiographic progression. Br J Rheumatol. 1998;37(11):1157–63.
42. Symmons D, Tricker K, Roberts C, Davies L, Dawes P, Scott DL. The British Rheumatoid Outcome Study Group (BROSG) randomised controlled trial to compare the effectiveness and cost-effectiveness of aggressive versus symptomatic therapy in established rheumatoid arthritis. Health Technol Assess. 2005;9(34):iii–iv. ix–x, 1–78.
43. Fefferman DS, Farrell RJ. Endoscopy in inflammatory bowel disease: indications, surveillance, and use in clinical practice. Clin Gastroenterol Hepatol. 2005;3(1):11–24.
44. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J. 1955;2(4947):1041–8.
45. Baron JH et al. Variation between observers in describing mucosal appearances in proctocolitis. Br Med J. 1964;1(5375):89–92.
46. Feagan BG et al. Treatment of ulcerative colitis with a humanized antibody to the alpha4beta7 integrin. N Engl J Med. 2005;352(24):2499–507.
47. Powell-Tuck J et al. A comparison of oral prednisolone given as single or multiple daily doses for active proctocolitis. Scand J Gastroenterol. 1978;13(7):833–7.
48. Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. BMJ. 1989;298(6666):82–6.
49. Hanauer S, Schwartz J, Robinson M, Roufail W, Arora S, Cello J, et al. Mesalamine capsules for treatment of active ulcerative colitis: results of a controlled trial. Pentasa Study Group Am J Gastroenterol. 1993;88(8):1188–97.
50. Hanauer SB, Robinson M, Pruitt R, Lazenby AJ, Persson T, Nilsson LG, et al. Budesonide enema for the treatment of active, distal ulcerative colitis and proctitis: a dose-ranging study. U.S. Budesonide enema study group. Gastroenterology. 1998;115(3):525–32.
51. Sutherland LR, Martin F, Greer S, Robinson M, Greenberger N, Saibil F, et al. 5-Aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. Gastroenterology. 1987;92(6):1894–8.
52. Naganuma M, Ichikawa H, Inoue N, Kobayashi T, Okamoto S, Hisamatsu T, et al. Novel endoscopic activity index is useful for choosing treatment in severe active ulcerative colitis patients. J Gastroenterol. 2010;45(9):936–43.
53. Matts SG. The value of rectal biopsy in the diagnosis of ulcerative colitis. Q J Med. 1961;30:393–407.
54. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987;317(26):1625–9.
55. Neumann H, Neurath MF. Ulcerative colitis: UCCIS—a reproducible tool to assess mucosal healing. Nat Rev Gastroenterol Hepatol. 2012;9(12):692–4.
56. Samuel S, Bruining DH, Loftus Jr EV, Thia KT, Schroeder KW, Tremaine WJ, et al. Validation of the ulcerative colitis colonoscopic index of severity and its correlation with disease activity measures. Clin Gastroenterol Hepatol. 2013;11(1):49–54.e1.

57. Travis SP, Schnell D, Krzeski P, Abreu MT, Altman DG, Colombel JF, et al. Reliability and initial validation of the ulcerative colitis endoscopic index of severity. Gastroenterology. 2013;145(5): 987–95.
58. Walsh A, Palmer R, Travis S. Mucosal healing as a target of therapy for colonic inflammatory bowel disease and methods to score disease activity. Gastrointest Endosc Clin N Am. 2014;24(3):367–78.
59. D'Haens G, Feagan B, Colombel JF, Sandborn WJ, Reinisch W, Rutgeerts P, et al. Challenges to the design, execution, and analysis of randomized controlled trials for inflammatory bowel disease. Gastroenterology. 2012;143(6):1461–9.
60. Samaan MA, Mosli MH, Sandborn WJ, Feagan BG, D'Haens GR, Dubcenco E, et al. A systematic review of the measurement of endoscopic healing in ulcerative colitis clinical trials: recommendations and implications for future research. Inflamm Bowel Dis. 2014;20(8):1465–71.
61. Kamm MA, Sandborn WJ, Gassull M, Schreiber S, Jackowski L, Butler T, et al. Once-daily, high-concentration MMX mesalamine in active ulcerative colitis. Gastroenterology. 2007;132(1):66–75. quiz 432–3.
62. Feagan BG, Sandborn WJ, D'Haens G, Pola S, McDonald JW, Rutgeerts P, et al. The role of centralized reading of endoscopy in a randomized controlled trial of mesalamine for ulcerative colitis. Gastroenterology. 2013;145(1):149–57.e2.
63. Travis SP et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). Gut. 2012;61(4):535–42.
64. Daperno M, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc. 2004;60(4):505–12.
65. Annese V, Daperno M, Rutter MD, Amiot A, Bossuyt P, East J, et al. European evidence based consensus for endoscopy in inflammatory bowel disease. J Crohns Colitis. 2013;7(12):982–1018.
66. Daperno M, Castiglione F, de Ridder L, Dotan I, Farkkila M, Florholmen J, et al. Results of the 2nd part Scientific Workshop of the ECCO. II: Measures and markers of prediction to achieve, detect, and monitor intestinal healing in inflammatory bowel disease. J Crohns Colitis. 2011;5(5):484–98.
67. Tontini GE, Bisschops R, Neumann H. Endoscopic scoring systems for inflammatory bowel disease: pros and cons. Expert Rev Gastroenterol Hepatol. 2014;8(5):543–54.
68. Hebuterne X, Lemann M, Bouhnik Y, Dewit O, Dupas JL, Mross M, et al. Endoscopic improvement of mucosal lesions in patients with moderate to severe ileocolonic Crohn's disease following treatment with certolizumab pegol. Gut. 2013;62(2):201–8.
69. Laharie D, Reffet A, Belleannee G, Chabrun E, Subtil C, Razaire S, et al. Mucosal healing with methotrexate in Crohn's disease: a prospective comparative study with azathioprine and infliximab. Aliment Pharmacol Ther. 2011;33(6):714–21.
70. Rutgeerts P, Van Assche G, Sandborn WJ, Wolf DC, Geboes K, Colombel JF, et al. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. Gastroenterology. 2012;142(5):1102–11.e2.
71. Lemann M, Mary JY, Colombel JF, Duclos B, Soule JC, Lerebours E, et al. A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. Gastroenterology. 2005;128(7):1812–8.
72. Colombel JF, Rutgeerts PJ, Sandborn WJ, Yang M, Camez A, Pollack PF, et al. Adalimumab induces deep remission in patients with Crohn's disease. Clin Gastroenterol Hepatol. 2014;12(3): 414–22.e5.
73. Sipponen T, Bjorkesten CG, Farkkila M, Nuutinen H, Savilahti E, Kolho KL. Faecal calprotectin and lactoferrin are reliable surrogate markers of endoscopic response during Crohn's disease treatment. Scand J Gastroenterol. 2010;45(3):325–31.
74. Sipponen T, Karkkainen P, Savilahti E, Kolho KL, Nuutinen H, Turunen U, et al. Correlation of faecal calprotectin and lactoferrin with an endoscopic score for Crohn's disease and histological findings. Aliment Pharmacol Ther. 2008;28(10):1221–9.
75. Louis E, Mary JY, Vernier-Massouille G, Grimaud JC, Bouhnik Y, Laharie D, et al. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. Gastroenterology. 2012;142(1):63–70.
76. Aomatsu T, Yoden A, Matsumoto K, Kimura E, Inoue K, Andoh A, et al. Fecal calprotectin is a useful marker for disease activity in pediatric patients with inflammatory bowel disease. Dig Dis Sci. 2011;56(8):2372–7.
77. Dignass A, Stoynov S, Dorofeyev AE, Grigorieva GA, Tomsova E, Altorjay I, et al. Once versus three times daily dosing of oral budesonide for active Crohn's disease: a double-blind, double-dummy, randomised trial. J Crohns Colitis. 2014;8(9):970–80.
78. Moskovitz D, Deaperno M, Van Assche G. Defining and validating cut-off's for the simple endosocpic score for Crohn's disease. Gastroenterology. 2007;132(4):A173–S1097.
79. Ferrante M et al. Validation of endoscopic activity scores in patients with Crohn's disease based on a post hoc analysis of data from SONIC. Gastroenterology. 2013;145(5):978–86.e5.
80. Rutgeerts P et al. Natural history of recurrent Crohn's disease at the ileocolonic anastomosis after curative surgery. Gut. 1984;25(6): 665–72.
81. Sandborn WJ et al. Delayed-release oral mesalamine 4.8 g/day (800-mg tablet) is effective for patients with moderately active ulcerative colitis. Gastroenterology. 2009;137(6):1934–43. e1–3.
82. Adult inflammatory bowel disease (IBD). Presented at the Gastroenterology regulatory endopoints and the advancement of therapeutics (GREAT) workshop; Maryland: http://www.Regulations.Gov/-!Documentdetail;d=fda-2012-n-0001-0093.
83. Peyrin-Biroulet L et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): determining therapeutic goals for treat-totarget. Am J Gastroenterol. 2015;110:1324–38.
84. Bouguen G et al. Treat to target: a proposed new paradigm for the management of Crohn's disease. Clin Gastroenterol Hepatol. 2015;13:1042–50.e2.

1.5 TREATMENT TARGETS IN IBD: HISTOLOGIC HEALING

Over recent years, due to the evidence summarised above, endoscopic mucosal healing has been recognized as an important prognostic marker in IBD and increasingly thought of as a potential treatment target. However, despite the benefits of achieving endoscopic mucosal healing, endoscopic mucosal assessment only surveys the macroscopic surface layer of the bowel. Microscopic evidence of inflammation is common, even in patients with clinically and endoscopically quiescent disease, and CD is a transmural disease that involves the mesenteric lymphatic system. Therefore, more recently, there has been growing interest in the significance of histologic healing, as perhaps an even "deeper" marker of disease control compared to endoscopic mucosal healing.(2) Up to 63% of patients with IBD in clinical and endoscopic remission will have ongoing histologic inflammation and it is increasingly being recognised that persistent histologic inflammation is associated independently with a worse prognosis over time.(18-20) However, there is still very limited information on the characteristics that identify patients who may continue to have smouldering microscopic activity despite clinical and endoscopic or mucosal normalisation and only limited information on the benefits of histologic remission in patients with Crohn's disease.

Despite some concerns over the practicality of assessing for and achieving histologic healing, the consideration of such a goal of therapy is gaining popularity. While more research is needed into clinical outcomes, initial evidence of histologic healing in UC suggest that it is more predictive of improved outcomes than historical measures, including mucosal healing, as histologic healing has been associated with decreased risk of relapse, hospitalization, need for colectomy and risk for colorectal neoplasm compared to mucosal healing alone.(2, 15, 27-30) In CD, however, there have been very few studies evaluating the impact of histologic activity

and outcomes. Although it has been demonstrated that histologic remission can be achieved with azathioprine, methotrexate and infliximab, the correlation of histologic healing with endoscopic findings and improved outcomes is still not clear.(31, 32) The value of histologic healing in CD will be examined in this thesis.

Currently there is no standardised reporting system to grade histologic activity. When grading histology in IBD, it is a common perception that, following a diagnosis of IBD, structural abnormalities of the mucosa persist. This idea has become so established that when histology has been described in UC, normalisation is not generally defined as an independent outcome and histologic healing is described as the absence of inflammation.(2, 7, 29, 33) However, perhaps with improvements in treatment modalities, complete histologic normalisation of previously affected mucosa had been increasingly noted in patients with UC. The rates, predictors of and prognostic value of this normalisation will also be examined as part of this thesis.

1.6 DEFINING HISTOLOGIC HEALING AND HISTOLOGICAL SCORING SYSTEMS IN IBD

Histologic healing does not have a validated definition, but is most commonly defined as the absence of residual mucosal inflammation with distinctive changes in crypt architecture distortion and/or atrophy, or completely normal mucosa.(34) A systematic review by Bryant et al demonstrated that there were 22 different histological scoring systems for IBD, none of which were fully validated.(35) Since that review two partially validated scores for UC have been developed and are the most studied indices: the Nancy Index and the Robarts Histopathologic Index.(36-38) These two indices have excellent intra- and inter-observer agreement. The

Robarts Index was based on a RAND consensus process for which specific scoring descriptors from the Geboes score and modified Riley score were selected based on their reproducibility and reliability and their correlation with a visual analogue scale of severity.(37) The final index scores lamina propria chronic inflammation, lamina propria neutrophils, neutrophils in the epithelium and surface epithelial injury. Although it was specifically designed to be responsive and reproducible, it requires assessment of 4 features to arrive at a calculated score, which may reduce its clinical usefulness. The Nancy index is a stepwise 5-item index that evaluates lamina propria chronic inflammation (defined as lymphocytes, plasma cells and eosinophils), neutrophilic inflammation and ulcers.(38) The worst feature present determines the final score. These indices correlate with clinical remission and disease activity as well as the Mayo endoscopic score and faecal calprotectin concentrations.(39) Even with these partially validated indices, there is currently no agreed definitions for histologic healing, response or remission. Due to the lack of a standardised approach, the International Organization of Inflammatory Bowel Disease (IOIBD) has recommended the following definition for histologic healing: 1) absence of neutrophils (both in crypts and lamina propria), 2) absence of basal plasma cells and ideally reduction of lamina propria plasma cells to normal and 3) normal numbers of lamina propria eosinophils.(40) With the growing evidence of the utility of histology in predicting patient outcomes, UC histologic remission is now considered an adjunctive goal of care and its use is incorporated into most clinical trials.(41)

The most commonly utilised histological scoring system in CD is the Colonic and Ileal Global Histologic Disease Activity Score (GCHAS or IGHAS).(42) It incorporates epithelial damage, architectural changes, mononuclear or polymorphonuclear cells in the lamina propria and epithelium, presence of erosions/ulcers and granulomata as well as the number of segmental biopsy specimens affected. It is not validated so its role remains undefined and whether treating

to histologic remission is possible in CD remains unknown. Therefore, no guidelines currently incorporate CD histologic outcomes into a treatment target strategy currently.

1.7 EMERGING ENDPOINTS AND SURROGATE MARKERS OF INFLAMMATION

Current paradigms have endoscopic assessment as the preferred target in designing therapeutic strategies.(41) However, endoscopy is an invasive and expensive test, not free from risks, and is relatively unfriendly to patients particularly as it should be repeatedly applied in the algorithms suggested.(43) There is also the issue that, as outlined above, endoscopy only surveys the mucosal surface of colon and terminal ileum despite Crohn's disease being a transmural disease that involves the mesenteric lymphatic system. There is, therefore, clearly the need for reliable surrogate markers upon which monitoring and subsequent decisions can be based and the need for endoscopic assessment reduced.

1.7.1 Blood Biomarkers: C-reactive protein

C-reactive protein (CRP) is produced by hepatocytes and increased levels can often be seen following inflammatory stimulation. CRP rises sharply following the onset of inflammation but once the inflammatory stimuli disappears, the levels falls rapidly due to its short half-life of 19 hours.(44) CRP is a well-known marker of disease activity in CD(45) and several studies have demonstrated the correlation between CRP with clinical and endoscopic activity.(46-49) A prospective longitudinal study that evaluated 101 patients with CD showed that CRP was reproducible and reliable, and CRP concentrations decreased as the disease went into clinical remission.(50) A higher rate of clinical relapse was observed in patients with a persistently elevated CRP(50) and separately CRP $\geq$ 5 mg/L has been found to be a risk factor for clinical

relapse.(51) Finally a review by Schnitzler et al(52) of 614 CD patients treated with infliximab and followed for a median time frame of 55 months found that patients had improved outcomes if CRP fell and remained less than 3 mg/L. However, despite these promising findings, CRP is an insensitive marker of disease activity for mild to moderate endoscopic inflammation in CD.(53)

Although CD patients have a stronger CRP response compared to those with UC(44, 54), CRP elevations are also significantly associated with severe clinical activity and active disease at ileocolonoscopy in patients with UC.(3, 48) Correlation between endoscopy activity and CRP was evaluated in a prospective study, in which CRP and leucocyte count were able to discriminate mild from moderately active endoscopic disease but neither from inactive to mild nor from moderate to highly active endoscopic disease.(55)

Overall CRP does have some value in detecting asymptomatic disease activity(47), but up to one-third of patients with intestinal inflammation do not have an elevated CRP concentration.(50, 56) In addition, its low sensitivity in detecting mild disease from inactive disease limit its use.(53, 55) Therefore, although it can be useful if elevated in the individual patient, the assessment of CRP levels should not be solely relied upon to assess for mucosal inflammation.

1.7.2 Faecal Biomarkers: Faecal calprotectin or lactoferrin

A novel way of detecting inflammation in the bowel is measuring faecal calprotectin or lactoferrin which are predominantly derived from neutrophils. Calprotectin is the most commonly utilized with some studies suggesting slightly greater sensitivity and specify when compared to lactoferrin in certain clinical situations.(57) Calprotectin is stable at room

temperature for up to 7 days(58) and has been found to correlate well with endoscopic activity in UC and CD.(59, 60) In UC, calprotectin > 250 μg/g gives a sensitivity of 71% and specificity of 100% (PPV 100% and NPV 47%) in detecting active mucosal disease (Mayo > 0) and is significantly correlated with clinical symptoms ($r=0.561$, $p< 0.001$).(60) Other studies have had similar conclusions, with one study of 228 patients finding that, of clinical assessment, CRP and calprotectin, calprotectin correlated most highly with endoscopic activity. In addition, as endoscopic disease activity increased so did the value of the calprotectin.(55, 59) Elevated calprotectin levels are also useful in predicting which patients are responding to therapy and which patients are at increased risk of clinical disease relapse.(61, 62) De Vos and colleagues studied calprotectin levels in patients receiving treatment with infliximab; Patients with an 80% decrease in calprotectin level between the baseline measurement and the measurement at two weeks or a calprotectin level of less than 50 μg/g at two weeks after initiating therapy were found to have achieved mucosal healing at week ten of therapy with infliximab with a sensitivity of 54% and specificity of 67%.(63) In a separate study of patients receiving infliximab, they found that those patients who achieved deep remission at 52 weeks (defined as both clinical (partial Mayo score < 3) and endoscopic (endoscopic Mayo Score of 0) remission) had consistently very low levels of calprotectin throughout the follow-up period. Additionally, two consecutive calprotectin levels greater than 300 μg/g one month apart was predictive of clinical disease relapse while on treatment with a sensitivity of 62% and specificity of 100%.(64)

In patients with CD, calprotectin and lactoferrin also correlate with clinical and endoscopic disease activity and predict favourable clinical outcomes of patients following anti-tumour necrosis factor (anti-TNF) therapy.(65-67) At a cut-off of 250 μg/g, calprotectin can be used to indicate the presence of large ulcers in CD with a sensitivity of 60% and specificity of 80%

(PPV 78% NPV 62%)(60) and can predict endoscopic remission (CDEIS ≤ 3) with 94% sensitivity and 62% specificity (PPV 49% and NPV 97%).(60) In addition, calprotectin levels correlate well with endoscopic improvement as measured by the Rutgeert's score in the postoperative setting in CD. Sorrentino et al(68) found that, in patients with disease recurrence on stopping anti-TNF therapy in the postoperative setting, mucosal injury corresponded to calprotectin levels. In addition, those patients who responded to re-initiation of anti-TNF therapy with endoscopic improvement had improvement of calprotectin.(68) Finally, normalisation of calprotectin following induction therapy with anti-TNF therapy can predict favourable clinical outcomes in CD after anti-TNF therapy with Molander et al finding that at a cut-off of 139 μg/g, calprotectin had a sensitivity of 72% and specificity of 80% to predict clinically active disease at 1 year.(69)

More recently, calprotectin has been found to be associated with even deeper levels of remission than endoscopic mucosal healing alone. In a study of 59 patients who had achieved clinical and endoscopic remission (Mayo 0 or 1), patients with ongoing histologic inflammation had significantly higher median levels of calprotectin; calprotectin > 155 μg/g was able to predict ongoing histologic inflammation with a sensitivity of 78%, specificity of 71% and an area-under-the-receiver-operator curve (AUC) of 0.754.(70) A further study of 72 patients with a Mayo endoscopic score of 0 at surveillance colonoscopy concluded that higher calprotectin levels were associated with a significantly increased risk of clinical relapse on follow-up; calprotectin < 56 μg/g predicted absence of relapse during follow-up with 64% sensitivity and 100% specificity and was a stronger predictor of relapse than histologic scoring.(71)

Calprotectin is an important addition to the assessment tools available in the management of IBD, but it does have limitations. The test characteristics are good but the test is not completely

able to rule in or out the presence or absence of mucosal or transmural healing.(59) If one were to use calprotectin instead of endoscopic and histologic evaluation for monitoring disease activity exclusively there would be patients who have achieved mucosal and histologic healing that have a negative test for healing and patients who have not achieved mucosal and histologic healing who have a positive test for healing. Its utility is also currently impacted as there are still no defined optimal cut-off points for ruling out intestinal inflammation or for treatment management (ie. Escalation of medical therapy) in the IBD patient.(72) It also does not provide information on the location or distribution of inflammation or the presence of disease complications including strictures or fistulas. In summary, the test characteristics of calprotectin for predicting clinical course are not strong enough to be relied upon alone with complete certainty.(61-64) However it is increasingly being shown to be useful as an adjunct test in a treat-to-target strategy(73) and should be incorporated alongside other markers of disease activity into routine management of patients with IBD.

1.7.3 Cross-sectional imaging

Cross-sectional imaging with computed tomography or magnetic resonance imaging is of interest, and has increasing utility to assess for response to therapy and confirmation of achievement of mucosal healing in CD patients, but has limited use in UC.(74, 75) At this stage, magnetic resonance enterography (MRE) is the most validated cross-sectional tool and is recommended to assess and confirm healing of inflammation in those who cannot have their disease assessed by endoscopy.(41) MRE is accurate at detecting activity, severity and complications of CD.(76) The accuracy of MRE for detecting disease activity and assessing severity was validated in a prospective study in 50 CD patients where it was found that a magnetic resonance index of activity correlated with global CDEIS ($r=0.83$, $p<0001$)(77) and had a sensitivity of 87% and specificity of 87% for diagnosing endoscopically active

disease.(75, 77) In a systematic review, Panes et al reported that the overall sensitivity of MRE for detection of disease activity in CD is 80% (95% CI 77%-83%) and specificity is 89% (95% CI 93-96%).(78) In addition, MRE has been shown to be accurate at assessing response to therapy and confirming bowel healing in patients with CD. In a study of 48 CD patients who had ileocolonoscopy and MRE at baseline and after 12 weeks of treatment, MRE determined ulcer healing with 90% accuracy and endoscopic remission with 83% accuracy.(74) MRE was as reliable as endoscopy in assessing healing.(74) In UC, although not used as routinely, magnetic resonance colonography (MRC) is also accurate at assessing disease activity and severity.(75) A segmental simplified MRC index enabled detection of endoscopic inflammation with high diagnostic accuracy with a sensitivity of 87% and specificity of 88% (AUC 0.95, $p<0.001$).(75) However, the requirement for rectal contrast and water insufflation makes this procedure less practical.(75)

Overall MRE is an attractive alternative to endoscopy as it reduces discomfort and complications relative to ileocolonoscopy. However, its use is currently limited due to lack of widespread availability, cost, the fact that it can be poorly tolerated by some patients and the lack of data on long-term outcomes of patients stratified by disease activity on the basis of MRE or MRC assessment.(47, 74)

Intestinal ultrasonography (IUS) is sensitive at detecting mucosal inflammation in both UC and CD and can diagnose post-operative recurrence in CD.(79-81) In addition, it can assess treatment response and can detect complications of disease including fistulae, strictures and abscesses, but is user-dependent and expertise is not available in many parts of the world.(82) In a systematic review of 68 publications conducted by Panes et al, the reported overall sensitivity and specificity of IUS in assessing CD activity was 85% and 91%,

respectively.(78) In addition contrast-enhanced IUS may be able to classify the severity identified at endoscopy significantly better than Doppler US.(83) There are less studies looking at the utility of IUS in UC. A prospective study of 83 patients with UC demonstrated that there was high concordance between IUS score and endoscopic score at 3 months following steroid therapy and that IUS was the strongest predictor of outcomes of disease at 15 months.(79) Another prospective study of 253 patients with UC found that patients had improvement of bowel wall thickness on IUS as early as week 2 following treatment intensification. Furthermore, clinical responders showed a significant reduction in bowel wall thickness in the sigmoid or descending colon at week 12 from baseline when compared to the reduction in bowel wall thickness in clinical non-responders.(84) A systematic review concluded that, despite limited evidence, IUS has a viable role in the routine assessment and management of patients in UC.(85) IUS use is likely to increase as treating to objective targets is further embraced, as it can be used as an accurate alternative to regular endoscopic assessment in IBD and it is cheap, safe and can be used as a point-of-care test.

A few small studies have demonstrated the benefit of positron emission tomography scanning for detection of subclinical inflammation and in assessment of treatment response in IBD.(86, 87) However, the cost, lack of accessibility and radiation exposure of such an exam limits its use.

1.8 MEDICATIONS USED FOR INDUCTION AND MAINTENANCE OF HISTOLOGIC HEALING

1.8.1-Aminosalicylates (5-ASA)

5-aminosalicylates (5-ASA) compounds (oral and topical) are the first-line therapy to induce and maintain clinical remission in mild to moderate UC.(88) Although there is a paucity of controlled trial data comparing their efficacy to placebo, several studies have demonstrated the ability of 5-ASA agents to induce both mucosal and histologic remission. A meta-analysis of 5-ASA clinical trials found that 37% of patients with UC on oral 5-ASA (graulates and tablets) and 50% of those using rectal 5-ASA (suppositories, enemas, and foam) achieve mucosal healing with no difference in efficacy between the different formulations in each category.(89) Dosage however, may influence treatment response. A pooled analysis of the ASCENT 1 and 2 trials demonstrated that rates of mucosal healing may be dose-dependent with at least some 5-ASA formulations, with mucosal healing achieved in 80% of patients with mild to moderate UC on 4.8 g/day of delayed-release oral mesalazine compared to 68% on 2.4 g daily at 6 weeks ($p=0.012$).(90) A meta-analysis also found a significantly higher mucosal healing rate with any oral 5-ASA formulation $\geq$ 3g, but only demonstrated a trend toward a dose-response with rectal therapy.(89)

Both oral and topical 5-ASA agents are also able to induce histologic healing. A large study comparing once or thrice daily oral dosing of 3 g/d mesalamine granules found that histologic healing was achieved in 35% of those on single dosing and 41% of those on thrice daily dosing.(91) A study of topical mesalamine vs budesonide reported histologic remission in approximately 50% of patients randomised to topical mesalamine(92) and a Cochrane review concluded that rectal 5-ASA medications are more likely to induce histologic remission

compared to placebo (Odds Ratio (OR), 6.28; 95% confidence interval (95%CI), 2.74-14.40; p<0.0001).(93)

In contrast to UC, 5-ASA agents have limited efficacy in CD and there is no clear evidence that 5-ASA induce mucosal or histologic healing in CD.

1.8.2 Corticosteroids

Corticosteroids are used as a short-term treatment to induce clinical remission in both CD and UC.

There is some evidence that corticosteroids are able to induce mucosal healing in UC. In the 1955 landmark paper by Truelove and Witt's, it was concluded that, after 2-6 weeks of therapy, mucosal healing was achieved in 30% of UC patients randomised to cortisone 100 mg/day compared to only 11% of those randomised to placebo.(94) Supporting these findings, a more recent study of 157 newly diagnosed UC patients prescribed systemic corticosteroid therapy reported a mucosal healing rate of 38% after three months of therapy.(95) Similar rates of mucosal healing have been reported with budesonide therapy with a Cochrane review finding that 27% of patients treated with budesonide achieve mucosal healing at week 8 compared to 18% of patients treated with placebo.(96) The evidence for the ability of corticosteroids to achieve histologic remission in UC is varied. A study of 343 patients randomised to either oral budesonide or oral mesalamine found that 48% of patients randomised to budesonide achieved histologic remission at week eight compared to 59% of those on mesalamine.(97) However, a pooled analysis of two phase III placebo-controlled studies only demonstrated a 10% histologic healing rate in those placed on budesonide at week eight.(98) For topical therapies delivered per rectum, a study of 237 patients with active left-sided UC compared mesalamine enemas

with budesonide enemas and found that histologic remission was achieved in 43% of those on rectal budesonide compared to 47% of those on mesalamine enemas.(92)

In CD, a non-randomised, prospective study of 142 patients treated with high-dose prednisolone (1 mg/kg) for up to 7 weeks demonstrated that of the 131 patients who achieved clinical remission, endoscopic remission was achieved in 29% of patients when remission was defined as only minor lesions and in 13% of patients when it was defined as complete healing.(22) Of note, this only equates to approximately 12% of the overall cohort achieving true mucosal healing following prednisolone treatment. Furthermore, most other studies have found that corticosteroids are not effective at inducing and/or maintaining mucosal healing when compared with placebo.(22, 99) As mucosal healing is assumed to be an earlier target than histologic healing, it is likely that corticosteroids also have limited efficacy at inducing histologic healing in CD.

1.8.3 Thiopurines and Methotrexate

Data on the ability of thiopurines (azathioprine and 6-mercaptopurine) and methotrexate to achieve mucosal and histologic healing in IBD are scarce. Overall, it appears that azathioprine may have a modest effect in inducing mucosal and histologic remission in both UC and CD, and methotrexate may have a limited benefit in CD but not UC.(100, 101) However, it must be noted, that there is delayed onset of action.

For UC, the best evidence of azathioprine's ability to achieve mucosal healing is from the UC SUCCESS randomized controlled trial of azathioprine, infliximab or combination therapy, which found that mucosal, healing, was achieved in 37% of patients randomized to azathioprine alone at week 16.(100) The METEOR trial, comparing 25 mg/week of parenteral methotrexate

with placebo in corticosteroid dependent patients, demonstrated no increase in mucosal healing rates with methotrexate compared to placebo (35% vs 25% in placebo, p=0.28).(102)

In regard to histologic healing, a study of 32 patients on azathioprine and 10 patients on methotrexate found that 75% of those on azathioprine and 60% of those on methotrexate achieved histologic remission.(103) However, these rates seem curiously high, given the lack of efficacy in regard to rates of mucosal healing determined in other studies and, therefore, require confirmation in further prospective studies.

In CD, there are several studies that address the ability of immunomodulators and methotrexate and their ability to achieve mucosal healing. The strongest evidence for mucosal healing comes from the well-designed SONIC study where patients were randomised to azathioprine, infliximab or combination therapy. Of those that were placed on azathioprine, 36% withdrew before week 26. Amongst the remaining patients, only 17% were found to achieve mucosal healing.(104) There are no data on the ability of thiopurines to induce histologic remission in CD. For methotrexate, again there are only limited data in its ability to achieve mucosal healing. A non-randomised study of methotrexate given to 14 patients demonstrated mucosal healing in 5 patients and histologic normalisation in 4.(105) In addition, a prospective cohort study of 51 patients with known mucosal ulceration who were placed on methotrexate, azathioprine or infliximab and achieved clinical remission, demonstrated that mucosal healing was achieved in 11% of those on methotrexate compared to 50% of those on azathioprine and 60% of those on infliximab.(106) There were no histologic outcomes reported.

1.8.4 Calcineurin Inhibitors

Cyclosporin is the most frequently utilized calcineurin inhibitor and is an effective salvage therapy for acute severe UC refractory to intravenous corticosteroids.(107) Tacrolimus is also

an effective therapy for steroid-resistant UC and CD is most often utilized in the outpatient setting.(108) Despite their efficacy at inducing clinical remission, adverse side-effects including hypertension, diabetes, renal dysfunction, infection and tremor limit their utility as maintenance agents.(107, 108)

There are limited data on the efficacy of cyclosporin and tacrolimus in achieving mucosal or histologic remission in UC and a complete paucity of data in CD.

For UC, evidence suggests that cyclosporin is effective at inducing mucosal healing. A randomised controlled trial of 110 patients comparing cyclosporin with infliximab in acute severe UC patients refractory to intravenous corticosteroids demonstrated that mucosal healing was achieved in 47% of patients randomised to cyclosporin at day 98 compared to 45% in the infliximab arm (p=0·85).(107) Similarly, a randomised controlled trial of oral tacrolimus vs placebo for active UC found that tacrolimus is effective at rapidly inducing mucosal healing, with 44% (14/32) of patients achieving mucosal healing by week 2 compared to 13% (4/30) in the placebo group (p=0.012).(108) A study comparing methylprednisolone and cyclosporin did demonstrate histologic improvement with both therapies but no study has reported on rates of histologic healing in UC with either tacrolimus or cyclosporin.(109)

Although there is some evidence for the clinical utility of cyclosporin and tacrolimus in CD, there are no reports on mucosal healing or histologic healing rates with these therapies.(110)

1.8.5 Anti-Tumour Necrosis Factor Treatment

The anti-TNF biologics (infliximab, adalimumab and golimumab) utilised in the treatment of IBD are efficacious in achieving both mucosal and histologic healing and their addition to the armamentarium of medical therapies has transformed clinical care.

In UC, the original ACT1 and ACT2 trials on moderate to severe ulcerative colitis demonstrated that 61% of patients receiving infliximab achieved mucosal healing at week 8 versus 33% of those who were given placebo ($p<0.01$).(13) For adalimumab, the ULTRA1 trial, which only included anti-TNF naïve UC patients, failed to demonstrate any benefit in regards to achieving mucosal healing at week 8 compared to placebo (47% vs 41%, p=NS).(111) However, the ULTRA2 trial, that included both TNF-exposed and naïve patients, did demonstrate a marginal benefit for adalimumab with 41% of those on adalimumab achieving mucosal healing at week 8 vs 32% of placebo patients ($p=0.014$).(112) Rates of mucosal healing with golimumab were similar to adalimumab in the seminal trials, with the PURSUIT study demonstrating that 44% of patients on golimumab achieved mucosal healing at week 6 vs 29% of those who were placed on placebo ($p <0.002$).(113)

There are few data on the rates of histologic healing achievement in UC. In a study by Molander et al of 62 patients who achieved both clinical and endoscopic remission after being on infliximab or adalimumab for more than 11 months, 93% of the patients also achieved histologic remission.(114)

In CD, the ACCENT 1 trial found that 31% of patients who received standard 5 mg/kg dosing of infliximab at weeks 0, 2 and 6 achieved mucosal healing at week 10 vs 0% of those who received a single dose at baseline ($p=0.006$).(115) The SONIC trial which compared azathioprine, infliximab and combination therapy also demonstrated that infliximab resulted in approximately 30% of patients achieving mucosal healing at week 26, which significantly increased to 44% in those receiving combination therapies with infliximab and azathioprine.(104) For adalimumab, the CHARM study demonstrated that mucosal healing at

week 12 was achieved in 27% of those who were given standard dosing of adalimumab versus 13% of those who received induction dosing at week 0 and 2 and were then randomised to placebo (p=006).(116)

Several studies have demonstrated histologic improvement with anti-TNF treatment but few have focused on healing.(23, 117, 118) In a study of 183 CD patients treated with infliximab or adalimumab, 43% achieved a combination of clinical and mucosal healing and, of these, 75% also achieved histologic remission.(114)

1.8.6 Anti-integrin Treatment: Vedolizumab

Vedolizumab is a monoclonal antibody to alpha-4 beta-7 integrin and has been approved for both induction and maintenance of remission for UC and CD. Although there are only limited data available, vedolizumab appears effective at inducing mucosal and histologic remission in both UC and CD.

In UC, mucosal healing was reported in 52% and 56% of patients receiving vedolizumab every 8 and 4 weeks respectively in the GEMINI 1 study, which was significantly greater than the 20% seen in those who received placebo.(119) Furthermore, in a post-hoc analysis of 41 patients from this study, 55% of those who achieved endoscopic healing (defined as a Mayo endoscopic sub-score 0-1) also achieved histologic healing (defined as Geboes grade 0-1).(120)

Mucosal healing was not an endpoint in the CD GEMINI 2 trial.(121) Nevertheless, a retrospective, multi-centre, real-world study reported an accumulative mucosal healing rate of 63% in CD patients treated with vedolizumab.(122) However, there were significant shortcomings in this study, particularly as the rates did not appear to take into account patient

drop-out and hence this figure is likely an overestimate. More recently, in a prospective, open-label, single-armed study of 101 CD patients commenced on vedolizumab, 12% achieved endoscopic remission by 6 months, which increased to 18% at one year.(123) This study also reported on histologic outcomes and found that 24% and 38% of patients achieved histologic response in the colon and ileum respectively by 6 months.(123) At one year, this had decreased to 21% response rate in the colon but increased to 34% in the ileum. There was no placebo group with which these outcomes could be compared.

1.8.7 Ustekinumab

Ustekinumab is a monoclonal antibody to the p40 subunit of IL-12 and IL-23 and has recently been approved for the induction and maintenance of remission in CD. There is some limited evidence that it may be effective at inducing both mucosal and histologic remission in CD and UC.

The UNIFI studies, evaluating the safety and efficacy of ustekinumab in moderate-to-severe UC, were the first major pharmaceutical studies including a combined histo-endoscopic mucosal healing endpoint. In these studies, ustekinumab was significantly more likely to achieve histo-endoscopic mucosal healing compared to placebo with 39%, and 46% of patients treated with ustekinumab every twelve ($p=0.002$), and eight ($p=0.001$) weeks respectively, achieving histo-endoscopic mucosal healing compared with 24% in the placebo arm.(124) The individual rates of mucosal and histologic healing achieved were, unfortunately, not reported. For CD, the UNITI studies evaluating ustekinumab safety and efficacy in moderate to severe CD did not include an endoscopic endpoint.(125) However, in an endoscopy sub-study of 334 patients, there was a significant decrease in the SES-CD score in those who received ustekinumab compared to placebo but no difference in endoscopic mucosal healing rates.(126)

9% and 17% of patients treated with ustekinumab 90mg 8-weekly achieved endoscopic mucosal healing by week 8 and week 44 respectively which was not statistically significantly better than the 4% at both times points in the placebo treatment arm. It was however found that a significantly greater proportion of patients achieved histologic improvement (50% in those randomized to 8-weekly ustekinumab vs 0% in the pooled placebo groups, p = 0.0137). The number of patients who achieved complete histologic healing in each treatment arm was not reported.(127)

1.9 RECURRENT CD: MEDICAL PROPHYLAXIS

This book chapter reviews the medical options in the post-operative CD patient and reviews risk factors for disease recurrence and repeat surgery. It assesses options for maintaining patients in a disease-free state (aiming for mucosal and histologic healing) and reviews the medical therapies and their efficacy at preventing mucosal disease recurrence. The chapter concludes with an assessment and treatment algorithm to maintain patient's wellbeing discussing the objective targets that should be monitored to improve their long-term outcomes.

Recurrent CD: Medical Prophylaxis

16

Britt Christensen and David T. Rubin

Abbreviations

CD	Crohn's disease
FC	Fecal calprotectin
IMM	Immunomodulator

Introduction

Following surgical resection in Crohn's disease (CD), post-operative recurrence remains a significant problem. Endoscopic recurrence rates at or proximal to the surgical anastomosis are reported to be between 70 and 90 % within 1 year [1, 2]. In addition, up to 50 % of patients will require a repeat operation for recurrence within 5 years and up to 70 % will require repeat surgery within 20 years [3–6]. Prevention of this post-operative recurrence is essential to prevent both disease relapse and a second negative outcome such as surgery [7]. However optimal monitoring and medical management of patients with CD after surgery is still controversial.

B. Christensen, BSc, MBBS, MPH • D.T. Rubin, MD (✉)
Section of Gastroenterology, Hepatology and Nutrition, The University of Chicago Medicine, 5841 S. Maryland Avenue, MC4076, Room M410, Chicago, IL 60637, USA
e-mail: britt.christensen@uchospitals.edu; drubin@medicine.bsd.uchicago.edu

Relapse Rates and Predictors of Relapse

Clinical relapse rates at 1 year are estimated to be between 10 and 38 % [8]. However clinical relapse is much less frequent than endoscopic recurrence with studies suggesting an endoscopic recurrence rate as high as 90 % in those not receiving medical prophylaxis 1 year after surgery [1, 2]. Endoscopic findings that indicate recurrence include small aphthous ulcers, deep linear ulcers, mucosal inflammation, fistulae, and strictures [9]. These varying degrees of endoscopic disease activity may be seen within 3 months of surgery in more than 70 % of patients [2]. The most common site of recurrence is the surgical anastomosis, especially the proximal side of the anastomosis [1]. The cause of recurrence at this location is believed to be due to luminal contents, specifically intestinal flora [10].

The most consistently recognized risk factors for recurrence include smoking cigarettes, perforating type disease, perianal fistula, prior CD surgery, and ileocolonic disease compared with colonic and small intestinal disease patterns [11–15]. Shorter disease duration till first operation, and younger age at first operation are also likely risk factors [11]. It is unclear if having clear margins at the time of surgery, having a smaller length of resection or if the types of anastomosis are associated with improved outcomes [12, 14–16].

A. Fichera and M.K. Krane (eds.), *Crohn's Disease: Basic Principles*,
DOI 10.1007/978-3-319-14181-7_16,

Bacteria and gut contents play a significant role in post-operative recurrence. If a patient is diverted proximal to the anastomosis, a sustained remission at the anastomosis is achieved without medical therapy [17]. In a study by D'Haens et al. of patients with an ileal resection and primary anastomosis but with proximal diversion of luminal contents by a diverting ileostomy, no recurrence was noted by endoscopy [17]. However following reinfusion of ileostomy contents into the diverted distal ileum, there was histologic evidence of inflammation within 1 week, thus demonstrating the critical role of luminal contents in reactivation of CD [17].

Assessing Post-Operative Recurrence Risk

Patients with any of the risk factors mentioned have a high likelihood of recurrence and are the patient subgroup in which prophylactic medical therapy should be strongly considered. The assessment of post-operative risk recurrence should occur pre-operatively. All available options should be discussed with the patient. In addition open communication between the GI physicians and the surgical teams needs to occur with clarification of the type, extent and severity of disease, and discussion regarding plans for immune suppression. Due to the high recurrence rates seen it is worthwhile being proactive and to institute preventative strategies in high-risk patient groups. Post-operative ileocecectomy should be seen as the ideal opportunity for prevention of symptomatic disease and complications from the disease.

Assessment of Recurrence

Clinical symptoms should not be relied upon to assess for post-operative recurrence. Inflammation is often present in asymptomatic patients and there is poor correlation between clinical and endoscopic findings in the post-operative setting [18, 19]. The most commonly used endoscopic scoring system to assess disease recurrence after ileal or ileocolonic resection in CD is the Rutgeerts' score (Fig. 16.1) [1]. This score looks at the presence and severity of recurrence in the

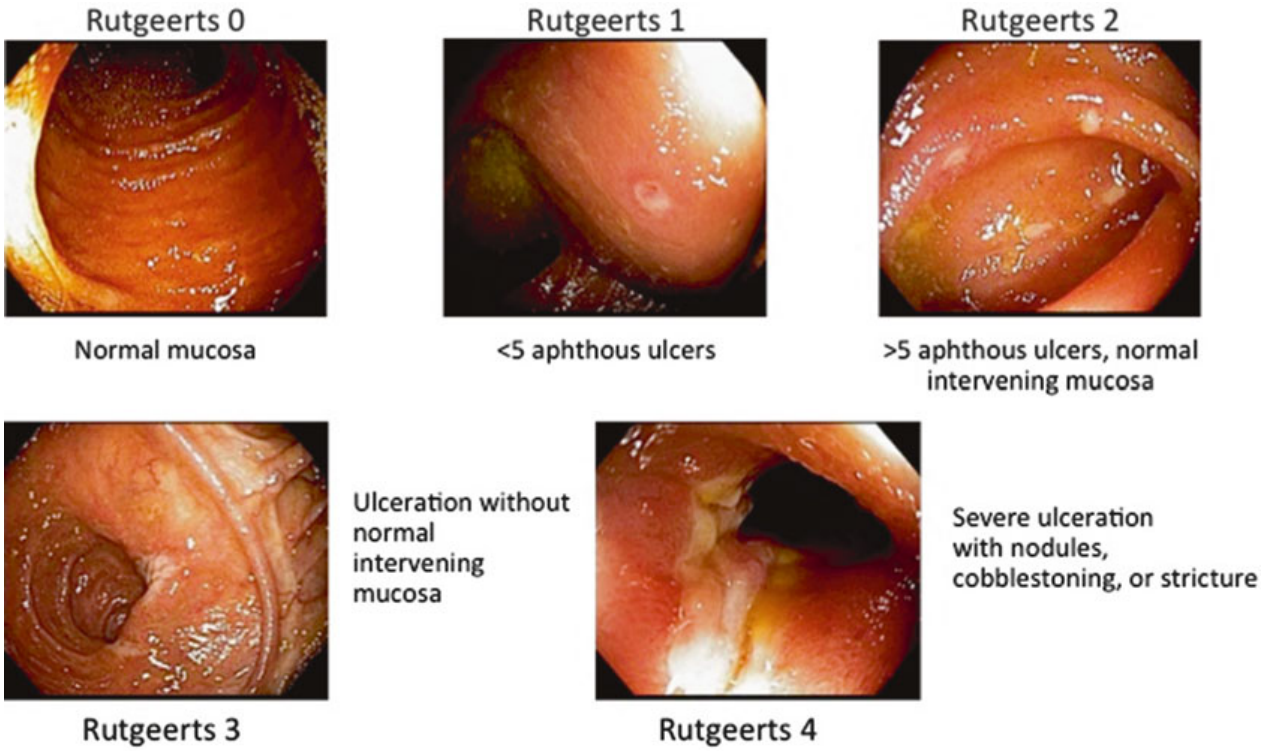


Fig. 16.1 Rutgeerts' score for post-operative endoscopic recurrence

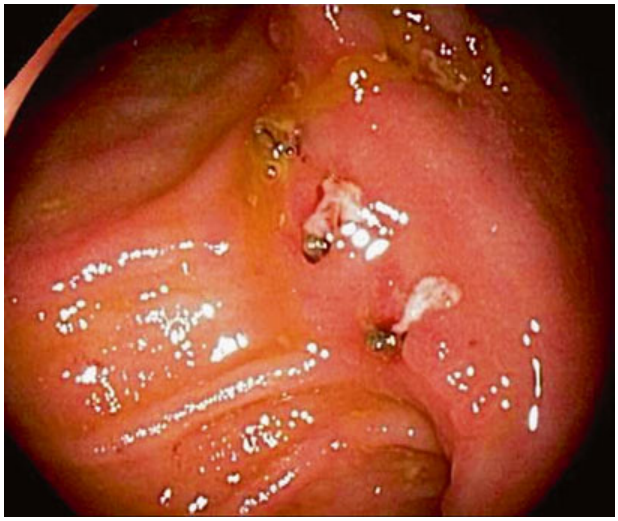


Fig. 16.2 Suture related trauma at the post-operative anastomosis

neoterminal ileum and at the ileocolonic anastomosis. When utilizing this scoring system it is important to acknowledge that ulcers at the anastomosis may not always be related to disease recurrence. It is quite common to have suture related trauma (Fig. 16.2) or marginal ulceration/ischemia at this location and such ulcers should be excluded from the scoring system. Rutgeerts' score is used to determine initiation of medical therapy as it has been found to correlate with the prognosis of clinical disease recurrence with those having a score of i-0 or i-1 having less than 5 % chance of clinical recurrence within 3 years. This is in comparison with i-2, i-3, and i-4, which correlate with a clinical recurrence risk of 14 %, 40 %, and 90 %, respectively [1, 20]. Due to the fact that endoscopic recurrence precedes clinical recurrence and that most recurrence occurs within the first year [20] it is recommended that an ileocolonoscopy be performed within 6–12 months of surgery.

Fecal Calprotectin for Assessing Post-Operative Recurrence

As endoscopy is an invasive test that potentiates a risk to the patient, there has been interest in the use of surrogate markers to monitor for disease recurrence in the post-operative setting. The most promising is that of fecal calprotectin (FC). FC levels correlate well with endoscopic recurrence as measured by the Rutgeerts' score [21, 22]. Sorrentino et al. measured FC in 25 patients every 2 months following surgery and found that FC corresponds to endoscopic recurrence [22]. Additionally, patients that received anti-TNF therapy to treat this recurrence and had endoscopic improvement also had improvement of their FC [22]. Another study by Wright et al. of 136 patients who had a calprotectin measured pre-operatively and at 6 months post-operatively found that a cutoff of 100 μg/g FC could be used to monitor for disease recurrence with a sensitivity of 0.89 and a negative predictive value of 91 %, concluding that the use of fecal calprotectin to monitor patients in the post-operative setting may allow for 41 % of patients to avoid colonoscopy [23]. This has also been demonstrated by Lobaton et al. who found that the medium FC for those with i0–i1 disease was 98 μg/g versus 234.5 μg/g in those with i2–i4 disease [24]. Finally in a study by Yamamoto and Kotze, a cutoff value of 170 μg/g for FC had a sensitivity of 0.83 and a specificity of 0.93 to predict clinical recurrence [25]. Although at this stage it is premature to rely on FC alone to monitor for disease recurrence, growing evidence suggests it will play an increasing role in the future, with colonoscopy reserved for patients with an elevated FC.

Symptoms After Crohn's Surgery Are Not Always Inflammatory

It is important to note that patients may have diarrhea or pain following their operation that may not be due to CD recurrence (Table 16.1). Therefore before treating symptomatic disease recurrence in the post-operative setting, objective markers of disease activity should be sought. Ideally this is with endoscopy, although FC may be a viable substitute. As clinical symptoms and endoscopic activity poorly correlate, treatment should be based on endoscopic activity or a surrogate marker, not on clinical symptoms in order to prevent both over- and under-treatment of the patient.

Table 16.1 Symptoms, etiology, and treatment of problems post CD surgery

Symptoms	Cause	Treatments
Post-operative pain	Mucosal pain/healing	Limited analgesia, regional anesthesia when possible
Diarrhea	Post-resection "diarrhesis" (rapid transit due to absence of obstruction and muscular hypertrophy)	Anti-diarrheals
Diarrhea	Bile salts	Bile acid sequestrant
Abdominal pain ± bloating, nausea, vomiting, and constipation	Narcotic bowel	NO narcotics!
Bloating, diarrhea	Bacterial overgrowth	Antibiotics

Medical Prophylaxis Options

A resection often clears all disease in a patient with CD and provides an ideal opportunity to prevent further symptomatic disease. The risks of medical over-treatment need to be acknowledged, however, under-treatment in the post-operative setting will lead to disease recurrence in the majority of patients. In the current era of treatment for IBD, our aims include the prevention of progressive disease, disability, and future surgical intervention. Therefore prophylactic therapy should be considered in most patients.

Minimal Benefit: Probiotics/5-ASA Medications/Corticosteroids

As antibiotics prevent recurrent disease it has been hypothesized that changing the microbiotica may have benefits in preventing recurrence. However studies have failed to demonstrate any benefit in the post-operative setting with the use of probiotics [26, 27]. 5-ASA medications are also appealing due to their minimal side effect profile and low cost, however results are inconsistent and their effect on clinical and endoscopic outcomes is mild at best [28–30]. Corticosteroids (both systemic and budesonide) have shown little benefit in preventing post-operative recurrence [31, 32].

Moderate Benefit: Antibiotics/ Immunomodulators

Due to the evidence that suggests that bacteria are in part responsible for recurrence of CD following resection there have been a number of studies looking at the role of antibiotics to prevent recurrence. Nitroimidazole antibiotics (metronidazole and ornidazole) are the most commonly studied medication. Rutgeerts et al. demonstrated that recurrence, defined as i2 or greater, was decreased at 3 months from 75 % in the placebo group to 52 % ($p = 0.09$) in those taking metronidazole and severe recurrence decreased from 43 to 13 % ($p = 0.02$). Clinical recurrence was also decreased at 12 months (25 % versus 4 %, $p = 0.044$) [33]. In addition metronidazole seems to have a beneficial effect when added to azathioprine as combination therapy at preventing post-operative recurrence with rates of endoscopic recurrence at 12 months of 44 % in the combination therapy group compared to 69 % in those on monotherapy with azathioprine ($p = 0.048$) [34]. Patients were also more likely to have no lesions seen at 12 months (22 % no lesions in combination group versus 3.5 % no lesions seen in the azathioprine monotherapy group, $p = 0.03$). We therefore recommend that if patients can tolerate it that most be placed on 3 months of metronidazole in the post-operative setting. The dose should not be higher than 1 g/day to minimize the risk of neuropathy.

Immunomodulator (IMM) monotherapy also seems to have a modest effect on reducing post-operative recurrence. A meta-analysis of 433 patients who were placed on immunomodulators versus placebo found that thiopurines were more effective than placebo at preventing severe endoscopic recurrence at 1 year (i2–4) (mean diff 15 %, 1.8–29 %, $p=0.026$, NNT = 7) but were not more effective at preventing very severe (i3–4) recurrence [35]. In regard to clinical relapse, thiopurines were more effective than placebo in preventing clinical relapse at 1 year (mean difference 8 %, CI 95 %: 1–15 %, $p=0.021$, NNT = 13) and 2 years (mean difference 13 %, CI 95 %: 2–24 %, $p=0.018$, NNT = 8) [35].

High Benefit: Biological Therapy

Biological therapies have been found to have the greatest impact in decreasing post-operative recurrence in CD. An initial study by Regueiro et al. demonstrated that anti-TNF therapy could decrease endoscopic recurrence from 84.6 % in the placebo arm to 9.1 % in those receiving infliximab at 1 year (endoscopic recurrence i2–4) [36]. In the second year of follow-up, patients were offered open access infliximab and it was found that remission was maintained over the 2-year period in those who continued on infliximab. In addition, anti-TNF naïve patients who developed endoscopic CD recurrence 1 year after their respective surgery had endoscopic improvement but not cure with infliximab and those who stopped their infliximab at 1 year in the setting of no recurrence developed endoscopic recurrence at 2 years [36, 37]. This demonstrates the need for early and prolonged treatment in such high-risk patients.

Adalimumab also appears to be effective in the post-operative setting. A study of 51 patients by Savarino et al. demonstrated that recurrence of CD was only 6.3 % at 2 years in patients treated with adalimumab post-operatively compared to 64.7 % in patients treated with azathioprine alone and 83.3 % in patients treated with mesalamine alone [7]. Preliminary data from the POCER study has also shown benefit with adalimumab therapy demonstrating that at 6 months 94 % of high-risk patients treated with post-operative adalimumab remain in endoscopic remission (i0–i1) versus 62 % treated with a thiopurine ($p=0.02$) [38].

There is currently no data in the post-operative setting for cetolizumab pegol, natalizumab, or vedolizumab.

A Proposed Monitoring and Treatment Algorithm for Post-Operative CD

Treatment in the post-operative should be individualized for each patient. The benefits of early assessment and titration of medical therapy based on disease recurrence are evident in the preliminary results from the POCER study [39]. This study found that at risk patients treated immediately after surgery followed by colonoscopy performed at 6 months and treatment step-up if recurrence occurred had significantly better outcomes compared to patients treated immediately after surgery with optimal drug therapy but followed without early colonoscopy assessment (Fig. 16.3).

Low risk patients are those that have long-standing CD (>10 years) who are undergoing their first surgical resection for a short (<10 cm), fibrostenotic lesion. These patients progress slowly, so no chronic therapy is required initially. In high-risk patients including those who smoke, have penetrating disease or perianal disease, or have a history of previous resection, initiating or continuing anti-TNF therapy with IMM immediately in the post-operative setting should be considered. Moderate risk patients are those who do not fit into the aforementioned categories and in these patients we treat with an IMM monotherapy in the post-operative period.

In regard to monitoring patients in the post-operative setting, there is currently no standardized approach. As calprotectin levels remain high for the first 2 months and then lower in those patients who do not have CD recurrence it is our practice to measure FC in patients at 3 months post surgery. As FC < 100 mg/kg has a high specificity

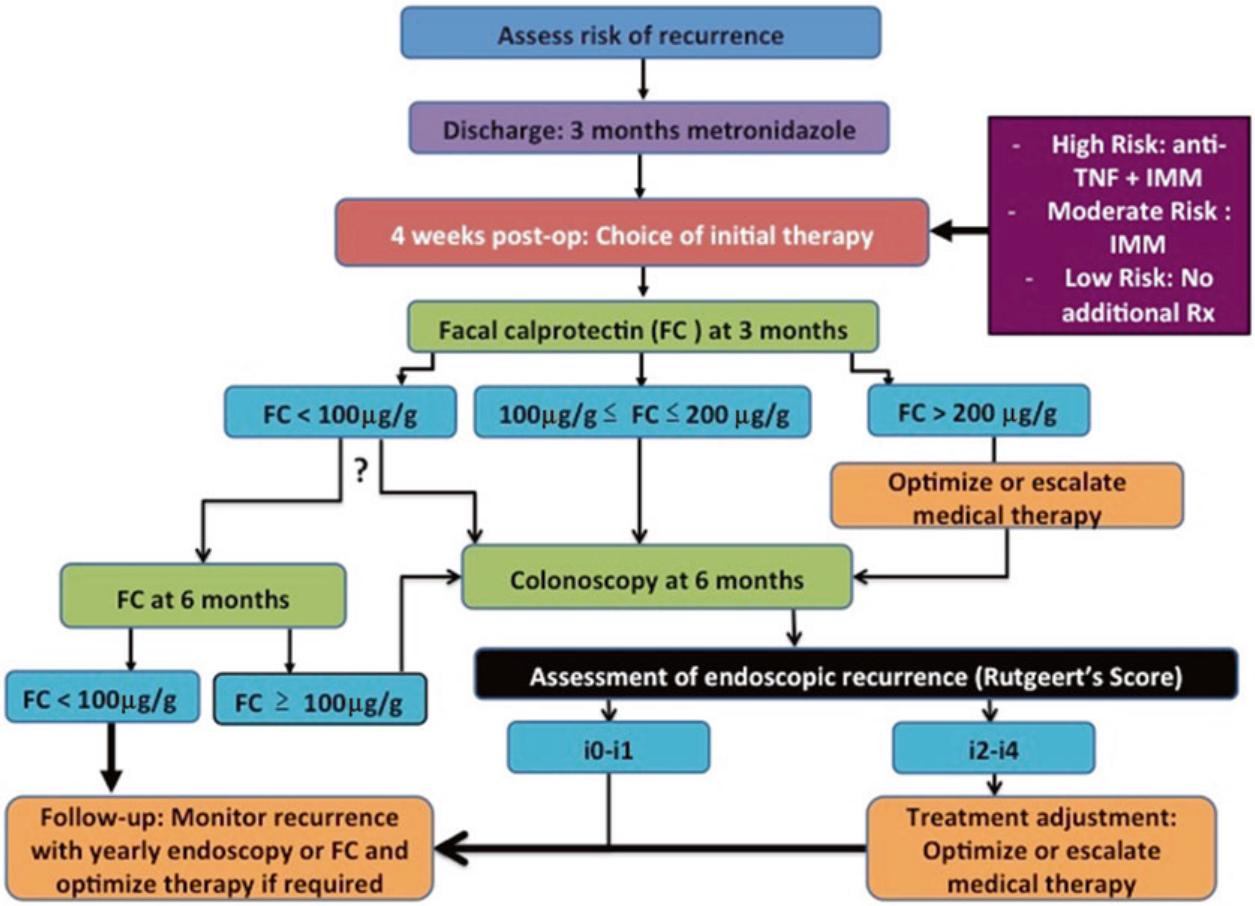


Fig. 16.3 An updated algorithm for predicting and preventing recurrence of post-operative CD

for lack of mucosal lesions, in patients who have an FC < 100 mg/kg we continue to monitor and either repeat an FC or perform a colonoscopy at 6 months. If the FC is still below 100 mg/kg or the colonoscopy shows i0–i1 disease at 6 months, we continue the patients' current medical regimen.

Evidence suggests that patients with a calprotectin higher than 100 mg/kg should have a colonoscopy at 6 months [23]. However we risk-stratify these patients depending on the level of their calprotectin. In the study by Sorrentino et al. [22], patients who had no post-operative recurrence had FC levels below 200 mg/kg. Therefore if patients have an FC level higher than 200 mg/kg, we optimize or escalate their medical therapy at 3 months with a view to then perform a colonoscopy at 6 months. In patients who have an FC of between 100 and 200 mg/kg we con-tinue their current medical therapy and perform a colonoscopy at 6 months.

At colonoscopy, in patients with i0–i1 disease, current medical therapy may be continued and in patients with i2 or greater recurrence, then initiation, optimization, or escalation of therapy should occur. This can be in the form of commencing IMM or anti-TNF therapy and optimizing dosage of current IMM or anti-TNF therapy. To confirm that IMMs are not under-dosed, the metabolic profile should be assessed with dose increase if required or if shunting is present considering the use of allopurinol. In regard to therapeutic monitoring of anti-TNF therapies, depending on the anti-TNF level and the presence or not of antibodies, options include increasing the dose, decreasing the dosing interval, switching therapy to another drug within the same class or switching therapy to a drug outside the class, or adding a drug to the ongoing treatment regimen. The choice of which strategy to employ is based on careful assessment of the

patient by history, examination, and increasingly therapeutic drug monitoring.

Once a patient has had their medical therapy optimized and their post-operative recurrence is stable we review them on a 6–12 monthly basis utilizing a 12 monthly objective marker of recurrence being either that of FC or colonoscopy. If objective evidence of recurrence occurs, then we recommend further optimizing therapy using the techniques discussed.

Conclusion

Surgical resection is an appropriate treatment option in many patients with CD and should be embraced. However, post-operative recurrence of CD is very common. The post-operative setting should be viewed as an ideal opportunity to prevent recurrence of symptomatic disease. It is therefore imperative to understand the patient's risk of recurrence, weigh the risks and benefits of long-term treatment based on this risk and be proactive in preventing recurrence. Antibiotics, immunomodulators, and anti-TNF therapies have all been shown to have efficacy in the post-operative setting. However, there is also increasing evidence for an approach that includes assessment with a 3-month FC and a 6-month colonoscopy to further risk-stratify patients. Although the optimal approach to monitoring and therapy is still unknown, an individualized approach based on a patients' risk profile is most appropriate. We propose an updated algorithm approach to risk stratification and prevention.

References

1. Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. Gastroenterology. 1990;99:956–63.
2. Olaison G, Smedh K, Sjodahl R. Natural course of Crohn's disease after ileocolic resection: endoscopically visualised ileal ulcers preceding symptoms. Gut. 1992;33:331–5.
3. Michelassi F, Balestracci T, Chappell R, Block GE. Primary and recurrent Crohn's disease. Experience with 1379 patients. Ann Surg. 1991;214:230–8. discussion 8–40.
4. Terdiman JP. Prevention of postoperative recurrence in Crohn's disease. Clin Gastroenterol Hepatol. 2008;6:616–20.
5. Sachar DB. Patterns of postoperative recurrence in Crohn's disease. Scand J Gastroenterol Suppl. 1990;172:35–8.
6. Sachar DB. The problem of postoperative recurrence of Crohn's disease. Med Clin North Am. 1990;74:183–8.
7. Savarino E, Bodini G, Dulbecco P, Assandri L, Bruzzone L, Mazza F, et al. Adalimumab is more effective than azathioprine and mesalamine at preventing postoperative recurrence of Crohn's disease: a randomized controlled trial. Am J Gastroenterol. 2013;108:1731–42.
8. Renna S, Camma C, Modesto I, Cabibbo G, Scimeca D, Civitavecchia G, et al. Meta-analysis of the placebo rates of clinical relapse and severe endoscopic recurrence in postoperative Crohn's disease. Gastroenterology. 2008;135:1500–9.
9. Cho SM, Cho SW, Regueiro M. Postoperative management of Crohn disease. Med Clin North Am. 2010;94:179–88.
10. Cameron JL, Hamilton SR, Coleman J, Sitzmann JV, Bayless TM. Patterns of ileal recurrence in Crohn's disease. A prospective randomized study. Ann Surg. 1992;215:546–51. discussion 51-2.
11. Whelan G, Farmer RG, Fazio VW, Goormastic M. Recurrence after surgery in Crohn's disease. Relationship to location of disease (clinical pattern) and surgical indication. Gastroenterology. 1985;88:1826–33.
12. Bernell O, Lapidus A, Hellers G. Risk factors for surgery and recurrence in 907 patients with primary ileocaecal Crohn's disease. Br J Surg. 2000;87:1697–701.
13. D'Haens GR, Gasparaitis AE, Hanauer SB. Duration of recurrent ileitis after ileocolonic resection correlates with presurgical extent of Crohn's disease. Gut. 1995;36:715–7.
14. Greenstein AJ, Lachman P, Sachar DB, Springhorn J, Heimann T, Janowitz HD, et al. Perforating and nonperforating indications for repeated operations in Crohn's disease: evidence for two clinical forms. Gut. 1988;29:588–92.
15. Bernell O, Lapidus A, Hellers G. Risk factors for surgery and postoperative recurrence in Crohn's disease. Ann Surg. 2000;231:38–45.
16. Lautenbach E, Berlin JA, Lichtenstein GR. Risk factors for early postoperative recurrence of Crohn's disease. Gastroenterology. 1998;115:259–67.
17. D'Haens GR, Geboes K, Peeters M, Baert F, Penninckx F, Rutgeerts P. Early lesions of recurrent Crohn's disease caused by infusion of intestinal contents in excluded ileum. Gastroenterology. 1998;114:262–7.
18. McLeod RS, Wolff BG, Steinhart AH, Carryer PW, O'Rourke K, Andrews DF, et al. Prophylactic mesalamine treatment decreases postoperative recurrence of Crohn's disease. Gastroenterology. 1995;109:404–13.

19. Calabrese E, Petruzziello C, Onali S, Condino G, Zorzi F, Pallone F, et al. Severity of postoperative recurrence in Crohn's disease: correlation between endoscopic and sonographic findings. Inflamm Bowel Dis. 2009;15:1635–42.
20. Rutgeerts P, Geboes K, Vantrappen G, Kerremans R, Coenegrachts JL, Coremans G. Natural history of recurrent Crohn's disease at the ileocolonic anastomosis after curative surgery. Gut. 1984;25: 665–72.
21. Sorrentino D, Paviotti A, Terrosu G, Avellini C, Geraci M, Zarifi D. Low-dose maintenance therapy with infliximab prevents postsurgical recurrence of Crohn's disease. Clin Gastroenterol Hepatol. 2010;8:591–9 e1; quiz e78–9.
22. Sorrentino D, Terrosu G, Paviotti A, Geraci M, Avellini C, Zoli G, et al. Early diagnosis and treatment of postoperative endoscopic recurrence of Crohn's disease: partial benefit by infliximab—a pilot study. Dig Dis Sci. 2012;57:1341–8.
23. Wright E, De Cruz P, Kamm M, Hamilton A, Hamilton K, Ritchie K, et al. Feacal calprotectin is superior to feacal lactoferrin and S100A12 as a surrogate marker for post-operative Crohn's disease endoscopic recurrence. Prospective longitudinal endoscopic validation. Results from the POCER study. Gastroenterology. 2014;146:S-174.
24. Lobaton T, Lopez-Garcia A, Rodriguez-Moranta F, Ruiz A, Rodriguez L, Guardiola J. A new rapid test for fecal calprotectin predicts endoscopic remission and postoperative recurrence in Crohn's disease. J Crohns Colitis. 2013;7:e641–51.
25. Yamamoto T, Kotze PG. Is fecal calprotectin useful for monitoring endoscopic disease activity in patients with postoperative Crohn's disease? J Crohns Colitis. 2013;7:e712.
26. Prantera C, Scribano ML, Falasco G, Andreoli A, Luzi C. Ineffectiveness of probiotics in preventing recurrence after curative resection for Crohn's disease: a randomised controlled trial with Lactobacillus GG. Gut. 2002;51:405–9.
27. Chermesh I, Tamir A, Reshef R, Chowers Y, Suissa A, Katz D, et al. Failure of Synbiotic 2000 to prevent postoperative recurrence of Crohn's disease. Dig Dis Sci. 2007;52:385–9.
28. Cottone M, Camma C. Mesalamine and relapse prevention in Crohn's disease. Gastroenterology. 2000; 119:597.
29. Caprilli R, Cottone M, Tonelli F, Sturniolo G, Castiglione F, Annese V, et al. Two mesalazine regimens in the prevention of the post-operative recurrence of Crohn's disease: a pragmatic, double-blind, randomized controlled trial. Aliment Pharmacol Ther. 2003; 17:517–23.
30. Sutherland LR, Martin F, Bailey RJ, Fedorak RN, Poleski M, Dallaire C, et al. A randomized, placebo-controlled, double-blind trial of mesalamine in the maintenance of remission of Crohn's disease. The Canadian Mesalamine for Remission of Crohn's Disease Study Group. Gastroenterology. 1997;112: 1069–77.
31. Steinhart AH, Ewe K, Griffiths AM, Modigliani R, Thomsen OO. Corticosteroids for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2003:CD000301.
32. Hellers G, Cortot A, Jewell D, Leijonmarck CE, Lofberg R, Malchow H, et al. Oral budesonide for prevention of postsurgical recurrence in Crohn's disease. The IOIBD Budesonide Study Group. Gastroenterology. 1999;116:294–300.
33. Rutgeerts P, Van Assche G, Vermeire S, D'Haens G, Baert F, Noman M, et al. Ornidazole for prophylaxis of postoperative Crohn's disease recurrence: a randomized, double-blind, placebo-controlled trial. Gastroenterology. 2005;128:856–61.
34. D'Haens GR, Vermeire S, Van Assche G, Noman M, Aerden I, Van Olmen G, et al. Therapy of metronidazole with azathioprine to prevent postoperative recurrence of Crohn's disease: a controlled randomized trial. Gastroenterology. 2008;135:1123–9.
35. Peyrin-Biroulet L, Deltenre P, Ardizzone S, D'Haens G, Hanauer SB, Herfarth H, et al. Azathioprine and 6-mercaptopurine for the prevention of postoperative recurrence in Crohn's disease: a meta-analysis. Am J Gastroenterol. 2009;104:2089–96.
36. Regueiro M, Schraut W, Baidoo L, Kip KE, Sepulveda AR, Pesci M, et al. Infliximab prevents Crohn's disease recurrence after ileal resection. Gastroenterology. 2009;136:441–50. quiz 716.
37. Regueiro M, Kip KE, Baidoo L, Swoger JM, Schraut W. Postoperative therapy with infliximab prevents long-term Crohn's disease recurrence. Clin Gastroenterol Hepatol. 2014;12:1494–502.
38. De Cruz P, Kamm MA, Hamilton AL, Ritchie KJ, Gorelik A, Liew D, et al. 1161 adalimumab prevents post-operative Crohn's disease recurrence, and is superior to thiopurines: early results from the POCER study. Gastroenterology. 2012;142:S-212.
39. De Cruz P, Kamm MA, Hamilton AL, Ritchie KJ, Krejany S, Gorelik A, et al. 925j optimising postoperative Crohn's disease management: best drug therapy alone versus colonoscopic monitoring with treatment step-up. The POCER study. Gastroenterology. 2013;144:S-164.

1.10 IBD-PRIMARY SCLEROSING CHOLANGITIS (PSC): A DIFFICULT-TO-TREAT IBD PHENOTYPE

1.10.1 IBD-PSC Phenotype

Primary sclerosing cholangitis (PSC) is a chronic, inflammatory condition of the biliary epithelium that results in multifocal scarring of the bile ducts.(128) This scarring can lead to stricturing and blockage of bile ducts and result in hepatic cirrhosis, liver failure and/or sepsis.(128) In addition, patients with PSC are at significantly increased risk of developing cholangiocarcinoma.(129) PSC is closely associated with IBD; approximately 70-80% of patients who are diagnosed with PSC also have a diagnosis of IBD and up to 8.1% of IBD patients will have PSC.(130, 131)

Adults with comorbid PSC and IBD often present with clinically quiescent disease involving predominantly the right side of the colon. The phenotype is distinct with frequent reports of rectal sparing, backwash ileitis and minimal endoscopic disease despite more active histologic inflammation.(132) Unfortunately, rates of colorectal cancer are high in comparison to those without PSC, potentially driven in part by the frequent presence of histological inflammation affecting the entirety of the colon.(130) The overall survival in patients with IBD-PSC is worse than in those without PSC, driven mostly by increased rates of colorectal cancer, hepatic failure, and cholangiocarcinoma.(130)

Even in children there is now evidence that, despite an overall decreased need for biologics, sub-clinical endoscopic activity is more common in those with PSC than those without PSC and patients are more likely to experience growth impairment.(133)

1.10.2 IBD-PSC Therapies

Since chronic inflammation is the driver for liver and bowel injury and carcinogenesis, therapy to minimise such inflammation would be central to prevention of such complications. While treatment of the bowel component of IBD-PSC follows the same algorithms as IBD without PSC, healing has been generally difficult to achieve. Thus, vigilant objective surveillance by colonoscopy is needed. For the biliary disease, there is no cure or specific treatment for PSC apart from liver transplantation.(134). The need for effective therapy is reflected in the poor prognosis of the PSC component in IBD-PSC with a three-fold increase in the mortality rate in patients with a diagnosis of PSC compared with that of the general population.(130)

Although the pathogenesis of PSC is not completely understood, serum levels of TNF- α are elevated in patients with PSC.(135, 136) In addition, mucosal addressin cell adhesion molecule-1 (MadCAM-1) is induced in inflamed endothelium of the portal vein and its activity correlates with histologic inflammatory activity of the liver in PSC.(135, 136) MAdCAM-1 interacts with the alpha-4 beta-7 integrin on lymphocytes and promotes extravasation of lymphocytes into affected tissues, which, in the case of IBD-PSC, is thought to result in periductal inflammation, cholangiocyte damage and progressive fibrosis.(137)

However, despite PSC resulting from inflammation of the bile duct epithelium and reports of increased levels of serum TNF-α in patients with PSC,(138) to date glucocorticoids, tacrolimus, cyclosporin, azathioprine, methotrexate, anti-tumour necrosis factor alpha agents and ursodeoxycholic acid (UCDA) have not demonstrated any benefit in treating or improving the prognosis of PSC.(137)

As previously discussed, vedolizumab is a monoclonal antibody to alpha-4 beta-7 integrin and therefore, theoretically may reduce the inflammation in the liver and colon in patients with IBD-PSC by blocking migration of lymphocytes into both. It, therefore, offers a potential treatment to halt the progression of IBD-PSC. In this PhD, the role of vedolizumab in controlling inflammation in both the liver and colon in patients with IBD-PSC is explored.

1.11 OVERALL RESEARCH DESIGN

This thesis aims to answer several questions regarding the prognostic value of histology in UC and CD, and the impact of a relatively new biologic medicine, vedolizumab, on treatment outcomes in IBD.

1.11.1 Overall Thesis Hypotheses

1. That complete histologic normalisation in UC occurs and is associated with improved clinical outcomes compared to patients who only achieve histologic quiescence
2. That regression of histologic disease extent in UC occurs and is associated with improved clinical outcomes
3. That histologic healing occurs in CD and is associated with improved clinical outcomes compared to endoscopic healing alone
4. That vedolizumab is an effective biologic agent that induces clinical, endoscopic and histologic healing in both UC and CD
5. That calcineurin inhibitors can be used in combination with vedolizumab as an effective therapy for patients with moderate-severe CD or UC
6. That vedolizumab is effective at treating primary sclerosing cholangitis and mucosal inflammation in patients with IBD-PSC

1.11.2 Thesis Aims

This thesis has two overall aims, each with several specific aims.

OVERALL AIM 1. To determine the clinical prognostic value of histologic assessment of healing in patients with IBD.

Specific aims:

1. To determine if histologic normalisation occurs in UC patients and, if so, what predicts this occurrence
2. To determine if histologic normalisation is associated with improved long-term outcomes in UC patients
3. To identify if histologic regression of disease extent occurs in UC and, if so, whether it is associated with clinical outcomes in UC patients
4. To determine if histologic healing occurs in CD patients and, if so, to define predictors of this healing and its association with long-term outcomes

OVERALL AIM 2: To define, in a real-world setting, the effectiveness of the new, gut-selective anti-integrin approach with vedolizumab perform in reaching the targets of therapy for IBD and PSC.

Specific aims:

1. To determine clinical, endoscopic and histologic outcomes in a real-world setting in patients with IBD treated with vedolizumab
2. To determine if combination therapy with a calcineurin-inhibitor followed by maintenance vedolizumab is an effective and safe treatment strategy in IBD

3. To determine if vedolizumab improves liver biochemistry and mucosal inflammation in patients with IBD-PSC

1.11.3 Details of the Studies in this Thesis

Chapter 2.2 Histologic normalization occurs in ulcerative colitis and is associated with improved clinical outcomes

A retrospective case-control study assessing the frequency and predictors of complete histologic normalisation in patients with UC and its impact on long-term clinical outcomes.

Chapter 2.3 Segmental histologic normalisation occurs in ulcerative colitis but does not improve clinical outcomes

A retrospective study assessing the pattern and frequency of disease regression in UC and its impact on long-term clinical outcomes.

Chapter 2.4 Histologic healing is more strongly associated with clinical outcomes in ileal Crohn's disease than endoscopic healing

A retrospective study assessing the frequency of histologic healing in CD and its impact on long-term clinical outcomes.

Chapter 3.2: Vedolizumab as induction and maintenance for inflammatory bowel disease: 12-month effectiveness and safety

A prospective study following patients commenced on vedolizumab in a large-tertiary centre looking at the efficacy of vedolizumab in inducing and maintaining clinical, endoscopic and histologic improvement and remission up to 12 months of therapy.

Chapter 3.3: Safety and efficacy of combination treatment with calcineurin inhibitors and vedolizumab in patients with refractory inflammatory bowel disease

A retrospective study of a prospective database following patients treated with combination calcineurin inhibitors and vedolizumab. The efficacy of this treatment regime on long term steroid and calcineurin free clinical remission and endoscopic improvement or remission was assessed.

Chapter 3.4: Vedolizumab in patients with concurrent primary sclerosing cholangitis and inflammatory bowel disease does not improve liver biochemistry bus is safe and effective for the bowel disease

A retrospective study of a prospective database on the impact of vedolizumab on liver biochemistry and clinical outcomes on patients with PSC-IBD.

Part 2: Histologic healing in IBD: A New Target to Improve Outcomes in IBD

2.1 INTRODUCTION

Part 2 of this thesis explores histology as a treatment endpoint in IBD. As discussed in Part 1, endoscopic healing has become the standard treatment goal in IBD as patients who achieve mucosal healing ultimately have improved clinical outcomes in both UC and CD. Histology has emerged as a more stringent target in IBD however, up to this point, research on this endpoint as a prognostic factor has been limited. Although histologic quiescence has previously been demonstrated to improve outcomes in UC, normalisation of histology has not been described or studied extensively. In addition, disease extension is known as a poor prognostic marker in UC, however there is limited evidence on the impact of disease regression. Finally, the role of histology as a treatment endpoint in CD has not been studied. This part of the thesis includes three papers that explore the role of histology as a treatment endpoint in IBD. The first two papers look at both partial (disease regression) and complete normalisation of histology as an endpoint in UC and its role as a prognostic biomarker. Finally, the novel role of histology in CD is explored.

2.2 HISTOLOGIC NORMALIZATION OCCURS IN ULCERATIVE COLITIS AND IS ASSOCIATED WITH IMPROVED CLINICAL OUTCOMES

It has previously been shown that mucosal healing improves outcomes in inflammatory bowel disease and increasingly that histologic quiescence in UC improves outcomes. However, normalization of histology has not been reported, nor whether it improves outcomes. This study was a retrospective study that determined that 1) histologic normalisation is possible in UC and occurs in approximately 10% of patients and 2) histologic normalization is associated with improved clinical outcomes when compared to histologic quiescence and endoscopic mucosal healing.

Clinical Gastroenterology and Hepatology 2017;15:1557–1564

Histologic Normalization Occurs in Ulcerative Colitis and Is Associated With Improved Clinical Outcomes

Britt Christensen,[*,‡,¶] Stephen B. Hanauer,[§] Jonathan Erlich,[*] Olufemi Kassim,[*] Peter R. Gibson,[‡] Jerrold R. Turner,[*,‖] John Hart,[*,‖] and David T. Rubin[*]

[*]Inflammatory Bowel Disease Center, University of Chicago Medicine, Chicago, Illinois; [‡]Department of Gastroenterology, Alfred Hospital and Monash University, Melbourne, Australia; [§]Northwestern University Feinberg School of Medicine, Chicago, Illinois; [‖]Department of Pathology, University of Chicago Medicine, Chicago, Illinois; and [¶]Department of Gastroenterology, The Royal Melbourne Hospital, Melbourne, Australia

BACKGROUND & AIMS: **Mucosal healing, determined by histologic analysis, is a potential therapeutic target for patients with ulcerative colitis (UC). However, the histologic features of tissue normalization, as an outcome of treatment, have not been well described. We examined the prevalence and predictive values of normalization of the colonic mucosa, based on histologic analysis (histologic normalization) in patients with UC, and determined its association with risk of clinical relapse, compared with histologic disease quiescence and endoscopic mucosal healing.**

METHODS: **We performed a retrospective study of 646 patients with confirmed UC who underwent colonoscopy at a tertiary medical center from August 2005 through October 2013. We reviewed reports from pathology analyses of random mucosal biopsies from each colon segment, and categorized them into 3 groups based on histology findings: (1) normalization (completely normal mucosa with no features of chronicity present), (2) quiescence (crypt atrophy or branching without signs of active inflammation including erosions, abscesses, or focal neutrophil infiltration), or (3) active disease (epithelial infiltration by neutrophils, crypt abscesses, erosions, or ulceration). Histology findings were compared with clinical and endoscopic findings. We assessed variables associated with histology findings and, in patients in clinical remission (Simple Clinical Colitis Activity Index score ≤2 and subscore of ≤1 for stool frequency or rectal bleeding), predictive values for clinical relapse at follow-up evaluations 6 months later or more were calculated.**

RESULTS: **Of the 646 patients included in the study, 60% had endoscopic mucosal healing, 40% had histologic quiescence, and 10% had histologic normalization. The level of agreement between mucosal and histologic activity was moderate (agreement for 68% of samples; $\kappa = 0.50$; $P < .001$). On multivariate analysis, only proctitis associated with histologic normalization ($P = .002$). Of 310 patients in clinical remission at initial review, 25% had a clinical relapse, after a median time of 16 months (interquartile range, 10–23 months). Histologic normalization was independently associated with increased odds of relapse-free survival compared with histologic quiescence (hazard ratio, 4.31; 95% confidence interval, 1.48–12.46; $P = .007$) and histologic activity (hazard ratio, 6.69; 95% confidence interval, 2.16–20.62; $P = .001$); mucosal healing was not associated with increased odds of relapse-free survival compared with no mucosal healing (hazard ratio, 1.02; 95% confidence interval, 0.56–1.85; $P = .954$).**

CONCLUSIONS: **Histologic normalization of colonic mucosa can be used as a clinical endpoint for patients with UC. We associated histologic normalization with increased odds of relapse-free survival compared with endoscopic healing or histologic quiescence. Further studies are needed to determine whether histologic normalization should be a goal of treatment for patients with UC.**

Keywords: Histopathology; Mucosal Healing; Inflammatory Bowel Disease; Normalization.

Abbreviations used in this paper: CHN, complete histologic normalization; IBD, inflammatory bowel disease; MH, mucosal healing; UC, ulcerative colitis.

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2017.02.016

Most current article

Ulcerative colitis (UC) is a chronic inflammatory disease characterized by periods of disease activity alternating with periods of quiescence. The primary treatment goal in UC has been to limit these periods of activity and maintain clinical remission, traditionally defined as cessation of rectal bleeding and normalization of stool frequency.[1] In recent years endoscopic mucosal healing (MH) in UC has been associated with improved clinical outcomes compared with achieving clinical remission alone.[2–5] In fact, MH has been associated with prolonged remission, fewer hospitalizations and colectomies, and an improved quality of life.[2–8]

Despite such improved outcomes associated with MH, up to 40% of patients with MH have persistent histologic inflammatory activity.[3,9–12] Therefore, there is interest in the significance of histologic remission, as a "deeper" marker of disease control compared with MH. Although more research is needed into the practicality and validity of histologic assessment, it is known that reduced histologic activity is associated with decreased risks of relapse, hospitalization, corticosteroid use, colectomy, and colorectal neoplasia.[3,9–18]

It has been a common understanding that, following a diagnosis of UC, histologic abnormalities of the mucosa persist. This idea has been so established that when histologic grading has been described in UC, normalization has not generally been defined as an outcome that is distinct from quiescence; and histologic healing is generally described simply as absence of active inflammation.[3,9,14,19] Furthermore, in 2 recently described histologic indices, the focus has been on short-term treatment responsiveness and architectural abnormalities have been excluded in their assessment.[20,21]

Although there are infrequent descriptions of histologic normalization in the literature,[22] it remains incompletely defined in the context of clinical outcomes. In addition, patient, disease, and treatment characteristics associated with histologic normalization have not been studied, and it had not been determined if complete histologic normalization (CHN) is associated with improved clinical outcomes compared to histologic remission or endoscopic MH alone.

The aims of this study were to examine the prevalence and predictors of histologic normalization in patients with confirmed UC, and to determine if normalization is associated with improved clinical outcomes compared with ongoing histologic activity, histologic quiescence, and endoscopic MH.

Methods

A retrospective case-control study was performed and approved by the institutional review board (13-1063). All patients who underwent colonoscopy at University of Chicago between August 2005 and October 2013 for UC were identified by 1 or more of the International Classification of Diseases, Ninth revision, Clinical Modification codes for UC (556.0, 556.2, 556.3, 556.5, 556.6, 556.8, 556.9). Patients were eligible for inclusion if they had an established diagnosis of UC at the time of this "follow-up" colonoscopy and documentation of previous complete colonoscopy and segmental biopsies obtained in at least the rectum, left colon, and right colon that showed chronic changes (with or without acute changes) consistent with a histologic diagnosis of UC more than 1 year prior. Patients who had inadequate documentation, had undergone a colectomy, or had confirmed *Clostridium difficile* infection at time of follow-up colonoscopy were excluded.

Medical Records Abstraction

Endoscopy reports were retrieved through the electronic documentation system for endoscopic reports (Provation, Minneapolis, MN). Demographic, clinical, histologic, and biochemical data were collected from our electronic medical record system (EPIC, Verona, WI), including age of diagnosis, disease duration, smoking history, and previous and current use of anti-inflammatory agents and/or immunosuppressant therapy (steroids, immunomodulators, anti–tumor necrosis factor agents) at time of follow-up colonoscopy.

Endoscopic and Histologic Assessment

The bowel was divided into 3 segments as per the Montreal classification for UC[23]: (1) proctitis (E1, rectum only), (2) left-sided (E2, rectum to splenic flexure), or (3) extensive colitis (E3, disease proximal to splenic flexure). Disease extent was determined using a modified Montreal classification in that, rather than endoscopic appearance, histology was used on most proximal biopsy showing evidence of disease, whether acute or chronic inflammation, or chronic architectural changes (ie, crypt branching/shortening, decreased crypt densities, and irregular mucosal surfaces). Maximal disease extent was determined at any colonoscopy performed over the patient's history. The endoscopic and histologic severity and number of biopsies taken from each segment at follow-up endoscopy were recorded.

Endoscopic Mucosal Assessment

An academic inflammatory bowel disease (IBD) expert gastroenterologist with minimum 5 years' experience performed all endoscopies, during which endoscopic photographs were obtained from each segment of bowel, with targeted photographs of areas of mucosal activity. An independent reviewer classified patients into 3 distinct groups of endoscopic grade of inflammation using the endoscopic subscore of the Modified Mayo Disease Activity Index.[24] A score of 0 (no friability, granularity, and intact vascular pattern) was classified as normal, 1 (mild erythema or decreased vascular

pattern) as quiescent mucosa, and a score of ≥2 (any of moderate or marked erythema, absent vascular pattern, friability, erosions, ulceration, or contact/spontaneous bleeding) as mucosal activity. Endoscopic MH was defined by either completely normal or quiescent mucosa (Modified Mayo Disease Activity Index endoscopic subscore ≤1).

Histologic Assessment

As is routine in this unit, random mucosal biopsies were obtained from each colon segment, targeting the area of most significant mucosal disease activity. Two pathologists who specialize in gastrointestinal histology routinely assess all biopsies and report histology using a standardized scale that includes histologically normal, quiescent, mild, moderate, or severe disease. We reviewed these pathologic reports and categorized histology specimens into 3 distinct groups using the modified Riley score as described by Bryant et al[16], but with the subcategorization of histologic remission into histologic normalization and histologic quiescence based on the absence or presence of architectural changes, respectively. Based on the maximum inflammation score at each segment, patients were categorized as (1) histologic normalization: completely normal mucosa with no features of chronicity present; (2) histologic quiescence: features of chronicity including crypt atrophy or branching but no active inflammation, such as erosions, crypt abscesses, or focal neutrophil infiltration; and (3) histologic activity: presence of any epithelial infiltration by neutrophils, crypt abscesses, erosions or ulceration.

As previously reported, the interobserver agreement for interpretation of UC histology between our pathologists using a 6-point scale that classifies varying severities of inflammatory activity (including normal) was very good (kappa = 0.6).[13] In this study, an additional 150 samples were regraded by 1 of the expert pathologists (J.H.) who was blinded to the prior official reads of these specimens; 50 were histologically normal, 50 quiescent, and 50 had active histology. All 150 samples were interpreted correctly (kappa = 1.0).

The primary outcome of CHN was defined by normalization of mucosa without histologic features of chronicity in all bowel segments on follow-up colonoscopy in a patient with previous structural changes on biopsy consistent with UC.

Assessment of Clinical Relapse-Free Survival

Patients in clinical remission at follow-up colonoscopy with ≥6 months of follow-up at the University of Chicago from this colonoscopy until September 2014 were included in a separate analysis of clinical relapse-free survival. At each patient clinic visit, the Simple Clinical Colitis Activity Index was calculated.[25] Clinical remission was defined as Simple Clinical Colitis Activity Index ≤2 and subscore of ≤1 for stool frequency or rectal bleeding as determined from physician records. Clinical relapse-free survival was defined as time from colonoscopy to period of clinical relapse, with clinical relapse defined at clinical follow-up as Simple Clinical Colitis Activity Index >2, subscore >1 for stool frequency or rectal bleeding, or medication escalation for symptoms, hospitalization for UC relapse, or colectomy for refractory UC.

Statistical Analysis

Continuous variables were summarized using medians and interquartile ranges. Categorical variables were expressed as percentage and number of cohort. Cohen kappa coefficient (κ) was calculated to measure agreement between mucosal and histologic activity.

Univariate analysis of baseline characteristics was performed to identify predictive factors for CHN. The Mann-Whitney *U* test and analysis of variance were used to compare continuous variables, and Pearson chi-square test was used to compare categorical variables. Multivariate analysis to identify independent factors associated with histologic outcomes was performed using logistic regression.

Kaplan-Meier analysis was performed to compare clinical relapse-free survival in those with and without CHN and MH and log-rank statistics were performed to compare subgroups of interest. Cox proportional hazards regression analysis was performed to identify independent predictors of clinical regression.

All variables with $P < .20$ on univariate analysis were retained and integrated into the multivariate models. A 2-sided $P \leq .05$ was considered statistically significant. All data analyses were performed using Stata 12.0 (StataCorp, College Station, TX).

Results

Patients

A total of 646 patients fulfilled the entry criteria and were included in the analysis. Baseline characteristics at time of follow-up colonoscopy are shown in Table 1. Using endoscopic criteria, 40% (n = 261) had endoscopic mucosal activity, 35% (n = 228) mucosal quiescence, and 24% (n = 157) mucosal normalization on follow-up colonoscopy. Using histologic criteria, 50% (n = 321) had ongoing activity, 40% (n = 260) histologic quiescence, and 10% (n = 65) had CHN.

The level of agreement between mucosal and histologic activity was moderate (68%; $\kappa = 0.50$; $P < .001$). A total of 12% (19 of 157) of patients with mucosal normalization had histologic activity and 27% (61 of 228) of patients with mucosal quiescence had histologic activity. No patient (0 of 65) with histologic normalization had mucosal activity but 8% (20 of 260) of patients with histologic quiescence had mucosal activity.

Table 1. Clinical Characteristics at Baseline

Baseline characteristics (N = 646)	Median (IQR) or percentage (n)
Age at diagnosis of UC (*y*)	29 (22–41)
Gender (male)	50.2% (n = 324)
Greatest disease extent seen, %	
Proctitis	10.1 (n = 65)
Left-sided	30.5 (n = 197)
Pancolitis	59.4 (n = 384)
Duration of disease (*y*)	13 (7–22)
Smoking status (current smoker), %	6.6 (n = 41)
Endoscopic mucosal disease activity, n (%)	Mucosal healing 385 (59.6)
Mucosal normalization	157 (24.3)
Mucosal quiescence	228 (35.3)
Mucosal activity	261 (40.4)
Histologic disease activity, n (%)	Histologic healing 325 (50.3)
Histologic normalization	65 (10.1)
Histologic quiescence	260 (40.2)
Histologic activity	321 (49.7)
Medications, n (%)	
Oral steroid exposure	394 (66.8)
Current oral steroid	54 (98.6)
Mesalamine exposure	637 (99.5)
Current mesalamine	517 (81.6)
Immunomodulator exposure	294 (48.1)
Current immunomodulator	190 (30.1)
Previous cyclosporine salvage	25 (4.2)
Anti-TNF exposure	109 (18.1)
Current anti-TNF	82 (13.0)

IQR, interquartile range; TNF, tumor necrosis factor.

Complete Histologic Normalization

A total of 10% (n = 65) of patients had complete normalization of their histology in all segments that had previously shown changes (ie, CHN). The mean number of biopsies taken at each endoscopy was 20 (standard deviation, 9.5) and the number of biopsies taken was not significantly different in patients achieving CHN and in those who did not (Supplementary Table 1).

CHN was identified in 9% (n = 35) of patients with extensive colitis, 8% (n = 15) with left-sided disease, and 23% (n = 15) with proctitis alone. By univariate analysis, CHN was associated with less extensive disease at baseline ($P = .001$), disease duration >10 years ($P = .029$), and negatively associated with previous steroid ($P = .041$) and anti–tumor necrosis factor therapy ($P = .031$) (Table 2). On multivariate analysis, a diagnosis of proctitis compared with left-sided (E2) (adjusted odds ratio, 3.63; 95% confidence interval, 1.56–8.46; $P = .003$) and extensive (E3) colitis (adjusted odds ratio, 2.81; 95% confidence interval, 1.32–5.96; $P = .007$) remained significantly and independently associated with CHN. There was a trend for patients with disease duration of more than 10 years to achieve CHN (adjusted odds ratio, 1.81; 95% confidence interval, 0.98–3.35; $P = .058$).

Table 2. Univariate Analysis of Predictors of Complete Histologic Healing in UC

Characteristic (N = 646)	CHN (n = 65)	No CHN (n = 581)	*P* value
Age, n (%)			.071[a]
≤16 *y*	11 (17)	49 (9)	
17–39 *y*	39 (61)	357 (63)	
≥40 *y*	14 (22)	160 (28)	
Gender, male, n (%)	40 (46)	294 (51)	.496
Current smoker, n (%)	5 (8)	36 (6)	.666
Disease extent at baseline, n (%)			.001[b]
E1	15 (23)	50 (9)	
E2	15 (23)	182 (31)	
E3	35 (54)	349 (60)	
Disease >10 *y*, n (%)	47 (73)	336 (59)	.029[b]
Oral steroid exposure, n (%)	33 (55)	361 (68)	.041[b]
Mesalamine monotherapy, n (%)	40 (63)	291 (51)	.082
Previous immunomodulator, n (%)	22 (36)	272 (50)	.033[b]
Current immunomodulator, n (%)	15 (23)	175 (31)	.220
Previous cyclosporine salvage, n (%)	4 (7)	21 (4)	.340
Previous anti-TNF, n (%)	5 (8)	104 (19)	.031[b]
Current anti-TNF Rx, n (%)	5 (8)	77 (14)	.192[a]
Current immunomodulator and anti-TNF, n (%)	4 (6)	26 (5)	.555

TNF, tumor necrosis factor.
[a]Incorporated into multivariate analysis as $P < .2$.
[b]Significant $P < .05$.

Clinical Relapse-Free Survival

A total of 310 patients who were in clinical remission at follow-up colonoscopy were assessed for clinical relapse-free survival. Baseline characteristics are shown in Table 3. Using endoscopic criteria, 25% (n = 80) had ongoing endoscopic mucosal activity, 41% (n = 127) quiescence, and 33% (n = 103) mucosal normalization. Using histologic criteria, 35% (n = 108) had histologic activity, 51% (n = 157) quiescence, and 15% (n = 45) CHN.

Median follow-up was 22 (interquartile range, 14–34) months and 25% (n = 77) patients experienced clinical relapse at median time 16 (interquartile range, 10–23) months. Patients with CHN had lower rates of clinical relapse compared with those with histologic quiescence and activity (Figure 1*A*) and patients with endoscopic MH had lower rates of clinical relapse rates compared with those with mucosal activity (Figure 1*B*). In patients who had MH and were in clinical remission, histologic normalization remained protective against clinical relapse (Figure 1*C*).

By univariate analysis, the only factors associated with improved clinical relapse-free survival were the achievement of endoscopic MH compared with no MH, and CHN compared with both histologic quiescence and histologic activity (Table 4). By multivariate analysis, only CHN compared with histologic quiescence (hazard ratio, 4.31 [1.48–12.46]; $P = .007$), CHN compared with histologic activity (hazard ratio, 6.69 [2.16–20.62]; $P = .001$), and no previous exposure to cyclosporine ($P = .034$) predicted clinical relapse-free survival

Table 3. Baseline Characteristics of Those in Clinical Remission at Baseline

Patients	N = 310
Sex, n (%), male	159 (51.3)
Age, median (IQR), *y*	48.4 (36.6–58.8)
Age of diagnosis, median (IQR), *y*	29 (22–41)
Active smoking status, n (%)	21 (6.8)
Duration of disease, median (IQR), *y*	14 (1–52 or 8–49)
Disease extent, n (%)	
E1	34 (11.0)
E2	89 (28.7)
E3	187 (60.3)
Endoscopic mucosal disease activity, n (%)	
Endoscopic mucosal activity	80 (25.0)
Endoscopic mucosal quiescence	127 (41.0)
Endoscopic mucosal normalization	103 (33.2)
Histologic disease activity, n (%)	
Histologic activity	108 (34.8)
Histologic quiescence	157 (50.7)
Complete histologic normalization	45 (14.5)
Medications, n (%)	
Past oral steroid exposure	185 (66.3)
Current oral steroids	15 (4.9)
Past mesalamine exposure	303 (99.3)
Current mesalamine therapy	242 (79.3)
Past IMM therapy exposure	156 (52.9)
Current IMM therapy	110 (36.2)
Past anti-TNF therapy exposure	57 (19.5)
Current anti-TNF therapy	49 (16.2)
Previous cyclosporine salvage therapy	12 (4.1)

IMM, immunomodulator; IQR, interquartile range; TNF, tumor necrosis factor.

(Table 4). MH was not independently associated with lower rate of clinical relapse.

Discussion

We have demonstrated that histologic normalization of the colon in UC is possible and is characterized by statistically superior clinical relapse-free survival. A total of 1 in 10 of our cohort achieved CHN.

This is the first study to describe complete normalization of histology in UC. A study by Kleer and Appelman[26] did demonstrate that areas of histologic chronic colitis became normal at some point in 22 of 41 patients (54%). However, this study only described the rate of normalization of a single point in the bowel, and did not look at complete normalization of the bowel or examine patient characteristics that predicted this normalization.

Most descriptions of histologic normalization have been reported as rectal sparing. Levine et al[27] found that, of 24 asymptomatic patients with UC, 2 (8%) normalized their rectal biopsy on follow-up. Odze et al[22] looked at 14 patients treated with either mesalamine or placebo enemas and found that, in patients on mesalamine rectal therapy, 36% of rectal biopsies normalized (defined as "complete absence" of any of the characteristic features of chronic UC). However, only 1 patient (7%) normalized all their rectal biopsies. Finally, Bernstein et al[28] showed that 2 of 39 (5%) patients with UC have histologic evidence of absolute rectal sparing at some point during their disease. None of these studies looked at proximal colon histologic normalization or patient or disease characteristics associated with histologic normalization.

We found that CHN was associated with less extensive disease. It has previously been described that

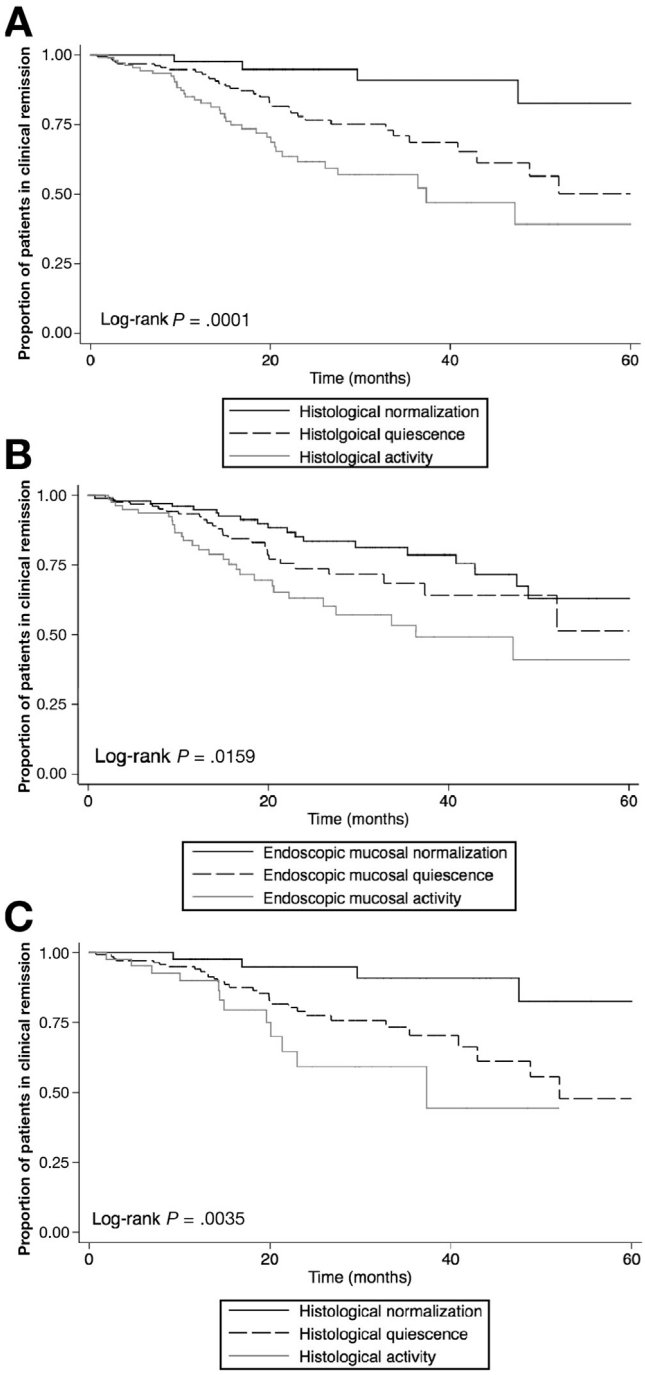


Figure 1. Kaplan-Meier analysis of effect of endoscopic mucosal and histologic activity on clinical relapse-free survival. (*A*) Clinical relapse-free survival versus histologic healing. (*B*) Clinical relapse-free survival versus endoscopic mucosal healing. (*C*) Clinical relapse-free survival versus histologic healing in patients with endoscopic mucosal healing.

Table 4. Univariate and Multivariate Analysis For Factors Associated With Clinical Relapse-Free Survival

Risk factor	Univariate analysis: HR[a] (95% CI)	*P* value[b]	Multivariate analysis: HR[a] (95% CI)	*P* value[b]
Sex (female)	1.15 (0.74–1.81)	.533		
Older age at colonoscopy	0.99 (0.97–1.00)	.152[c]	0.99 (0.98–1.01)	.408
Older age of diagnosis	0.99 (0.98–1.01)	.436		
Current smoker	1.19 (0.51–2.75)	.687		
Longer duration of disease	0.99 (0.96–1.01)	.301		
Disease extent				
E2 vs E1	1.33 (0.59–2.98)	.487		
E3 vs E1	1.41 (0.66–3.01)	.369		
Endoscopic MH				
Quiescent disease vs normalization	1.56 (0.87–2.76)	.131		
Active disease vs normalization	2.44 (1.37–4.36)	.002		
No endoscopic MH	1.93 (1.21–3.07)	.006[d]	1.02 (0.56–1.85)	.954
Histologic healing				
Quiescent disease vs normalization	3.79 (1.34–10.68)	.012[d]	4.31 (1.48–12.46)	.007[d]
Active disease vs normalization	6.76 (2.39–19.14)	< .001[d]	6.69 (2.16–20.62)	.001[d]
Current oral steroids	0.72 (0.23–2.30)	.582		
Current mesalamine therapy	1.19 (0.67–2.14)	.555		
Current anti-TNF therapy	0.88 (0.44–1.78)	.724		
Current duel therapy (IMM + anti-TNF)	1.42 (0.61–3.27)	.416		
Current IMM therapy	1.37 (0.86–2.17)	.183[c]	1.21 (0.72–2.04)	.469
Past anti-TNF therapy exposure	0.81 (0.42–1.54)	.522		
Past IMM therapy exposure	1.32 (0.83–2.09)	.236		
Past cyclosporine salvage therapy	2.34 (0.99–5.52)	.052[c]	2.71 (1.07–6.82)	.034[d]
Past oral steroid exposure	1.08 (0.67–1.74)	.749		

CI, confidence interval; HR, hazard ratio; IMM, immunomodulator; TNF, tumor necrosis factor.
[a]HR for each risk factor in Cox model (estimate and 95% CI).
[b]Significance level.
[c]Incorporated into multivariate analysis as $P < .2$.
[d]Significant $P < .05$.

extensive colitis is a risk factor for more complicated disease outcomes with the rate of colectomy in these patients of about 19% at 10 years compared with 5% of those who have proctitis.[29]

Our study demonstrates that histologic normalization is associated with improved clinical outcomes when compared with histologic quiescence and activity, and is more predictive of improved outcomes than endoscopic MH alone or histologic quiescence alone. Several studies have now confirmed the value of histologic features of colitis predicting clinical relapse in UC.[9,11,12,16,18] Riley et al[9] found in 82 patients with UC that an acute inflammatory cell infiltrate, crypt abscess, and mucin depletion were significantly higher in those who subsequently relapsed within 12 months. Bitton et al[11] reported on 74 patients in clinical and endoscopic remission with rectal biopsy specimens and demonstrated that basal plasmacytosis was associated with UC relapse with a hazard rate of 4.5. In addition, Feagins et al[18] described 51 patients in clinical remission and reported that basal lymphoplasmacytosis, erosions/ulceration of the epithelial, or moderate to marked architectural distortion significantly predicted clinical flares by 6 and 12 months and was more accurate at predicting flares compared with endoscopic assessment alone. Finally, Bryant et al[16] demonstrated that histologic remission predicted corticosteroid use and acute severe colitis requiring hospitalization over 6 years and, similar to our study, endoscopic MH did not. Although our data confirm the importance of histologic healing in improving clinical outcomes in patients with UC over and beyond that of endoscopic MH, it is novel in that we identify histologic normalization as a stronger predictor of a decreased risk of relapse in patients with either quiescent endoscopic mucosal or histologic UC.

Despite our findings, one must be guarded in translating these associations into clinical practice. The findings cannot yet justify increasing therapy for the sole purpose of achieving histologic normalization. It is important, however, to acknowledge that this level of "deeper remission" is associated with improved outcomes. Patients who achieve histologic normalization can be informed of their improved prognosis and may represent a cohort requiring less stringent clinical surveillance and follow-up. Furthermore, whether this is a subgroup of patients that may benefit from stable de-escalation of medical therapy or require less intensive cancer surveillance remains to be determined. Finally, similar to other recent reports,[12,16] a total of 27% of patients in this study with mucosal quiescence had persistent microscopic inflammation. Because histologic assessment seems superior to endoscopic assessment in predicting clinical outcomes, this disparity between histologic and endoscopic outcomes indicates that one

should consider incorporating histologic surveillance into clinical practice.

This study lends further evidence to the importance of histologic assessment in prognosticating a patient's future disease course, and has implications for the design of future clinical trials. In fact, the United States Food and Drug Administration has pointed to the possibility of requiring documentation of histologic disease activity at inclusion and as an outcome measure in future clinical trials.[30] Clarification of a standardized and validated reporting system for histologic disease severity is needed in UC. There are current international efforts being undertaken to develop such an index.[20,21] This study suggests any such index should include histologic normalization as a separate and independent grade.

There are several notable strengths and several limitations to this study. As with any retrospective analysis, there may be inaccuracies in data collection. However, the extensive experience of the involved clinicians and overlapping data sources (electronic records, endoscopy, and pathology reports) should minimize this limitation. The generalizability of the data is also uncertain, because this is a single-center study based in a tertiary hospital setting where experts in the area of IBD manage patients. It is unclear whether this selection issue would make normalization of histology more or less likely; although patients may be treated for their disease more aggressively, they also most likely represent a more complex range of patients with more severe disease phenotypes compared with the general community. The tertiary nature of the setting is also in part its strength, because there is standardized reporting for endoscopy and pathology at the center. In addition, although we do use a standardized approach to sampling the mucosa in our patients with UC, it is possible that these results may represent a sampling bias. We believe this limitation was minimized based on the fact that there was no significant difference in biopsy number per patient when comparing cases and control subjects (histologic normalization compared with no normalization). There is also minimal variability between biopsies within each colonic segment with the same percentage of intrasegment biopsies with the same histologic inflammatory activity score being 80% or greater across all segments of the large bowel.[31] Furthermore, although our histologic activity and quiescence definitions are similar to those previously described by others,[3,14,16,32] the histologic scale used here to assess histologic normalization has not undergone independent validation. Finally, given the limitations of this retrospective review, dose and duration of medication exposures were not obtained. Although understanding more about therapies and how they may achieve histologic normalization is of interest, we suggest that this should be assessed in future trials, along with the potential for controlled de-escalation of therapies in patients who achieve CHN.

In conclusion, we demonstrate that histologic normalization is an outcome in patients with UC and have found that it occurs more often in association with less extensive disease. We demonstrate for the first time that CHN in UC is associated with improved clinical outcomes and provide further evidence that, despite the introduction and search for other predictive biomarkers in IBD, traditional histopathology may well be the most reliable. We propose that histologic assessment of disease activity should be part of endoscopic assessment in IBD. In addition, future standardized and validated histologic indices include histologic normalization as a unique outcome and encourage these findings to be incorporated into future clinical trials and clinical practice.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2017.02.016.

References

1. D'Haens G, Sandborn WJ, Feagan BG, et al. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. Gastroenterology 2007; 132:763–786.
2. Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. Gut 2012;61:1619–1635.
3. Truelove SC, Richards WC. Biopsy studies in ulcerative colitis. Br Med J 1956;1:1315–1318.
4. Froslie KF, Jahnsen J, Moum BA, et al. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. Gastroenterology 2007;133:412–422.
5. Colombel JF, Rutgeerts P, Reinisch W, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology 2011; 141:1194–1201.
6. Sandborn WJ, Rutgeerts P, Feagan BG, et al. Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. Gastroenterology 2009;137:1250–1260.
7. Feagan BG, Reinisch W, Rutgeerts P, et al. The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients. Am J Gastroenterol 2007;102:794–802.
8. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): determining therapeutic goals for treat-to-target. Am J Gastroenterol 2015;110:1324–1328.
9. Riley SA, Mani V, Goodman MJ, et al. Microscopic activity in ulcerative colitis: what does it mean? Gut 1991;32:174–178.
10. Bessissow T, Lemmens B, Ferrante M, et al. Prognostic value of serologic and histologic markers on clinical relapse in ulcerative colitis patients with mucosal healing. Am J Gastroenterol 2012; 107:1684–1692.
11. Bitton A, Peppercorn MA, Antonioli DA, et al. Clinical, biological, and histologic parameters as predictors of relapse in ulcerative colitis. Gastroenterology 2001;120:13–20.
12. Park S, Abdi T, Gentry M, et al. Histological disease activity as a predictor of clinical relapse among patients with ulcerative colitis: systematic review and meta-analysis. Am J Gastroenterol 2016;111:1692–1701.

13. Rubin DT, Huo D, Kinnucan JA, et al. Inflammation is an independent risk factor for colonic neoplasia in patients with ulcerative colitis: a case-control study. Clin Gastroenterol Hepatol 2013;11:1601–1608.
14. Gupta RB, Harpaz N, Itzkowitz S, et al. Histologic inflammation is a risk factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. Gastroenterology 2007; 133:1099–1105.
15. Hefti MM, Chessin DB, Harpaz NH, et al. Severity of inflammation as a predictor of colectomy in patients with chronic ulcerative colitis. Dis Colon Rectum 2009;52:193–197.
16. Bryant RV, Burger DC, Delo J, et al. Beyond endoscopic mucosal healing in UC: histological remission better predicts corticosteroid use and hospitalisation over 6 years of follow-up. Gut 2016;65:408–414.
17. Peyrin–Biroulet L, Bressenot A, Kampman W. Histologic remission: the ultimate therapeutic goal in ulcerative colitis? Clin Gastroenterol Hepatol 2014;12:929–934.
18. Feagins LA, Melton SD, Iqbal R, et al. Clinical implications of histologic abnormalities in colonic biopsy specimens from patients with ulcerative colitis in clinical remission. Inflamm Bowel Dis 2013;18:1477–1482.
19. Geboes K, Riddell R, Öst A, et al. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. Gut 2000;47:404–409.
20. Marchal-Bressenot A, Salleron J, Boulagnon-Rombi C, et al. Development and validation of the Nancy histological index for UC. Gut 2017;66:43–49.
21. Mosli MH, Feagan BG, Zou G, et al. Development and validation of a histological index for UC. Gut 2017;66:50–58.
22. Odze R, Antonioli D, Peppercorn M, et al. Effect of topical 5-aminosalicylic acid (5-ASA) therapy on rectal mucosal biopsy morphology in chronic ulcerative colitis. Am J Surg Pathol 1993; 17:869–875.
23. Satsangi J, Silverberg M, Vermeire S, et al. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut 2006;55:749–753.
24. Scherl EJ, Pruitt R, Gordon GL, et al. Safety and efficacy of a new 3.3 g bid tablet formulation in patients with mild-to-moderately-active ulcerative colitis: a multicenter, randomized, double-blind, placebo- controlled study. Am J Gastroenterol 2009; 104:1452–1459.
25. Walmsley RS, Ayres RC, Pounder RE, et al. A simple clinical colitis activity index. Gut 1998;43:29–32.
26. Kleer CG, Appelman HD. Ulcerative colitis: patterns of involvement in colorectal biopsies and changes with time. Am J Surg Pathol 1998;22:983–989.
27. Levine TS, Tzardi M, Mitchell S, et al. Diagnostic difficulty arising from rectal recovery in ulcerative colitis. J Clin Pathol 1996; 49:319–323.
28. Bernstein CN, Shanahan F, Anton PA, et al. Patchiness of mucosal inflammation in treated ulcerative colitis: a prospective study. Gastrointest Endosc 1995;42:232–237.
29. Solberg IC, Lygren I, Jahnsen J, et al. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort. Scand J Gastroenterol 2009; 44:431–440.
30. U.S. Department of Health and Human Services Food and Drug Adminstration Center for Drug Evaluation and Research (CDER). Ulcerative colitis: clinical trial endpoints guidance for industry. Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm515143.pdf. Accessed September 4, 2016.
31. Mikolajczyk AE, Watson S, Ackerman MT, et al. Assessment of the degree of variation of histologic inflammation in ulcerative colitis. Gastroenterology 2014;146:S-232.
32. Hanauer S, Schwartz J, Robinson M, et al. Mesalamine capsules for treatment of active ulcerative colitis: results of a controlled trial. Am J Gastroenterol 1993;88:1188–1197.

Reprint requests
Address requests for reprints to: David T. Rubin, MD, AGAF, 5841 South Maryland Avenue, MC4076, Room M410, Chicago, Illinois 60637. e-mail: drubin@medicine.bsd.uchicago; fax: (773) 702–2182.

Conflicts of interest
The authors disclose no conflicts.

Funding
Funded in part by the Digestive Disease Research Core Center of the University of Chicago (grant number P30DK42086).

Supplementary Table 1. Biopsies in Each Segment of the Colon by Healing Status

	CHN	No CHN	
	Median biopsy (IQR)		*P* value
Right colon, n	6 (4–10)	7 (4–11)	.237
Left colon, n	6 (4–9)	7 (4–10)	.412
Rectum, n	3 (2–4)	4 (2–5)	.089

2.3 SEGMENTAL HISTOLOGIC NORMALISATION OCCURS IN ULCERATIVE COLITIS BUT DOES NOT IMPROVE CLINICAL OUTCOMES

We have shown in chapter 2.2 that normalisation of the entire bowel improves outcomes and is possible. This paper demonstrates that a lesser outcome, segmental normalization also occurs in patients with UC, usually in a distal to proximal direction, however, is not associated with improved outcomes assessed.

Journal of Crohn's and Colitis, 2020, 1–9
doi:10.1093/ecco-jcc/jjaa068
Advance Access publication April 8, 2020
Original Article

Original Article

Segmental Histological Normalisation Occurs in Ulcerative Colitis but Does Not Improve Clinical Outcomes

Britt Christensen,[a,b,c] Stephen B. Hanauer,[d] Peter R. Gibson,[c] Jerrold R. Turner,[f] John Hart,[a,e] David T. Rubin[a]

[a]Inflammatory Bowel Disease Center, University of Chicago Medicine, Chicago, IL, USA [b]Department of Gastroenterology, Royal Melbourne Hospital, Melbourne, VIC, Australia [c]Department of Gastroenterology, Alfred Hospital and Monash University, Melbourne, VIC, Australia [d]Digestive Disease Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA [e]Department of Pathology, University of Chicago Medicine, Chicago, IL, USA [f]Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Corresponding author: Britt Christensen, MBBS MPH, Royal Melbourne Hospital, Gastroenterology Department, 300 Grattan St, Parkville, VIC, Australia. Tel.: +61 3 9342 7000; email: britt.christensen@mh.org.au

Abstract

Background and Aims: Complete histological normalisation and reduction of inflammation severity in patients with ulcerative colitis are associated with improved clinical outcomes, but the clinical significance of normalisation of only segments of previously affected bowel is not known. We examined the prevalence, pattern, predictors, and clinical outcomes associated with segmental histological normalisation in in patients with ulcerative colitis.

Methods: Medical records of patients with confirmed ulcerative colitis and more than one colonoscopy were sought. Segmental histological normalisation was defined as histological normalisation of a bowel segment [rectum, left-sided or right-sided colon] that had previous evidence of chronic histological injury. We assessed the variables influencing these findings and whether segmental normalisation was associated with improved clinical outcomes.

Results: Of 646 patients, 32% had segmental and 10% complete histological normalisaton when compared with their maximal disease extent. Most [88%] had segmental normalisation in a proximal-to-distal direction. Others had distal-to-proximal or patchy normalisation. On multivariate analysis, only current smoking [$p = 0.040$] and age of diagnosis ≤16 years [$p = 0.028$] predicted segmental histological normalisation. Of 310 who were in clinical remission at initial colonoscopy, 77 [25%] experienced clinical relapse after median 1.3 [range 0.06–7.52] years. Only complete histological normalisation of the bowel was associated with improved relapse-free survival (hazard ratio [HR] 0.23; 95% confidence interval [CI] 0.08–0.68; $p = 0.008$].

Conclusions: Segmental histological normalisation occurs in 32% of patients with ulcerative colitis and is increased in those who smoke or were diagnosed at younger age. Unlike complete histological normalisation, segmental normalisation does not signal improved clinical outcomes.

Key Words: Histology; mucosal healing; disease activity; disease regression; histological healing

1. Introduction

Ulcerative colitis [UC] is characterised by chronic mucosal inflammation that nearly always affects the rectum and involves continuous inflammation for variable lengths of the colon proximal to this. The disease is regionally classified according to disease extent, using the Montreal classification system, into ulcerative proctitis [limited to the rectum—E1], left-sided [extending up to the splenic flexure—E2], and extensive colitis [extending beyond the splenic flexure—E3].[1] Approximately one-third of patients present with ulcerative proctitis, one-third present with left sided UC, and another one-third present with extensive colitis.[2]

Reasons for such a classification are that disease extent is associated with both therapeutic strategy and prognosis. Thus, first-line treatment of patients with limited colitis is usually delivered topically via rectal instillation, whereas patients with more extensive disease require orally delivered therapy.[3] Patients with active extensive colitis are more likely to need colectomy[4] and are at greater long-term risk of developing colorectal cancer.[5] However, despite the Montreal classification system and the importance of classifying disease extent at diagnosis, changes in disease extent over time have been identified. Half of patients with limited disease at diagnosis may progress to more extensive disease and these patients have a worse prognosis with higher overall rates of surgery.[6] Conversely, disease extent may regress with treatment or over time. Older studies relied on radiological data or do not describe what method they used to identify regression.[7] A more recent study identified that 16% of patients have disease regression over a mean duration of 9 [4–16] years,[8] but disease regression was based solely on endoscopic findings and did not include evaluation of histological disease extent. In addition, whether patients had improved clinical outcomes with disease regression was not explored.

What is meant by disease regression requires clarification. Quiescence of disease activity more proximally [as shown radiologically or by histological 'quiescence'] is not disease regression. Strictly, regression requires evidence of histological normalisation, such that microscopic evidence of chronic injury is no longer visible. Both complete histological normalisation and a reduction in severity of endoscopic and histological inflammation in the most severely affected segment of bowel in UC have been associated with improved clinical outcomes.[9–12] However, data on incomplete histological remission or disease regression [i.e., segmental normalisation] are sparse and the clinical implications and associations of patient, disease, and treatment characteristics of such a definition of disease regression are not known. Thus, the aims of the current study were to examine both the prevalence and the predictors of segmental histological normalisation in UC patients, and to determine the association of such normalisation with clinical outcomes.

2. Methods

2.1. Protocol

A retrospective cohort study was performed as previously described[9] and was approved by the Institutional Review Board [IRB13-1063]. Segmental or complete histological normalisation was evaluated in colonoscopic biopsies, and the rates and associations were examined. In this cohort, approximately 10% previously had demonstrated complete normalisation of their bowel histology and found to have improved clinical outcomes.[9] Briefly, all patients with UC who underwent a colonoscopy at the University of Chicago between August 2005 and October 2013, with biopsies obtained in at least the rectum, left colon, and right colon, which showed chronic changes consistent with a histological diagnosis of UC [index colonoscopy] and who had a subsequent colonoscopy [final colonoscopy] more than 1 year later, were studied. Where patients had had more than one previous colonoscopy, the colonoscopy with the maximal disease extent on histology was classified as the index colonoscopy [see below]. Patients who had inadequate documentation, had undergone a colectomy, or had confirmed *Clostridioides difficile* infection at the time of follow-up colonoscopy, were excluded.

Demographic, clinical, endoscopic, histological, and biochemical data were collected from the electronic medical record system, including the date of onset of disease, duration of disease, smoking history, and previous and current use of anti-inflammatory agents and/or immunosuppressant therapy (steroids, immunomodulators, anti-tumour necrosis factor [TNF] agents) at the time of follow-up colonoscopy.

The endoscopic and histological severity and the number of biopsies taken from each segment were recorded. The maximal disease extent was defined by the most proximal biopsy showing evidence of disease, whether acute or chronic inflammation or chronic architectural changes [i.e., crypt branching/shortening, decreased crypt densities, and irregular mucosal surfaces] at any previous endoscopy. At each colonoscopy, patients were classified on histological findings as per the Montreal classification,[22] with the baseline or index disease extent classified as the most extensive Montreal classification found on any previous endoscopy.

All colonoscopies were performed by an academic inflammatory bowel disease [IBD] expert gastroenterologist with a minimum of 5 years' experience. Photographs were taken of each segment of the bowel, with targeted photographs of the areas of mucosal activity. An independent reviewer classified the segments of the colon according to the endoscopic sub-score of the Modified Mayo Disease Activity Index [MMDAI] scoring system.[13] Endoscopic mucosal healing was defined by an MMDAI endoscopic sub-score ≤1 [normal or mild erythema or decreased vascular pattern] throughout the bowel, and endoscopic disease activity as an MMDAI ≥2 [any of moderate or marked erythema, absent vascular pattern, friability, erosions, ulceration, or contact/spontaneous bleeding]. Endoscopic normalisation was defined as an MMDAI endoscopic sub-score = 0.

Mucosal biopsies from each segment of the colon, targeting the area of most significant mucosal disease activity, were assessed by two pathologists who specialise in gastrointestinal histopathology. Their reporting uses a standardised scale that leads to conclusions that each region of the colon examined is histologically normal, quiescent, mild, moderate. or severe disease, as previously described.[9] The criteria used had not changed over the period of the study. For the purposes of the current study, histopathological findings were dichotomised into either: 1] histologically normal: completely normal mucosa with no features of chronicity; or active inflammation 2] not histologically normal: presence of any feature of chronicity, including crypt atrophy or branching, or any active inflammation including erosions, crypt abscesses, or focal neutrophil infiltration. The inter-observer agreement between the pathologists when grading histological scores on a 6-point scale of inflammation severity has previously been reported as very good [kappa = 0.6].[25]

The primary outcome of segmental histological normalisation was defined by normal mucosa on histology in at least one bowel segment [right side, left side, or rectum] on final colonoscopy that had previously identified histological evidence of UC on index colonoscopy. Segmental histological normalisation was further divided into complete histological normalisation, proximal histological

normalisation, distal histological normalization, and patchy histological normalisation [Table 1]. Disease extension or progression was not looked at as a separate category, because the patient's index disease extent was classified according to the most extensive disease they had previously recorded at any endoscopy.

2.2. Assessment of clinical relapse-free survival

Patients in clinical remission at follow-up colonoscopy, and who had ≥6 months of clinical follow-up at the University of Chicago from their last colonoscopy until September 2014, were included in a separate analysis of clinical relapse-free survival. At each patient clinic visit at the University of Chicago, the Simple Clinical Colitis Activity Index [SCCAI] was calculated.[26] Clinical remission was defined as an SCCAI ≤2 and sub-score of ≤1 for stool frequency or rectal bleeding as determined from physician records. Clinical relapse-free survival was defined as time from follow-up colonoscopy to period of clinical relapse, with clinical relapse defined at clinical follow-up as an SCCAI > 2, sub-score of >1 for stool frequency or rectal bleeding, or medication escalation for symptoms, hospitalisation for UC relapse, or colectomy for refractory UC.

2.3. Statistical analysis

Continuous variables were summarised using medians and interquartile ranges [IQR]. Categorical variables were expressed as the percentage and number of the cohort. Univariate analysis of baseline characteristics was performed to identify possible predictive factors for histological regression. The Mann-Whitney U test and analysis of variance were used to compare continuous variables, and Pearson's chi square test was used to compare categorical variables. Multivariable analysis to identify independent factors associated with histological outcomes was performed using logistic regression.

Clinical relapse-free survival was compared between those with and without histological regression, using log-rank testing; Kaplan-Meier analysis was performed to compare clinical relapse-free survival in those with and without segmental and complete normalisation; and Cox-proportional hazard regression analysis was performed to compare sub-groups of interest and to identify independent predictors of segmental normalisation. All variables with p-values <0.2 on univariate analysis were retained and integrated into the multivariate models. A two-sided p-value ≤0.05 was considered statistically significant. All data analyses were performed using Stata 12.0 [StataCorp., College Station, TX].

3. Results

3.1. Patients

In all, 646 patients fulfilled the entry criteria and were included in the analysis. Their demographic and clinical details are outlined in Table 2: 50% were men, and the median age at diagnosis of UC was 29 [IQR 22–41] years with a median duration of disease at final colonoscopy of 13 [7–22] years. Of these patients, 59% had extensive colitis at the index colonoscopy.

3.2. Disease regression

Segmental histological normalisation was identified in 32% [n = 208] of patients on follow-up and, of these, 10% [n = 65] had complete normalisation of their histology in all segments that had previously shown changes.

Complete histological normalisation was identified in 9% [n = 35] of patients with extensive colitis, 8% [n = 15] of those with left-sided disease, and 23% [n = 15] of those with proctitis alone [Figure 1a]. Of those who achieved segmental normalisation, histological normalisation was seen in a proximal to distal direction [proximal histological normalisation] in 118 patients, with 25% [n = 29] of these patients regressing from extensive colitis to proctitis, 24% [n = 28] from left-sided colitis to proctitis, and 52% [n = 61] from extensive to left-sided disease [Figure 1a]. An additional 4% [n = 25] of patients normalised a distal segment of their bowel, but had evidence of proximal disease [distal histological normalisation or patchy histological normalisation]; 24 had rectal normalisation, two of whom had extension of their disease proximally [Figure 1b].

By univariate analysis, segmental histological normalisation of any kind was associated with diagnosis of UC for ≤16 years [p = 0.016], current smoking [p = 0.017], and more extensive disease extent at baseline [p = 0.002] [Table 3]. On multivariate analysis, age of diagnosis ≤16 years (adjusted odds ratio [AOR] 1.84; 95% CI 1.03–3.30; p = 0.040) and current smoking [AOR 2.40; 95% CI 1.24–4.64; p = 0.010] were significantly and independently associated with segmental histological normalisation.

3.3. Clinical relapse-free survival

Of patients who were in clinical remission at the time of their final colonoscopy, 310 were assessed for their clinical relapse-free survival time over the subsequent median 1.8 [IQR 1.1–2.9] years of

Table 1. Criteria used to define segmental histological normalisation.

Histological regression type	Definition
Complete histological normalisation	Normal mucosa by biopsy in all bowel segments which previously had identified histological evidence of UC in prior index colonoscopy
Proximal histological normalisation	Disease regression in proximal to distal direction: normal mucosa by biopsy in most proximal bowel segments [i.e., right-side colon] which previously had identified histological evidence of UC in prior index colonoscopy with ongoing histological evidence of UC in most distal bowel segments [i.e., rectum]
Distal histological normalisation	Disease regression in distal to proximal direction: normal mucosa by biopsy in most distal bowel segments [i.e., rectum or rectum/left-side bowel] which previously had identified histological evidence of UC in prior index colonoscopy with ongoing histological evidence of UC in most proximal bowel segments [i.e., right side colon]
Patchy histological normalisation	Disease regression in patchy pattern: normal mucosa by biopsy in patchy bowel segments [i.e., left-side bowel] which previously had identified histological evidence of UC in prior index colonoscopy with ongoing histological evidence of UC in more proximal and distal bowel segments [i.e., right side colon and/or rectum]

UC, ulcerative colitis.

Table 2. Clinical characteristics at baseline.

Baseline characteristics [$n = 646$]	Median [min-max] or percentage [n]
Age at diagnosis of UC [years]	29 [5–82]
Gender [male]	50% [$n = 324$]
Greatest disease extent seen:	
Proctitis	10% [$n = 65$]
Left-sided	31% [$n = 197$]
Extensive colitis	59% [$n = 384$]
Duration of disease [years]	13 [1–52]
Smoking status [current smoker]	7% [$n = 41$]
Endoscopic mucosal healing on follow-up	57% [$n = 368$]
Segmental histological normalisation on follow-up	32% [$n = 208$]

UC, ulcerative colitis; min-max, minimum to maximum.

follow-up: 51% were male, with median age 29 years [IQR 22–41] and median duration of disease of 14 years [IQR 8–49].

Maintenance medications at time of follow-up colonoscopy included systemic oral steroids [5%], 5-aminosalicylate [5-ASA] [79%], immunomodulators [36%], and anti-TNF [16%]. Most patients [60%] had extensive colitis as their most extensive previous disease; 74% [$n = 230$] had endoscopic mucosal healing; and 36% [$n = 113$] had segmental histological normalisation of the disease.

Clinical relapse occurred in 77 [25%] patients after 1.3 [range 0.6–7.5] years. Of these, 58 had their medication regimen escalated, 11 were hospitalised, and one proceeded to colectomy. As shown in Figure 2a, patients who did not achieve segmental histological normalisation had higher rates of clinical relapse than those who did. However, when the type of normalisation was separated into partial [including proximal and distal/patchy histological normalisation] and complete sub-groups, only patients who achieved complete histological normalisation had a decreased risk of clinical relapse [Figure 2b]. Those who had incomplete segmental normalisation relapsed at a similar rate as those without any evidence of segmental histological normalisation [Figure 2b].

By univariate analysis, the achievement of complete mucosal healing [MMDAI ≤1], endoscopic mucosal normalisation [MMDAI ≤0], and segmental histological normalisation were associated with improved clinical relapse-free survival [Table 4]. When segmental histological normalisation was divided into sub-types, only complete normalisation was associated with decreased risk of clinical relapse[Table 4]. As there was collinearity between segmental normalisation and the sub-groups of normalisation based on direction, segmental normalisation was removed from the multivariable analysis. Therefore, only complete histological normalisation (HR 0.23; [0.08–0.68]; $p = 0.008$] was associated with clinical-relapse free survival [Table 4]. Incomplete segmental normalisation including proximal, distal, and patchy histological normalisation was not associated with improved clinical-relapse free survival on multivariable analysis.

4. Discussion

We have demonstrated that histological normalisation of previously inflamed segments of the large bowel, with consequent regression of disease extent, is possible with current management of UC. One in 10 of our cohort achieved complete histological normalisation and one in three demonstrated segmental histological normalisation with normalisation/regression of at least one segment of the colon, in the vast majority [88%] in a proximal-to-distal direction. The remaining 12% normalised a distal segment, most commonly the rectum. Incomplete segmental histological normalisation or regression of a segment by itself did not have an impact on clinical outcomes, with only those achieving complete histological normalisation having statistically superior clinical relapse-free survival.

The frequency and associated clinical impact of segmental histological normalisation has not been previously studied, but there are previous reports of disease regression in UC, all with differing definitions. Previous work has examined change in the distribution of active inflammation, either radiologically[14] or using undefined clinical criteria.[8] In the former study, 60% of 1161 patients with barium-defined extensive colitis had radiological regression after 9 years,[14] whereas the prospective Swiss latter study reported that 16% of patients had regression of their disease on follow-up over 9 years.[8] Histological normalisation was not part of either study. It might be anticipated that loss of inflammation is the first process in regression. Indeed, the regression rates reported were greater in these two studies than we have reported, consistent with that concept. For example, in the Swiss study 19% of patients with extensive colitis regressed to left-sided colitis and 9.4% of patients regressed to proctitis,[8] compared with the 16% and 8%, respectively, that we encountered. Only proximal-to-distal regression was analysed and complete regression was not examined, as the authors needed an actively inflamed segment to enable assessments to be made.

True segmental normalisation can only be determined when the mucosa becomes histologically normal. This is well documented to occur in descriptive studies, such as that by Kleer and colleagues[15] who reported that areas of histological chronic colitis became normal at some point in 22 of 41 patients [54%]. However, this study only described the rate of normalisation of a single point in the bowel, and did not look at complete normalisation of the bowel or rates of regression overall, nor did it examine patient characteristics that predicted this normalisation. Most descriptions of histological regression have been reported as 'rectal sparing'. Levine and colleagues[16] found that, of 24 asymptomatic patients with UC, two [8%] had normalisation of their rectal biopsy on follow-up. Odze and colleagues[17] looked at 14 patients treated with either 5-ASA or placebo enemas and found that, in the patients on 5-ASA rectal therapy, 36% of the rectal biopsies normalised [defined as 'the complete absence' of any of the characteristic features of chronic UC] with no lamina propria mixed inflammatory infiltrate, crypt architectural abnormalities, basally lymphoid aggregates or plasmacytosis, or Paneth cell metaplasia. However, only one patient [7%] had normalisation of all of their rectal biopsies. Finally, a study by Bernstein and colleagues[18] showed that two of 39 [5%] patients with UC had histological evidence of absolute rectal sparing at some point during their disease. These studies have slightly lower rates of rectal normalisation when compared with our study, in which 14% experienced rectal histological normalisation, although in our study only 24 [4%] experienced a form of rectal sparing. None of the above small studies looked at proximal colon histological normalisation, or at patient or disease characteristics associated with histological normalisation, or whether this normalisation was associated with improved outcomes.

The large cohort examined in the current study enabled predictive factors to be identified. The first factor was that patients with younger age of diagnosis were more likely to have segmental histological normalisation of their disease. This finding is in contrast to previous studies that have shown that younger age of diagnosis is associated with UC disease extension.[6,19] However, it has been reported

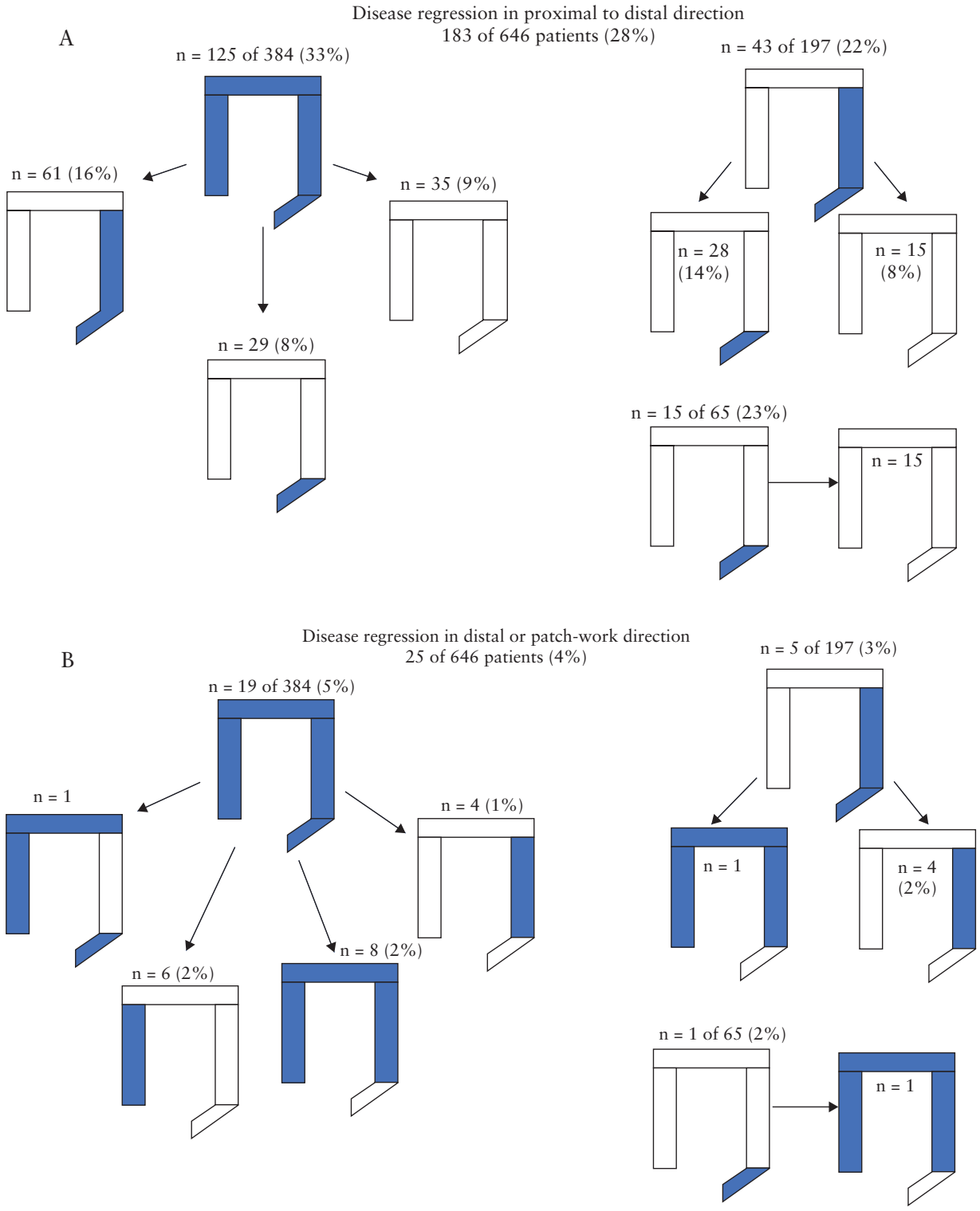


Figure 1. Diagram demonstrating degrees of and patterns of histological normalisation in ulcerative colitis. A] Proximal histological normalisation: histological normalisation in proximal-to-distal direction. B] Distal and patchy histological normalisation: histological normalisation in a distal-to-proximal or patchy direction/pattern.

that colonic inflammation may be less severe in children than in adults with UC, and that children have less severe and less diffuse architectural abnormalities and often have no architectural features of chronicity.[20] A study by Robert and colleagues[21] determined that these findings were only seen proximal to the rectum, which may explain why patients with younger age of diagnosis of UC were more likely to have segmental histological normalisation in this study but not complete normalisation in other studies.[9]

The second factor was cigarette smoking, segmental histological normalisation being associated with current cigarette smokers at the time of final colonoscopy; almost one in two smokers had segmental histological normalisation, compared with less than one in three of

Table 3. Univariate analysis of predictors of histological regression in UC

Characteristic [n = 646]	Histological regression [*n* = 208]	No histological regression [*n* = 438]	*p*-value
Age, y, *n* [%]			
≤16 y	29 [14]	31 [7]	
17–39 y	118 [58]	278 [65]	0.016**
≥40 y	58 [28]	116 [27]	
Gender, m, *n*[%]	97 [47]	227 [52]	0.218
Current smoker, *n* [%]	20 [10]	21 [5]	0.017**
Disease extent baseline, *n* [%]			
E1	16 [8]	49 [11]	0.002**
E2	48 [23]	149 [34]	
E3	144 [69]	240 [55]	
Disease > 10 y, *n* [%]	73 [64]	251 [59]	0.199*
Oral steroid exposure, *n* [%]	129 [69]	265 [66]	0.517
5-ASA monotherapy, *n* [%]	104 [51]	227 [53]	0.607
Previous immunomodulator, *n* [%]	103 [53]	192 [46]	0.147*
Current immunomodulator, *n* [%]	71 [35]	119 [28]	0.076*
Previous cyclosporine salvage, *n* [%]	12 [6]	13 [3]	0.086*
Previous anti-TNF, *n* [%]	32 [16]	77 [19]	0.470
Current anti-TNF therapy, *n* [%]	26 [13]	56 [13]	0.915
Current immunomodulator and anti-TNF, *n* [%]	9 [4]	21 [5]	0.790

UC, ulcerative colitis; y, years; m, male; 5-ASA, 5-aminosalicylate; TNF, tumour necrosis factor.

*Incorporated into multivariate analysis as *p*-value <0.2.

**Significant *p*-value <0.05.

the ex- and never-smokers. This unique observation adds to the previously reported protective effect of smoking in patients with UC. Smokers with UC have fewer relapses and hospitalisations, and a reduced need for oral corticosteroids or immunomodulator therapy for management of their disease, compared with ex- and never-smokers.[22–26] Consistent with our novel findings was the observation by Aldous and colleagues,[26] that a higher proportion of smokers than ex- or never-smokers had a decrease in disease extent between diagnosis and follow-up, both macroscopically and histologically, with 22% of current smokers compared with 9% of ex-smokers and 6% of never-smokers having less extensive disease 5 years after diagnosis [$p = 0.001$]. However, this was no longer significant at 10 years [$p = 0.086$]. Their study was limited by not describing how they assessed disease extent, merely stating that it was classified by 'endoscopic and histological assessment', which do not always correlate. In our study, the rates of segmental normalisation were much higher,

One factor that was not associated with segmental histological normalisation was anti-TNF therapy, which has more recently been associated with higher rates of mucosal healing in UC compared with conventional therapies.[27] However, the 'follow-up' colonoscopy in this study occurred between 2005 to 2013, and at this time anti-TNF therapy was not as readily available for the treatment of UC, with infliximab having only just become available in 2005 and adalimumab only receiving FDA approval in 2012. Therefore, only 13% of patients were receiving infliximab and the study may be underpowered to evaluate this association. In addition, many patients at this time only received intermittent dosing or may have been under-dosed, since assessments of serum concentrations were not yet prevalent. It would be of interest to study the association between histological normalisation and regression with biologic use, in a prospective fashion.[28,29] Unfortunately, data on use of 5-ASA suppositories or enemas were not collected. In future studies, it would be of interest to see if this predicted distal histological normalisation. As previously mentioned, only 4% of our patients did experience rectal sparing on follow-up, which is similar to previous reports. However, it is important to note that only six patients of the 646 [0.15%] had complete left-sided and rectal sparing with residual ongoing disease activity in the right colon. Hence, this suggests that even in patients with previous disease proximal to the sigmoid colon, flexible sigmoidoscopy is adequate to confirm histological normalisation in the majority of patients, as long as left-sided colon biopsies are taken.

One of the primary motivational factors to perform this study was to determine the prognostic value of incomplete remission or segmental histological normalisation in terms of major clinical outcomes such as relapse. Several studies have confirmed the role of disease progression on poorer outcomes, with patients who develop disease progression more likely having a steroid-refractory course requiring thiopurines, cyclosporine, or infliximab, and having a higher incidence of surgery and development of neoplasia.[30] In addition, it has been previously demonstrated that complete histological normalisation[9,10] and reduction in severity of the worst-affected segment histologically[12] and endoscopically[11] are associated with improved clinical outcomes. As previously described, patients in this study with complete histological normalisation were 80% less likely to have clinical relapse compared with those who did not achieve complete histological normalisation. However, incomplete segmental normalisation of any kind was not associated with improved outcomes. In other words, patients who achieve rectal sparing or a reduction in extent of disease and/or number of affected segments without the achievement of complete histological normalisation are just as likely to develop clinical relapse as those who achieve no histological normalisation at all. Furthermore, although further studies are required to confirm these findings and explore the association in parallel with the evolution of the inflammation in the segments that remain affected, this study supports the current use of the most commonly used endoscopic scoring systems, the Mayo endoscopic score[13,31] and the Ulcerative Colitis Endoscopic Index of Severity [UCEIS][30] that rely on assessing the severity of inflammation in the most affected segment, without taking into consideration disease extent.

This study provides further evidence that histology, more than endoscopic assessment, predicts a patient's risk of clinical relapse.[9,12] As only moderate correlation between histological and endoscopic findings exists, with approximately one-quarter of patients having persistent histological inflammation in the setting of endoscopic healing,[9,12] it is increasingly suggested that histological assessment should be incorporated into clinical practice and trials.[32] Despite this, the confidence by which histological normalisation on a small sample of biopsies can be extrapolated to the whole segment is not certain. It is reassuring that previous studies have demonstrated minimal variability between biopsies within each colonic segment and among different segments.[33] In addition, biopsies were obtained from each bowel segment in every patient. However, clarifying the technical approaches, developing histological assessment guidelines, and validating a biopsy approach in UC should be prioritised.[34]

There are a number of strengths and several limitations to this study. As with any retrospective analysis, there may be inaccuracies in data collection and reporting that affect results. The overlapping

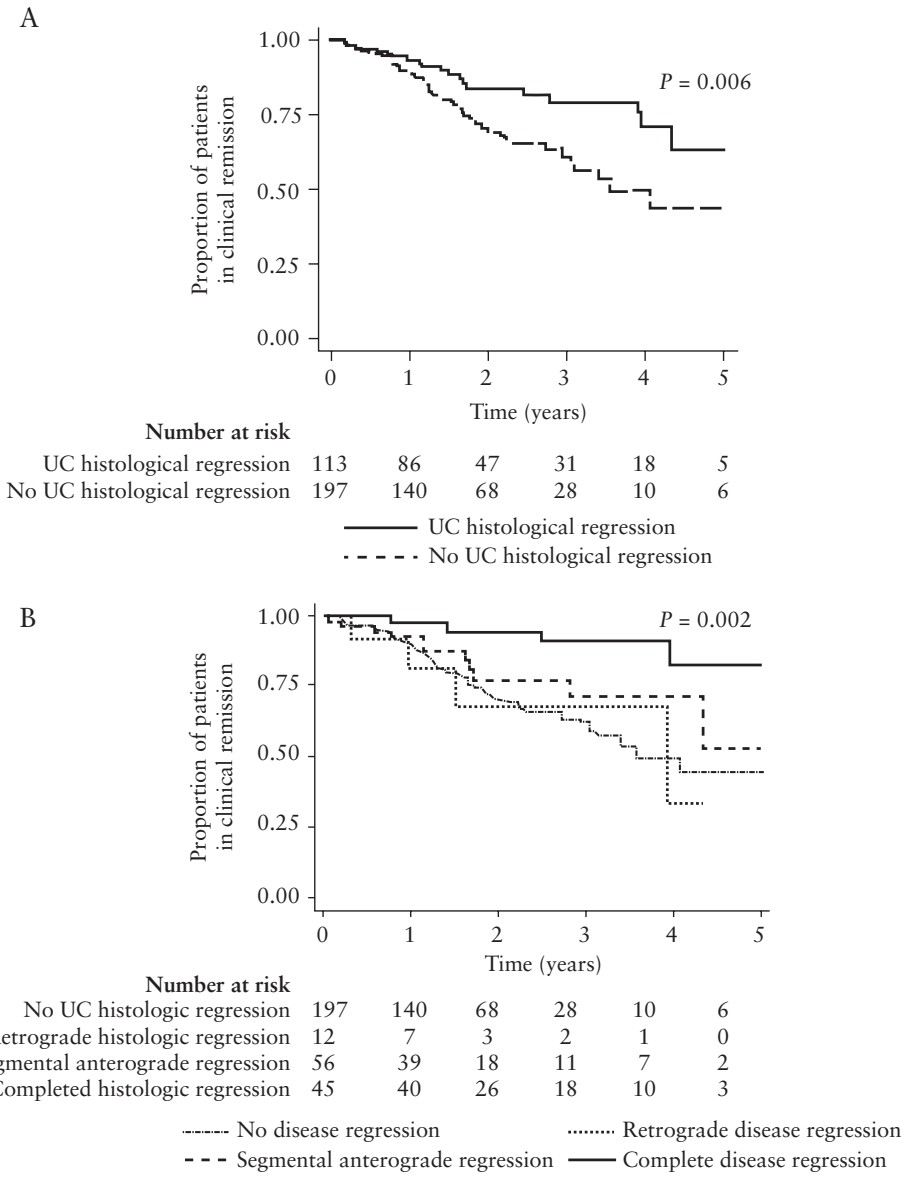


Figure 2. Association of segmental histological normalisation and clinical relapse-free survival. A] Clinical relapse-free survival in patients with and without segmental histological normalization. B] Clinical relapse-free survival in patients with no segmental histological normalisation, distal or patchy histological normalisation, proximal histological normalization, and complete histological normalisation.

data sources [electronic records, endoscopy records, and pathology reports], the extensive experience of the clinicians involved, and the fact that there is standardised reporting for endoscopy and pathology at our centre, should minimise this limitation. In addition, although our histological activity definitions are similar to those previously described by others,[3,14,16] the histological scale used here to assess histological normalisation has not undergone independent validation. In addition, the score does not take into consideration basal plasmacytosis that has been shown to predict patient outcomes. However, the focus of this study was on complete normalisation of mucosa, and our score was simply constructed to confirm normality or not. Also, given the limitations of this retrospective review, dose and duration of medication exposures were not obtained and data on topical therapies were not collected. Understanding more about therapies and how they may achieve histological regression is of interest, particularly the impact of topical therapies on distal histological remission, and we suggest that this should be assessed in future trials. The increased emphasis on and interest in histological assessments in clinical trials are limited by the current approach of assessing histological activity in a single location rather than throughout the entire colon. Therefore, future assessment of the response of therapy on regression in UC will require more extensive data collection. Finally, although this study demonstrates that response in regards to disease extent or number of affected bowel segments does not appear to be associated with clinical outcomes, future studies looking at this, in parallel with the evolution of the inflammation in the segments that remain affecte and their associated inflammation intensity in relationship to clinical outcomes, should be looked at. It may be that histological regression in patients with similar degrees of inflammation in the remaining affected segments does in fact impact on clinical outcomes.

In conclusion, we demonstrate that segmental histological normalisation occurs in UC and is associated with younger age of diagnosis and current cigarette smoking. We confirm the benefit of achieving complete histological normalisation, and demonstrate that partial or segmental normalisation of disease in any pattern is not

Table 4. Univariate and multivariate analysis for factors associated with clinical relapse-free survival.

Risk factor	Univariate analysis HR[a] [95% CI]	p–value[b]	Multivariate analysis HR[a] [95% CI]	p–value[b]
Sex [female]	1.15 [0.74–1.81]	0.533		
Older age at colonoscopy	0.99 [0.97–1.00]	0.152*	0.99 [0.97–1.01]	0.276
Older age at diagnosis	0.99 [0.98–1.01]	0.436		
Current smoker	1.19 [0.51 – 2.75]	0.687		
Longer duration of disease	0.99 [0.96–1.01]	0.301		
Disease extent:				
E2 vs E1	1.33 [0.59–2.98]	0.487		
E3 vs E1	1.41 [0.66–3.01]	0.369		
Endoscopic healing [MMDAI ≤ 1]_	0.49 [0.30–0.78]	0.003**	0.69 [0.40–1.18]	0.174
Endoscopic healing [MMDAI ≤0]	0.47 [0.28–0.81]	0.006**	0.79 [0.45–1.39]	0.420
Segmental histological normalisation	0.48 [0.28,0.81]	0.006**		
Complete histological normalisation	0.22 [0.08–0.60]	0.003**		
Histological normalisation:				
Distal or patchy histological normalisation vs no normalisation	1.30 [0.47–3.60]	0.612	1.43 [0.43–4.73]	0.353
Proximal histological normalisation vs no normalisation	0.65 [0.34–1.25]	0.194	0.66 [0.34–1.29]	0.226
Complete histological normalisation vs no histological normalisation	0.20 [0.07–0.56]	0.002**	0.23 [0.08–0.68]	0.008**
Steroids	0.72 [0.23–2.30]	0.582		
5-ASA therapy	1.19 [0.67–2.14]	0.555		
Anti-TNF therapy	0.88 [0.44–1.78]	0.724		
Dual therapy [IMM + anti-TNF]	1.42 [0.61–3.27]	0.416		
IMM therapy	1.37 [0.86–2.17]	0.183*	1.22 [0.71–2.10]	0.469
Past anti-TNF therapy exposure	0.81 [0.42–1.54]	0.522		
Past IMM therapy exposure	1.32 [0.83–2.09]	0.236		
Past cyclosporine salvage therapy	2.34 [0.99–5.52]	0.052*	2.61 [0.98–6.96]	0.056
Past oral steroid exposure	1.08 [0.67–1.74]	0.749		

F, female; 5-ASA, 5-aminosalicylate; TNF, tumour necrosis factor; HR, hazard ratio; CI, confidence interval; MMDAI, Modified Mayo Disease Activity Index; IMM, immunomodulator.

[a]Hazard ratio for each risk factor in Cox model [estimate and 95% CI]

[b]Significance level [p <0.05].

*Incorporated into multivariate analysis as p-value <0.2.

**p-value <0.05.

associated with improved clinical outcomes. In addition, normalisation does not always occur in a proximal to distal fashion and results in complete left-sided normalisation with residual right-sided disease activity in less than 0.2% of patients. This suggests that, if left colonic biopsies are taken, flexible sigmoidoscopy is adequate to determine histological healing and prognosticate future risk of relapse in almost all cases of UC.

Funding

This work was supported by the Digestive Disease Research Core Center of the University of Chicago [NIH grant number DK42086]. BC receives support through an Australian Government Research Training Program Scholarship.

Conflict of Interest

COI forms are available as supplementary files.

Acknowledgments

We would like to thank Jonathon Erlich and Olufemi Kassim for helping with data collection.

Author Contributions

BC: study concept and design, acquisition of the data, analysis and interpretation of the data, drafting of the manuscript, statistical analysis. JE:acquisition of data and drafting of the manuscript. OK: scquisition of data. SBH: study concept and design and critical revision of the manuscript. PRG: study concept and design, drafting of the manuscript, critical revision of the manuscript, and study supervision. JRT: pathology review and critical revision of the manuscript. JH: pathology review and critical revision of the manuscript. DTR: tudy concept and design, study supervision, drafting of the manuscript, and critical revision of the manuscript.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

References

1. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006;**55**:749–53.
2. Ordás I, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. *Lancet* 2012;**380**:1606–19.
3. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG Clinical Guideline: Ulcerative Colitis in Adults. *Am J Gastroenterol* 2019;**114**:384–413.
4. Moum B, Ekbom A, Vatn MH, Elgjo K. Change in the extent of colonoscopic and histological involvement in ulcerative colitis over time. *Am J Gastroenterol* 1999;**94**:1564–9.
5. Ekbom A, Helmick C, Zack M, Adami HO. Ulcerative colitis and colorectal cancer. A population-based study. *N Engl J Med* 1990;**323**:1228–33.
6. Farmer RG, Easley KA, Rankin GB. Clinical patterns, natural history, and progression of ulcerative colitis. A long-term follow-up of 1116 patients. *Dig Dis Sci* 1993;**38**:1137–46.

7. Langholz E, Munkholm P, Davidsen M, Nielsen OH, Binder V. Changes in extent of ulcerative colitis: a study on the course and prognostic factors. *Scand J Gastroenterol* 1996;**31**:260–6.
8. Safroneeva E, Vavricka S, Fournier N, *et al.*; Swiss IBD Cohort Study Group. Systematic analysis of factors associated with progression and regression of ulcerative colitis in 918 patients. *Aliment Pharmacol Ther* 2015;**42**:540–8.
9. Christensen B, Hanauer SB, Erlich J, *et al.* Histological normalization occurs in ulcerative colitis and is associated with improved clinical outcomes. *Clin Gastroenterol Hepatol* 2017;**15**:1557–64.e1.
10. Israel A, Christensen B, El Jurdi K, *et al.* Follow-up of patients with ulcerative colitis and histological normalization. *Clin Gastroenterol Hepatol* 2020;**18**:987–8.e1.
11. Colombel JF, Rutgeerts P, Reinisch W, *et al.* Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology* 2011;**141**:1194–201.
12. Bryant RV, Burger DC, Delo J, *et al.* Beyond endoscopic mucosal healing in UC: histological remission better predicts corticosteroid use and hospitalisation over 6 years of follow-up. *Gut* 2016;**65**:408–14.
13. Scherl EJ, Pruitt R, Gordon GL, *et al.* Safety and efficacy of a new 3.3 g b.i.d. tablet formulation in patients with mild-to-moderately-active ulcerative colitis: a multicenter, randomized, double-blind, placebo-controlled study. *Am J Gastroenterol* 2009;**104**:1452–9.
14. Langholz E, Munkholm P, Davidsen M, Nielsen OH, Binder V. Changes in extent of ulcerative colitis: a study on the course and prognostic factors. *Scand J Gastroenterol* 1996;**31**:260–6.
15. Kleer CG, Appelman HD. Ulcerative colitis: patterns of involvement in colorectal biopsies and changes with time. *Am J Surg Pathol* 1998;**22**:983–9.
16. Levine TS, Tzardi M, Mitchell S, Sowter C, Price AB. Diagnostic difficulty arising from rectal recovery in ulcerative colitis. *J Clin Pathol* 1996;**49**:319–23.
17. Odze R, Antonioli D, Peppercorn M, Goldman H. Effect of topical 5-aminosalicylic acid [5-ASA] therapy on rectal mucosal biopsy morphology in chronic ulcerative colitis. *Am J Surg Pathol* 1993;**17**:869–75.
18. Bernstein CN, Shanahan F, Anton PA, Weinstein WM. Patchiness of mucosal inflammation in treated ulcerative colitis: a prospective study. *Gastrointest Endosc* 1995;**42**:232–7.
19. Solberg IC, Lygren I, Jahnsen J, *et al.*; IBSEN Study Group. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort [IBSEN Study]. *Scand J Gastroenterol* 2009;**44**:431–40.
20. Glickman JN, Bousvaros A, Farraye FA, *et al.* Pediatric patients with untreated ulcerative colitis may present initially with unusual morphologic findings. *Am J Surg Pathol* 2004;**28**:190–7.
21. Robert ME, Tang L, Hao LM, Reyes-Mugica M. Patterns of inflammation in mucosal biopsies of ulcerative colitis: perceived differences in pediatric populations are limited to children younger than 10 years. *Am J Surg Pathol* 2004;**28**:183–9.
22. Harries AD, Baird A, Rhodes J. Non-smoking: a feature of ulcerative colitis. *Br Med J* 1982;**284**:706.
23. Calkins BM. A meta-analysis of the role of smoking in inflammatory bowel disease. *Dig Dis Sci* 1989;**34**:1841–54.
24. Bridger S, Lee JC, Bjarnason I, Jones JE, Macpherson AJ. In siblings with similar genetic susceptibility for inflammatory bowel disease, smokers tend to develop Crohn's disease and non-smokers develop ulcerative colitis. *Gut* 2002;**51**:21–5.
25. Samuelsson SM, Ekbom A, Zack M, Helmick CG, Adami HO. Risk factors for extensive ulcerative colitis and ulcerative proctitis: a population based case-control study. *Gut* 1991;**32**:1526–30.
26. Aldhous MC, Drummond HE, Anderson N, *et al.* Smoking habit and load influence age at diagnosis and disease extent in ulcerative colitis. *Am J Gastroenterol* 2007;**102**:589–97.
27. Panaccione R, Ghosh S, Middleton S, *et al.* Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. *Gastroenterology* 2014;**146**:392–400.e3.
28. Pouillon L, Rousseau H, Busby-Venner H, *et al.* Vedolizumab trough levels and histological healing during maintenance therapy in ulcerative colitis. *J Crohns Colitis* 2019;**13**:970–5.
29. Papamichael K, Rakowsky S, Rivera C, Cheifetz AS, Osterman MT. Infliximab trough concentrations during maintenance therapy are associated with endoscopic and histological healing in ulcerative colitis. *Aliment Pharmacol Ther* 2018;**47**:478–84.
30. Etchevers MJ, Aceituno M, García-Bosch O, *et al.* Risk factors and characteristics of extent progression in ulcerative colitis. *Inflamm Bowel Dis* 2009;**15**:1320–5.
31. Travis SP, Schnell D, Krzeski P, *et al.* Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity [UCEIS]. *Gut* 2012;**61**:535–42.
32. Peyrin-Biroulet L, Sandborn W, Sands BE, *et al.* Selecting Therapeutic Targets in Inflammatory Bowel Disease [STRIDE]: determining therapeutic goals for treat-to-target. *Am J Gastroenterol* 2015;**110**:1324–38.
33. Mikolajczyk AE, Watson S, Ackerman MT, *et al.* Sa1213 Assessment of the degree of variation of histological inflammation in ulcerative colitis. *Gastroenterology* 2014;**146**:S232.
34. Marchal Bressenot A, Riddell RH, Boulagnon-Rombi C, *et al.* Review article: the histological assessment of disease activity in ulcerative colitis. *Aliment Pharmacol Ther* 2015;**42**:957–67.

2.4 HISTOLOGIC HEALING IS MORE STRONGLY ASSOCIATED WITH CLINICAL OUTCOMES IN ILEAL CROHN'S DISEASE THAN ENDOSCOPIC HEALING

It has been demonstrated that mucosal healing in CD improves outcomes, however there is little research on histology in CD. This paper explores whether histologic healing occurs in CD. Due to the patchy nature of CD and the difficulty in studying histology in these patients we focused only on patients with ileal CD. We demonstrated that histologic healing does occur in patients with ileal CD and is a stronger predictor of improved clinical outcomes on follow-up when compared to mucosal healing.

Clinical Gastroenterology and Hepatology 2020;18:2518–2525

Histologic Healing Is More Strongly Associated with Clinical Outcomes in Ileal Crohn's Disease than Endoscopic Healing

Britt Christensen,[*,‡,§] Jonathan Erlich,[*] Peter R. Gibson,[§] Jerrold R. Turner,[*,‖] John Hart,[*,‖] and David T. Rubin[*]

*Inflammatory Bowel Disease Center, University of Chicago Medicine, Chicago, Illinois; [‡]Department of Gastroenterology, Royal Melbourne Hospital, Melbourne, Australia; [§]Department of Gastroenterology, Alfred Hospital and Monash University, Melbourne, Australia; and [‖]Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

BACKGROUND & AIMS: **Deep remission, based on clinical remission and evidence of healing during endoscopic evaluation, are goals of medical treatments for Crohn's disease (CD). We investigated whether histologic healing is associated with outcomes of patients with CD ileitis.**

METHODS: **We performed a retrospective study of 101 patients with CD (52% male) isolated to the terminal ileum who had a colonoscopy between September 2005 and June 2015. Our analysis included patients in clinical remission at colonoscopy who had biopsies collected from colon and ileum. The ileum was evaluated for endoscopic healing (no ulceration) and histologic evidence of healing (no active inflammation, erosions, ulceration, or neutrophil infiltration). We compared times of clinical relapse-free survival, medication escalation, corticosteroid use, or hospitalization secondary to disease activity between patients with and without histological and endoscopic healing, followed for a median 21 months. We identified factors associated with survival using Kaplan Meier analysis and Cox proportional hazard model.**

RESULTS: **At ileo-colonoscopy, 63% of patients had endoscopic healing and 55% had histologic evidence of healing. The level of agreement between endoscopic and histologic activity was fair (62%, K = 0.2250, $P = .0064$). Forty-two patients had clinical relapse, 45 had medication escalation, 30 required corticosteroids, and 17 were hospitalized (3 required surgery). On multivariate analysis, only histologic healing was associated with decreased risk of clinical relapse (hazard ratio [HR], 2.05; 95% CI, 1.07–3.94; $P = .031$), medication escalation (HR, 2.17; 95% CI, 1.2–3.96; $P = .011$), and corticosteroid use (HR, 2.44; 95% CI, 1.17–5.09; $P = .018$). No factors were associated with hospitalization.**

CONCLUSIONS: **In patients with ileal CD in clinical remission, histologic healing but not endoscopic healing is associated with decreased risk of clinical relapse, medication escalation, or corticosteroid use.**

Keywords: Inflammatory Bowel Disease; Mucosal Healing; Histology; Histopathology; Prognostic Factor.

See editorial on page 2430; See related article on page 2510.

In patients with Crohn's disease (CD), persistent inflammation leads to bowel damage. Cumulative bowel damage, described as progressing from inflammatory to stricturing and then to a penetrating phenotype, may predict long-term disability and can lead to clinical symptoms and need for surgery.[1]

Historically, treatment of CD aimed to control clinical symptoms. However, clinical symptoms poorly correlate with endoscopic mucosal disease activity, and resolution of symptoms alone fails to alter this natural progression of CD and cumulative bowel damage.[2] On the other hand, mucosal healing is associated with better long-term outcomes; patients who achieve mucosal healing have lower rates of hospitalization and surgery and are less likely to have a clinical flare on follow-up.[3–6] Therefore, deep remission, defined as clinical remission and endoscopic healing without bowel ulceration, has emerged as the recommended goal of treatment therapy.[7,8]

Histologic inflammation may persist in the setting of mucosal healing. In UC, histologic inflammation is a

Abbreviations used in this paper: **CD, Crohn's disease; EH, endoscopic healing; HBI, Harvey-Bradshaw Index; HR, hazard ratio; IGHAS, Ileal Global Histological Disease Activity Score; IQR, interquartile range; UC, ulcerative colitis.**

Most current article

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2019.11.056

stronger predictor of clinical flares, corticosteroids use, and hospitalization for disease activity than mucosal healing.[9,10] In addition, histologic normalization has been associated with improved long-term clinical outcomes when compared with histologic quiescence.[11] This has led to suggestions that histologic assessment in UC should be used as an adjunct to mucosal disease assessment in standard care.[11,12]

The role of histologic assessment in CD has been poorly explored. Despite the recent appreciation for the value of endoscopic assessment in CD, there is little evidence as to whether microscopic examination of the mucosa adds any further prognostic information. Histologic healing is achievable in CD,[13,14] but because of the patchy nature of the disease, it is often believed that histologic assessment is subject to too much biopsy bias and is too difficult to study.[15] In addition, there is currently no consensus on the use of a specific scoring system when assessing histologic changes in CD.

The aims of this study were to explore whether histologic healing (Supplementary Table 1) provides any further prognostic information in regard to clinical outcomes, hospitalization, and medication escalation in patients with ileal CD when compared with endoscopic healing (EH) alone.

What You Need to Know

Background

Deep remission, based on clinical remission and evidence of healing on endoscopic evaluation are goals of medical treatments for Crohn's disease (CD).

Findings

In patients with ileal CD in clinical remission, histologic healing, but not endoscopic healing, indicates that patients have decreased risk of clinical relapse, medication escalation, or corticosteroid use.

Implications for patient care

Patients in remission from CD should be evaluated for histologic evidence of healing.

Methods

An exploratory retrospective case-control study of patients with CD limited to the terminal ileum was performed and was approved by the Institutional Review Board (IRB13-1063). All patients who underwent colonoscopy for CD at the University of Chicago between September 2005 and June 2015 were identified. For patients with a confirmed diagnosis of CD based on clinical and histologic information, the electronic medical record was then reviewed. Inclusion criteria comprised a colonoscopy to the terminal ileum, biopsies of both the colon and terminal ileum with disease limited to the terminal ileum both macroscopically and microscopically throughout the duration of their disease, clinical remission at the time of the colonoscopy, and $\geq$6 months of clinical follow-up after colonoscopy. Patients with inadequate documentation, inflammation present in the colon, undergone a colectomy, or confirmed *Clostridioides difficile* infection at the time of follow-up colonoscopy were excluded.

Medical Records Abstraction

Endoscopy reports were retrieved through an electronic documentation system (Provation, Minneapolis, MN). Demographic, clinical, histologic, and biochemical data were collected from the electronic medical record system (EPIC, Verona, WI), including date of disease onset, disease duration, smoking history, CD phenotype according to Montreal classification (B1, inflammatory; B2, stricturing; B3, penetrative), disease location (ileal disease only included), and previous and current use of anti-inflammatory agents and/or immunosuppressant therapy (steroids, immunomodulators, anti–tumor necrosis factor agents) at the time of colonoscopy.

Endoscopic Assessment

An academic IBD expert gastroenterologist with minimum of 5 years of experience performed all endoscopies, during which endoscopic photographs were obtained from each bowel segment, with targeted photos of the areas of endoscopic activity. As per the inclusion criteria, patients could not have evidence of past or present colonic CD. Consistent with recent large clinical trials and the STRIDE guidelines, EH was defined as the presence of no mucosal ulceration including aphthae,[12,16,17] which was confirmed by both the endoscopic report and photographic evidence.

Histologic Assessment

Within the unit, mucosal biopsies from both the ileum and colon are routinely taken targeting the area of most significant mucosal inflammation. Patients were excluded if there was histologic evidence of CD in the colon.

The histopathology reports from all diagnostic, screening, and surveillance endoscopic biopsies contained in the patient's electronic medical records were reviewed. Two pathologists (J.R.T., J.H.) who specialize in gastrointestinal histology and whose agreement has been previously described[18] routinely assessed all biopsies and reported the worst affected area. There are several histologic scoring schemes that have been used in CD; however, none of these have been validated.[19–21]

In the absence of a validated histologic grading score in CD, histologic healing was assessed by using a modified Ileal Global Histological Disease Activity Score (IGHAS).[14] The IGHAS is the most commonly used histologic index in CD and assesses and scores 2 features of chronicity (architectural changes and infiltration of

mononuclear cells in the lamina propria) and 5 features of activity (epithelial damage, polymorphonuclear cells in the lamina propria, polymorphonuclear cells in the epithelium, presence of erosions and/or ulcers, epithelial granuloma). For the purposes of the current study, histologic assessment was dichotomized to histologic healing, where none of the features of activity above were present, and histologic activity, where 1 or more of the features were present. Severity of inflammation was not scored, as stated in Supplementary Table 1.

Assessment of Clinical Outcomes

At every patient clinic visit at the University of Chicago, the Harvey-Bradshaw Index (HBI) is calculated.[22] All patients who were in clinical remission at the time of the colonoscopy, defined as HBI $\leq$4, and who had $\geq$6 months of follow-up were included. Clinical relapse-free survival, medication escalation–free survival, corticosteroid-free survival, and hospitalization-free survival were calculated and defined as time from colonoscopy to event. Clinical relapse was defined at clinical follow-up as HBI >4 that resulted in alteration or addition of medical therapy, hospitalization, or surgery. Escalation of medication was defined as need for a course of corticosteroid or change in medication maintenance including change of biologic agent or escalation of dose, addition or change of immunomodulator in combination therapy for CD, or escalation from immunomodulator to biologic agent. Corticosteroid use was defined as the requirement for an increase in dosage or new course of oral corticosteroids including budesonide for active CD symptoms. Hospitalization was recorded if required for disease activity or refractory disease including need for surgery.

Statistical Analysis

Continuous variables were summarized by using medians and interquartile ranges (IQRs). Categorical variables were expressed as the percentage and number of cohort. Cohen's kappa coefficient (κ) was calculated to measure agreement between endoscopic and histologic activity.

Kaplan-Meier analyses were performed to compare clinical relapse-free survival, medication escalation–free survival, corticosteroid-free survival, and hospitalization-free survival in those with and without EH and with and without histologic healing. Univariate and multivariate Cox proportional hazard regression analysis was performed to identify predictors of clinical relapse, medication escalation, corticosteroid use, and hospitalization. All variables with P values $\leq$.10 on univariate analysis were retained and integrated into the multivariable models. A two-sided P value of .05 or less was considered statistically significant. All data analyses were performed by using Stata 12.0 (StataCorp, College Station, TX).

Results

Patients

Of 1287 patients with documented CD and a colonoscopy, 150 fulfilled entry criteria with disease limited to the terminal ileum, normal colonoscopic biopsies, and evaluable biopsies from the ileum. Of these, 101 were in clinical remission at the time of colonoscopy and were included in the study (Figure 1).

The patients' demographics and clinical characteristics are shown in Table 1. Fifty-two percent of patients were male, with median age of diagnosis of 25 years and median duration of disease at time of colonoscopy of 12 years. Eighty-six percent of patients had 2 or more sets of biopsies taken of the terminal ileum. At colonoscopy, 64 patients (63%) had EH, and 55% had achieved histologic healing. The level of agreement between endoscopic activity and histologic activity was fair at 62% (κ = 0.2250; P = .011).

Clinical Relapse-Free Survival

Median follow-up time was 21 months (IQR, 12–40). Clinical relapse occurred in 42% of patients (n = 42) after median time of 16 months (IQR, 7–26). As shown in Figure 2, patients with EH and histologic healing were less likely to experience clinical relapse (Figure 2*A* and *B*). By univariate analysis, no other factors were associated with improved clinical relapse-free survival (Table 2). By multivariable analysis, only histologic activity remained associated with clinical relapse-free survival with hazard ratio (HR) 2.05 (1.07–3.94; P = .031; Table 2). EH did not independently predict a lower rate of clinical relapse.

Medication Escalation–Free Survival

The medication regimen was escalated in 45% of patients (n = 45), two of whom were in clinical remission but had moderate or severe endoscopic disease activity on colonoscopy. Thirty-two patients required a course of oral corticosteroids (budesonide or prednisolone), 19 required a new biologic agent, 1 had escalation of biologic agent dosing, and 6 patients had an immunomodulator added to their biologic therapy. Patients with histologic healing were less likely to have medication escalation (Figure 2*C*). EH was not significantly associated with a lower rate of medication escalation (Figure 2*D*). The only factor associated with improved medication escalation–free survival was the achievement of histologic healing compared with histologic activity, with HR 2.17 (1.20–3.96; P = .011) on univariate analysis and HR 2.08 (1.14–3.80; P = .017) on multivariable analysis (Table 2).

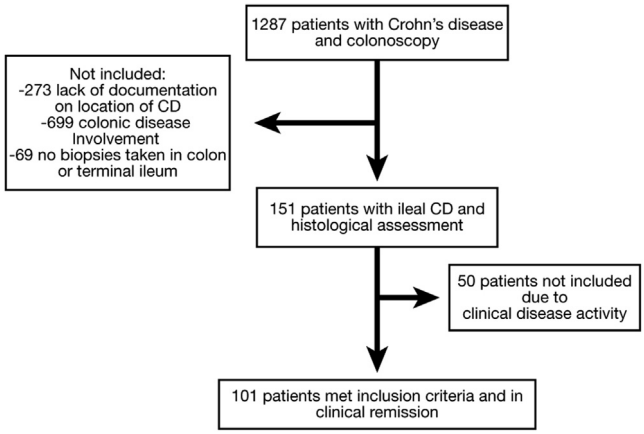


Figure 1. Flowchart of patients included in the study. CD, Crohn's disease.

Corticosteroid-Free Survival

Patients with histologic healing, but not EH, were less likely to have a requirement for salvage therapy with corticosteroids (Figure 3*A* and *B*). By univariate and multivariable analyses, the only factor associated with corticosteroid-free survival was the achievement of histologic healing compared with histologic activity (HR 2.44 [1.17–5.09]; $P = .018$; Table 2).

Hospitalization-Free Survival

Seventeen percent of patients (n = 17) were hospitalized, and 3 patients proceeded to ileocecectomy. Because of small numbers, predictors of surgery could not be analyzed. No factor was associated with hospitalization-free survival. EH and histologic healing did not protect from hospitalization on follow-up (Figure 3*C* and *D*).

Discussion

Recently, there has been increased emphasis placed on objective markers of disease activity. In CD particularly, the association with clinical symptoms and bowel damage is poor.[3] This may, in part, explain why despite the advent of many new therapies, the natural history of the disease has barely changed up until recently.[23] Recently, expert consensus has stated that the target of treatment for CD should be EH, as defined by lack of ulceration, to attempt to prevent ongoing bowel damage.[12] Unlike UC, where histologic healing has been defined as an adjunct to EH[24] and the combination of both has been proposed as a new endpoint of interest,[25] the role of histology in CD beyond diagnosis is poorly defined. In the current exploratory study, the prognostic value of histology in patients with CD restricted to the ileum has clearly shown that histologic remission is associated with superior clinical relapse–free survival and reduced need for medication escalation and corticosteroids. Moreover, the results indicate the poor performance of EH alone as a prognostic predictor.

As in UC, this study demonstrates that there is a disparity between EH and histologic remission. We found that the level of agreement between endoscopic activity and histologic activity was only fair at 63% ($\kappa = 0.2250$). Microscopic inflammation persisted in 36% of those who achieved EH. This is similar to previous reports of persistent microscopic inflammation in the setting of EH between 25% and 37%[8,26] and emphasizes the need to consider histologic outcomes separate to endoscopic measures of remission in CD.

Several studies have demonstrated the effect of medical therapy on histologic healing in patients with CD; azathioprine, methotrexate, and the biologics can all

Table 1. Clinical Characteristics at Baseline

	Patients with histologic healing N = 56	Patients without histologic healing N = 45
Baseline characteristics (N = 101)	Median (IQR) or percentage (n)	
Age at diagnosis of CD (*y*)	24 (16–31)	27 (19–34)
Gender (male)	48% (n = 27)	58% (n = 26)
Duration of disease (*y*)	14 (9–25)	9 (3–19)
Disease phenotype		
B1 (inflammatory)	14% (n = 8)	38% (n = 17)
B2 (stricturing)	61% (n = 34)	40% (n = 18)
B3 (penetrating)	25% (n = 14)	22% (n = 10)
Medications at time of colonoscopy		
Oral prednisolone/budesonide	20% (n = 11)	18% (n = 8)
5-Aminosalicylic acid	9% (n = 5)	11% (n = 5)
6-Mercaptopurine/azathioprine	45% (n = 25)	38% (n = 17)
Methotrexate	11% (n = 6)	9% (n = 4)
Anti–tumor necrosis factor	32% (n = 18)	31% (n = 14)
Ustekinumab	2% (n = 1)	0% (n = 0)
Vedolizumab	7% (n = 4)	4% (n = 2)
Endoscopic healing	73% (n = 41)	51% (n = 23)

CD, Crohn's disease; IQR, interquartile range.

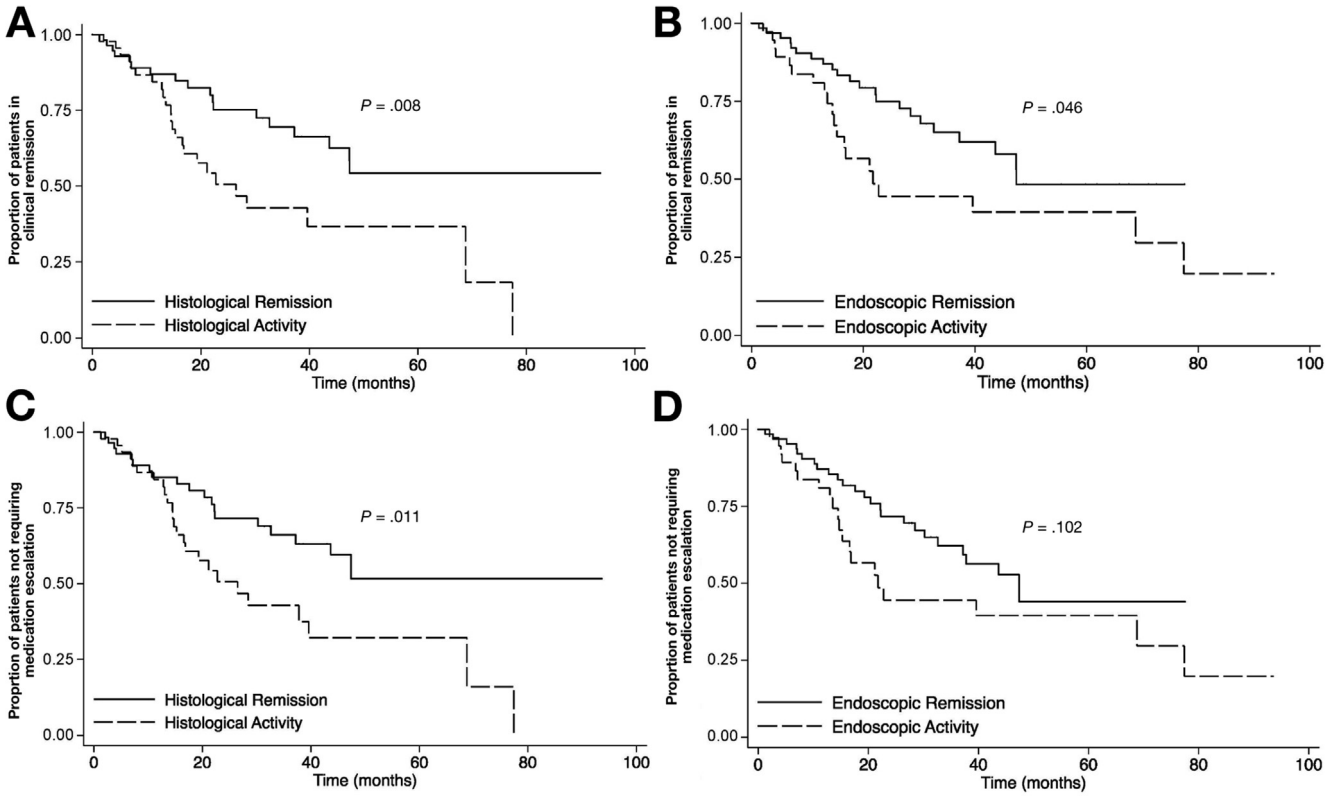


Figure 2. Kaplan-Meier analysis of effect of endoscopic and histologic activity on (*A*) clinical relapse-free survival versus histologic healing, (*B*) clinical relapse-free survival versus endoscopic healing, (*C*) medication escalation–free survival versus histologic healing, and (*D*) medication escalation–free survival versus endoscopic healing.

result in histologic healing.[13,14,16,17,27] A subanalysis of 13 patients from the ACCENT 1 study established that histologic improvement after 54 weeks of infliximab was associated with a consistent decrease in the expression of inflammatory markers including CD68 and gelatinase B in the colonic mucosa.[28] The relationship of histology to chance of relapse was explored in a study of 46 patients with Crohn's colitis undergoing surveillance colonoscopy, and histology and/or active mucosal disease did not predict chance of relapse.[20] This study also found similar lack of association in patients with UC. However, a recent article on 62 CD patients in clinical remission demonstrated that histologic inflammation was strongly associated with an increased risk of clinical flares within 1–2 years and that endoscopic activity alone did not predict clinical flares on follow-up.[19] Two recent studies have also specifically examined the link between histologic remission and outcomes in UC and found that histologic disease activity was linked to an increased chance of clinical relapse. Bryant et al[10] demonstrated that histologic remission predicted reduced corticosteroid use and episodes of acute severe colitis requiring hospitalization in a cohort of 91 patients with UC during a period of 6 years. In a large cohort of 310 patients from Chicago, histologic normalization was also found to be achievable, and this predicted a lower chance of clinical relapse during the ensuing 16 months.[11] Because of such studies, routine histologic assessment is now recommended in UC.[12] This exploratory study on ileal CD demonstrates that histologic assessment in CD patients is also clinically relevant, despite the patchy nature of the disease. Therefore, we recommend that routine ileal biopsies be obtained when patients with terminal ileal disease are being assessed.

As we strive to achieve deeper markers of disease control, histologic healing may emerge as a treatment target in CD. However, this aspiration raises several issues. Dichotomously scoring the histopathology of individual biopsies as healed versus inflamed by using the criteria applied in the current study should be relatively easy, as opposed to scoring the severity of inflammation. It is the patchy nature of inflammation in CD with the implications around what should be defined as healed that provides the uncertainty and controversy. Studies of where the biopsies should be taken and how many are needed to confidently make such a decision are required so a validated and reproducible histologic index can be established. Despite this, the results of the current study have clearly demonstrated that the goal of gaining meaningful prognostic information from assessing histologic healing in the terminal ileum is achievable.

Even if these guidelines existed, it is as yet unclear whether it is even possible to achieve histologic healing in the majority of patients or whether treating our patients more aggressively with medical therapy will improve rates of histologic healing. Hence, although

Table 2. Univariable Predictors of Clinical Outcome Measures in Patients With Crohn's Disease

Variable	Clinical relapse, n = 42[a] HR (95% CI), *P* value	Medication escalation, n = 45[a] HR (95% CI), *P* value	Corticosteroid requirement, n = 32[a] HR (95% CI), *P* value	Hospitalization for severe disease, n = 17[a] HR (95% CI), *P* value
Age at diagnosis of CD (*y*)	0.98 (0.95–1.01), .196	0.98 (0.95–1.00), .127	0.98 (0.95–1.01), .204	0.98 (0.94–1.03), .463
Sex (male)	0.66 (0.36–1.23), .197	0.60 (0.32–1.09), .095	0.65 (0.32–1.32), .239	0.49 (0.18–1.36), .171
Disease duration (*y from diagnosis to colonoscopy*)	0.99 (0.97–1.02), .569	0.99 (0.97–1.01), .656	0.99 (0.96–1.02), .637	1.00 (0.96–1.04), .980
Penetrative vs inflammatory (B2 v sB1)	0.78 (0.39–1.58), .493	0.89 (0.44–1.76), .729	1.08 (0.45–2.59), .860	1.95 (0.43–8.90), .391
Stricturing vs inflammatory (B3 vs B1)	0.44 (0.16–1.20), .111	0.45 (0.17–1.22), .120	0.62 (0.19–1.99), .422	1.06 (0.17–6.56), .947
Maintenance therapy				
- 5-ASA	1.21 (0.48–3.11), .682	1.13 (0.44–2.88), .794	0.90 (0.27–2.97), .861	1.8 (0.24–4.76), .923
- Immunomodulator	0.66 (0.35–1.25), .202	0.73 (0.39–1.36), .327	0.62 (0.30–1.27), .193	0.41 (0.13–1.25), .117
On oral corticosteroids at endoscopy	1.50 (0.73–3.05), .267	1.20 (0.47–3.05), .703	1.34 (0.47–3.88), .578	1.29 (0.29–5.72), .737
Ongoing histologic activity	2.31 (1.24–4.31), .008[b]	2.17 (1.20–3.96), .011[b]	2.36 (1.16–4.81), .018[b]	1.27 (0.47–3.43), .636
Ongoing endoscopic activity	1.87 (1.01–3.45), .046[b]	1.64 (0.91–2.99), .102	1.39 (0.68–2.85), .369	0.97 (0.35–2.67), .951

5ASA, 5-Aminosalicylic acid; CD, Crohn's disease; HR, hazard ratio.
[a]Cox regression univariate analyses presented.
[b]*P* value ≤.05 considered significant.

histologic healing might provide prognostic information, at this stage it cannot be recommended as a target on which therapeutic decisions in patients with ileal disease can be made. Although those who have a healed ileum have a better clinical outlook, whether this group who achieve this level of deeper remission need less stringent follow-up or monitoring or are less likely to have disease that progresses to a stricturing or penetrating phenotype requires further study.

CD causes chronic transmural inflammation of the gastrointestinal tract. There is evidence that patients who achieve transmural healing also have more favorable clinical outcomes on follow-up compared with patients who achieve EH alone.[29] It is unclear whether transmural inflammation persists in the setting of histologic healing as demonstrated on mucosal biopsies or whether achieving the potentially even deeper target of transmural healing could result in further improvement in clinical outcome compared with histologic healing alone, but this should be looked at in future research.

There are several limitations to this study. First, this is a retrospective analysis with a relatively small sample size, and there may be inaccuracies in data collection that affect results. The extensive experience of the involved clinicians and the overlapping data sources (electronic records, endoscopy records, and pathology reports) aim to minimize this limitation, but those patients in prolonged clinical remission may not be included because of not having had a colonoscopy or endoscopic biopsies. Second, the generalizability of the data is also uncertain; this is a single-center study based in a tertiary hospital setting where experts in the area of inflammatory bowel disease manage patients. Third, the findings are currently applicable only to patients with ileal CD. The patchiness of the disease makes histologic studies in patients with colonic or ileocolonic disease challenging. In the same way, however, the restriction to terminal ileal disease was a strength of the current study because it aimed to examine a concept with clearly positive results. It provides the impetus to expand the work to more extensive disease to determine whether normalization of histology has prognostic value as it does in ileal disease and UC. Fourth, even though the current histologic scale was not assessing severity of inflammation but rather the normality of biopsies, its application and reproducibility have not undergone independent validation. Because there are currently no validated histologic indices in CD, we focused on the absence of an active inflammatory infiltrate to represent the absence of histologic activity. The presence of acute inflammation, which is of clinical significance, is simple and reproducible and is the outcome that has been reported to improve after biologic treatment in previous CD trials.[14,16,17] Fifth, the use of clinical remission as an inclusion criterion for this study also has its own limitations. Patients with both histologic healing and EH may have clinical symptoms, so not all patients with EH would be included in this study. In addition, it is unclear what percentage of patients had an inflammatory relapse because the outcomes analyzed were clinical relapse and need for steroids or medication escalation, which may have occurred in some patients who had worsening symptoms despite no increase in inflammatory burden. Finally, it is noted that biomarker assessment at time of colonoscopy would strengthen this study and that future prospective studies should include calprotectin, C-reactive protein assessment, and perhaps intestinal ultrasound to

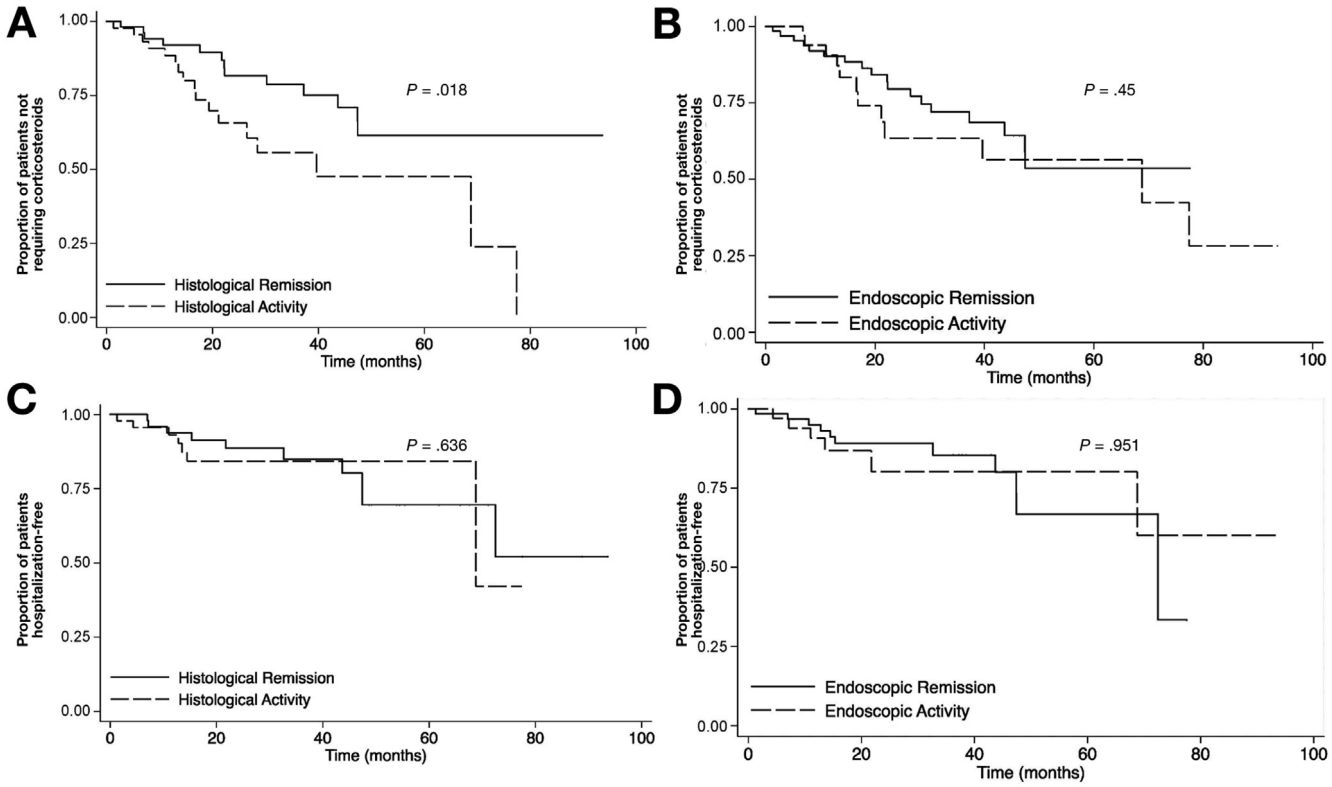


Figure 3. Kaplan-Meier analysis of effect of endoscopic and histologic activity on (*A*) corticosteroid-free survival versus histologic healing, (*B*) corticosteroid-free survival versus endoscopic healing, (*C*) hospitalization-free survival versus histologic healing, and (*D*) hospitalization-free survival versus endoscopic healing.

determine how they compare with histologic and endoscopic assessment alone.

In conclusion, we have demonstrated in patients with CD restricted to the terminal ileum the potential for histologic healing to act as a prognostic marker. It is associated with improved clinical outcomes, less chance of clinical relapse, and decreased need for medication escalation. We propose that histologic assessment of healing should be part of endoscopic assessment in CD. However, there is a clear need for standardized and validated histologic indices in CD, and the prognostic value of their application to CD affecting the colon and rectum requires evaluation.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2019.11.056.

References

1. Pariente B, Cosnes J, Danese S, et al. Development of the Crohn's disease digestive damage score, the Lemann score. Inflamm Bowel Dis 2011;17:1415–1422.
2. Cosnes J, Cattan S, Blain A, et al. Long-term evolution of disease behavior of Crohn's disease. Inflamm Bowel Dis 2002;8:244–250.
3. Solem CA, Loftus EV Jr, Tremaine WJ, et al. Correlation of C-reactive protein with clinical, endoscopic, histologic, and radiographic activity in inflammatory bowel disease. Inflamm Bowel Dis 2005;11:707–712.
4. Rutgeerts P, Diamond RH, Bala M, et al. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. Gastrointest Endosc 2006;63:433–442, quiz 464.
5. Schnitzler F, Fidder H, Ferrante M, et al. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. Inflamm Bowel Dis 2009;15:1295–1301.
6. Rutgeerts P, Feagan BG, Lichtenstein GR, et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. Gastroenterology 2004;126:402–413.
7. Colombel JF, Rutgeerts PJ, Sandborn WJ, et al. Adalimumab induces deep remission in patients with Crohn's disease. Clin Gastroenterol Hepatol 2014;12:414–422 e5.
8. Molander P, Sipponen T, Kemppainen H, et al. Achievement of deep remission during scheduled maintenance therapy with TNFalpha-blocking agents in IBD. J Crohns Colitis 2013;7:730–735.
9. Riley SA, Mani V, Goodman MJ, et al. Microscopic activity in ulcerative colitis: what does it mean? Gut 1991;32:174–178.
10. Bryant RV, Burger DC, Delo J, et al. Beyond endoscopic mucosal healing in UC: histological remission better predicts corticosteroid use and hospitalisation over 6 years of follow-up. Gut 2016;65:408–414.
11. Christensen B, Hanauer SB, Erlich J, et al. Histologic normalization occurs in ulcerative colitis and is associated with

improved clinical outcomes. Clin Gastroenterol Hepatol 2017; 15:1557–1564 e1.
12. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): determining therapeutic goals for treat-to-target. Am J Gastroenterol 2015;110:1324–1338.
13. Mantzaris GJ, Christidou A, Sfakianakis M, et al. Azathioprine is superior to budesonide in achieving and maintaining mucosal healing and histologic remission in steroid-dependent Crohn's disease. Inflamm Bowel Dis 2009;15:375–382.
14. D'Haens G, Van Deventer S, Van Hogezand R, et al. Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: a European multicenter trial. Gastroenterology 1999;116:1029–1034.
15. Bryant RV, Winer S, Travis SP, et al. Systematic review: histological remission in inflammatory bowel disease—is 'complete' remission the new treatment paradigm? an IOIBD initiative. J Crohns Colitis 2014;8:1582–1597.
16. Li K, Friedman JR, Chan D, et al. Effects of ustekinumab on histologic disease activity in patients with Crohn's disease. Gastroenterology 2019;157:1029–1031.
17. Danese S, Sandborn WJ, Colombel JF, et al. Endoscopic, radiologic, and histologic healing with vedolizumab in patients with active Crohn's disease. Gastroenterology 2019; 157:1007–1018.e7.
18. Rubin DT, Huo D, Kinnucan JA, et al. Inflammation is an independent risk factor for colonic neoplasia in patients with ulcerative colitis: a case-control study. Clin Gastroenterol Hepatol 2013;11:1601–1608 e1–e4.
19. Brennan GT, Melton SD, Spechler SJ, et al. Clinical implications of histologic abnormalities in ileocolonic biopsies of patients with Crohn's disease in remission. J Clin Gastroenterol 2017; 51:43–48.
20. Baars JE, Nuij VJ, Oldenburg B, et al. Majority of patients with inflammatory bowel disease in clinical remission have mucosal inflammation. Inflamm Bowel Dis 2012;18:1634–1640.
21. Naini BV, Cortina G. A histopathologic scoring system as a tool for standardized reporting of chronic (ileo)colitis and independent risk assessment for inflammatory bowel disease. Hum Pathol 2012;43:2187–2196.
22. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet 1980;1:514.
23. Jess T, Riis L, Vind I, et al. Changes in clinical characteristics, course, and prognosis of inflammatory bowel disease during the last 5 decades: a population-based study from Copenhagen, Denmark. Inflamm Bowel Dis 2007;13:481–489.
24. Vuitton L, Peyrin-Biroulet L, Colombel JF, et al. Defining endoscopic response and remission in ulcerative colitis clinical trials: an international consensus. Aliment Pharmacol Ther 2017; 45:801–813.
25. Sands BE, Sandborn WJ, Panaccione R, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2019;381:1201–1214.
26. Korelitz BI, Sommers SC. Response to drug therapy in Crohn's disease: evaluation by rectal biopsy and mucosal cell counts. J Clin Gastroenterol 1984;6:123–127.
27. Laharie D, Reffet A, Belleannee G, et al. Mucosal healing with methotrexate in Crohn's disease: a prospective comparative study with azathioprine and infliximab. Aliment Pharmacol Ther 2011;33:714–721.
28. Geboes K, Rutgeerts P, Opdenakker G, et al. Endoscopic and histologic evidence of persistent mucosal healing and correlation with clinical improvement following sustained infliximab treatment for Crohn's disease. Curr Med Res Opin 2005;21:1741–1754.
29. Serban ED. Treat-to-target in Crohn's disease: will transmural healing become a therapeutic endpoint? World J Clin Cases 2018;6:501–513.

Reprint requests
Address requests for reprints to: Britt Christensen, MBBS, MPH, The Royal Melbourne Hospital, Gastroenterology Department, 300 Grattan Street, Parkville, Victoria, Australia 3050. e-mail: britt.christensen@mh.org.au; fax: +61-3-9342-7848.

CRediT Authorship Contributions
Britt Christensen (Conceptualization: Lead; Data curation: Lead; Formal analysis: Lead; Investigation: Lead; Writing – original draft: Lead; Writing – review & editing: Lead)
Jonathan Erlich (Data curation: Equal; Writing – original draft: Equal)
Peter R. Gibson (Conceptualization: Equal; Writing – original draft: Equal; Writing – review & editing: Equal)
Jerrold R. Turner (Validation: Equal; Writing – original draft: Supporting)
John Hart (Validation: Equal; Writing – original draft: Supporting)
David T. Rubin, MD (Conceptualization: Equal; Supervision: Lead; Writing – original draft: Equal; Writing – review & editing: Equal)

Conflicts of interest
These authors disclose the following: Dr Christensen reports personal fees from Gilead, Novartis, Janssen, Takeda, Pfizer, and Abbvie, grants from Janssen, grants from Janssen and Ferring Pharmaceuticals; Dr Gibson reports personal fees from Allergan, Janssen, MSD, Pfizer, Anatara, Atmo Biosciences, Immunic Therapeutics, Novozymes, and Takeda, and grants from MSD; Dr Hanauer reports personal fees from AbbVie, Allergan, Amgen, Arena, Bristol Myers Squibb, Celgene, Celltrion, Genentech, Gilead, GSK, Janssen, Lilly, Merck, Nestle, Novartis, Pfizer, Progenity,Prometheus, Receptos, Salix, Samsung Bioepis, Seres Therapeutics, Takeda, Tigenex, UCB Pharma, VHsquared, grants from AbbVie, Allergan, Amgen, Celgene, Genentech, GSK, Janssen, Lilly, Novartis, Pfizer, Prometheus, Receptos, Takeda, UCB Pharma; Dr Rubin reports personal fees from Abbvie, Abgenomics, Allergan Inc, Boehringer Ingelheim Ltd, Bristol-Myers Squibb, Celgene Corp/Syneos, Check-cap, Dizal Pharmaceuticals GalenPharma/Atlantica, Genentech/Roche, Gilead Sciences, Ichnos Sciences, GlaxoSmithKline Group, Janssen Pharmaceuticals, Lilly, Narrow River Mgmt, Pfizer, Prometheus Laboratories, Reistone, Shire, Takeda, Techlab, Inc, and grants from Abbvie, Genentech/Roche, Janssen Pharmaceuticals, Prometheus Laboratories, Shire, Takeda. The remaining authors have nothing to disclose.

Funding
Supported in part by the Digestive Disease Research Core Center of the University of Chicago (DK42086). Britt Christensen receives support through an "Australian Government Research Training Program Scholarship".

Supplementary Table 1. Criteria Used to Distinguish Histologic Healing From Histologic Activity According to Modifications of the Ileal Global Histological Disease Activity Score[14]

Histologic healing	Histologic activity
None of the following: • Lamina propria infiltration by neutrophils • Epithelial infiltration by neutrophils • Crypt abscesses • Erosions • Ulcerations • Granulomas	Presence of any of the following: • Lamina propria infiltration by neutrophils • Epithelial infiltration by neutrophils • Crypt abscesses • Erosions • Ulcerations • Granulomas

Part 3: Vedolizumab: A new therapy to improve outcomes in IBD

3.1 INTRODUCTION

Part 1 and 2 of this thesis have analysed endoscopic and histologic treatment end-points in IBD. Part 3 of this thesis will explore options on how to achieve these endpoints and improve outcomes in IBD in a novel fashion. Treatment options are limited in IBD and there is a significant therapeutic gap. Anti-TNF therapies were the first biologic available for the induction and maintenance of remission in IBD and are still frequently used today. However, approximately one third of patients will have primary non-response to an anti-TNF therapy and another third will proceed to secondary loss of response.(139) There is therefore a significant need for additional therapeutic options to increase the effectiveness of treatment for our patients.

Vedolizumab is a monoclonal antibody to alph-4 beta-7 integrin which is involved in lymphocyte translocation into the bowel wall. It was approved for use in UC and CD in 2014 with no real-world data available regarding its efficacy.

This part of the PhD will explore the use of this medication in the real-world and its efficacy at inducing and maintaining clinical and endoscopic response and remission in patients with IBD. In addition, in the clinical trials it appeared its onset of action was moderate and increasing efficacy was seen up to week 14 of treatment. This limits the use of this medication in severe disease; we therefore investigated the efficacy and safety of concomitant vedolizumab and a calcineurin inhibitors which are fast acting but have limited long-term use in IBD due to side

effects. Finally, primary sclerosing cholangitis (PSC) is a debilitating disease associated with IBD with limited treatment options. Its pathogenesis has been hypothesized to involve the MADACAM-alhpa-4-beta 7 pathway. We therefore explored whether vedolizumab can improve liver biochemistry in patients with PSC and IBD.

3.2 VEDOLIZUMAB AS INDUCTION AND MAINTENANCE FOR INFLAMMATORY BOWEL DISEASE: 12-MONTH EFFECTIVENESS AND SAFETY

The major clinical trials demonstrate that vedolizumab is effective and safe at improving clinical outcomes in patients with IBD. This study looks at “real-world” data and prospectively follows patients utilizing this treatment. In addition, it explores both endoscopic and histologic outcomes of patients placed on this therapy, outcomes that were mostly ignored in the pivotal clinical trials. We demonstrate that vedolizumab is an effective agent in both UC and CD at inducing clinical and endoscopic response and remission.

Vedolizumab as Induction and Maintenance for Inflammatory Bowel Disease: 12-month Effectiveness and Safety

Britt Christensen, MBBS,[,†,‡] Ruben J. Colman, MD,[*] Dejan Micic, MD,[*] Peter R. Gibson, MBBS,[†] Sarah R. Goeppinger, BSc,[*] Andres Yarur, MD,[*] Christopher R. Weber, MD,[§] Russell D. Cohen, MD,[*] and David T. Rubin, MD[*]*

Background: Vedolizumab is approved for moderate to severe Crohn's disease (CD) and ulcerative colitis (UC). We present prospective, 1-year data of the real-world effectiveness and safety of vedolizumab in inflammatory bowel disease.

Methods: Consecutive patients receiving vedolizumab for treatment of UC or CD with at least 14 weeks of follow-up, regardless of outcome, were included. Patients had clinical activity scores (Harvey-Bradshaw Index [HBI] or Simple Clinical Colitis Activity Index [SCCAI]) and inflammatory markers prospectively measured at baseline and weeks 14, 30, and 52. Clinical response was defined as a reduction ≥3 in HBI or SCCAI, clinical remission as HBI ≤4 or SCCAI ≤2, steroid-free remission as clinical remission without the need for corticosteroids, and mucosal healing (assessed at 6 months) as a Mayo endoscopic subscore of 0 or 1 or CD-SES <3.

Results: A total of 132 patients were included: 61 (45%) male, 94 (71%) with CD, 42 (29%) with UC; 22% and 34% of CD and UC patients, respectively, achieved steroid-free remission by week 14. This increased to 31% in CD patients and plateaued at 35% in UC patients at 12 months. Increasing remission rates to 6 months were seen in patients with CD, but minimal improvements after 3 months of therapy occurred in those with UC. Mucosal healing was achieved in 52% of UC and 30% of CD patients. Most adverse events were minor; 74% remained on vedolizumab at 12 months.

Conclusions: In this real-world study, vedolizumab demonstrated similar efficacy and safety seen in pivotal trials, with sustained clinical response in the majority of patients. Similar rates of response were seen in UC and CD patients.

Key Words: vedolizumab, inflammatory bowel disease, alpha-4 integrin inhibitors, response to therapy, biological therapy

INTRODUCTION

Current treatment goals for patients with Crohn's disease (CD) or ulcerative colitis (UC) include the induction and maintenance of clinical remission of the disease and achievement of mucosal healing.[1] Anti–tumor necrosis factor (TNF)–α therapies are highly efficacious in the treatment of inflammatory bowel disease (IBD), and their availability has dramatically changed the treatment algorithm of IBD. However, despite their effectiveness, alternative therapies to anti-TNFα agents are essential, as a number of patients do not respond to these therapies and their use has been associated with loss of response and adverse effects such as infections and malignancy.[2, 3]

For intestinal inflammatory disease in patients with IBD, anti-integrin therapies target the adhesion and migration of leukocytes across the endothelium of inflamed tissues, and they are effective and safe in placebo-controlled trials.[4–6] Vedolizumab is a selective humanized immunoglobulin G1 monoclonal antibody to $\alpha_4\beta_7$ integrin that modulates gut lymphocyte trafficking[7] and has been approved by regulatory agencies in the United States, Europe, and Australia for use in moderate to severe CD and UC. To date, experience with real-world drug utilization and exposure has been limited to either short-term clinical follow-up, retrospective data, or data failing to report on endoscopic outcomes,[8–13] and there have been no real-world reports of histological outcomes.

Received for publications July 21, 2017; Editorial Decision October 2, 2017.

From the *Inflammatory Bowel Disease Center, University of Chicago Medicine, Chicago, Illinois; †Department of Gastroenterology, Alfred Hospital and Monash University, Melbourne, Australia; ‡Department of Gastroenterology, The Royal Melbourne Hospital, Melbourne, Australia; §Department of Pathology, University of Chicago Medicine, Chicago, Illinois.

Conflicts of interest: David T. Rubin has received institutional grant support from Abbvie, Janssen, and Takeda and served as a consultant for Abbvie, Janssen, Takeda, Amgen, Pfizer, and UCB. Russell D. Cohen has received institutional grant support from Abbvie, Janssen, and Takeda and served as a consultant for Abbvie, Janssen, Takeda, and UCB. Peter R. Gibson has served as consultant or advisory board member for AbbVie, Ferring, Janssen, Merck, Nestle Health Science, Danone, Allergan, Celgene, and Takeda. His institution has received speaking honoraria from AbbVie, Janssen, Ferring, Takeda, Fresenius Kabi, Mylan, and Pfizer. He has received research grants for investigator-driven studies from AbbVie, Janssen, Falk Pharma, Danone, and A2 Milk Company.

Britt Christensen has received travel grants from Takeda.

Supported by: This work was funded in part by the Digestive Diseases Research Core Center and a National Institute of Health Grant (grant number P30DK42086). Britt Christensen receives support through an "Australian Government Research Training Program Scholarship." This is an investigator-initiated study, and has no industry funding.

Address correspondence to: Britt Christensen, MBBS, The Royal Melbourne Hospital, 300 Grattan St, Parkville, Victoria, Australia, 3050 (britt.christensen@mh.org.au).

doi: 10.1093/ibd/izx067
Published online 23 February 2018

Here, we report our real-world vedolizumab experience in a high-volume tertiary care setting with patients who were followed prospectively for up to 52 weeks. Our aim was to characterize the clinical remission and response rates and durability of response while utilizing clinical, endoscopic, and histological outcome measures.

MATERIALS AND METHODS

Study Design and Setting

This was a prospective, single-center observational cohort study of adult patients (age 18 years or older) who commenced vedolizumab for the treatment of IBD at the University of Chicago Medicine IBD Center. Consent was obtained from consecutive patients initiating vedolizumab between its Food and Drug Administration (FDA) approval (May 20, 2014) and August 30, 2015, for the treatment of CD or UC. Patients were eligible to be included if they had a confirmed clinical, endoscopic, or histological diagnosis of CD or UC. Baseline characteristics were extracted from our IBD clinical registry and via chart review. Outcomes were collected prospectively at follow-up at weeks 14, 30, and 52. Patients who had at least 14 weeks of follow-up at University of Chicago Medicine from their first vedolizumab infusion, whether still maintained on vedolizumab or not, were included in the final analysis. Endoscopic reports at our center routinely include documentation of extent and severity of findings as described in the Simple Endoscopic Score for Crohn's disease (SES-CD) and the Mayo Endoscopic Subscore (Mayo score).

Intervention

All patients received vedolizumab according to the FDA-approved dosing regimen for IBD. Under this protocol, 300 mg of vedolizumab is administered via intravenous infusion over 30 minutes. Induction dosing occurred at weeks 0, 2, and 6, with standard maintenance dosing at 8-week intervals thereafter. Concomitant therapy, prior treatment exposure, and changes to the vedolizumab maintenance regimen (dose escalation) were recorded throughout the study duration. Dose escalation of vedolizumab was at the discretion of the treating physician and was commenced in patients with clinically active UC or CD, in those who were steroid dependent despite 8-weekly vedolizumab, and in those with moderate to severe endoscopic disease activity.

Outcomes

Baseline patient and disease characteristics were recorded, and outcomes were evaluated at weeks 14, 30, and 52 of treatment. Clinical disease activity was assessed with the Harvey-Bradshaw Index (HBI) for CD[14] and the Simple Clinical Colitis Activity Index (SCCAI) for UC.[15] Clinical disease activity was defined as an HBI score greater than 4 for CD and a SCCAI score greater than 2 for UC.

The primary outcome measure was steroid-free remission at week 52, which was defined as clinical remission (HBI score of 4 or less for CD and SCCAI score of 2 or less for UC) without oral glucorticoids (prednisolone or budesonide). Secondary outcomes were clinical response and clinical remission at weeks 14, 30, and 52, steroid-free remission at weeks 14 and 30, and rates of surgery and hospitalization during follow-up. Clinical response was defined as a reduction of at least 3 points in either HBI or SCCAI or achievement of clinical remission in those with clinical disease activity at baseline.

It is routine in our center to perform endoscopic assessment of mucosal healing at 6 months after commencement of biological treatment independent of clinical disease activity. Endoscopic response was assessed utilizing the SES-CD for CD[16] or Mayo endoscopic subscore for UC patients[17] in patients who had colonoscopic evaluations at baseline and at 6 months after initiation of vedolizumab. In CD, endoscopic improvement was defined as a reduction in the SES-CD of >50%, and mucosal healing (MH) as an SES-CD score <3. In UC, endoscopic improvement was defined as absolute reduction of ≥1 point in the Mayo endoscopic subscore, and MH as a Mayo endoscopic subscore of 0 or 1. Biopsies in CD and UC were interpreted by an expert gastrointestinal pathologist, and histological inflammation was scored on a 4-point scale as quiescent/normal (0), mild (1), moderate (2), or severe (3).[18] The highest histological score obtained during the examination was used as the representative score, and biopsies were targeted from areas of most active mucosal disease. Histological improvement was defined as an absolute reduction of at least 1 point, and histological remission as a score of 0. Additional available clinical outcomes were collected from standard of care visits, including laboratory values (C-reative protein [CRP] and fecal calprotectin).

At each visit, patients were questioned about adverse events including infections, infusion reactions, or other potential adverse events related to vedolizumab. Adverse events were graded as serious if they resulted in antibiotic treatment, discontinuation of vedolizumab, or hospitalization.

Statistical Methods

Patients were analyzed on an intent-to-treat basis, and cessation of vedolizumab for any reason, including adverse events or loss of response, was considered a treatment failure with failure to achieve clinical remission from that time forward. Descriptive statistics were provided to summarize demographic characteristics. Pre-treatment and post-treatment clinical activity scores and CRP were compared using the paired *t* test, pre-treatment and post-treatment endoscopic activity scores were compared using Wilcoxon signed-rank test, and within-group differences for clinical remission, response, steroid-free remission, and histological outcomes at different time points were determined using McNemar's test. For patients

who withdrew therapy prematurely, the last observation from the time of treatment failure was carried forward. Agreement between mucosal and histological outcomes was determined using the kappa statistic. Continuation of vedolizumab was compared between CD and UC patients, anti-TNFα-naive and non-anti-TNFα-naive patients, and patients on an immunomodulator and those on vedolizumab monotherapy using log-rank test and Kaplan-Meier analysis. Variables associated with week 52 glucocorticoid-free remission were explored using logistic regression. Multivariate analysis was performed on variables with a *P* value <0.2 on univariate analysis using backward step-wise logistic regression. A 2-sided *P* value of 0.05 or less was considered statistically significant. All data analyses were performed using Stata 12.0 (StataCorp, College Station, TX).

Ethical Considerations

The study was approved by the Research Ethics Committee at University of Chicago Hospital (Institutional Review Board: 14–1371). Written informed consent was obtained from all subjects.

RESULTS

Patients

A total of 184 patients were prescribed and received at least 1 vedolizumab infusion between May 2014 and August 2015; 136 patients had reached 14 weeks of follow-up at University of Chicago Medicine, consented to have their data collected, and were included in this analysis. All 136 were followed for at least 14 weeks from their first infusion, 130 had available week 30 clinical outcomes, and 113 patients had week 52 outcomes assessed (Figure 1). The patient baseline characteristics and indications for vedolizumab are shown in Table 1; 66% (n = 90) of patients had clinically active disease (HBI > 4 or SCCAI > 2) at vedolizumab commencement. Other indications for vedolizumab included corticosteroid dependence in 13% (n = 18), moderate/severe endoscopic disease activity in 11% (n = 15), and concerns regarding the safety of prior maintenance therapy in 6% (n = 8; natalizumab, n = 7; tacrolimus, n = 1).

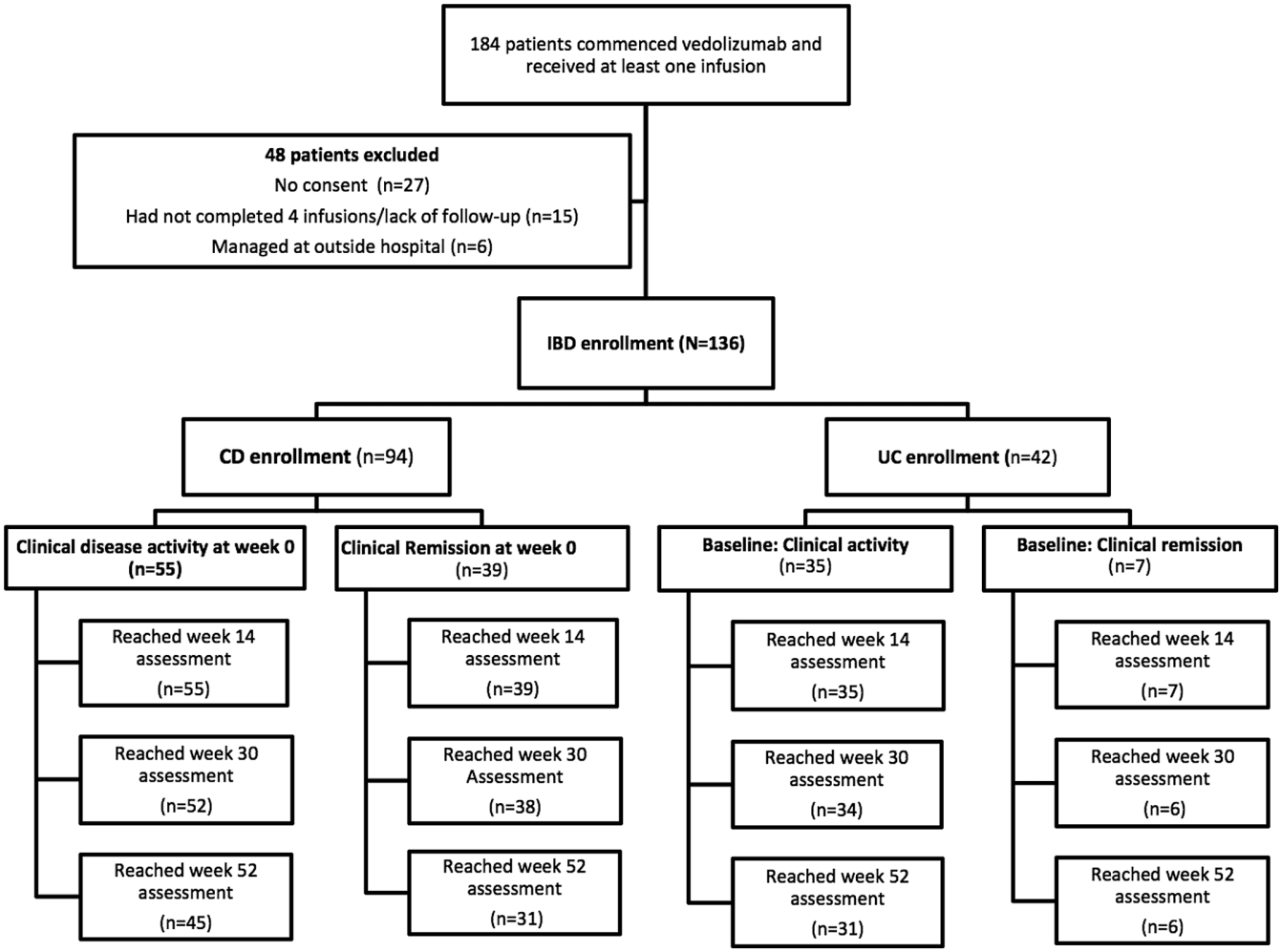


FIGURE 1. Flow chart of patients included in the vedolizumab study.

TABLE 1: Baseline Characteristics

Characteristic	IBD = 136	CD = 94 Patients	UC = 42 Patients
Age, median (IQR), y	39 (28–50)	41 (26–51)	37 (29–45)
Male sex, No. (%)	61 (45)	39 (41)	20 (52)
Body weight, median (IQR), kg	70 (58–84)	68.2 (56–83)	72 (61–88)
BMI, median (IQR), kg/m^2	24 (21–28)	24 (21–2)	24 (22–27)
Current smoker, No. (%)	8 (6)	8 (9)	0 (0.0)
Age at diagnosis, median (IQR), y	22 (15–30)	21 (15–30)	27 (20–35)
Duration of disease, median (IQR), y	12 (7–21)	14 (8–24)	9 (5–16)
Family history of IBD, No. (%)	42 (31)	31 (33)	11 (27)
Past surgery for CD, No. (%)	—	49 (52)	—
Previous *C. difficile* infection, No. (%)	20 (15)	14 (15)	6 (14)
Disease location, Montreal Classification, No. (%)			
	—	L1: 12 (13)	E1: 1 (2)
		L2: 28 (30)	E2: 11 (26)
		L3: 54 (57)	E3: 30 (71)
		L4: 11 (12) P: 34 (36)	—
Clinical disease activity at baseline, No. (%)	—	HBI: <5 (remission): 39 (41) 5–7 (mild): 31 (33) 8–16 (moderate): 20 (21) >16 (severe): 4 (4)	SCCAI: <3 (remission): 7 (17) 3–6 (mild): 22 (52) 7–10 (moderate): 9 (21) >10 (severe): 4 (9)
Hb, median (IQR)	13 (12.0–14.3)	12.7 (11.7–14.3)	13.7 (12.5–14.3)
WBC, median (IQR)	7.3 (5.9–9.5)	7.3 (5.8–9.7)	7(5.9–8.5)
Albumin, median (IQR)	4.2 (3.9–4.5)	4.3 (3.9–4.5)	4.1 (3.9–4.4)
Fecal calprotectin (n = 39), median (IQR)	431 (135–951)	414 (113–876)	474 (237–951)
C-reactive protein (n = 97), mean (SD)	13 (25)	12 (17)	14 (36)
Concomitant medications, No. (%)			
Oral prednisolone	57 (42)	35 (37)	22 (52)
Oral corticosteroid[a]	76 (56)	48 (51)	28 (67)
Thiopurines	35 (26)	27 (29)	8 (19)
Methotrexate	16 (12)	12 (13)	4 (10)
Calcineurin inhibitor	17 (12)	8 (9)	9 (21)
Prior anti-TNF therapy, No. (%)			
Naive	17 (13)	4 (4)	13 (31)
1 failure	40 (29)	22 (23)	18 (43)
>1 failure	79 (58)	68 (72)	11 (26)
Reason for failing anti-TNF therapy, No. (%)			
Primary nonresponse	35 (29)	23 (26)	12 (41)
Secondary LOR	52 (44)	40 (44)	12 (41)
Unacceptable side effects	32 (27)	27 (30)	5 (17)
Indication for vedolizumab, No. (%)			
Clinical disease activity	90 (66)	55 (59)	35 (83)
Clinical remission	46 (34)	39 (41)	7 (17)
Endoscopic disease activity	15 (11)	14 (15)	1 (2)
Safety concerns natalizumab/tacrolimus	8 (6)	7 (7)	1 (2)
Refractory perianal disease	1 (1)	1 (1)	0 (0)
SE from previous medication	3 (2)	1 (1)	2 (5)
Corticosteroid dependence	18 (13)	15 (6)	3 (7)
Budesonide dependence	9 (7)	7 (7)	2 (5)
Systemic corticosteroid dependence	9 (7)	8 (9)	1 (2)
Maintenance postreversal of diversion	1 (1)	1 (1)	0 (0)

BMI = body mass index; LOR = loss of response; SE = side effect; WBC = white blood cells.

[a]Includes budesonide.

Clinical Response and Remission

Crohn's disease

In CD patients with clinical disease activity at baseline (n = 55, 59%), 58% (n = 32) achieved clinical response by week 14, 73% (n = 38) by week 30, and 56% (n = 25) had a clinical response by week 52. Clinical remission was achieved in 38% (n = 21) by week 14, 62% (n = 32) by week 30, and 51% (n = 23) by week 52. Steroid-free clinical remission was achieved in 22% (n = 12) by week 14, 44% (n = 23) by week 30, and 31% (n = 14) by week 52. The increase in clinical remission and steroid-free remission rates was significant between weeks 14 and 30 (P = 0.02), but this cumulative benefit was lost by week 52 (Figure 2A).

Mean HBI significantly improved from a mean baseline score of 8.6 (SD, 4.4) to 5.6 (SD, 3.7) at week 14, 4.7 (SD, 4.2) at week 30, and 4.5 (SD, 4.2) at week 52. There was significant improvement between week 14 and week 52 but not between week 14 and week 30 or week 30 and week 52 (Figure 2B).

Of the 39 CD patients in clinical remission at baseline, 97% (n = 38) maintained remission at week 14, 89% (n = 34) by week 30, and 77% (n = 24) maintained remission at week 52; 53% of patients who were in clinical remission but steroid-dependent achieved corticosteroid-free remission on follow-up.

Overall, 48 patients were receiving glucocorticoids at vedolizumab initiation; 27% (n = 13) were steroid-free and 15% (n = 7) were in steroid-free remission at week 14, 57% (n = 25) were steroid-free and 39% (n = 18) were in steroid-free remission at week 30, and 48% (n = 19) were steroid-free and 33% (n = 13) were in steroid-free remission at week 52.

Ulcerative colitis

In UC patients with clinical disease activity at baseline (n = 35, 77%); 63% (n = 22) of patients achieved clinical response by week 14, 59% (n = 20) at week 30, and 52% (n = 16) at week 52. Clinical remission was achieved in 51% (n = 18) by week 14, 50% (n = 17) at week 30, and 45% (n = 14) were in clinical remission at 1 year. Steroid-free remission was achieved in achieved in 34% (n = 12) at week 14, 35% (n = 12) at week 30, and 35% (n = 11) by 1 year. There was no change in rates of remission or response between week 14 and weeks 30 or 52.

Mean SCCAI significantly improved from a baseline of 6.20 (SD, 2.58) to 3.11 (SD, 2.69) at week 14, 2.94 (SD, 2.79) at week 30, and 2.86 (SD, 2.85) at week 52. There was no significant improvement between week 14 and week 30 or week 14 and week 52 (Figure 2D).

Of the 7 UC patients in remission at baseline, 71% (n = 5) remained in remission at week 14, 50% (n = 3) at week 30, and 83% (n = 5) were in remission at 1 year. Of the 3 patients who were steroid-dependent at baseline, 1 achieved steroid-free remission.

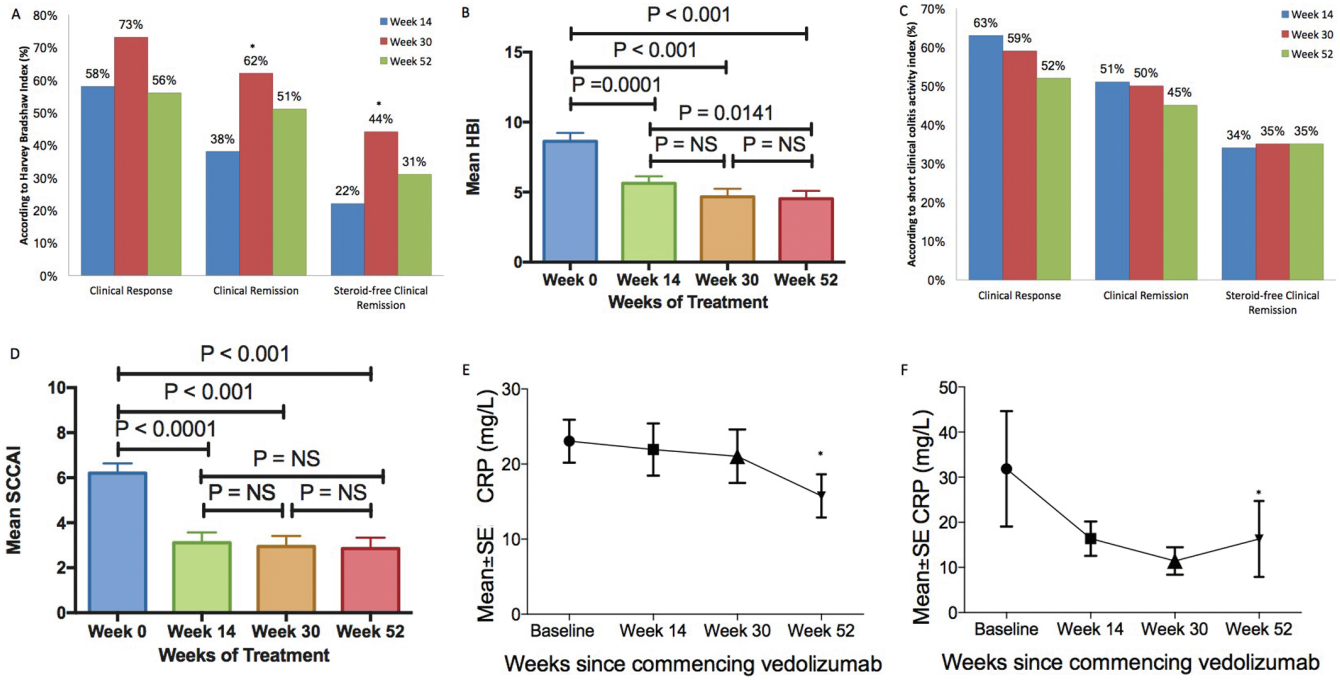


FIGURE 2. Change in clinical and biochemical markers of disease activity after vedolizumab treatment. A, Crohn's disease clinical response and remission rates. *Signifies $P < 0.05$ when comparing efficacy with week 14, determined using McNemar's test. B, Mean (SE) Harvey-Bradshaw Index. Clinical disease activity continued to improve to 52 weeks. C, Ulcerative colitis clinical response and remission rates. D, Mean SCCAI (SE). Clinical activity improved up to week 14 but then appeared to stabilize. E, Mean C-reactive protein (SE) at weeks 0, 14, 30, and 52 in CD patients with elevated CRP at baseline. F, Mean C-reactive protein (SE) at weeks 0, 14, 30, and 52 in UC patients with elevated CRP at baseline.

Overall, 28 UC patients were receiving oral glucocorticoids at vedolizumab initiation; 38% (n = 10) were steroid-free and 21% (n = 6) were in steroid-free remission by week 14, 72% (n = 13) were steroid-free and 22% (n = 6) were in steroid-free remission at week 30, and 35% (n = 9) were steroid-free and 24% (n = 6) were in steroid-free remission at week 52.

C-reactive reactive protein

Of 74 CD patients with serial C-reactive protein measurements, mean CRP decreased from week 0 to week 52 (P = 0.021), but not between week 0 and week 14 or week 0 and week 30. Of 37 patients who had elevated CRP at baseline (CRP > 5), 24% (n = 9) normalized their CRP by week 14, 30% (n = 11) by week 30, and 41% (n = 15/37) by 1 year. In these patients, CRP significantly decreased between week 0 and week 52 (Figure 2E).

Of 38 UC patients with serial CRP measurements, mean CRP did not significantly decrease with treatment; 31% (n = 5/16) of patients with elevated CRP at baseline normalized their CRP at week 14, 38% (n = 6/16) by week 30, and 44% (n = 7/16) at week 52. Change in CRP in these patients significantly decreased between week 0 and week 52 (Figure 2F).

Mucosal Healing

Sixty-six patients (22 UC, 44 CD) had baseline and postinduction endoscopic assessment at a median time of 6 months (interquartile range [IQR], 5–8). There was no difference between frequency of endoscopic assessment in those who continued vs those who ceased vedolizumab therapy (51% who continued vedolizumab to week 52 had endoscopic assessment vs 46% of those who ceased vedolizumab having endoscopic assessment, P = NS) or in those who achieved week 52 steroid-free remission vs those who did not (50% who achieved week 52 steroid-free remission underwent endoscopic assessment vs 56% of those who did not achieve week 52 steroid-free remission under-went endoscopic assessmemt). Endoscopic and histological scores before and after vedolizumab therapy are shown in Figure 3, A–D.

Of 44 patients with CD, 43 had active mucosal inflammation at baseline, of which 40% achieved endoscopic improvement and 30% MH. There was significant improvement in endoscopic activity, with the median SES-CD improving from 12 (IQR, 6–15) to 7 (IQR, 1–12; P < 0.001). Thirty-seven patients with CD had active histological inflammation at baseline and follow-up histology; 57% achieved histological improvement and 22% histological remission. The improvement in histological scores was significant (P = 0.016). There was a strong correlation between mucosal and histological healing, with a 92% agreement between the 2 outcomes (K, 0.79; $P \leq 0.001$). In the setting of mucosal healing, 72% of patients also achieved histological healing, compared with no patients achieving histological healing when endoscopic activity was present. Patients who achieved MH (81% vs 17%, P < 0.001), mucosal improvement (60% vs 20%, P = 0.010), histological improvement (57% vs 8%, P = 0.004), and histological healing (86% vs 26%, P = 0.004) had significantly higher rates of steroid-free remission at 1 year.

Of 22 patients with UC, 21 had a Mayo endoscopic score >0, and 18 patients had active endoscopic activity. Of these, 57% had endoscopic improvement and 52% achieved MH. There was significant improvement of endoscopic activity, with the median Mayo score decreasing from 2 (IQR, 2–3) to 1 (P = 0.011).[1–3] Seventeen patients had active histological inflammation at baseline and follow-up histology; 69% achieved histological improvement and 53% histological remission. The improvement in histological score with treatment was significant (P = 0.013). There was moderate correlation between mucosal and histological healing, with 79% agreement between the 2 outcomes (K, 0.57; P = 0.005). In the setting of mucosal healing, 75% of patients also achieved histological healing and 5% (n = 1) of patients appeared to have endoscopic activity despite histological healing. Week 52 steroid-free remission was greater in patients who achieved mucosal healing (70% week 52 steroid-free remission in those who achieved mucosal healing vs 20% in those who did not achieve mucosal healing, P = 0.025), and histological healing (78% week 52 steroid-free remission in those who achieved histological healing vs 13% in those who did not achieve histological healing, P = 0.0070) was achieved.

Ninety-six percent (n = 24/25) of patients with IBD who achieved MH at postinduction colonoscopy continued treatment with vedolizumab, and no patient required surgery at follow-up. Of the 42 patients who did not achieve MH, 36% ceased vedolizumab therapy and 19% proceeded to colectomy. Patients were more likely to continue on vedolizumab therapy at week 52 when MH was achieved on colonoscopy (96% vs 64%, P = 0.003) (Figure 4A).

Vedolizumab Dose Escalation

Forty-three patients (32%: 30 CD, 13 UC) underwent dose escalation of vedolizumab to Q4 (n = 40) or Q6 (n = 3) weeks; 36 (84%) were dose-escalated for active clinical disease, 5 (12%) for glucocorticoid dependence, and 2 (5%) for nonhealing perianal disease. At median follow-up of 6 months (IQR, 4–7 months) after dose escalation, 24 (56%) patients achieved clinical remission, of which 12 (26%: 8 CD, 4 UC) achieved glucocorticoid-free clinical remission. Eighteen (42%) patients had no clinical response, of which 10 (23%: 6 CD, 4UC) ceased vedolizumab. Of the 5 patients who were steroid-dependent before dose intensification, 2 (40%) achieved steroid-free remission. Neither patient with refractory perianal disease responded to the higher dose of vedolizumab.

Predictors of Response to Vedolizumab

Univariate and multivariate predictors of week 52 steroid-free remission are shown in Table 2.

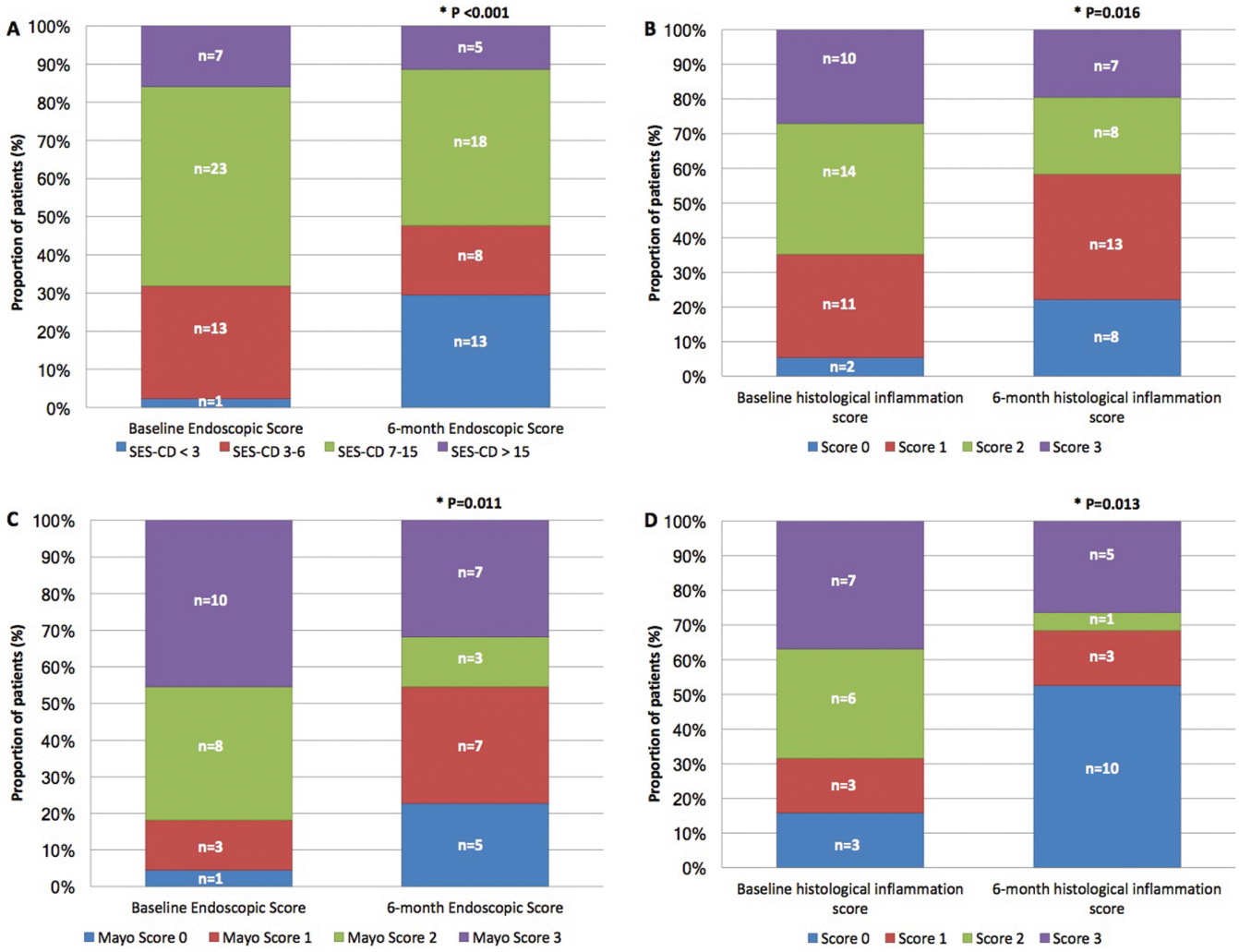


FIGURE 3. Endoscopic and histological scores before and after vedolizumab. Pre-treatment and post-treatment SES-CD scores and Mayo endoscopic subscores were compared using Wilcoxon signed-rank test and within group differences for histological outcomes were compared using McNemar's test. Significance level $P < 0.05$. A, SES-CD scores in CD patients before and after vedolizumab. B, Histological scores in CD patients before and after vedolizumab. C, Mayo endoscopic subscores in UC patients before and after vedolizumab. D, Histological scores in UC patients before and after vedolizumab.

In patients with CD, predictors of week 52 steroid-free remission on univariate analysis were corticosteroid use at baseline (odds ratio [OR], 0.375; 95% confidence interval [CI], 0.14–0.99; $P = 0.049$), lower baseline clinical disease activity score (HBI; OR, 0.84; 95% CI, 0.74–0.95; $P = 0.006$), and achieving week 14 clinical remission (OR, 3.13; 95% CI, 1.15–8.49; $P = 0.026$), week 14 steroid-free remission (OR, 4.34; 95% CI, 1.61–11.69; $P = 0.004$), week 30 clinical remission (OR, 5.44; 95% CI, 1.62–18.25; $P = 0.006$), and week 30 steroid-free remission (OR, 11.25; 95% CI, 3.71–34.11; $P < 0.001$).

Use of concomitant immunomodulators ($P = 0.97$) was not associated with week 52 steroid-free remission. Only 1 patient was anti-TNFα-naive, so this could not be assessed for prediction of response to therapy.

Because collinearity between week 14 and week 30 clinical outcomes was demonstrated, week 14 clinical outcomes and week 30 clinical remission were removed from the multivariate analysis. Multivariate analysis demonstrated that patients with increased clinical disease severity at baseline based on the HBI (adjusted odds ratio [AOR], 0.87; 95% CI, 0.76–0.99; $P = 0.038$) were less likely to achieve week 52 steroid-free remission, and achieving week 30 steroid-free remission (AOR, 9.55; 95% CI, 3.04–29.99; $P < 0.001$) predicted week 52 steroid-free remission.

In patients with UC, predictors of week 52 steroid-free remission included concomitant steroid use when commencing vedolizumab (OR, 0.12; 95% CI, 0.03–0.59; $P = 0.009$), achieving week 14 remission (OR, 13.36, 95% CI, 2.33–76.47; $P = 0.004$), week 14 steroid-free remission (OR, 23.33; 95% CI, 3.98–136.80; $P < 0.001$), week 30 clinical remission (OR, 13.36; 95% CI, 2.33–76.47; $P = 0.004$), and week 30 steroid-free remission (OR, 38.00; 95% CI, 4.53–318.78; $P = 0.001$). Being

TABLE 2: Univariate and Multivariate Predictors for Week 52 Steroid-Free Remission Following Treatment With Vedolizumab

	Crohn's Disease (N = 75)				Ulcerative Colitis (N = 37)			
Variables Predicting Week 52 Steroid-Free Remission	**Univariate Analysis OR (95% CI)**	***P*[a]**	**Multivariate Analysis AOR (95% CI)**	***P*[a]**	**Univariate Analysis OR (95% CI)**	***P*[a]**	**Multivariate Analysis AOR (95% CI)**	***P*[a]**
Age of diagnosis, y	0.98 (0.94–1.01)	0.226			1.04 (0.98–1.11)	0.179[b]		
Age commenced Rx, y	1.00 (0.97–1.03)	0.747			1.02 (0.96–1.08)	0.504		
Sex	1.31 (0.51–3.35)	0.569			2.67 (0.66–10.70)	0.167[b]		
Disease distribution	Colonic vs ileal: 0.87 (0.18–4.14) Ileocolonic vs ileal: 1.04 (0.25–4.40)	0.856 0.956			Extensive vs left-sided/ proctitis: 0.75 (0.16–3.44)	0.711		
Penetrating disease	0.86 (0.29–2.58)	0.790			NA			
Oral steroids at baseline	0.375 (0.14–0.99)	0.049[a]			0.12 (0.03–0.59)	0.009[a]		
On immunomodulator[c]	0.98 (0.39–2.47)	0.970			1.33 (0.30–5.96)	0.706		
Anti-TNF-naive	NA	NA			1.52 (0.37–6.29)	0.565		
Current smoker	0.48 (0.09–2.63)	0.396			0.91 (0.14–5.78)	0.920		
BMI, kg/m^2	1.05 (0.97–1.14)	0.254			1.01 (0.89–1.14)	0.928		
Clinical score (increase in HBI in CD and SCCAI in UC)	0.84 (0.74–0.95)	0.006[a]	**0.87 (.76–.99)**	**0.038[a]**	0.82 (0.66–1.06)	0.139[b]		
Week 14 clinical remission	3.13 (1.15–8.49)	0.026[a]			13.36 (2.33–76.47)	0.004[a]		
Week 14 steroid-free clinical remission	4.34 (1.61–11.69)	0.004[a]			23.33 (3.98–136.80)	< 0.001[a]	**23.33 (3.98–136.90)**	**< 0.001[a]**
Week 30 clinical remission	5.44 (1.62–18.25)	0.006[a]			13.36 (2.33–76.47)	0.004[a]		
Week 30 steroid-free clinical remission	11.25 (3.71–34.11)	<0.001[a]	**9.55 (3.04–29.99)**	**<0.001[a]**	38.00 (4.53–318.78)	0.001[a]		

BMI = body mass index.
[a]Significance level (significant $P < 0.05$).
[b]Incorporated into multivariate analysis as $P < 0.2$.
[c]Patients taking either methotrexate, azathioprine, or 6-mercaptopurine when commencing vedolizumab.

anti-TNFα-naive ($P = 0.565$) and use of concomitant immunomodulators ($P = 0.706$) were not associated with week 52 steroid-free remission.

Because collinearity between week 14 and week 30 clinical outcomes was demonstrated, week 14 clinical remission and week 30 clinical outcomes were removed from the multivariate analysis, which demonstrated that only week 14 steroid-free remission independently predicted week 52 steroid-free remission (AOR, 23.33; 95% CI, 3.98–136.80; $P < 0.001$).

Vedolizumab Discontinuation and Adverse Events

Thirty-five (26%) patients discontinued vedolizumab: 31 patients due to nonresponse and 4 due to side effects. There was no difference between vedolizumab discontinuation rates in patients with CD compared with UC, or among those previously exposed to anti-TNFα therapy or on an immunomodulator (Figure 4, B–D). Nineteen patients (14%: 11 CD, 8 UC) required an IBD-related surgery during the 52 weeks of follow-up. Surgical procedures included colectomies (n = 15, 8 UC), stricturoplasty (n = 1), ileal resection (n = 1), and diverting stoma (n = 22). Four of these patients continued vedolizumab.

Adverse events are summarized in Table 3. Over the 113 patient-years of follow-up, there was a total of 11 (9.7 per 100 person-years of follow-up [PYF]) serious noninfectious events and 17 (12.8 per 100 PYF) serious infectious events. Two patients discontinued treatment because of an infusion-related reaction: 1 described pruritus, swelling of the tongue and throat and rash, and 1 patient described severe flu-like symptoms and fever. Two patients ceased therapy secondary to an allergic-type rash. Seven patients developed new-onset arthropathy,

TABLE 3: Adverse Events on Vedolizumab

Event	Patients With Inflammatory Bowel Disease (n = 136)	Rate of Occurrence: per 100 Person-years of Follow-up
Adverse event: noninfectious		
Headache	3 total	2.7 per 100 PYF
Neurological complaints (n = 3)	3 total -1 paresthesia -1 eye floaters -1 photophobia	2.7 per 100 PYF
Paradoxical skin manifestation	6 total	5.3 per 100 PYF
Pruritis	4 total	3.5 per 100 PYF
GI bleed or drop in hemoglobin	4 total	3.5 per 100 PYF
Athralgia	14 total -7 new-onset arthralgia (1 ceased therapy) -7 worsening of previous arthralgia	12.4 per 100 PYF
Infusion related reaction	2 total	1.8 per 100 PYF
Cancer	2 BCCs No other cancer documented	1.8 per 100 PYF
Constipation	5 total	24.6 per 100 PYF
Perianal disease	10 total -3 new perianal fistula -1 new entero-vaginal fistula -5 worsening perianal fistula -1 worsening hidradenitis	4.4 per 100 PYF
Fatigue	1	0.9 per 100 PYF
Nausea	3	2.7 per 100 PYF
Any serious noninfectious event[a]	11 total	9.7 per 100 PYF
Adverse event: infections		
Enteric infection	8 total -6 *Clostridium difficile*: all responded to oral vancomycin -1 viral enteritis -1 CMV colitis All continued therapy after treatment	7.1 per 100 PYF
Flu or flu-like infection	5 total	4.4 per 100 PYF
URTI	3 total	2.6 per 100 PYF
Sinopulmonary infections	7 total -2 pneumonia -1 pharyngitis -4 sinusitis	6.2 per 100 PYF
Postoperative complications	2 total -1 postoperative stomal infection with muco-cutaneous separation -1 necrotic abdominal wound after creation of diverting stoma	1.8 per 100 PYF
Miscellaneous	4 total -1 hand-foot-mouth dx -1 G-tube site infection -1 herpes zoster -1 UTI	3.5 per 100 PYF
Sepsis	1 total	0.9 per 100 PYF
Any serious infection[a]	17 total	12.8 per 100 PYF

BCC = basel cell carcinoma; CMV = cytomegalovirus; GI = gastrointestinal; URTI = upper respiratory tract infection; UTI = urinary tract infection.
[a]A serious adverse event or infection was defined as any adverse event when leading to treatment interruption, antibiotic therapy, hospitalization, disability or persistent damage, colectomy, or death.

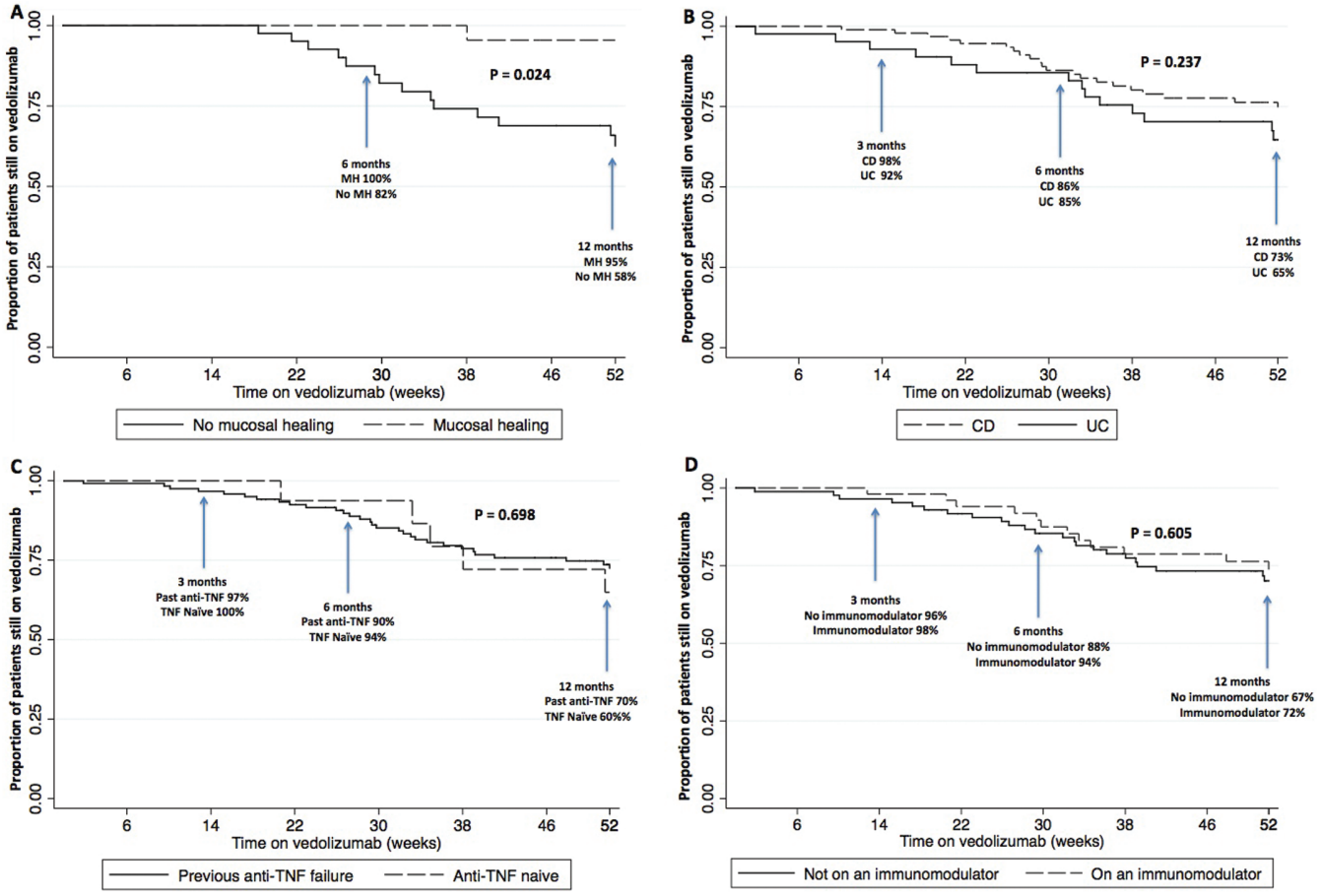


FIGURE 4. Proportion of patients remaining on vedolizumab during follow-up. A, Patients who achieve MH vs those with mucosal inflammation. B, Crohn's disease vs ulcerative colitis. C, Anti-TNFα-naive vs not anti-TNFα-naive. D, On concurrent treatment with immunomodulator vs not on concurrent immunomodulator.

and 1 required discontinuation of treatment. Two patients were diagnosed with basal cell carcinoma, and 4 patients required hospitalization for severe anemia or gastrointestinal bleeding, 2 of which required a blood transfusion. The majority of serious infections were enteric or sinopulmonary; 6 tested positive for *Clostridium difficile* by polymerase chain reaction assay of stool, and all these patients responded to treatment with oral vancomycin and remained on vedolizumab. One patient who was also receiving prednisolone, budesonide, and methotrexate developed *Candida glabrata* and *Staphylococcal epidermitidis* sepsis. This patient proceeded to colectomy but recommenced vedolizumab postoperatively.

DISCUSSION

This study confirms the long-term efficacy of vedolizumab in patients with CD and UC at a tertiary medical center. Currently, there are limited data on vedolizumab outcomes in clinical practice at 1 year.[12, 13] Our study differed from previous reports in that data were collected prospectively and that outcomes in patients with UC and both endoscopic and histological data were included.

We have demonstrated that vedolizumab is effective in UC and CD for inducing clinical response and remission, and for maintaining remission over 1 year. In both UC and CD, vedolizumab achieved steroid-free remission in one-third of patients with active disease at 1 year. This outcome was seen in patients with complex disease phenotypes, and in those who had previously failed biologic therapies. Unique findings for both CD and UC included the achievement of clinical remission in half of the patients at 1 year, maintenance of remission over long-term follow-up of those in clinical remission when commencing treatment, and induction of histological improvement and remission. Mucosal and histological healing was associated with steroid-free remission, and continued vedolizumab therapy and dose escalation were appropriate for some patients.

Our prospective study demonstrates similar efficacy and safety as seen in the pivotal trials,[5, 6] but our rates of remission after induction treatment are higher and similar to those reported in previously published cohort studies of week 14 outcomes.[8–12] This is likely due to the fact that we evaluated postinduction response and remission after 14 rather than 6

weeks, allowing more time for the mechanism of this therapy to effect a clinically measurable change. We found that 58% of CD patients achieved clinical response, 38% achieved clinical remission, and 22% achieved steroid-free remission by week 14. This is similar to previous cohort studies, with the largest cohort, by Amiot et al.,[10] demonstrating response rates of 64%, remission rates of 36%, and steroid-free remission rates of 31% at week 14. In our study, clinical remission and steroid-free remission significantly increased to a maximum level of 62% and 44%, respectively, by week 30 and then plateaued out to 51% and 31% at week 52. Our rates of steroid-free remission were similar to that reported by Dulai et al.[12] of 34% after 12 months of therapy and confirm their findings and those observed in the GEMINI trial, that the effectiveness of vedolizumab appears to be time-dependent in CD, with greatest benefit appearing after 6 months of therapy.[6, 19]

In the current study, UC patients had similar rates of efficacy to CD patients, with 63% achieving clinical response, 51% achieving clinical remission, and 34% steroid-free remission by week 14. Again, this is similar to that reported in previous cohort studies, with Amiot et al.[10] demonstrating response rates of 57%, remission rates of 39%, and steroid-free remission rates of 36% at week 14. Unlike in CD, remission rates in UC patients did not vary significantly after 14 weeks of therapy, with clinical remission and steroid-free remission rates of 50% and 35% at week 30 and 45% and 35% at week 52, respectively. Our study is the first to provide long-term follow-up on UC patients and demonstrates that, unlike CD, there is no increasing benefit beyond 14 weeks of follow-up. This is similar to what was demonstrated in the Gemini clinical trials and has important clinical implications regarding when clinicians should consider alternative mechanisms of management in the nonresponding patient.

Of patients with active endoscopic disease at baseline, 30% of CD and 52% of UC patients achieved MH with vedolizumab therapy. For UC, this is comparable to the results of the pivotal trial, which demonstrated rates of 41% for MH in induction and 54% in maintenance.[5] The pivotal trials for CD did not report MH, but a prospective study reported 30%, and a retrospective study found that 50% of patients with CD achieve MH.[8] The latter study had significant limitations due to the nonstandardized reporting of MH.

In addition to confirming vedolizumab as an effective agent to achieve endoscopic MH in CD patients, this study has uniquely demonstrated in both UC and CD, first, that MH is associated with continued vedolizumab treatment; second, that vedolizumab is effective at achieving histological improvement and remission; and third, that the majority of patients who achieve mucosal healing will also achieve histological healing. This is a clinically significant outcome of interest and of particular importance given the cellular-based mechanism of action of this therapy.

Unique in this study is that we report the benefit of dose escalation of vedolizumab, achieved by decreasing the interval between infusions, in both UC and CD. After a minimum of 3 months of dose escalation, 26% of 43 patients who were dose-escalated for clinical disease activity subsequently achieved glucocorticoid-free clinical remission. This is higher than the 13% reported previously, although reports of clinical response in this retrospective study were high (40%).[12] This finding supports the notion that, similar to our other monoclonal antibodies, increased dosing intervals for this therapy are beneficial in some patients.

Similar to the considerable safety information from the pivotal GEMINI studies and cohort studies,[20] we found vedolizumab to be very safe and associated with a low side effect profile, with the majority of adverse events being related to enteric or sinopulmonary infections or new-onset joint pain. Rarely did this result in the requirement of vedolizumab discontinuation.

The major limitations of our study were the sample size, particularly in regards to predictors of response to vedolizumab, and that, despite the prospective nature of the study, some data were missing from patients due to incomplete follow-up. In addition, given the tertiary setting and the expectation of this therapy arriving in the US market, this patient group likely has more medically resistant disease than in the general community, which may have underestimated the response rates of vedolizumab in less severe patients. Furthermore, as not all patients underwent endoscopic assessment, there is a possibility that the rates of mucosal healing are overestimated secondary to selection bias, with patients deemed primary nonresponders less likely to undergo endoscopic assessment. We believe that this bias is limited as patients may also have been selected to undergo endoscopic assessment when failing vedolizumab and rates of endoscopic assessment were no different in those who achieved week 52 steroid-free remission and in those who did not. In addition, reassuringly, our rates of mucosal healing are similar in UC to the large clinical trials[5] but are less than those reported in retrospective clinical studies for CD.[8] Finally, the histological scale used here to assess histological activity and quiescence has not undergone independent validation.

In conclusion, in our tertiary IBD practice, we demonstrate that vedolizumab is effective, durable, and safe in patients with complex and treatment-resistant CD and UC. We further confirm the efficacy in patients who are anti-TNFα-naive and those who are anti-TNFα-experienced, and we uniquely extend the data demonstrating durable efficacy to UC patients. We provide evidence for the benefit of dose intensification and introduce the role of endoscopic and histological improvement in this population.

ACKNOWLEDGEMENT

Thanks to Dania Saddiqui who helped with patient recruitment and data collection.

REFERENCES

1. Lichtenstein GR, Hanauer SB, Sandborn WJ; Practice Parameters Committee of American College of Gastroenterology. Management of Crohn's disease in adults. *Am J Gastroenterol*. 2009;104:465–83; quiz 464, 484.
2. Roda G, Jharap B, Neeraj N, Colombel JF. Loss of response to anti-tnfs: definition, epidemiology, and management. *Clin Transl Gastroenterol*. 2016;7:e135.
3. Bonovas S, Fiorino G, Allocca M, et al. Biologic therapies and risk of infection and malignancy in patients with inflammatory bowel disease: a systematic review and network meta-analysis. *Clin Gastroenterol Hepatol*. 2016;14:1385–397.e10.
4. Lobatón T, Vermeire S, Van Assche G, et al. Review article: anti-adhesion therapies for inflammatory bowel disease. *Aliment Pharmacol Ther*. 2014;39:579–94.
5. Feagan BG, Rutgeerts P, Sands BE, et al; GEMINI 1 Study Group. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2013;369:699–710.
6. Sandborn WJ, Feagan BG, Rutgeerts P, et al; GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for crohn's disease. *N Engl J Med*. 2013;369:711–21.
7. Soler D, Chapman T, Yang LL, et al. The binding specificity and selective antagonism of vedolizumab, an anti-alpha4beta7 integrin therapeutic antibody in development for inflammatory bowel diseases. *J Pharmacol Exp Ther*. 2009;330:864–75.
8. Vivio EE, Kanuri N, Gilbertsen JJ, et al. Vedolizumab effectiveness and safety over the first year of use in an IBD clinical practice. *J Crohns Colitis*. 2016;10:402–409.
9. Shelton E, Allegretti JR, Stevens B, et al. Efficacy of vedolizumab as induction therapy in refractory IBD patients: a multicenter cohort. *Inflamm Bowel Dis*. 2015;21:2879–885.
10. Amiot A, Grimaud JC, Peyrin-Biroulet L, et al; Observatory on Efficacy and of Vedolizumab in Patients With Inflammatory Bowel Disease Study Group; Groupe d'Etude Therapeutique des Affections Inflammatoires du Tube Digestif. Effectiveness and safety of vedolizumab induction therapy for patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2016;14:1593–1601.e2.
11. Baumgart DC, Bokemeyer B, Drabik A, et al; Vedolizumab Germany Consortium. Vedolizumab induction therapy for inflammatory bowel disease in clinical practice–a nationwide consecutive German cohort study. *Aliment Pharmacol Ther*. 2016;43:1090–1102.
12. Dulai PS, Singh S, Jiang X, et al. The real-world effectiveness and safety of vedolizumab for moderate-severe Crohn's disease: results from the US VICTORY consortium. *Am J Gastroenterol*. 2016;111:1147–155.
13. Stallmach A, Langbein C, Atreya R, et al. Vedolizumab provides clinical benefit over 1 year in patients with active inflammatory bowel disease - a prospective multicenter observational study. *Aliment Pharmacol Ther*. 2016;44:1199–1212.
14. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. *Lancet*. 1980;1:514.
15. Walmsley RS, Ayres RC, Pounder RE, et al. A simple clinical colitis activity index. *Gut*. 1998;43:29–32.
16. Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc*. 2004;60:505–12.
17. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med*. 1987;317:1625–629.
18. Joseph N, Weber C. Pathology of inflammatory bowel disease. In: Baumgart D, ed. *Crohn's Disease and Ulcerative Colitis*. New York: Springer; 2011:287–306.
19. Sands BE, Feagan BG, Rutgeerts P, et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. *Gastroenterology*. 2014;147:618–27.e3.
20. Colombel JF, Sands BE, Rutgeerts P, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. *Gut*. 2017;66:839–51.

3.3 SAFETY AND EFFICACY OF COMBINATION TREATMENT WITH CALCINEURIN INHIBITORS AND VEDOLIZUMAB IN PATIENTS WITH REFRACTORY INFLAMMATORY BOWEL DISEASE

Vedolizumab is an effective therapy for the treatment of moderate to severe UC and CD. However due to its mechanism of action, patient's response can be delayed with improving outcomes up to and even beyond 3 months in patients with UC and CD. These long wait times can preclude its use in patients with steroid-refractory or more severe disease. This paper explores the novel use of vedolizumab utilizing calcineurin inhibitors as a bridge to therapy. The paper examines both the safety and efficacy of this novel treatment protocol and demonstrates that calcineurin inhibitors bridging to vedolizumab is an effective and safe treatment option to add to your arsenal in IBD.

Clinical Gastroenterology and Hepatology 2019;17:486–493

Safety and Efficacy of Combination Treatment With Calcineurin Inhibitors and Vedolizumab in Patients With Refractory Inflammatory Bowel Disease

Britt Christensen,[*,‡,§] Peter R. Gibson,[§] Dejan Micic,[*] Ruben J. Colman,[*] Sarah R. Goeppinger,[*] Olufemi Kassim,[*] Andres Yarur,[*] Christopher R. Weber,[‖] Russell D. Cohen,[*] and David T. Rubin[*]

*Inflammatory Bowel Disease Center, ‖Department of Pathology, University of Chicago Medicine, Chicago, Illinois; ‡Department of Gastroenterology, The Royal Melbourne Hospital, Melbourne, Australia; §Department of Gastroenterology, Alfred Hospital, Monash University, Melbourne, Australia

BACKGROUND & AIMS: **Little is known about the efficacy and safety of induction therapy with calcineurin inhibitors in combination with vedolizumab for patients with Crohn's disease (CD) or ulcerative colitis (UC). We analyzed the outcomes of patients receiving vedolizumab along with calcineurin inhibitors.**

METHODS: **We collected data on patients with CD (n = 9) or UC (n = 11) who began treatment with vedolizumab from May 20, 2014, through March 30, 2015, and received calcineurin inhibitors (tacrolimus or cyclosporin) during the first 12 months of vedolizumab therapy. Clinical activity scores and inflammatory markers were measured at baseline and at weeks 14, 30, and 52 of vedolizumab treatment. Clinical remission was defined as a Harvey–Bradshaw index score ≤4 or short clinical colitis activity index score ≤2; steroid-free clinical remission was defined as clinical remission without corticosteroids.**

RESULTS: **By week 14 of treatment, 44% of the patients with CD and 55% of the patients with UC achieved steroid-free clinical remission; after 52 weeks of treatment, 33% of the patients with CD and 45% of the patients with UC were in steroid-free clinical remission. Seven patients received salvage therapy with a calcineurin inhibitor after primary nonresponse to vedolizumab—1 of the 2 patients with UC and 2 of 5 patients with CD stopped taking the calcineurin inhibitors and achieved steroid-free remission at week 52. In total, 16 patients (59%) received 52 weeks of treatment with vedolizumab. Three serious adverse events were associated with calcineurin inhibitors.**

CONCLUSIONS: **Combination therapy of vedolizumab with either cyclosporin or tacrolimus is effective and safe at inducing and maintaining clinical remission in patients with CD and UC with up to 52 weeks of follow-up evaluation. Larger studies of the ability of calcineurin inhibitors to induce remission in patients on vedolizumab are warranted.**

Keywords: HBI; SCCAI; α4 Integrin; Response to Therapy.

See related article on page 494.

A significant proportion of patients with inflammatory bowel disease (IBD) have steroid-resistant or steroid-dependent disease that requires treatment with biologic agents. However, even when biologic therapies are used, a significant proportion of patients have primary nonresponse or develop secondary loss of response. Potential reasons for this medically resistant disease include mechanistic challenges or inadequate exposure, either owing to underdosing or secondary to loss of serum protein, including monoclonal antibody therapies, through an inflamed gut.[1] Novel strategies that overcome these challenges are needed.

The calcineurin inhibitors tacrolimus and cyclosporin have shown short-term efficacy in Crohn's disease (CD) and ulcerative colitis (UC), are fast-acting, and may be an option in treatment-refractory patients.[2,3] In UC, cyclosporin has been used successfully as a rapidly acting bridge to the slower-acting immunomodulators in

Abbreviations used in this paper: CD, Crohn's disease; HBI, Harvey–Bradshaw index; IBD, inflammatory bowel disease; IV, intravenous; MH, mucosal healing; SCCAI, Short Clinical Colitis Activity Index; TNF, tumor necrosis factor; UC, ulcerative colitis.

Most current article

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2018.04.060

immunomodulatory-naive patients with short-term response rates in acute severe UC of greater than 80%.[2] In CD, reports of rapid response to intravenous (IV) and oral cyclosporin also have been reported with response rates up to 59%.[4,5] Tacrolimus also shows excellent short-term efficacy in IBD with short-term response rates of 61% to 96% in UC,[6] and partial and complete response rates of 39% and 29% in CD.[7] However, despite this evidence, protracted use of calcineurin inhibitors is limited by adverse events including infection, nephrotoxicity, hypercholesterolemia, and hypertension, and long-term prognosis is poor with high relapse rates on cessation of therapy.[4,6,8] Consequently, their use traditionally has been limited in IBD owing to a lack of an appropriate maintenance therapy.

Vedolizumab, a monoclonal antibody to $\alpha_4\beta_7$ integrin that blocks lymphocyte trafficking to gut mucosa,[9] is approved for use in moderate–severe CD and UC and has efficacy in inducing and maintaining remission in both in placebo-controlled trials.[10,11] However, improvement in clinical symptoms may be slow, with increasing response and remission rates shown at least over the course of the first 10 weeks.[10–12] Accordingly, the US prescribing guidelines suggest a minimum of 14 weeks of therapy before clinicians evaluate its efficacy. In addition, as observed with other monoclonal antibodies,[1] vedolizumab treatment in patients with severe disease theoretically is associated with increased drug loss and lower drug levels owing to protein loss via a leaky gut and, hence, reduced response may be associated with more severe disease. Indeed, patients with severe disease are at increased risk of failing biological therapy.[13]

The use of combination therapy in patients with IBD commenced on biologic therapies, most commonly achieved by using immunomodulator and anti–tumor necrosis factor (TNF) therapy, is associated with increased remission rates, increased anti-TNF drug levels, and reduced loss of response.[14,15] There are reports of patients with IBD tolerating concomitant anti-TNF and low doses of tacrolimus after liver transplant for primary sclerosing cholangitis.[16] However, because the combined immunosuppressive properties at therapeutic doses of these 2 agents can lead to adverse events including death,[17] concomitant administration to induce disease remission has been discouraged.

Because vedolizumab has impressive safety data, we hypothesized that combination therapy with a calcineurin inhibitor would not pose the same risks as combination therapy with a calcineurin inhibitor and (systemically active) anti-TNF agent. However, patients with exposure to calcineurin inhibitors were excluded from vedolizumab clinical trials and the success and safety of inducing remission and bridging from a calcineurin inhibitor to vedolizumab in IBD remains unknown. This study aimed to assess the short- and long-term responses, remission, steroid-free remission, and adverse event rates in patients treated concomitantly with a calcineurin inhibitor and vedolizumab, using prospectively collected data.

What You Need to Know

Background

Patients with exposure to calcineurin inhibitors have been excluded from vedolizumab clinical trials. We investigated the success and safety of induction therapy with a calcineurin inhibitor followed by longer-term treatment with vedolizumab in patients with CD or UC.

Findings

More than one third of patients with active CD or UC who received treatment with a combination of tacrolimus or cyclosporin along with vedolizumab achieved clinical remission without the need for concomitant steroid or calcineurin inhibitor treatment within 1 year. There were few side effects.

Implications for patient care

This was a small study. Initial treatment with either cyclosporin or tacrolimus is safe for patients who subsequently receive treatment with vedolizumab, which induces and maintains clinical remission in patients with severe IBD.

Methods

Study Design

Patients with established IBD who commenced vedolizumab at The University of Chicago Medicine Inflammatory Bowel Disease Center were invited to be included in the prospective University of Chicago Vedolizumab Database, part of the larger University of Chicago IBD Research Database. Among consenting patients, baseline patient and disease characteristics were recorded, and patient outcomes were evaluated prospectively at weeks 14, 30, and 52 of vedolizumab treatment. Clinical remission and response rates were assessed with the Harvey–Bradshaw Index (HBI)[18] for CD patients and the Simple Clinical Colitis Activity Index (SCCAI) for UC patients.[19]

We performed a subanalysis on patients who commenced vedolizumab treatment between its US Food and Drug Administration approval (May 20, 2014) and March 30, 2015, who received concomitant calcineurin inhibitors during the first 12 months of vedolizumab therapy. Patients were eligible if they had a confirmed clinical, endoscopic, or histologic diagnosis of CD or UC, had at least 3 months of follow-up evaluation after commencement of concurrent calcineurin inhibitor and vedolizumab therapy, and were followed up for 12 months from their first vedolizumab infusion.

Calcineurin inhibitors were commenced at the discretion of the primary treating physician in patients with refractory IBD. These included patients with severely active UC or CD despite high-dose oral or IV prednisolone and/or anti-TNF therapy, patients with

acute severe UC with the aim of bridging to vedolizumab, or patients who required a steroid-sparing agent. Baseline and outcome measures were extracted from the University of Chicago IBD Research Database. The University of Chicago Institutional Review Board approved the study (Institutional Review Board: 14-1371).

Intervention

Standard protocols for calcineurin inhibitor therapy induction dosing were used. Tacrolimus was initiated at 0.05 mg/kg twice daily. Dosage was adjusted according to trough level, aiming for a blood concentration of 10 to 15 ng/mL, clinical response and side effects. Trough levels, blood counts, and renal and liver profiles were measured 48 hours after treatment initiation, 1 to 2 weeks later, and every 2 to 3 weeks until steady-state trough levels were reached, after which laboratory data were checked monthly. Cyclosporin was administered intravenously at an initial dose of 2 mg/kg/d. Serum cyclosporin concentrations were measured every other day and dose was adjusted to a target level of 300 to 400 ng/mL. Intravenous therapy was continued for 5 to 7 days (up to 14 days) with dose adjustments based on C-reactive protein level, clinical symptoms, blood pressure, and renal function. Transition to oral therapy was performed when patients had improved clinical disease activity. Oral therapy was commenced at double the IV dose and was adjusted to reach similar trough concentrations as IV therapy. Outpatient cyclosporin levels, renal function, and liver function were monitored weekly.

All patients initiating calcineurin inhibitors received trimethoprim/sulfamethoxazole 800 mg/160 mg 3 times weekly for prophylaxis against *Pneumocystis jirovecii*. This was continued while patients remained on combination treatment with corticosteroids.

Calcineurin inhibitors were weaned after at least 6 weeks of therapy in patients who achieved clinical remission and, at the discretion of the primary treating physician, in patients who had significant clinical improvement. The initial calcineurin inhibitor dose was decreased by 50% for 2 weeks before discontinuation.

All patients received 300 mg of vedolizumab intravenously at weeks 0, 2, and 6, with maintenance dosing every 8 weeks thereafter as per standard-of-care guidelines and according to the Food and Drug Administration–approved dosing regimen for IBD. In patients commencing a calcineurin inhibitor as the induction agent, the first dose of vedolizumab was administered after initiation of calcineurin therapy.

Steroids were weaned at the discretion of the physician and baseline immunomodulators were continued throughout the study period.

Outcomes

Clinical remission was defined as HBI $\leq$ 4 or SCCAI $\leq$ 2, clinical response was defined as a reduction of $\geq$3 points in the HBI or SCCAI, and steroid-free clinical remission was defined as clinical remission without concomitant systemic corticosteroids.

When available, the endoscopic response was assessed using the Short Endoscopic Score[20] for CD patients or the Mayo endoscopic subscore[21] for UC patients after $\geq$3 months treatment with vedolizumab. Mucosal healing (MH) was defined by Short Endoscopic Score for CD score of $<$3 or resolution of all ulcers in CD, and in UC as a Mayo endoscopic subscore of 0/1.

At each visit patients were questioned about adverse events including infections, infusion reactions, or other potential adverse events related to vedolizumab. Adverse events were graded as serious if they resulted in antibiotic treatment, discontinuation of vedolizumab, or hospitalization.

Statistical Methods

Patients were analyzed on an intent-to-treat basis and cessation of vedolizumab for any reason was considered treatment failure. For patients who withdrew prematurely, the last observation was carried forward. Descriptive statistics were summarized using medians and interquartile ranges or means and SD and/or SEM for continuous variables. Categoric variables were expressed as a percentage and number of cohort. Univariate analysis was conducted using the chi-square or the Fisher exact tests for equal proportion. The Wilcoxon rank-sum test was used where appropriate. Pretreatment and post-treatment clinical activity scores were compared using the paired *t* test. A 2-sided *P* value $\leq$.05 was considered statistically significant. All data analyses were performed using Stata 12.0 (Stata Corp, College Station, TX).

Results

Of 31 patients who required concomitant tacrolimus or cyclosporin within the first 12 months of initiating vedolizumab therapy, 27 were included in the final analysis: 2 were excluded because they were on tacrolimus secondary to liver transplant and 2 were excluded because of inadequate documentation/follow-up evaluation (Figure 1). Baseline characteristics and indications for vedolizumab are shown in Table 1. A total of 96% (n = 26) failed therapy with at least 1 anti-TNF agent previously.

Co-induction With Vedolizumab and a Calcineurin Inhibitor

A calcineurin inhibitor was initiated before or at the time of commencing vedolizumab in 9 patients with CD (5 tacrolimus, 4 cyclosporin) and 11 patients with UC (4 tacrolimus, 7 cyclosporin). Fifteen patients (9 CD and 6 UC) were hospitalized at induction and failed intravenous

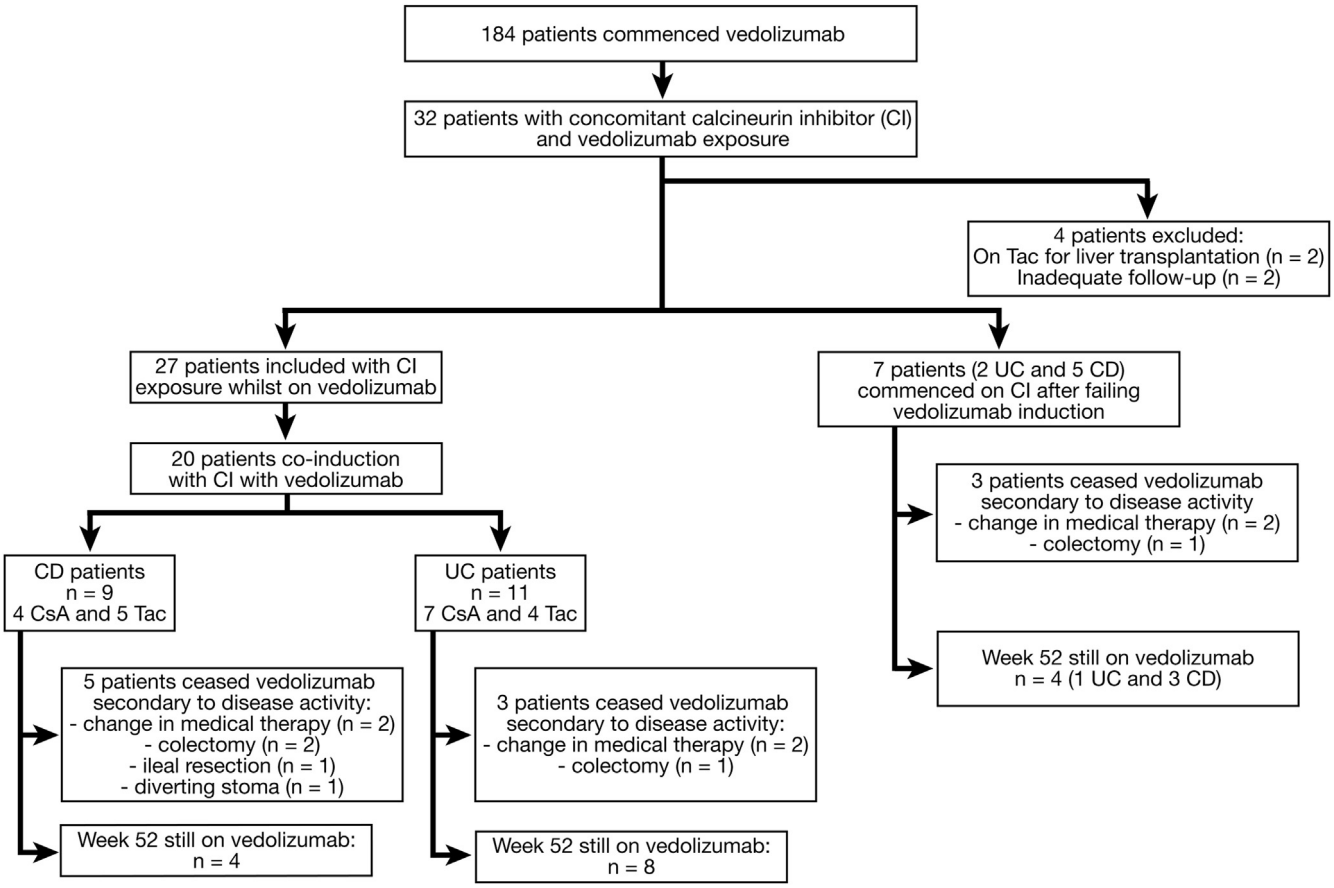


Figure 1. Patient flow chart. CsA, cyclosporin; CI, calcineurin inhibitor; Tac, tacrolimus.

steroids requiring salvage therapy with a calcineurin inhibitor (10 intravenous cyclosporine, 5 tacrolimus). The median duration of hospital admission was 10 days (IQR, 7–12 d). Patients commenced vedolizumab at a median of 30 days (IQR, 19–77 d) after their first dose of calcineurin inhibitor. All patients ceased the calcineurin inhibitor at 12 months. The average duration of combination therapy with a calcineurin inhibitor and vedolizumab was a median of 64 days (IQR, 42–87 d).

Crohn's Disease

As shown in Figure 2*A*, 67% (n = 6), 67% (n = 6), and 33% (n = 3) of 9 patients with CD had a clinical response, and 5, 4, and 3 of 9 patients achieved remission at weeks 14, 30, and 52, respectively. A total of 67% (n = 6) of patients weaned from calcineurin inhibitors by week 14, of whom 2 achieved calcineurin inhibitor–free clinical remission. Four patients were still on calcineurin inhibitors at week 30, 1 of whom had recommenced tacrolimus at week 14 after worsening disease activity after cessation at week 10. This patient eventually proceeded to surgery for treatment of refractory disease. By week 52 all patients were off calcineurin inhibitors. Thus, calcineurin inhibitor–free remission was achieved in 33% of patients at week 52.

All 9 CD patients were on prednisolone at baseline at a median dose of 40 mg/d (IQR, 20–50 mg/d). A total of 67% (n = 6), 67% (n = 6), and 100% (n = 9) were steroid-free and 4, 4, and 3 of 9 were in steroid-free clinical remission at weeks 14, 30, and 52, respectively.

The mean HBI significantly improved from a baseline score of 11.6 (SEM, 2.0) to 5.7 (SEM, 2.3) at week 14 ($P = .020$), and remained stable at 6.6 (SEM, 2.2) at week 30 and at 6.7 (SEM, 2.2) at week 52 ($P = .020$) (Figure 2*B*). In patients still on vedolizumab, the mean HBI was 3.0 (SEM, 1.29) at 12 months.

Ulcerative Colitis

As shown in Figure 2*C*, clinical response was achieved in 73% (n = 8), 82% (n = 9), and 64% (n = 7), and clinical remission was achieved in 55% (n = 6), 45% (n = 5), and 45% (n = 5) at weeks 14, 30, and 52, respectively. A total of 55% (n = 6) of patients were weaned from calcineurin inhibitors by week 14. Only 1 patient remained on a calcineurin inhibitor at week 30 and all patients were off calcineurin inhibitors by week 52. Thus, calcineurin inhibitor–free remission was achieved in 45% at week 52.

A total of 55% (n = 6) of patients were on corticosteroids at baseline at a median dose of 40 mg/d (IQR,

Table 1. Baseline Characteristics

Characteristic	IBD (N = 27)	CD (N = 14)	UC (N = 13)
Age, *y*, median (IQR)	33 (24–39)	31 (24–36)	29 (25–39)
Male sex, n (%)	13 (48)	6 (43)	7 (54)
Current smoker, n (%)	4 (15%)	1 (7%)	3 (23%)
Age at diagnosis, *y*, median (IQR)	21 (16–29)	18 (15–21)	29 (21–34)
Duration of disease, *y*, median (IQR)	7(4–20)	5 (2–8)	18 (6–23)
Family history of IBD, n (%)	10 (37%)	4 (29%)	6 (46%)
Past surgery for CD, n (%)		6 (22%)	
Disease location: Montreal Classification		L1: 1 (7%) L2: 5 (36%) L3: 8 (57%) L4: 1 (8%) P: 2 (17%)	E1: 1 (2%) E2: 11 (26%) E3: 30 (71%)
Clinical disease activity at baseline		HBI <5:2 (14%) 5–7:6 (43%) 8–16:4 (29%) >16:2 (14%)	SCCAI <3:0 (0%) 3–6:3 (23%) 7–10:5 (38%) >10:5 (38%)
Concomitant medications with vedolizumab, n (%)			
Glucocorticoids	21 (78%)	12 (86%)	9 (69%)
Thiopurines	7 (26%)	4 (29%)	3 (23%)
Methotrexate	2 (7%)	0 (0%)	2 (15%)
Prior anti-TNF therapy			
Naive	1 (4%)	0 (0%)	1 (8%)
1 failure	6 (22%)	0 (0%)	6 (46%)
>1 failure	20 (74%)	14 (100%)	6 (46%)

CD, Crohn's disease; IBD, inflammatory bowel disease; IQR, interquartile range; TNF, tumor necrosis factor; UC, ulcerative colitis.

25–50 mg/d). Of these, 100% (n = 6), 83% (n = 5), and 100% (n = 6) were steroid-free, but only 2, 0, and 2 were in steroid-free clinical remission at weeks 14, 30, and 52, respectively. Overall steroid-free remission was achieved in 55% (n = 6), 36% (n = 4), and 45% (n = 5) at weeks 14, 30, and 52, respectively.

The mean SCCAI decreased significantly from 8.2 (SEM, 0.82) at baseline to 2.0 (SEM, 0.65) at week 14 ($P < .001$), and then remained stable at 2.6 (SEM, 0.62) at week 30 and 1.8 (SEM, 0.58) at week 52 (Figure 2*D*). In patients still on vedolizumab, the mean SCCAI was 1.6 (SEM, 1.4) at 12 months.

Mucosal Healing After Co-induction

Of patients with a baseline and postinduction endoscopic assessment at a median of 5 months (range, 3–9 mo), MH was achieved in 1 of 7 with CD and in 4 of 7 with UC. Week 52 response rates were higher when MH was achieved (100% clinical response if MH was achieved vs 11% if no MH was achieved; $P = .003$) and week 52 steroid-free remission rates trended higher with MH (75% steroid-free remission if MH was achieved vs 25% if no MH was achieved; $P = .052$). MH was associated with vedolizumab continuation (100% vedolizumab continuation if MH was achieved vs 33% if no MH was achieved; $P = .016$).

Calcineurin Inhibitor Use in Patients Failing Induction With Vedolizumab

Seven patients (5 CD and 2 UC) commenced calcineurin inhibitor therapy after primary nonresponse to vedolizumab immunotherapy. Three patients (2 UC and 1 CD) commenced within 3 months of initiating vedolizumab. Two UC patients were hospitalized for IV corticosteroids and cyclosporin in the setting of clinical symptoms despite 40 mg prednisolone and vedolizumab for 3 months. One patient failed induction therapy with cyclosporin and proceeded to colectomy. The other patient weaned from cyclosporin after 51 days and remained in steroid- and calcineurin-free clinical remission at 12 months.

Tacrolimus salvage therapy was used in 5 patients with CD; 1 at 3 months and 4 at 6 months of vedolizumab therapy. All patients were steroid-dependent, 3 patients were on vedolizumab every 4 weeks and 2 patients required hospitalization for IV steroids with failure to achieve remission. One patient was changed to vedolizumab every 4 weeks at the time of commencing tacrolimus.

The mean duration of tacrolimus was 85 days (SD, 53 d). Of the 5 CD patients, 2 achieved steroid- and calcineurin inhibitor–free remission at 12 months and continued vedolizumab. One patient continued to have disease activity at 12 months despite tacrolimus and proceeded to loop ileostomy with no complications, with subsequent maintenance with vedolizumab monotherapy. Two patients ceased vedolizumab: 1 patient did not respond to tacrolimus and had a surgical resection, and the other patient ceased for inability to wean from tacrolimus despite response.

Vedolizumab Discontinuation and Adverse Events

Vedolizumab was discontinued for nonresponse after a median of 6 months (IQR, 6–7 mo) in 41% of patients (7 CD and 4 UC). Three patients with CD and 2 with UC were switched to a different therapeutic agent, and 6 patients proceeded to surgery with 4 colectomies (2 UC and 2 CD), 1 ileal resection (CD), and 1 diverting stoma (CD). There were no intraoperative complications. Postoperatively, 1 patient had delayed perineal healing after total proctocolectomy and 1 developed a mucocutaneous separation of the stoma, which subsequently healed with antibiotics. There were no other surgical complications.

Adverse events are summarized in Table 2. In addition to postoperative complications, there were 3 serious events in 2 patients. One patient described an infusion-related reaction with mild swelling of the tongue. This

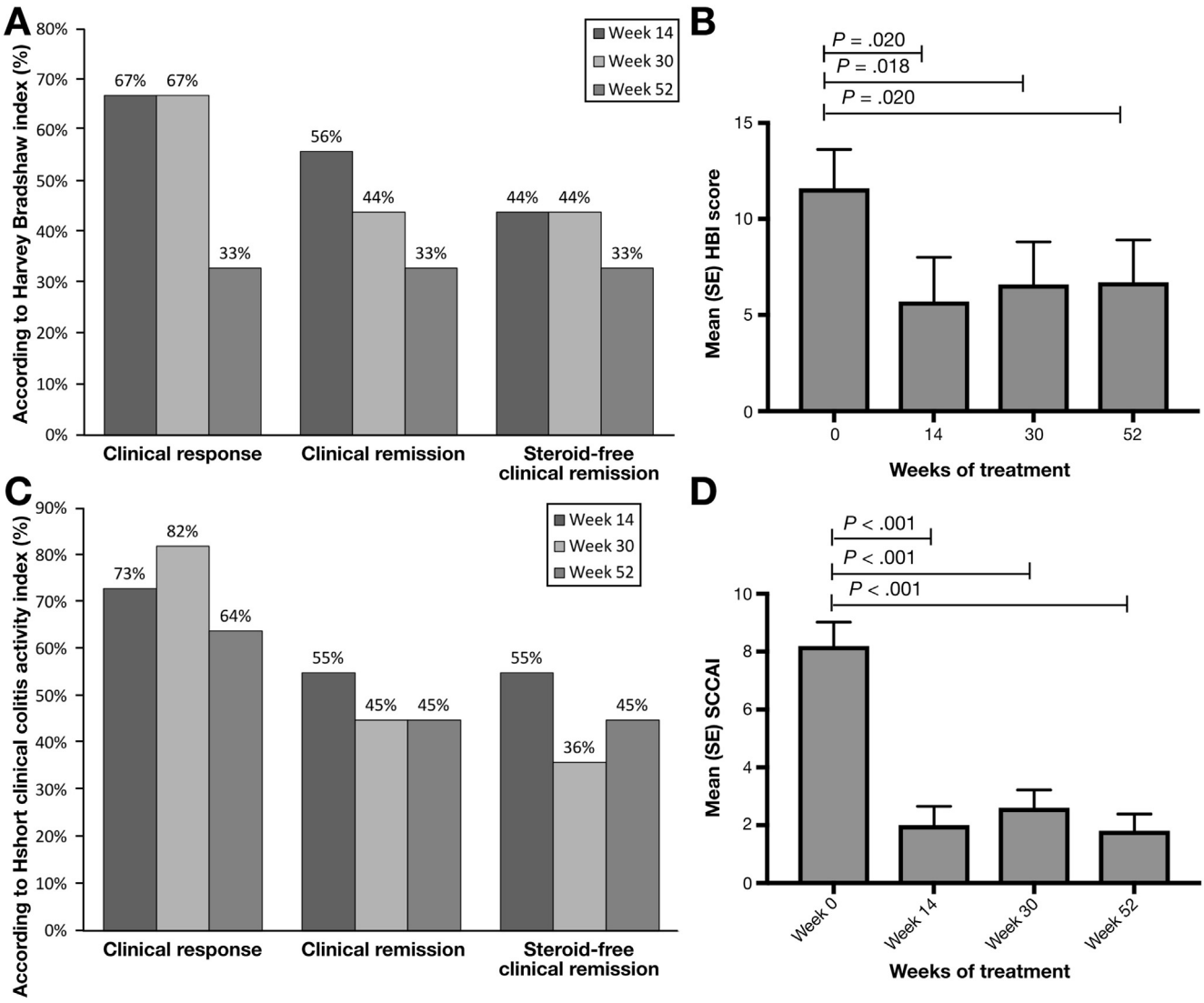


Figure 2. Change in markers of disease activity after vedolizumab. (*A*) Clinical response and remission rates and (*B*) mean (SEM) HBI in patients with CD. (*C*) Clinical response and remission rates and (*D*) mean (SEM) SCCAI in patients with UC.

patient had severely active disease, tested positive for *Clostridium difficile* and cytomegalovirus colitis with inclusion bodies on colon biopsy, ceased therapy, and proceeded to a colectomy. One patient developed viral gastroenteritis that required hospitalization, but recovered with conservative management.

Side effects possibly attributed to calcineurin inhibitor toxicity were minimal. One patient discontinued tacrolimus after 1 month owing to gum sensitivity, which resolved after tacrolimus cessation. Additional side effects that did not result in discontinuation included tremor (n = 2), migraine (n = 1), paresthesia (n = 1), leg cramps (n = 1), and fatigue (n = 1).

Discussion

In this prospective observational study, we show the efficacy and safety of a novel treatment approach for some patients with IBD: use of a calcineurin inhibitor in conjunction with vedolizumab. This strategy provides new options for many different clinical scenarios including failed corticosteroid therapy, failed or intolerance to thiopurine therapy, and hospitalized adults with severe IBD in whom we are concerned for gut loss of protein-based therapies and inadequate exposure. Calcineurin-based treatment also provides an induction option as a bridge to vedolizumab, to overcome the slower onset of action described for this biologic agent.

We show that using a combination of tacrolimus or cyclosporin with vedolizumab in patients with active IBD achieves steroid- and calcineurin inhibitor–free clinical remission in more than one third of patients at 1 year. The strategy also was effective when the induction therapy was introduced to patients who had failed vedolizumab monotherapy. Similar to previous reports of calcineurin inhibitor induction for UC and CD,[2,3] high initial response and remission rates were observed. Although these rates decreased over the follow-up period, 33% of CD and 45% of UC patients were in

Table 2. Adverse Events on Vedolizumab

Event	Patients with IBD (n = 27)
Adverse event: noninfectious	
Neurologic complaints (n = 4)	4 total: 1 paresthesia, 1 migraine, 2 mild tremor
Pruritis	1 total
Rheumatologic	2 total: 1 new-onset arthralgia, 1 leg cramps
Infusion-related reaction	1 infusion reaction[a]
Cancer	No cancer documented
Constipation	2 total
Perianal disease	1 total: worsening perianal fistula
Fatigue	1 total
Orofacial complications	1 total: gum sensitivity
Any serious noninfectious event[a]	1 total
Adverse event: infection	
Enteric infection	2 total: 1 viral enteritis,[a] 1 cytomegalovirus and *C difficile* colitis colectomy[a]
Sinopulmonary infections	1 sinusitis
Postoperative complications	2 total: 1 delayed perineal healing, 1 mucocutaneous separation of stoma
Miscellaneous	1 urinary tract infection
Any serious infection[a]	4 total

IBD, inflammatory bowel disease.
[a]A serious adverse event or infection was defined as any adverse event when leading to treatment interruption, antibiotic therapy, hospitalization, disability or persistent damage, colectomy, or death.

steroid-free remission at 1 year, which is similar to rates seen in the pivotal vedolizumab trials GEMINI 1 and 2,[10,11] despite the fact that this patient cohort likely represents a more treatment-resistant group. In addition, SCCAI and HBI scores improved significantly by week 14 in both CD and UC, and this improvement was maintained over 52 weeks despite patients ceasing corticosteroids and the calcineurin inhibitor. In fact, in our patient cohort, all patients who continued on vedolizumab were off corticosteroids and calcineurin inhibitors by 12 months. This suggests that calcineurin inhibitor therapy may be used as a bridge to vedolizumab in patients with moderately to severely active disease as well as a steroid-sparing therapy.

Endoscopically, 1 of 7 CD and 4 of 7 UC patients achieved MH. For UC, this is comparable with the results of the pivotal GEMINI 1 trial, which showed MH rates in initial responders of 54% in maintenance.[10] The pivotal GEMINI 2 trials for CD did not report on MH, but a real-world study showed a higher rate of 30% for MH.[22] MH was associated with continuation of vedolizumab ($P = .016$) and week 52 steroid-free remission rates trended higher when MH was achieved ($P = .052$). These findings support those from the anti-TNF clinical trials regarding the positive prognostic role that MH has after induction treatment on longer-term outcomes and are similar to the findings reported with standard vedolizumab therapy.[23]

All patients in our study were treatment-refractory and almost all had previously failed anti-TNF therapy. On this basis, it would be anticipated that few patients would have responded to re-induction therapy with standard anti-TNF therapy, but proof that the strategy of calcineurin inhibitors bridging to vedolizumab is more efficacious than re-treatment with a drug that had previously failed can be addressed definitively only by a randomized controlled trial. Whether such a study is ethical is dubious.

In patients who have primary nonresponse to vedolizumab monotherapy, despite adequate time for onset of action, a short duration of therapy with calcineurin inhibitors successfully salvaged patients who continued vedolizumab. At 6 months after calcineurin inhibitor salvage, 3 of 7 patients achieved steroid-free and calcineurin inhibitor–free clinical remission. Although the follow-up period was short, treatment options were limited in this patient cohort. These results therefore are promising and suggest that calcineurin inhibitor salvage may be a strategy to induce remission in this patient cohort, although clearly longer-term studies are required to determine the durability of this response. The mechanism of this response is not clear but there may be synergy of the different anti-inflammatory mechanisms of action or simply an additive benefit, followed by a more durable response to vedolizumab.

One hazard of multi-agent immunomodulator therapy in patients with IBD has been infection and other adverse events related to profound immune suppression.[8,24] In fact, combination therapy with a calcineurin inhibitor and anti-TNF therapy has been relatively contraindicated owing to severe infection risk and even mortality.[17] However, the predominantly gut-selective effect of vedolizumab on immune reactivity and minimal side effects and infection risk associated with its use as a monotherapy may imply that the addition of a systemically acting agent with broad immune-suppressing effects would not carry infective and other complications greater than that of the individual drugs. Indeed, no significant toxicity was observed in our series despite the fact that many patients were on quadruple immunosuppressive therapy, at least initially.

The major shortcoming of our study was the small sample size, which makes it more difficult to detect uncommon adverse effects and to define predictors of response to vedolizumab. In addition, despite the prospective nature of the study, some data were missing from patients. Finally, when vedolizumab first received regulatory approval in May 2014, many patients with very complex disease received it as end-of-the-line salvage therapy at our referral center. Therefore, this patient group most likely represents a population with more severe disease than might normally be placed on this therapy in the general community.

In conclusion, this study describes a novel treatment regimen for patients with moderate to severe UC or CD, and one that may be particularly useful in patients who are steroid-refractory or who have already failed an anti-TNF treatment. Cyclosporin and tacrolimus successfully

and rapidly induced response and remission in both CD and UC. We propose that this strategy can act as a bridge to maintenance vedolizumab treatment when applied to vedolizumab initiation or when there has been primary nonresponse to vedolizumab. On long-term follow-up evaluation, vedolizumab was able to maintain remission in 30% to 45% of IBD patients without the requirements for steroids or continuing the calcineurin inhibitor. Larger studies using short-term calcineurin inhibitors in conjunction with vedolizumab are warranted and planned.

References

1. Brandse JF, van den Brink GR, Wildenberg ME, et al. Loss of infliximab into feces is associated with lack of response to therapy in patients with severe ulcerative colitis. Gastroenterology 2015;149:350–355. e2.
2. Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. N Engl J Med 1994;330:1841–1845.
3. Thin LW, Murray K, Lawrance IC. Oral tacrolimus for the treatment of refractory inflammatory bowel disease in the biologic era. Inflamm Bowel Dis 2013;19:1490–1498.
4. Egan LJ, Sandborn WJ, Tremaine WJ. Clinical outcome following treatment of refractory inflammatory and fistulizing Crohn's disease with intravenous cyclosporine. Am J Gastroenterol 1998;93:442–448.
5. Brynskov J, Freund L, Rasmussen SN, et al. A placebo-controlled, double-blind, randomized trial of cyclosporine therapy in active chronic Crohn's disease. N Engl J Med 1989; 321:845–850.
6. Matsuoka K, Saito E, Fujii T, et al. Tacrolimus for the treatment of ulcerative colitis. Intest Res 2015;13:219–226.
7. McSharry K, Dalzell AM, Leiper K, et al. Systematic review: the role of tacrolimus in the management of Crohn's disease. Aliment Pharmacol Ther 2011;34:1282–1294.
8. Moskovitz DN, Van Assche G, Maenhout B, et al. Incidence of colectomy during long-term follow-up after cyclosporine-induced remission of severe ulcerative colitis. Clin Gastroenterol Hepatol 2006;4:760–765.
9. Soler D, Chapman T, Yang LL, et al. The binding specificity and selective antagonism of vedolizumab, an anti-alpha4beta7 integrin therapeutic antibody in development for inflammatory bowel diseases. J Pharmacol Exp Ther 2009;330:864–875.
10. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2013;369:699–710.
11. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med 2013;369:711–721.
12. Sands BE, Feagan BG, Rutgeerts P, et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. Gastroenterology 2014;147:618–627. e3.
13. Sandborn WJ, Rutgeerts P, Feagan BG, et al. Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. Gastroenterology 2009;137:1250–1260; quiz 1520.
14. Maser EA, Villela R, Silverberg MS, et al. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. Clin Gastroenterol Hepatol 2006;4:1248–1254.
15. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med 2010;362:1383–1395.
16. Singh S, Loftus EV Jr, Talwalkar JA. Inflammatory bowel disease after liver transplantation for primary sclerosing cholangitis. Am J Gastroenterol 2013;108:1417–1425.
17. Maser EA, Deconda D, Lichtiger S, et al. Cyclosporine and infliximab as rescue therapy for each other in patients with steroid-refractory ulcerative colitis. Clin Gastroenterol Hepatol 2008;6:1112–1116.
18. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet 1980;1:514.
19. Walmsley RS, Ayres RC, Pounder RE, et al. A simple clinical colitis activity index. Gut 1998;43:29–32.
20. Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc 2004; 60:505–512.
21. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987; 317:1625–1629.
22. Vivio EE, Kanuri N, Gilbertsen JJ, et al. Vedolizumab effectiveness and safety over the first year of use in an IBD clinical practice. J Crohns Colitis 2016;10:402–409.
23. Christensen B, Colman RJ, Micic D, et al. Vedolizumab as induction and maintenance for inflammatory bowel disease: 12-month effectiveness and safety. Inflamm Bowel Dis 2018; 24:849–860.
24. Minozzi S, Bonovas S, Lytras T, et al. Risk of infections using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a systematic review and meta-analysis. Expert Opin Drug Saf 2016;15:11–34.

Reprint requests
Address requests for reprints to: Britt Christensen, MBBS, Gastroenterology Department, The Royal Melbourne Hospital, 300 Grattan Street, Parkville, Victoria, Australia 3050. e-mail: britt.christensen@mh.org.au; fax: (61) 3 9342 7848.

Acknowledgments
The authors thank Dania Saddiqui for help with patient recruitment and data collection.

Conflicts of interest
These authors disclose the following: David T. Rubin has received institutional grant support from AbbVie, Janssen, and Takeda, and has served as a consultant for AbbVie, Janssen, Takeda, Amgen, Pfizer, and UCB; Russell D. Cohen has served on the speaker's bureau for AbbVie, Takeda, and Pfizer, has served as a consultant or on the advisory or scientific advisory boards for AbbVie, Celgene, Eli Lilly, Hospira, Janssen, Pfizer, Sandoz Biopharmaceuticals, Takeda, and UCB Pharma, and has been the principal investigator in clinical trials for Astra-Zeneca, Celgene, Gilead Sciences, Medimmune, Mesoblast Ltd, Osiris Therapeutics, Pfizer, Receptos, RedHill Biopharma, Sanofi-Aventis, and UCB Pharma; Peter R. Gibson has served as consultant or advisory board member for AbbVie, Ferring, Janssen, Merck, Nestle Health Science, Danone, Allergan, Celgene, and Takeda, his institution has received speaking honoraria from AbbVie, Janssen, Ferring, Takeda, Mylan, and Pfizer, and has received research grants for investigator-driven studies from AbbVie, Janssen, and A2 Milk Company; Andres Yarur has received research grants from Takeda, served as a consultant for Takeda Pharmaceuticals and Prometheus Laboratories, and is on the speaker's bureau for AbbVie and Prometheus Laboratories; and Britt Christensen has received education grants from Takeda and Pfizer and speaking honoraria from Abbvie and Janssen. The remaining authors disclose no conflicts.

Funding
Funded in part by the Digestive Disease Research Core Center of the University of Chicago (DK42086), and by an Australian Government Research Training Program Scholarship (B.C.).

3.4 VEDOLIZUMAB IN PATIENTS WITH CONCURRENT PRIMARY SCLEROSING CHOLANGITIS AND INFLAMMATORY BOWEL DISEASE DOES NOT IMPROVE LIVER BIOCHEMISTRY BUS IS SAFE AND EFFECTIVE FOR THE BOWEL DISEASE

Primary sclerosing cholangitis is a chronic inflammatory condition of the bile ducts that can progress to strictures, leading to cholangitis and is associated with a significant increase in risk of cholangiocarcinoma. Two-thirds of cases of primary sclerosing cholangitis are associated with inflammatory bowel disease and there is currently no effective therapy available to treat the cholangitis and prevent progression of disease. When vedolizumab first became available on the market it was hoped that through preventing the translocation of white cells into the bile ducts by blocking the alpha4beta7 integrin antibody it may halt and even reverse the inflammatory process of the disease. This study explores the use of vedolizumab in patients with primary sclerosing cholangitis and inflammatory bowel disease but unfortunately demonstrates no efficacy of vedolizumab in this debilitating condition.

Received: 30 September 2017 | First decision: 16 October 2017 | Accepted: 29 December 2017

DOI: 10.1111/apt.14525

WILEY AP&T Alimentary Pharmacology & Therapeutics

Vedolizumab in patients with concurrent primary sclerosing cholangitis and inflammatory bowel disease does not improve liver biochemistry but is safe and effective for the bowel disease

B. Christensen[1,2,3] | D. Micic[4] | P. R. Gibson[1] | A. Yarur[5] | E. Bellaguarda[4] | P. Corsello[6] | J. N. Gaetano[3] | J. Kinnucan[6] | V. L. Rao[3] | S. Reddy[4] | S. Singh[5] | J. Pekow[3] | D. T. Rubin[3]

[1]Alfred Hospital and Monash University, Melbourne, Australia

[2]Royal Melbourne Hospital, Melbourne, Australia

[3]University of Chicago Medicine Inflammatory Bowel Disease Center, Chicago, IL, USA

[4]Northwestern University Feinberg School of Medicine, Chicago, IL, USA

[5]Division of Gastroenterology and Hepatology, Medical College of Wisconsin, Milwaukee, WI, USA

[6]University of Michigan Health System, Ann Arbor, MI, USA

Correspondence
Dr. B Christensen, Gastroenterology Department, The Royal Melbourne Hospital, Parkville, Victoria, Australia.
Email: britt.christensen@mh.org.au

Funding information
NIH, Grant/Award Number: P30DK42086, K08DK090152

Summary

Background: Blocking of lymphocyte trafficking to bile ducts is a potential mechanism to alter the disease course of patients with primary sclerosing cholangitis (PSC).

Aim: To describe the effect of the $\alpha_4\beta_7$ integrin antibody, vedolizumab, on liver biochemistry and disease activity in patients with PSC and inflammatory bowel disease (IBD).

Methods: This is a retrospective multi-centre study of adult patients with a diagnosis of both IBD and PSC. The primary outcome was change in serum alkaline phosphatase level at weeks 14 and 30. Secondary outcomes included changes in other liver biochemistries and in clinical outcomes for the bowel disease. A safety analysis for adverse events was performed.

Results: Thirty-four patients (16 Crohn's disease, 18 ulcerative colitis) were included. Nine (26%) had a history of liver transplant. Median follow-up on vedolizumab was 9 months (IQR: 7-16). There was no overall change in serum alkaline phosphatase level with vedolizumab therapy (median 268 [IQR: 105-551] IU/L at baseline versus 249 [IQR: 183-634] IU/L, $P = 0.99$ at week 30). No significant changes in other liver biochemistries or the Mayo PSC Risk Score were demonstrated at week 30. Clinical remission was achieved at week 30 in 55% of Crohn's disease and 29% of ulcerative colitis patients. Seven (21%) patients ceased vedolizumab; six patients stopped therapy due to persistent IBD activity and one for worsening of liver biochemistries.

Conclusion: Vedolizumab treatment in patients with PSC and IBD did not improve liver biochemistry but was associated with improvement in bowel disease and a favourable safety profile.

The Handling Editor for this article was Professor Jonathan Rhodes, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

Primary sclerosing cholangitis (PSC) causes chronic and progressive injury to the bile ducts characterised by inflammatory and obliterative periductal fibrosis, and is the classic hepatobiliary extra-intestinal manifestation of inflammatory bowel disease (IBD).[1] With disease progression, progressive biliary strictures can lead to cholangitis, biliary cirrhosis and end-stage liver disease.[1] Two-thirds of cases of PSC cases are associated with IBD[2] and, although patients are commonly asymptomatic at the time of diagnosis, they have a shorter than average survival compared to matched controls in the general population.[3,4]

As PSC is associated with significant morbidity and mortality, various therapies have been examined in an effort to mitigate the progressive nature of the disease. Immunosuppressive agents including corticosteroids, tacrolimus, ciclosporin, azathioprine, methotrexate and anti-tumour necrosis factor (TNF) therapies have not shown clinical benefit in PSC.[3] Ursodeoxycholic acid, a hydrophilic bile acid that is often employed to treat cholestatic liver diseases,[3,5] has demonstrated improvement in alkaline phosphatase and other liver biochemistry in patients with PSC but has not favourably influenced key endpoints that include death, liver transplantation or progression to cirrhosis.[1,3,6,7]

Vedolizumab is a selective humanised monoclonal antibody to the $\alpha_4\beta_7$ integrin expressed on lymphocytes. The binding of the $\alpha_4\beta_7$ integrin to MadCAM-1, which is expressed on intestinal endothelial vessels, allows for gut lymphocyte trafficking.[8] Thus vedolizumab modulates the ability of lymphocytes to enter the gastrointestinal epithelium, reducing inflammation and inducing mucosal healing in patients with moderate-severe Crohn's disease (CD) and ulcerative colitis (UC).[9-11] Although MAdCAM-1 is not expressed in normal liver tissue, it is induced in the portal tract endothelium of inflamed and cirrhotic livers, and its activity correlates with histological inflammatory activity in PSC.[12,13] It has therefore been postulated that vedolizumab could also be of therapeutic benefit in patients with PSC. However, experience with vedolizumab in patients with PSC has been limited to individual-center case series.[14,15]

We studied the use of vedolizumab in a multi-centre, multinational cohort of patients with PSC and IBD with a primary focus on change in liver biochemistry. Secondary outcomes assessed for changes in prognostic models of PSC and clinical outcomes and safety of vedolizumab in patients with chronic liver disease and IBD including patients with orthotopic liver transplant.

2 | MATERIALS AND METHODS

2.1 | Participants

Electronic medical records at participating sites were reviewed for adult patients with an established diagnosis of concurrent IBD and PSC (IBD-PSC) based on clinical, biochemical, imaging and endoscopic information and who had been initiated on vedolizumab between June 2014 and January 2016. Data were collected until August 2016. Participating sites included: University of Chicago Medicine (n = 11), Medical College of Wisconsin (n = 9), University of Michigan (n = 7), Northwestern University (n = 4) and Alfred Hospital, Melbourne, Australia (n = 3). These sites were identified by a pre-existing collaborative group without prior knowledge to the number of patients that would meet the inclusion criteria. All patients that met the inclusion criteria from each site were included in the study. Institutional review board approval was granted at the individual participating sites.

2.2 | Study design

A retrospective cohort study was performed. Baseline demographic information abstracted from the medical record included age, sex, dates of diagnosis, disease phenotype based on the Montreal classification,[16] and previous and current use of ursodeoxycholic acid, anti-inflammatory agents and/or immunosuppressant therapy (steroids, immunomodulators, anti-TNF agents). Changes to immunomodulator therapy and UDCA dosing were monitored throughout the study. Results of orthotopic liver transplant, endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP) and liver biopsy before and during vedolizumab treatment were recorded. Clinical scores, laboratory values and endoscopic outcomes were collected from standard-of-care visits. In addition, all adverse events including hospitalisations, surgeries, infusion reactions or infections after initiation of vedolizumab were documented.

2.3 | Outcomes

The primary outcome of interest was a decrease in alkaline phosphatase level at weeks 14 and 30 in those with active PSC (patients with PSC who had not undergone orthotopic liver transplant and those who underwent orthotopic liver transplant with recurrent PSC in the transplanted liver). Secondary outcomes of interest included changes in total bilirubin, Mayo PSC Risk Score,[17] alanine aminotransferase and aspartate aminotransferase at weeks 14 and 30 from baseline in those with active PSC, and the development of adverse events at any time. Adverse events were defined as any clinically significant event that occurred from the date of commencing vedolizumab to the last follow-up. Adverse events were graded as serious if they resulted in discontinuation of vedolizumab, hospitalisation or death.

Clinical activity was assessed using the Harvey-Bradshaw Index (HBI) for CD[18] and the Simple Clinical Colitis Activity Index (SCCAI) for UC.[19] In those with clinical disease activity at baseline, rates of clinical remission and corticosteroid-free remission at week 14 and 30 were determined. Clinical remission was defined as a HBI ≤ 4[18] or a SCCAI ≤ 2.[19] Corticosteroid-free remission was defined as clinical remission without need for concomitant corticosteroids.

In patients with baseline endoscopy and follow-up colonoscopy after at least 3 months of vedolizumab, endoscopic response was

assessed utilising the SES-CD for CD patients[20] or Mayo endoscopic subscore for UC.[21] In CD, endoscopic improvement was defined as reduction in the SES-CD > 50% and mucosal healing as SES-CD score < 3. In UC, endoscopic improvement was defined as absolute reduction ≥ 1 point in the Mayo endoscopic subscore and mucosal healing as Mayo endoscopic subscore of 0 or 1. Biopsies in CD and UC were scored on a 4-point scale as quiescent/normal (0), mild (1), moderate (2) or severe (3).[22] Histological improvement was defined as an absolute reduction of 1 point or more and histological remission as score of 0.

2.4 | Statistical methods

Patients were analysed on an intent-to-treat basis and cessation of vedolizumab for any reason was considered treatment failure. Descriptive statistics were provided to summarise demographic characteristics using mean (95% confidence interval [CI]) or median (interquartile range [IQR]) for continuous variables, and number and percentage for categorical variables. As the differences between liver biochemistry were not normally distributed, the Wilcoxon's signed-rank test was used for statistical analysis of response to treatment. Pre-treatment and post-treatment biochemical indices and Mayo PSC Risk Scores were compared between week 0 and week 14 and week 0 and week 30. For patients who withdrew prematurely, the last observation was carried forward. A two-sided *P*-value ≤ 0.05 was considered statistically significant. All data analyses were performed using Stata 12.0 (STATACORP, College Station, TX, USA).

3 | RESULTS

3.1 | Baseline characteristics

Demographics, baseline characteristics and medication usage of the 34 patients with PSC-IBD who met inclusion criteria are shown in Table 1. Included patients and clinical outcomes assessed are outlined in Figure 1. Of the nine (26%) patients who had undergone orthotopic liver transplantation for PSC prior to initiation of vedolizumab, 3 had recurrent PSC demonstrated on liver biopsy. Thus, 28 patients (71% large duct) had active PSC at the time of treatment with vedolizumab.

Vedolizumab was commenced for IBD clinical disease activity in the majority of patients (n = 27, 79%). Other indications for vedolizumab included possible therapeutic benefit in active PSC (n = 3), intolerance of previous maintenance medication (n = 1), transition from natalizumab (n = 1) and severe endoscopic disease activity despite clinical remission (n = 1). Median clinical follow-up while on vedolizumab was 9 (IQR: 7-16) months and 28 (82%) patients had at least 6 months of clinical follow-up.

At commencement of vedolizumab, 7 patients were on long-term ursodeoxycholic acid, the dose of which did not change in these patients throughout the study period. Two patients commenced ursodeoxycholic acid during the study period.

3.2 | Efficacy

3.2.1 | Alkaline phosphatase

Alkaline phosphatase levels from all patients with active PSC and biochemical testing before and after vedolizumab are shown in Table 2 and Figure 2. Overall, there was no significant change in alkaline phosphatase levels before and after treatment with vedolizumab at week 14 or 30. Median alkaline phosphatase activities were 268 (IQR: 105-551) IU/L before treatment, 234 (IQR: 126-396) IU/L, $P = 0.346$ at week 14 and 249 (IQR: 183-634) IU/L, $P = 0.990$ at week 30. The median percentage change from baseline in alkaline phosphatase was 0% [IQR: −17%, 10%] at week 14 and −1% [IQR: -20%, 21.7%] at week 30.

Of the 18 patients (69%) with an elevated alkaline phosphatase at baseline, 11 patients (61%) improved but none achieved a normal alkaline phosphatase at week 30 (Figure 2A). Alkaline phosphatase did significantly fall with treatment at week 14 from median 475 (IQR: 241-757) IU/L at baseline to 322.5 (IQR: 220-651) IU/L at week 14 ($P = 0.025$). However, two patients potentially confounded this analysis with a fall associated with the commencement of ursodeoxycholic acid (where alkaline phosphatase activities fell by 75% and 13%, respectively, as shown in Figure 2A). At week 30, median alkaline phosphatase activities only trended down to 283 (IQR: 207-658) IU/L ($P = 0.267$). When patients who were commenced on ursodeoxycholic acid during vedolizumab treatment were excluded, the decrease in alkaline phosphatase only trended to significance at week 14 ($P = 0.070$) and was again not significant at week 30 ($P = 0.866$). The median percentage change in alkaline phosphatase among individuals with an elevated baseline level was −10% [IQR: −38%, 0%] at week 14 and −12% [IQR: −24%, 2%] at week 30. In most cases, improvement was evident by week 14; only one patient with transient worsening of their alkaline phosphatase at week 14 achieved improvement in their alkaline phosphatase at week 30. No clear demographic or clinical characteristics, including the duration of PSC, type of PSC (small-duct vs large-duct) and type of IBD (CD vs UC), defined patients with alkaline phosphatase improvement (data not shown).

Of the eight patients (31%) with normal alkaline phosphatase at baseline, four (50%) had a subsequent increase in its activity to abnormal levels over the 30 weeks of treatment (Figure 2B). Overall, in these eight patients, there was a significant increase in alkaline phosphatase from a baseline median of 98 (IQR: 77-102) IU/L to 110 (IQR: 102-183) IU/L, $P = 0.019$ at week 14 and to 146 (IQR: 90-203) IU/L, $P = 0.036$ at week 30. The median percentage change among individuals with a normal baseline alkaline phosphatase was +20% (IQR: 5%, 80%) at week 14 and +48% (IQR: 4%, 94%) at week 30.

3.2.2 | Total bilirubin, aspartate aminotransferase, alanine aminotransferase and Mayo PSC Risk Score

As shown in Table 2 and Figure 3, there were no significant changes in the median serum total bilirubin, aspartate aminotransferase or

TABLE 1 Baseline characteristics of patients with primary sclerosing cholangitis (PSC) and inflammatory bowel disease (IBD)

Characteristic	Crohn's disease, n = 16	Ulcerative colitis, n = 18
All patients: n = 34 Male gender, n (%)	9 (56%)	15 (83%)
Median age IBD diagnosis, y (IQR)	19.5 (17-24)	22 (18-39)
Median age, y (IQR)	34 (25.5-38.5)	37 (23-46)
Median duration of disease, y (IQR)	10.5 (7.5-18.5)	10 (3-15)
Disease Location-Montreal Classification	L1-0 (0%) L2-3 (19%) L3-13 (81%) P-2 (13%)	16 (100%) pan-colitis
Current smoker, n (%)	2 (13%)	0 (0%)
Clinical disease activity at baseline, n (%)	HBI <5 (remission): 5 (31%) 5-7 (mild): 5 (31%) 8-16 (moderate): 6 (38%) >16 (severe): 0 (0%)	SCCAI <3 (remission): 4 (22%) 3-6 (mild): 8 (44%) 7-10 (moderate): 4 (22%) >10 (severe): 2 (11%)
History of liver transplant, n (%)	2 (13%)	7 (39%)
Recurrent PSC in transplanted liver, n (%)	1 (50%)	2 (25%)
Active PSC at vedolizumab commencement, n (%)	15 (94%)	13 (72%)
Anti-TNF treatment naïve, n (%)	1 (6%)	6 (33%)
Concomitant medications at commencement, n (%)		
Tacrolimus	2 (13%)	7 (39%)
Immunomodulator	6 (38%)	7 (39%)
Glucocorticoids	4 (25%)	8 (44%)
Antibiotics	1 (6%)	1 (6%)
Median prednisolone equivalent dose, mg (IQR)	40 (30-40)	15 (10-40)
Patients with PSC and biochemical testing before and after vedolizumab: n = 26		
Median age of PSC diagnosis, y (IQR)	24 (20-29)	22 (20-43)
Median duration of PSC, y (IQR)	8 (3-10)	3 (1-8)
Cirrhosis, n (%)	2 (14%)	0 (0%)
History of biliary stricture dilation, n (%)	5 (36%)	4 (33%)
On UDCA, n (%)	5 (36%)	2 (17%)
Median daily urosodeoxycholic acid dose, mg (IQR)	900 (900-1000)	1000 (1000-1000)
Biochemistry at baseline, median (IQR)		
Alkaline phosphatase (IU/L) (normal <120)	268 (99-551)	283 (108-618)
Aspartate aminotransferase (IU/L) (normal <30)	34 (24-98)	81 (50-111)
Alanine aminotransferase (IU/L) (normal <120)	42 (20-144)	86 (27-139)
Albumin (g/dL) (normal 3.9-4.4)	3.5 (2.9-4.5)	4.1 (3.9-4.3)
Total bilirubin (mg/dl)	0.5 (0.4-0.6)	0.8 (0.6-1.6)
Baseline Mayo Risk Score, mean (95% CI)	−0.55 (−1.38-0.27)	−0.26 (−0.81-0.29)

alanine aminotransferase over 14 or 30 weeks' therapy with vedolizumab. The calculated Mayo PSC Risk Score for PSC did improve significantly from baseline to week 14 from mean -0.40 [95% CI: −0.85, 0.05] at baseline to -0.59 [95% CI: −0.99, -0.18] at week 14 ($P = 0.03$). This difference was no longer significant at week 30 with a Mayo PSC Risk Score of −0.38 [95% CI: −0.83, 0.08] ($P = 0.90$) (Figure 3D).

3.3 | Clinical activity of intestinal disease

All 34 patients had clinical assessment of their intestinal disease activity before and after vedolizumab therapy was initiated and 25 patients (11 CD; 14 UC) had clinically active IBD (HBI > 4 or SCCAI > 2) at baseline. Among those with CD, 5 (45%) patients achieved clinical remission by week 14, increasing to 6 (55%) by week 30. In those with

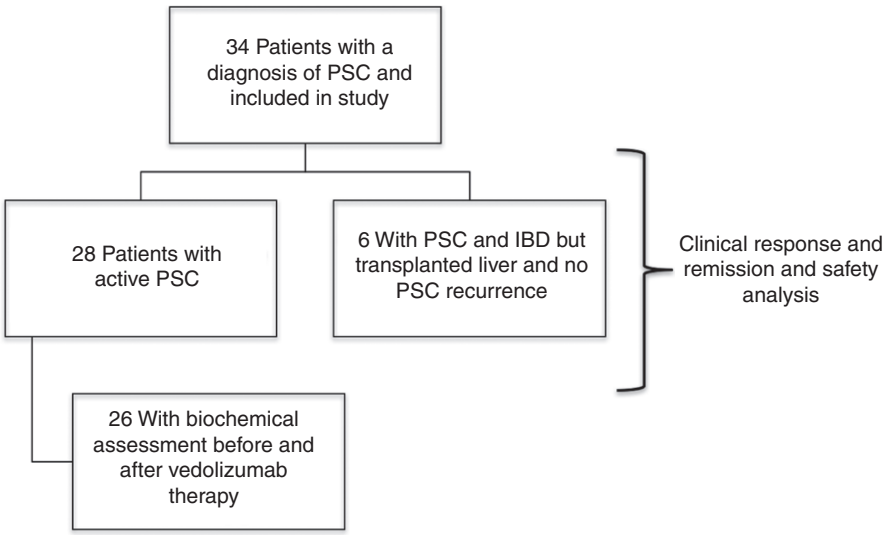


FIGURE 1 Flow chart of study design and included patients

TABLE 2 Change in liver biochemistry and Risk Score with vedolizumab

	Baseline	Wk 14	*P*-value: difference from baseline	Wk 30	*P*-value: difference from baseline
Alkaline phosphatase (IU/L) median (IQR)	268 (105, 551)	265 (176, 508)	0.346	236 (183, 634)	0.990
Bilirubin (IU/L) median (IQR)	0.6 (0.4, 0.9)	0.7 (0.4, 1)	0.619	0.7 (0.4, 1.3)	0.960
AST (IU/L) median (IQR)	54 (27, 98)	37 (23, 75)	0.215	46 (39, 93)	0.693
ALT (IU/L) median (IQR)	63 (20, 144)	50 (31, 107)	0.459	58 (39, 154)	0.809
Mayo PSC Risk Score Mean (95% CI)	−0.40 (−0.85-0.05)	−0.59 (−0.99 to −0.18)	0.030[a]	−0.38 (−0.83-0.08)	0.879

[a]Signifies statistical significant difference.

UC, 3 (21%) achieved clinical remission by week 14, increasing to four (29%) by week 30. Of the 12 patients (4CD; 8UC) who were on corticosteroid therapy at baseline, 10 (83%) (3CD; 7UC) were weaned from corticosteroids during follow-up and 4 (33%) (2CD; 2UC) achieved corticosteroid-free remission by week 30 (Figure 4A). Eight of 9 (89%) patients in clinical remission at initiation of therapy remained in clinical remission through to 30 weeks.

3.4 | Mucosal healing

Thirteen patients (6CD; 7UC) had baseline endoscopic disease activity and follow-up assessment for mucosal healing at median time of 6 (IQR: 5, 10) months. Of the 6 CD patients, two (33%) achieved endoscopic improvement, but none achieved mucosal healing. None of five patients with CD who had histological assessment showed histological improvement or healing. Of the seven UC patients, two (29%) achieved endoscopic improvement and one (14%) mucosal healing. Six of those patients had histological assessment; 3 (50%) achieved histological improvement and 1 (17%) histological remission (Figure 4B). There was no association between mucosal improvement and change in serum alkaline phosphatase activity, with 33% and 29% of those who had deterioration and improvement of their alkaline phosphatase, respectively, achieving endoscopic improvement with vedolizumab treatment ($P = 1.00$).

3.5 | Safety and adverse events

Median follow-up was 9 (IQR: 7, 16) months. Seven (21%) patients ceased vedolizumab after a median of 8 (IQR: 5, 8) months, six for ongoing clinical disease activity and one for deteriorating LFTs. The patient with worsening LFTs had normal liver biochemistry at baseline; the alkaline phosphatase increased to 351 IU/L and alanine aminotransferase 264 IU/L at week 14. This patient proceeded to liver biopsy with histological findings consistent with a drug reaction thought secondary to vedolizumab. Vedolizumab was ceased at week 16 and the liver biochemistries returned to normal over the following 3 months. Two further patients had liver-related complications and were hospitalised for cholangitis, but continued on vedolizumab. Of these, one was found to have a dominant stricture that was dilated at ERCP, and the other patient proceeded to liver transplantation. One patient was hospitalised for poorly controlled intestinal disease, resulting in colectomy.

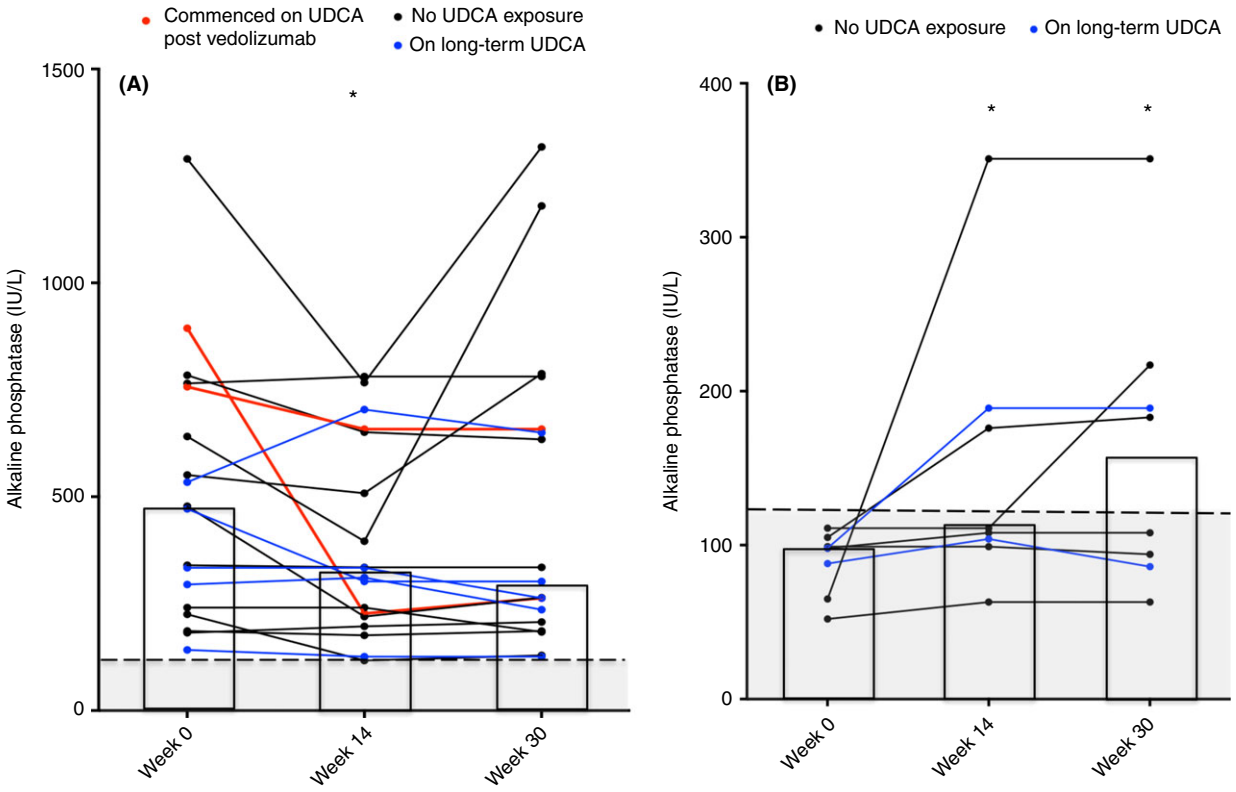


FIGURE 2 Change in Alkaline Phosphatase following treatment with vedolizumab. *Indicates significant decrease ($P < 0.05$) from wk 0 level. Shaded region represents normal range of alkaline phosphatase (<120 IU/L). The columns indicate the median value for each group. (A) Patients with elevated alkaline phosphatase (≥ 120 IU/L) level at baseline. There was a statistically significant decrease at wk 14 ($P = 0.025$). This decrease was no longer statistically significant at wk 30 ($P = 0.267$). (B) Patients with normal alkaline phosphatase activities at baseline. There was a significant increase at week 14 ($P = 0.02$) and 30 ($P = 0.04$)

There were four (12%) minor adverse events that did not require hospitalisation, change in therapy, or medical intervention. They included one patient who developed an upper respiratory tract infection, one with headaches, one dental abscess and one with diarrhoea associated with *Aeromonas* on stool culture.

4 | DISCUSSION

Despite multiple studies investigating treatment options for PSC, currently there is no effective medical therapy. It has been postulated that vedolizumab, a selective $\alpha_4\beta_7$ integrin antibody, may alter the disease course of progressive PSC by blocking lymphocyte trafficking to bile ducts, which, during chronic inflammation, express MadCAM-1. However, the findings of the current multi-centre, multi-national cohort suggest that vedolizumab has little impact on liver biochemistry or the Mayo PSC Risk Score in the vast majority of patients with PSC. Some patients did demonstrate a small and persistent decrease in the serum alkaline phosphatase following initiation of vedolizumab, but likewise there were several patients who commenced the study with normal alkaline phosphatase levels and also had small subsequent increases in their alkaline phosphatase.

While our findings support a tendency in patients with elevated alkaline phosphatase and PSC-IBD to decrease the enzymes concentration early in follow-up, the effect was not sustained through 30 weeks, nor did it represent a clinically meaningful change in only 10% difference in alkaline phosphatase following vedolizumab treatment. In addition, four of eight patients with normal alkaline phosphatase at commencement of therapy developed abnormal levels over 30 weeks of therapy and the overall increase in alkaline phosphatase levels in these patients was statistically significant at both week 14 and week 30. Of note, this increase was not due to the PSC in all patients and, despite this increase, only one patient required cessation of vedolizumab secondary to drug-induced liver damage and not progression of their PSC. However, the overall changes in alkaline phosphatase, both up and down, were small and appeared clinical inconsequential. Certainly, the short-term biochemical effects in this study do not inspire confidence that longer term results will be any more impressive.

Whether vedolizumab slows the progression of alkaline phosphatase increase cannot be ascertained without a control group. Reduction in alkaline phosphatase has been associated with longer survival in PSC, and a recent PSC study group consensus statement identified alkaline phosphatase as a potentially promising surrogate endpoint for PSC clinical trials.[23] However, the potential that changes in liver biochemical profile do not reflect long-term progression of liver disease must be taken into account in interpreting the current results. Lessons from experience with ursodeoxycholic acid,

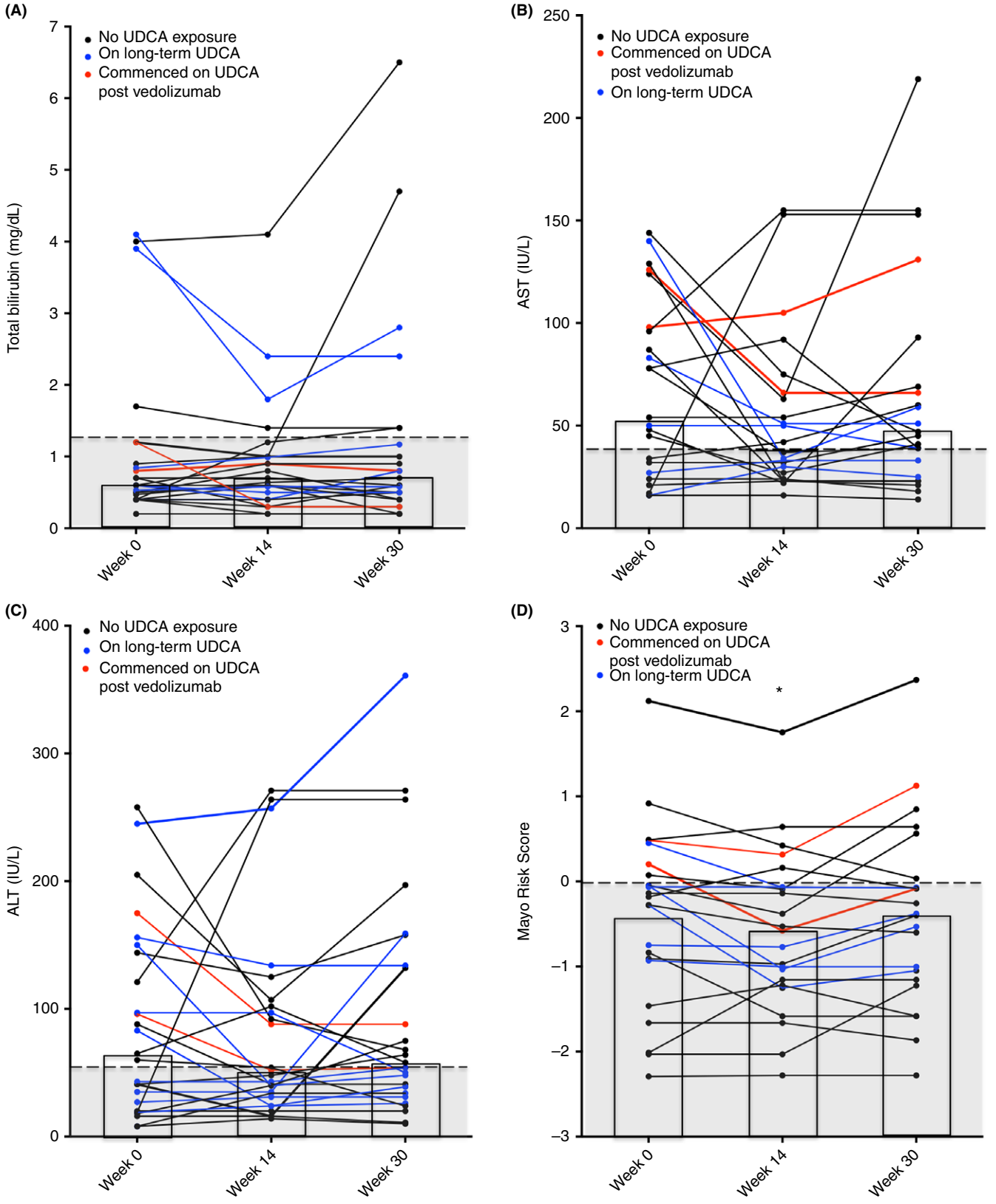


FIGURE 3 Liver biochemistry and Mayo PSC Risk Score before and following 14 and 30 wk' treatment with vedolizumab in patients with IBD-PSC. *Indicates significant decrease ($P < 0.05$) from wk 0 level. Shaded region represents normal range of factor. The columns indicate the median value for total bilirubin, AST and ALT and mean value for Mayo PSC Risk Score. (A) Total bilirubin: no change in total bilirubin with treatment. (B) Aspartate aminotransferase (AST) activities; no change with treatment. (C) Alanine aminotransferase (ALT) activities: no change with treatment. (D) Mayo PSC Risk Scores: improvement in Mayo PSC Risk Score from baseline to week 14 ($P = 0.03$), but not to wk 30 ($P = 0.90$)

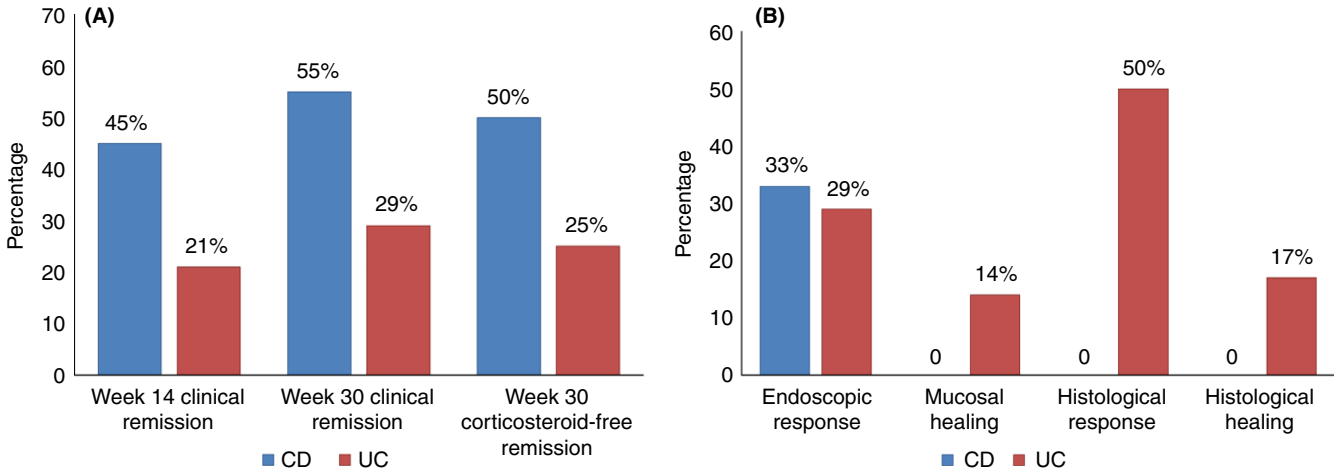


FIGURE 4 Effects of vedolizumab on disease activity in patients with clinically active disease on initiation of therapy. (A) Proportion of patients in clinical remission and corticosteroid-free clinical remission. (B) Proportion of patients with endoscopic response or healing following vedolizumab therapy

the most well described treatment for PSC, indicate that significant improvement in liver biochemistries in patients with decrease serum alkaline phosphatase activities by up to 67%[6,24-26] have not been reflected in improved clinical outcomes and in fact, more recently, high-dose ursodeoxycholic acid has been associated with worsening clinical outcomes and the development of colorectal cancer.[27,28]

Whether PSC itself is at all reversible is something that is yet to be determined. In this short-term study, we have relied on improvement in liver biochemistry to determine the utility of vedolizumab in patients with PSC. It is therefore presumed that, in part at least, the damage and increase in alkaline phosphatase in PSC is reversible. This may not be the case and is a limiting factor in all studies examining treatment options for PSC. Currently, trials in PSC therapeutics have been severely hampered by the time taken to reach clinically significant end-points and that there is no well-defined early surrogate marker for disease outcomes.[29] This study is no different and longer term, multi-centre and case-control studies of patients with PSC and IBD treated with vedolizumab will be required to determine if exposure to vedolizumab alters the rate of development of advanced liver disease, need for liver transplant, colorectal cancer and cholangiocarcinoma despite seeming to have little benefit on liver biochemistry.

In this study, IBD-PSC patients who had active intestinal disease achieved rates of clinical remission with vedolizumab similar to those previously reported.[11,30-33] However, despite vedolizumab being clinically effective in the IBD-PSC patient cohort, we found low rates of mucosal healing and histological remission. It has previously been reported that vedolizumab achieves mucosal healing in 50% of UC patients[9,31] and 20%-30% of CD patients.[11,31] In our study, no patient with CD and PSC achieved mucosal or histological healing and only one of seven with UC achieved mucosal healing and histological remission. How these rates compare directly to IBD-PSC patients on other therapies is unknown but a recent paper by Krugliak Cleveland et al[34] did demonstrate that UC patients with PSC who were in clinical remission were significantly more likely to have endoscopic and histological inflammation compared to UC patients without PSC. This warrants further attention as ongoing histological inflammatory activity[35] and PSC[36] are associated with an increased risk of bowel neoplasia. Furthermore, a theoretical concern with the use of vedolizumab is an increased risk of colorectal cancer due to decreased immune surveillance of the gut. Reassuringly, no associated increased risk of colorectal cancer has been found in long-term safety studies on vedolizumab compared to the general IBD population.[37]

Our study has shown that vedolizumab is safely administered to patients with IBD-PSC. In this cohort, seven (21%) patients ceased vedolizumab therapy after a median of 8 months (IQR: 5.5, 8) of which six were for primary nonresponse to vedolizumab. One patient had normal liver function tests prior to commencing vedolizumab but developed drug-related hepatotoxicity and was required to cease vedolizumab. Two further patients did develop cholangitis, one of which required liver transplantation for deterioration of liver disease and recurrent cholangitis after 7 months of therapy. The second patient had an elevated liver function profile at baseline that failed to improve after 3 months of vedolizumab therapy and was found to have a dominant biliary stricture on ERCP that required dilation. There were no other severe adverse events associated with vedolizumab use in this population, and the 12% of patients with minor adverse event were expected and similar as those reported in previous studies.[11,30,31]

There are a number of notable limitations to this study. First, all data collection was performed retrospectively, but, since the included centres are all major referral centres for IBD and liver disease, we were able to collect data obtained from routine clinic visits. Although we strengthened the data quality using objective outcome assessments where possible, there may still be bias present in the clinical follow-up of patients. Secondly, the sample size was small, which may have contributed, for example, to the failure to observe statistical significance in changes in liver biochemistry, particularly at week 30 outcomes where large interquartile ranges are observed.

However, the absolute difference in the primary outcomes of alkaline phosphatase levels does not appear to be clinically significant even if larger patient numbers were able demonstrates a statistically significant difference. The small sample size, however, also did not allow comparison of liver biochemistry improvement between different sub-groups including those with intra versus extrahepatic PSC or history of liver transplant to be adequately explored. The patients included in this study were also more likely to have CD than UC which is not reflective of the ratios of CD versus UC in the general PSC population. This is likely secondary to the fact that at the time of this study vedolizumab was primarily used to treat the intestinal disease activity rather than the PSC and in some centres, including the University of Chicago, the majority of patients commenced on vedolizumab had CD.[30,38,39,40] There is also the possibility that changes in ALP were secondary to other causes like low vitamin D status. Unfortunately, vitamin D levels were not assessed in this study but it is felt the likelihood of this altering the results significantly is low as all patients were treated at large academic centres where Vitamin D levels are routinely assessed and aggressively replaced. Finally, this study is limited by its short duration of follow-up. Changes in liver biochemistries were only assessed to week 30 of therapy and, therefore, longer term outcomes such as need for liver transplantation, development of cirrhosis or cancer incidence were unable to be assessed. Clearly larger, prospective, multi-centre studies are required to look at this question in more detail.

In conclusion, our study did not demonstrate sustained improvement in liver biochemistries in patients with UC and PSC treated with vedolizumab, and in fact revealed a modest increase in alkaline phosphatase in patients who had normal levels prior to vedolizumab commencement. This increase rarely resulted in discontinuation of vedolizumab, and we have demonstrated that vedolizumab therapy appears safe in patients with PSC, advanced liver disease and a history of orthotopic liver transplantation. In addition, clinical response and remission in IBD activity seems to be similar to the population of patients with IBD without PSC, although rates of mucosal healing may be lower. Future registry studies should focus more on whether vedolizumab can improve long-term clinical outcomes in PSC patients including decreasing the development of new biliary strictures, cirrhosis, need for transplantation and cancer incidence.

ACKNOWLEDGEMENTS

Declaration of personal interests: Joel Pekow has received grant support from Takeda. David Rubin has received institutional grant support from Abbvie, and consulting or advisory board funding from Verastem, Pfizer and Janssen. Janssen and Takeda and served as a consultant for Abbvie, Janssen, Takeda, Amgen, Pfizer and UCB. Peter R. Gibson has served as consultant or advisory board member for AbbVie, Ferring, Janssen, Merck, Nestle Health Science, Danone, Allergan, Celgene and Takeda. His institution has received speaking honoraria from AbbVie, Janssen, Ferring, Takeda, Fresenius Kabi, Mylan and Pfizer. He has received research grants for investigator-driven studies from AbbVie, Janssen, Falk Pharma, Danone and A2 Milk Company. Britt Christensen has received grants from Takeda and Pfizer. There are no other expressed conflicts of interest with respect to the submitted work. Writing assistance: No support provided.

Declaration of funding interests: This work was supported by the NIH [grant numbers P30DK42086, K08DK090152 to JP].

AUTHORSHIP

Guarantor of article: Britt Christensen.

Author contributions: B. Christensen contributed to conception and design, acquisition, analysis or interpretation, drafting of manuscript and approved final version to be submitted. D. Micic contributed to conception and design, acquisition, analysis or interpretation, drafting of manuscript and approved final version to be submitted. P. R. Gibson contributed to conception and design, acquisition, analysis or interpretation, drafting of manuscript and approved final version to be submitted. A. Yarur contributed to conception and design, acquisition, analysis or interpretation, drafting of manuscript and approved final version to be submitted. E. Bellaguarda contributed to acquisition, analysis or interpretation, critical review of manuscript and approved final version to be submitted. P. Corsello contributed to acquisition, analysis or interpretation, critical review of manuscript and approved final version to be submitted. J. N. Gaetano contributed to acquisition, analysis or interpretation, critical review of manuscript and approved final version to be submitted. J. Kinnucan contributed to acquisition, analysis or interpretation, critical review of manuscript and approved final version to be submitted. V. L. Rao contributed to acquisition, analysis or interpretation, critical review of manuscript and approved final version to be submitted. S. Reddy contributed to acquisition, analysis or interpretation, critical review of manuscript and approved final version to be submitted. S. Singh contributed to acquisition, analysis or interpretation, critical review of manuscript and approved final version to be submitted. D. T. Rubin contributed to conception and design and critical review of manuscript and approved final version to be submitted. J. Pekow contributed to conception and design, acquisition, analysis or interpretation, drafting of manuscript and approved final version to be submitted. All authors approved the final version of the manuscript.

ORCID

B. Christensen http://orcid.org/0000-0002-8746-4275

REFERENCES

1. Hirschfield GM, Karlsen TH, Lindor KD, et al. Primary sclerosing cholangitis. *Lancet*. 2013;382:1587-1599.
2. Boonstra K, van Erpecum KJ, van Nieuwkerk KM, et al. Primary sclerosing cholangitis is associated with a distinct phenotype of inflammatory bowel disease. *Inflamm Bowel Dis*. 2012;18:2270-2276.
3. Eaton JE, Talwalkar JA, Lazaridis KN, et al. Pathogenesis of primary sclerosing cholangitis and advances in diagnosis and management. *Gastroenterology*. 2013;145:521-536.

4. Porayko MK, Wiesner RH, LaRusso NF, et al. Patients with asymptomatic primary sclerosing cholangitis frequently have progressive disease. *Gastroenterology*. 1990;98:1594-1602.
5. Paumgartner G, Beuers U. Ursodeoxycholic acid in cholestatic liver disease: mechanisms of action and therapeutic use revisited. *Hepatology*. 2002;36:525-531.
6. Lindor KD. Ursodiol for primary sclerosing cholangitis. Mayo Primary Sclerosing Cholangitis-Ursodeoxycholic Acid Study Group. *N Engl J Med*. 1997;336:691-695.
7. Lindor KD, Kowdley KV, Luketic VA, et al. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. *Hepatology*. 2009;50:808-814.
8. Lobaton T, Vermeire S, van Assche G, et al. Review article: anti-adhesion therapies for inflammatory bowel disease. *Aliment Pharmacol Ther*. 2014;39:579-594.
9. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2013;369:699-710.
10. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2013;369:711-721.
11. Dulai PS, Singh S, Jiang X, et al. The real-world effectiveness and safety of vedolizumab for moderate-severe Crohn's disease: results from the US VICTORY Consortium. *Am J Gastroenterol*. 2016;111:1147-1155.
12. Eksteen B, Grant AJ, Miles A, et al. Hepatic endothelial CCL25 mediates the recruitment of CCR9+ gut-homing lymphocytes to the liver in primary sclerosing cholangitis. *J Exp Med*. 2004;200:1511-1517.
13. Hillan KJ, Hagler KE, MacSween RN, et al. Expression of the mucosal vascular addressin, MAdCAM-1, in inflammatory liver disease. *Liver*. 1999;19:509-518.
14. Lim TY, Pavlidis P, Gulati S, et al. Vedolizumab in inflammatory bowel disease associated with autoimmune liver disease pre- and postliver transplantation: a case series. *Inflamm Bowel Dis*. 2016;22:E39-E40.
15. Damas OM, Estes DE, Pena Polanco NA, et al. Sa1580 treatment of inflammatory bowel disease with vedolizumab for patients with coexisting primary sclerosing cholangitis: report of a nested case-control study. *Gastroenterology*. 2016;150:S1074.
16. Satsangi J, Silverberg MS, Vermeire S, et al. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut*. 2006;55:749-753.
17. Dickson ER, Grambsch PM, Fleming TR, et al. Prognosis in primary biliary cirrhosis: model for decision making. *Hepatology*. 1989;10:1-7.
18. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. *Lancet*. 1980;1:514.
19. Walmsley RS, Ayres RC, Pounder RE, et al. A simple clinical colitis activity index. *Gut*. 1998;43:29-32.
20. Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc*. 2004;60:505-512.
21. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med*. 1987;317:1625-1629.
22. Joseph N, Weber C. Pathology of Inflammatory Bowel Disease. In: Baumgart D, ed. *Crohn's Disease & Ulcerative Colitis*. New York: Springer; 2011:287-306.
23. Rupp C, Rossler A, Halibasic E, et al. Reduction in alkaline phosphatase is associated with longer survival in primary sclerosing cholangitis, independent of dominant stenosis. *Aliment Pharmacol Ther*. 2014;40:1292-1301.
24. Beuers U, Spengler U, Kruis W, et al. Ursodeoxycholic acid for treatment of primary sclerosing cholangitis: a placebo-controlled trial. *Hepatology*. 1992;16:707-714.
25. Mitchell SA, Bansi DS, Hunt N, et al. A preliminary trial of high-dose ursodeoxycholic acid in primary sclerosing cholangitis. *Gastroenterology*. 2001;121:900-907.
26. Olsson R, Boberg KM, de Muckadell OS, et al. High-dose ursodeoxycholic acid in primary sclerosing cholangitis: a 5-year multicenter, randomized, controlled study. *Gastroenterology*. 2005;129:1464-1472.
27. Eaton JE, Silveira MG, Pardi DS, et al. High-dose ursodeoxycholic acid is associated with the development of colorectal neoplasia in patients with ulcerative colitis and primary sclerosing cholangitis. *Am J Gastroenterol*. 2011;106:1638-1645.
28. Imam MH, Sinakos E, Gossard AA, et al. High-dose ursodeoxycholic acid increases risk of adverse outcomes in patients with early stage primary sclerosing cholangitis. *Aliment Pharmacol Ther*. 2011;34:1185-1192.
29. Goode EC, Rushbrook SM. A review of the medical treatment of primary sclerosing cholangitis in the 21st century. *Ther Adv Chronic Dis*. 2016;7:68-85.
30. Amiot A, Grimaud JC, Peyrin-Biroulet L, et al. Effectiveness and safety of vedolizumab induction therapy for patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2016;14:e2.
31. Vivio EE, Kanuri N, Gilbertsen JJ, et al. Vedolizumab effectiveness and safety over the first year of use in an IBD clinical practice. *J Crohns Colitis*. 2015;10:402-409.
32. Baumgart DC, Bokemeyer B, Drabik A, et al. Vedolizumab induction therapy for inflammatory bowel disease in clinical practice–a nationwide consecutive German cohort study. *Aliment Pharmacol Ther*. 2016;43:1090-1102.
33. Stallmach A, Langbein C, Atreya R, et al. Vedolizumab provides clinical benefit over 1 year in patients with active inflammatory bowel disease - a prospective multicenter observational study. *Aliment Pharmacol Ther*. 2016;44:1199-1212.
34. Cleveland NK, Rubin DT, Hart J, et al. 'Patients with ulcerative colitis and primary sclerosing cholangitis frequently have subclinical inflammation in the proximal colon'. *Clin Gastroenterol Hepatol*. 2017; in press.
35. Rutter M, Saunders B, Wilkinson K, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. *Gastroenterology*. 2004;126:451-459.
36. Kornfeld D, Ekbom A, Ihre T. Is there an excess risk for colorectal cancer in patients with ulcerative colitis and concomitant primary sclerosing cholangitis? *A population based study*. *Gut*. 1997;41:522-525.
37. Colombel JF, Sands BE, Rutgeerts P, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. *Gut*. 2016;66:839-851.
38. Kopylov U, Ron Y, Avni-Biron I, et al. Efficacy and safety of vedolizumab for induction of remission in inflammatory bowel disease-the Israeli real-world experience. *Inflamm Bowel Dis*. 2017;23:404-408.
39. Shelton E, Allegretti JR, Stevens B, et al. Efficacy of vedolizumab as induction therapy in refractory IBD patients: a multicenter cohort. *Inflamm Bowel Dis*. 2015;21:2879-2885.
40. Christensen B, Goeppinger SR, Colman RJ, et al. Tu1350 vedolizumab in the treatment of IBD: the University of Chicago experience. *Gastroenterology*. 2015;148:S-866.

How to cite this article: Christensen B, Micic D, Gibson PR, et al. Vedolizumab in patients with concurrent primary sclerosing cholangitis and inflammatory bowel disease does not improve liver biochemistry but is safe and effective for the bowel disease. *Aliment Pharmacol Ther*. 2018;47:753–762. https://doi.org/10.1111/apt.14525

Part 4: Conclusion and integrated discussion

4.1 SUMMARY OF FINDINGS

4.1.1 Histologic healing in IBD

Histology has emerged as a key prognostic marker in IBD and is emerging as a treatment target in UC. Yet, there has been a historical transatlantic divide in the utilisation of histology in clinical practice. In both North America and Europe, histology has been employed for the diagnosis of IBD and for the post-diagnostic assessment of dysplasia.(140) However, although assessment of histologic healing has, in some European countries, been considered useful as a prognosticate marker in UC, routine assessment has generally been limited.(141) In 2016, a shift in interest occurred when the Food and Drug Administration (FDA) announced that in clinical trials, the claim of endoscopic mucosal healing must be supported by histologic assessment.(142) This prompted pharmaceutical trials to include histologic endpoints and resulted in an expanded interest in histologic outcomes in IBD. However, despite this, evidence confirming why histologic outcomes are important in IBD have been required.

The University of Chicago IBD prospective database has defined care and clinical data outcomes in IBD patients and provided an excellent opportunity to address some of these issues. Despite the limitations of a retrospective analysis and the unvalidated scoring systems for histopathological assessment of biopsies, interrogation of this database enabled key information on the clinical meaning of histologic outcomes in IBD to be defined.

The major findings from this thesis and clinical implications include:

Complete histologic normalisation is possible in patients with UC

Histologic normalisation occurs in 10% of patients with ulcerative colitis and is associated with limited disease extent.

Complete histological normalisation is associated with improved clinical outcomes compared to histologic quiescence

Histologic normalisation in UC, when complete, leads to improved clinical outcomes and reduced rates of clinical relapse above that of endoscopic healing or histologic quiescence. Further research from our group has since determined that this normalisation does not represent a cure and may be transient, however in this setting the finding is still associated with a favourable prognosis.(Supplementary 1)(122) Hence histologic normalisation of colonic mucosa can be used as a clinical endpoint in UC.

Segmental disease regression occurs in patients with ulcerative colitis but is not associated with improved outcomes

Incomplete normalisation or regression of disease in UC occurs in one third of patients but unlike complete histologic normalisation, is not associated with improved clinical outcomes. This is an important observation confirming that widespread histologic healing in UC is required and sampling multiple colonic segments is important to confirm histologic remission based on location. Furthermore, normalisation when patchy, usually occurs in a proximal to distal direction and results in complete left-sided normalisation with residual right-sided activity in less than 0.2% of patients. These findings, although focusing on histologic outcomes, verify current guidelines on endoscopic reporting in UC clinical trials, where the worst affected segment is assessed and reported, not the cumulative bowel damage or inflammation.

Furthermore, these findings support that this current endoscopic strategy be extended to histologic indices in UC, as is the case in the recently validated Nancy and Robarts's histological indices.(37, 38) In addition, this study verifies that flexible sigmoidoscopy is adequate to determine histologic healing and prognosticate future risk of relapse in almost all cases of UC.

Histologic healing is possible in ileal Crohn's disease and is associated with improved clinical outcomes

Half of patients with ileal CD in clinical remission achieve histologic healing and this healing, not endoscopic healing, is associated with a decreased risk of clinical relapse, medication escalation and corticosteroid use. This suggests that histologic assessment in CD should be utilised as a prognostic biomarker in clinical practice and incorporated into clinical trial endpoints.

These studies have contributed to a major move to incorporate histology into protocols for trials and momentum is gathering to incorporate histologic endpoints into real-world practice, particularly when treating UC.

4.1.2 Vedolizumab: A new therapy to improve outcomes in IBD

As noted above, over the last few years there has been a paradigm shift in IBD treatment goals to that of endoscopic mucosal healing plus or minus histologic healing. However, a limiting factor when trying to achieve this goal is that a proportion of patients will have primary non-response or secondary loss of response to any one treatment or may need to cease therapy secondary to side-effects. There is, therefore, an unmet need for additional medical therapies that can enable healing themselves or in conjunction with other currently used approaches.

Recently there has been a several new medications that have been approved for the treatment of IBD. Vedolizumab was approved by the FDA in 2013 at the commencement of this research project. Vedolizumab has an advantage of a favourable safety profile due to its relative gut-selective mechanism of action. However, disadvantages include perhaps a more gradual onset of action in more severe disease when compared with the relatively rapid effects of other biologic therapies. This thesis looked at efficacy and safety of vedolizumab when used as sole therapy in the "real world", the utility of combination therapy with a calcineurin inhibitor in more severe patients and its potential as a treatment in those with IBD-PSC where there is no currently proven therapy for the biliary disease.

A prospective database with defined care and clinical data was developed. Patients consented and had their clinical and disease characteristics collected. The strengths of this dataset were the large sample size for a real-world study, and the tertiary setting and expertise of the doctors involved. Mucosal and histologic healing outcomes with standard and escalated dosing regimens and when combined with other immunomodulating drugs, and the efficacy and safety of vedolizumab in the IBD-PSC patient cohort were assessed.

The major findings from this thesis and implications for clinical practice include:

Vedolizumab is an effective and safe medication for the treatment of CD and UC in the real-world

First, similar to clinical trials, it was found that one-third of patients achieve long-term steroid-free clinical remission in both UC and CD.(143) The percentage of patients who achieved week-14 clinical remission appeared superior to the week-6 major clinical trial end-points with half of UC patients and one third of CD patients achieving clinical remission compared to 17% and 15% respectively in the GEMINI studies.(119, 144) This is likely secondary to the cumulative benefit of vedolizumab over the first three months of therapy, which has been described as having a slower onset of action compared to some other commonly-used biologic medications.(122)

Second, mucosal healing is achieved in one half of UC and one third of CD patients following 12 months of vedolizumab therapy. Just less than one quarter of CD patients and half of UC patients achieve histologic remission. More recent studies have reported either similar or only slightly lower rates of both mucosal and histologic healing confirming the efficacy of vedolizumab in controlling inflammation at a microscopic level.(120, 123, 145)

Third, the benefit of dose escalation by decreasing intervals between vedolizumab infusions was confirmed. One quarter of patients who receive dose escalation achieved glucocorticoid-free clinical remission supporting the notion that, similar to other monoclonal antibodies, increased dosing intervals with vedolizumab are beneficial in some patients. Subsequent studies confirm that higher vedolizumab levels are also associated with increased rates of mucosal and histologic healing.(146)

Fourth, unlike the increased response rates seen with combination therapy when using anti-TNF therapies, no additional benefit in terms of clinical remission, endoscopic mucosal healing or histologic healing is seen with the addition of an immunomodulator when treating patients with vedolizumab therapy. This has since been confirmed in other studies.(144, 145, 147)

In addition, it was found that vedolizumab is similarly effective in both anti-TNF naïve and anti-TNF experienced patients. However, other studies including the large clinical trials, have demonstrated that vedolizumab is less effective in patients who have previously failed anti-therapy.(148) The reasons for the discrepancy are unclear but may be secondary to sample size. Therefore, where possible, vedolizumab should be used as a first-line biologic therapy for enhanced therapeutic effect.

Finally, week-14 steroid-free clinical remission was associated with week-52 steroid-free clinical remission and achievement of mucosal healing after 6 months of therapy was associated with ongoing vedolizumab treatment. These findings confirm the role of early clinical and objective assessment of treatment response and endoscopic healing to predict improved clinical outcomes in the longer term.

Combination therapy with vedolizumab and a calcineurin inhibitor is safe and effective in the treatment of UC and CD

Calcineurin inhibitors are safe and effective as a bridge to long-term maintenance with vedolizumab. Utilising this algorithm, almost half of treatment-refractory UC patients and one third of CD patients can eventually achieve steroid-free and calcineurin inhibitor-free clinical remission. In addition, patients who have primary non-response or secondary loss of response to vedolizumab can successfully and safely undergo salvage therapy with a calcineurin

inhibitor, and then transition successfully back to vedolizumab maintenance in the longer term.(149) This has been confirmed in several small UC studies (150-152) and become a standard therapeutic treatment option for steroid-refractory or intolerant patients who have failed anti-TNF therapy and in those with severe or complex disease. Further research from this original study has also confirmed that this treatment strategy can be used in patients specifically with severe steroid-refractory ulcerative colitis. (Supplementary 2)(104) In this cohort, calcineurin inhibitors rapidly induce response and remission and vedolizumab effectively maintains that remission. This combination can lead to colectomy avoidance and should be utilized by IBD specialists.

Vedolizumab is not useful in the treatment of liver inflammation in patients with IBD-PSC

Despite making mechanistic sense, vedolizumab does not lead to improved liver enzyme tests in patients with PSC-IBD.(6) This study has been critical at informing treatment decision-making in this patient cohort. Of note, vedolizumab did not appear to significantly worsen the liver disease and was effective at improving bowel disease in patients with IBD-PSC with similar rates of clinical remission achieved when compared to non-PSC patients.(6) However, as previously reported with other medical therapies, very few patients with IBD-PSC treated with vedolizumab achieved mucosal and/or histologic healing, which therefore requires close monitoring given the increased risk of bowel cancer in these patients.(Supplementary 3)(6, 153, 154)

4.2 UNANSWERED QUESTIONS AND FUTURE DIRECTIONS

There remain multiple unanswered questions in addition to new questions that can be posed following the data outlined in this thesis.

4.2.1 Treatment Targets and Optimising Current Therapies

Expert guidelines now recommend a target of endoscopic healing in both UC and CD when a treat-to-target strategy is utilized.(41) In UC, the agreed endoscopic target is endoscopic remission defined as a Mayo Score of 0-1.(41) There is a push for this to be further tightened to a Mayo Score or UCEIS score of 0 as it has been recognised that more stringent endoscopic disease control leads to improved clinical outcomes.(155) In CD, the current agreed endoscopic target is resolution of ulceration at ileo-colonoscopy.(41) However, before aggressively implementing strategies to reach such targets, there are a few key questions that should be addressed. These include whether a healed mucosa is an achievable target, whether such strategies lead to over-treatment with implications of increased cost and adverse effects of both the therapy and the psychological effects on the patients, and in whom such a strategy should apply.

Since the commencement of this PhD, there has been an explosion of publications on the role of histology and outcomes in IBD. The utility of histologic assessment in UC is now firmly established. Many studies have since demonstrated that quiescent histology leads to improved outcomes and validated histologic indices have been developed.(37, 38, 156) Histology as an outcome is now integrated into pharmaceutical clinical trials and histologic assessment in UC have been recommended as an adjunct to mucosal healing in clinical care.(41)

However, few studies have looked at the role of histology in therapeutic decision-making or prognosis in patients with CD and assessment of histologic outcomes it is yet to be established as important to clinical care. Our study was one of the first to establish that there may be utility of histologic assessment in CD with improved clinical outcomes in ileal CD patients who achieve histological healing over endoscopic healing alone. Although, this study was on a highly restricted patient cohort it suggests that histological treatment targets should be explored in other CD phenotypes and further studies on the impact of histologic outcomes on prognosis are required.

Can we treat to histologic healing?

Evidence is emerging that rates of endoscopic mucosal healing in CD are improved with frequent objective disease monitoring and subsequent adjustment and escalation of therapy when this monitoring signals endoscopic healing has not been achieved. A small cohort-study demonstrated that CD patients who underwent repeated endoscopy procedures within 26 weeks of treatment with adjustment of therapy when mucosal healing was not observed were more likely to achieve mucosal healing on follow-up.(157) Further, in the setting of curative intestinal resection, De Cruz and colleagues demonstrated that patients who were actively assessed after surgery and had escalation of medical therapy if found to have significant anastomotic recurrence were more likely to achieve mucosal healing (22% vs 8%, p=0.03) on further follow up compared to those who were managed according to standard of care and clinical symptoms.(158) Finally, Colombel et al(73) prospectively demonstrated that tight objective monitoring and adjustment of therapy based on clinical and objective markers (CDAI ≥150, CRP ≥5 mg/L or faecal calprotectin ≥ 250 μg/g) was associated with increased rates of mucosal healing on follow-up compared with relying on clinical symptoms alone. Week 56 mucosal healing rates were significantly higher in those managed in the tight

control group compared to those managed on clinical symptoms alone (46% vs 30%, p=0.010), and patients in the tight control group had fewer CD-related hospitalisations and were more likely to achieve symptomatic remission. These studies now need to be replicated to determine if histologic healing can be achieved with escalation or optimisation of medical therapy in CD patients.

Regular assessment with adjustment of therapy also appears to improve the likelihood of achieving mucosal and histologic healing in patients with UC. In a retrospective analysis of patients undergoing colonoscopy, dose adjustment or escalation of medical therapy if mucosal healing was not observed was associated with better outcomes, including the cumulative probability of reaching mucosal healing and histologic healing than those who were managed expectantly(159). Factors independently associated with mucosal and histologic healing after referral were disease duration $\leq$ 2 years, familial history of IBD, anti-TNF therapy at baseline and any adjustment in medical therapy in cases of persistent endoscopic activity (hazard ratio, 5.05; 95% confidence interval, 1.67-19.04; p=0.0031).

Thus, earlier, more effective use of medication may increase the likelihood of achieving mucosal and histologic healing and the assessment of endoscopic disease activity with adjustment of medical therapy to target mucosal healing is feasible in clinical practice and is of benefit. Despite this, it is important to note that mucosal healing may not be a realistic treatment goal in all patients and histologic remission, by its nature, occurs later than endoscopic mucosal remission. Therefore, given the efficacy of our existing medications and concern that patients would burn through limited therapeutic options, histologic healing is currently more appropriately utilised as a prognostic biomarker in IBD and not as the ultimate treatment target.

What can be done if a patient is in clinical remission and found to have mucosal or histologic inflammation?

As discussed above, symptoms are a poor guide to the presence of ongoing inflammation in the intestine.(160, 161) If a patient who is in clinical remission is found on objective criteria to have mucosal or histologic inflammation, an open dialogue and shared decision-making is necessary in order to plan future therapy. Some patients may describe clinical remission, but on closer questioning, have normalized their active symptoms or developed learned helplessness in relation to their active disease.(21) In the discussion about achieving mucosal healing, symptom control and the side effects of therapy should be acknowledged, but a discussion about the risks of uncontrolled inflammation and resulting progressive disease should also occur, including the short and long-term goals of disease control and a modified natural history of disease progression.

There are several reasons a patient may not accomplish mucosal or histologic healing in IBD. This can be due to changing patterns of their disease over time, ineffective therapies including mechanisms that do not work, inter-patient variation, wrong dosing of medications, or lack of patient adherence. The clinical approach should, therefore, be targeted to optimising therapy.

First, adherence to therapy should be assessed and barriers addressed. Up to 60% of IBD patients are nonadherent to their prescribed oral medication and nonadherence is associated with up to a 5.5 times increased chance of disease flare compared to adherent patients.(162, 163) Education focusing on IBD, symptoms and medication regime, dose simplification and behavioural strategies including reminder systems can all improve adherence.(164)
Secondly, dosage and/or mode of delivery of current medication should be evaluated. This may be in the form of giving the optimal dose or formulation of 5-ASA medications or

adding rectal therapy. For thiopurines, anti-TNF monoclonal antibodies and increasingly the newer biologics including anti-integrin and anti-IL23 therapies, the principles of therapeutic drug monitoring should be applied. Assessing the metabolites of azathioprine or mercaptopurine enables non-adherence, under-dosing, inefficacy and so-called shunting to methylated, inefficacious metabolites (corrected by the use of allopurinol) to be identified, and subsequent optimisation strategies to be effected.(165, 166) Trough levels of biologics will provide key information as to optimisation by increasing the dose or decreasing the dosing interval of the current therapy, switching therapy to another drug within the same class or switching therapy to a drug outside the class, or adding a drug to the ongoing treatment regimen (for example an immunomodulator if patients are on monotherapy with a biologic).(167) Thirdly, increasing dosage (not on a TDM basis), or introducing new therapies as replacement or addition needs to be addressed. At this stage combination therapy with two biologics is not standard of care, but there is some evidence for efficacy of this approach in case series and we await clinical trial data from combination biologics including anti-TNF and vedolizumab (EXPLORER – Registered with ClinicalTrials.gov Trial Identifier: NCT02764762) and anti-TNF and IL-23 (VEGA – Registered with ClinicalTrials.gov Trial Identifier: NCT03662542).(168) These combinations are the most obvious due to the considerable safety profile of vedolizumab and anti-L23 therapies.(168) Fourthly, the use of adjunct therapies that might enhance the action of current therapies should be considered. As this thesis demonstrates, the combination of biologics and calcineurin inhibitors is an effective treatment strategy to achieve mucosal and histologic healing, and allows transition to long-term monotherapy with vedolizumab.(149) Enteral nutrition is also a therapeutic option and there is emerging evidence for dietary intervention with other low inflammatory diets in Crohn's disease.(6, 104, 169) Finally, if inflammation is mild, supplemental products

like fish oil, turmeric, mindfulness and other complementary and alternative therapies, could be considered.(170)

What is the risk benefit of over-treatment versus under-treatment?

Although it is thought that mucosal and histologic healing will improve long-term outcomes, it is still unclear just how much healing is required to impact outcomes.(167) While this thesis has demonstrated that the depth of healing seems to dictate outcomes(171, 172), whether the achievement of such healing by escalating therapy above standard approaches on the basis of ongoing inflammation rather than symptoms has only been shown in a few studies, even though it is intuitively likely. As previously discussed in this thesis, the data on feasibility of achieving mucosal and particularly histologic healing are limited. In any medication adjustment, the risks of medical escalation must be weighed against the benefits of achieving mucosal healing. Such escalation has the potential to increase the risks of adverse effects of the medication or level of immune suppression achieved. It might also increase the cost of therapy, especially with the use of patented small molecules or of biologics, which are inherently expensive. Furthermore, the anxiety created in the patient related to the desire to heal in order to prevent complications is very real; anxiety and depression has been found to be increased in patients with coeliac disease who have achieved mucosal healing which is hypothesized to be mediated through more vigilant compliance with a gluten-free diet.(112) It is therefore of concern that aiming and achieving the goal of mucosal and histologic healing may result in an increased risk of a mood disorder.(112)

How should we incorporate treatment targets into clinical practice?

Current targets of therapy should include endoscopic and histologic assessment but treating to histologic healing is currently not feasible and without evidence. Whilst treating to clinical symptoms in IBD is important to aid a patient's immediate quality of life, it alone does not

provide optimal long-term outcomes or prevent disability when used as a stand-alone treatment target. To improve long-term outcomes, it is now established that treating to mucosal healing is required. As mentioned, there is a growing body of evidence that mucosal healing is an achievable treatment goal in patients with IBD.

To achieve mucosal healing, the treatment algorithm begins with a baseline assessment of disease activity with endoscopic evaluation including histologic assessment. (See Figure 1)

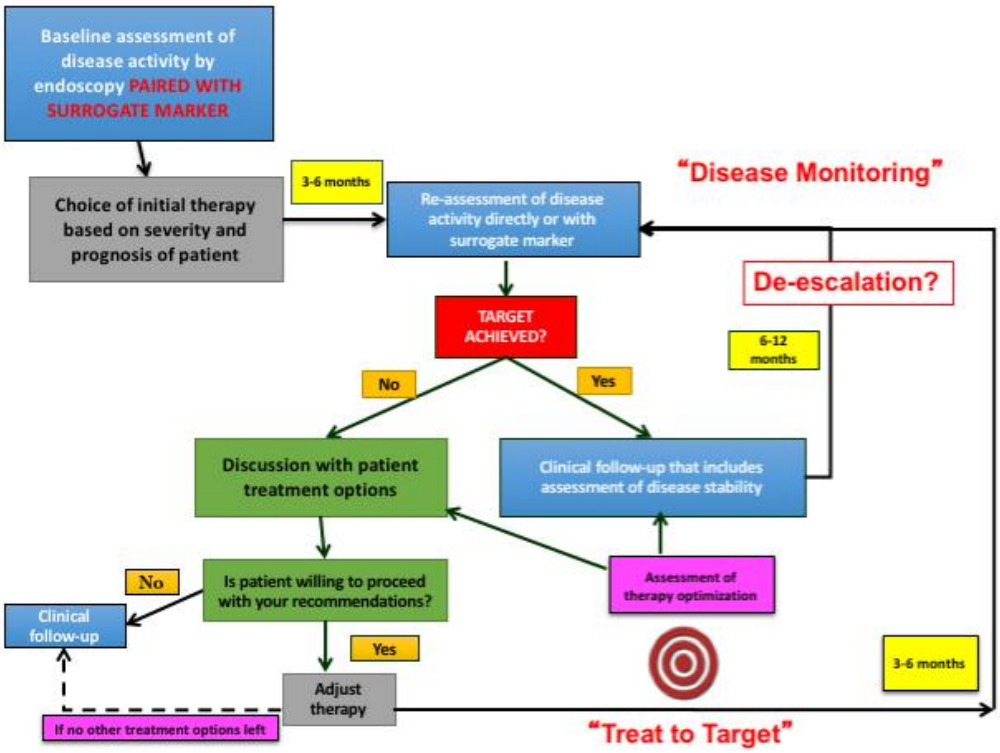


Figure 1: Treat to target in IBD: A treatment algorithm (173)

This baseline evaluation can be paired with a surrogate marker, such as CRP if the patient increases their CRP with inflammation, or a faecal marker. To achieve mucosal healing, patients require the introduction of more intensive treatment initiated early in the course of the disease. The choice of therapy should be based on the severity and prognosis of the patient

using an effective therapy to achieve early disease response and limiting patient's exposure to steroids. Between three to six months (earlier if the faster acting anti-TNF therapies are utilized and later if the slower acting anti-metabolite medications are used) reassessment should occur. Currently this is ideally with endoscopic assessment including histologic assessment, but other surrogate markers including CRP if previously increased or serial calprotectin, MR or US may have a role. If on reassessment, mucosal healing (or significant improvement) has not been achieved, a discussion about treatment options and goals should take place with the patient. If the patient has active clinical symptoms and mucosal inflammation, and the patient is agreeable, escalation of medical therapies should occur. If there is significant mucosal inflammation, then consideration of up-titration of medical therapy should be given irrespective of the symptomatic status of the patient. This should start with optimization of the existing therapy, with dose adjustments and pharmacokinetic optimisation using therapeutic drug monitoring as a consideration. Due to the lower risk, if histologic inflammation is present in the absence of mucosal healing, one could also confirm optimisation of current therapies however there is no current evidence to support escalating to a new therapy or switching therapies. Any adjustment of therapy must be re-assessed in another 3-6 months. If a treatment adjustment has not achieved the desired goal, de-escalation of that therapy should be considered.

Where patients have achieved mucosal healing but continue to have ongoing clinical symptoms, more stringent control of inflammation and achievement of histological healing has not demonstrated improved symptom relief.(174) In these patients it is important to recognise that non-inflammatory changes, bowel damage and irritable bowel syndrome can result in chromic symptom persistence.(174) Possible therapies in this scenario can include a trial of a low FODMAP diet with careful attention to nutritional adequacy, psychological therapies,

osmotic and stimulant laxatives in those with chronic constipation, hypomotility agents or bile-acid sequestrants for those with chronic diarrhoea, antispasmodics, neuropathic-directed agents and anti-depressants for those with abdominal pain in addition to probiotics, pelvic floor therapy and/or physical exercise.(175)

Once mucosal healing is achieved, then frequent clinical and objective monitoring with surrogate markers of mucosal healing should occur to assess for disease drift or early relapse every 6-12 months. To confirm maintenance of mucosal healing, endoscopic evaluation of the mucosa should also be considered every 1-2 years.(167) At this stage, biopsies to assess histology should be undertaken to further prognosticate the patient.

4.2.2 Novel treatment strategies to improve clinical outcomes in IBD

Vedolizumab is a safe and effective medication in the treatment of IBD, but a large percentage of patients will fail to have an adequate treatment response. The last decade has seen major advances in the treatment of IBD and many new therapies have become available. Despite this, a significant proportion of patients will fail to achieve clinical remission and there is currently no way of determining which medication will give the optimal outcome for the individual patient. Position of existing therapies requires a wholistic approach taking into consideration the individualised needs of the patient. In addition, novel treatment strategies may need to be explored. There are several key areas that require exploration in this space.

How do you position existing and emerging biologics?

There is a lack of head-to-head trials between the different biologics. The drought was broken by the recent VARSITY study that demonstrated that vedolizumab may be more effective at inducing and maintaining clinical remission and endoscopic healing when compared to adalimumab in both anti-TNF naïve patients and those that have previously failed therapy.(176) However, this study was hampered by major limitations including no forced corticosteroid wean and no ability to dose escalate or add an immunomodulator in patients on adalimumab. Hence, at the end of the trial, more patients were actually in steroid-free clinical remission with adalimumab than with vedolizumab (21.8% vs 12.6%). Therefore, several questions remain unanswered and the data need to be interpreted with caution. More rigorous trials comparing outcomes between the different biologics are required and predictors of treatment response in regard to the placement of those medications requires exploration.

Without head-to-head randomised controlled trials to compare efficacy, comparative observational effectiveness studies and network meta-analysis have tried to answer some of these questions but with differing conclusions.(177-182) It is important to note that these comparisons are indirect and this information should be combined with our own clinical experience, knowledge around patients disease phenotype and genotype and consideration of patients priorities and concerns. More work in this space needs to occur and genetic and disease specific predictors of response to the individual medications needs to be explored. Currently recommendations are based on expert opinions rather than high-quality evidence due to this lack of head-to-head trials.(183) Therefore, the optimal position of therapies in these algorithms remains unclear.

What is the efficacy and safety of combination therapies with biologics or small molecules?

The concept of combined therapies that have additive or synergistic modes of action to optimise benefits has been utilised for many years. In fact, the tendency to accumulate rather than replace medicine has been criticised in the use, for example, of aminosalicylates with thiopurines or other anti-inflammatory therapies.(184, 185) In the biologic era, combination therapy has been the recommended optimal way to achieve efficacy and longevity with anti-TNF agents, namely with thiopurines or methotrexate.(186, 187) However, beyond concomitant immunomodulators, there has been a reluctance to combine biologics with biologics or with other small molecules with seemingly potent effects. Reasons for this are not entirely clear, except for the obvious drug costs they entail. Concerns regarding the possible side-effects of combining these therapies are also cited however this seems overly cautious given the known safety profile of particularly the newer biologics like vedolizumab and ustekinumab.(188) Response rates with current therapies are sub-optimal and combining biologics and small molecule therapies with different modes of action in IBD has the potential to increase the proportion of patients who achieve clinical remission and mucosal healing. Further studies exploring the efficacy and safety profile of combination therapies in IBD are therefore urgently needed.

We broke some barriers by combining vedolizumab with calcineurin inhibitors and found such a strategy in challenging clinical situations to be an effective treatment strategy. However, the side effect profile limited such use due to the toxicity of calcineurin inhibitors, but, we believe, not due to the combination. Given the safe side-effect profile of vedolizumab and the low likelihood that it will synergise with other therapies in terms of adverse effects, other combination therapeutic strategies with this biologic require assessment including:

- Combination therapy for induction of clinical remission with a JAK-inhibitor (tofacitinib) bridging to maintenance vedolizumab in those with acute-severe or moderate to severe ulcerative colitis. This would be particularly attractive in patients who have previously failed anti-TNF therapy or who have a contraindication to long-term treatment with an anti-TNF.
- Combination therapy with ustekinumab or anti-TNF therapy in patients with severe or treatment refractory IBD.

Due to the safety profile of vedolizumab, this is the most attractive biologic to consider first line as a combination therapy with another biologic or small molecule agent. However, case reports with ustekinumab and anti-TNF therapies also appear safe and may have an efficacy signal in the rheumatoid and dermatological spaces so are also worth exploring in IBD patients.(168)

Are there emerging treatment strategies for IBD-PSC?

Currently, there are no definitive medical treatments for PSC. Research in this area has been hampered by a slow and variable disease process, no clear surrogate biomarker of disease severity or response and low patient numbers. To date, multiple studies on medication targeting the immune system, including our study on vedolizumab and IBD-PSC(189), have failed to demonstrate any benefit in the inflammatory component of the liver inflammation in IBD-PSC. Until we know the cause of PSC or at least have a better understanding of its pathogenesis, determining therapeutic strategies will remain challenging. Currently trials looking into the role of genetics, the microbiome, gut permeability and toxic bile and how they influence disease progression are being undertaken.(190) Regarding treatment, it seems future studies will need to determine if a combination of anti-inflammatory therapies, bile acid based

therapies and anti-fibrotic therapies can hamper or halt PSC disease progression. In addition, determining novel biomarkers that can easily be tested to define disease severity, to predict disease course and to be responsive to modulation of hepatic inflammation related to the PSC are required. Currently change or normalisation of alkaline phosphatase (ALP) is the most widely used primary efficacy end point to measure response to therapy in PSC and is employed in the majority of clinical trials including the study in this thesis.(191) Supporting this, normalisation and reduction of ALP has been associated with improved clinical outcomes(192) and expert consensus endorse its current use as a surrogate endpoint.(193) However, thresholds that predict improved clinical outcomes still need to be clarified and it utility is limited as ALP levels do not accurately predict need for liver transplant or the development of cholangiocarcinoma and colorectal cancer.

4.2.3 Future Directions

In light of the results of the studies reported in this thesis, many research questions have emerged. In Table 1, questions with regards to further establishing the role of histologic assessment and the position and placement of biologics into routine clinical and trial settings future research needs are outlined. Those research questions have a common goal of optimising personalized medicine in IBD. There are many new and emerging medications with varied mechanisms of actions in IBD and patients have different disease phenotypes. It can be difficult to know when and how to use each medication at an individual patient level. Research is required exploring the best treatment strategy for the individual patient utilising personalised biomarkers to select the most effective medication to improve treatment outcomes and to optimise the treatment target in that individual patient.

Table 1: Future Research Directions

Histologic outcomes in IBD	Development of a validated CD histological index
	Establish validated guidelines on biopsy protocols including the number and location of biopsies required in both UC and CD and the timing of such assessment in line with therapy commencement
	Confirm the limitations of histologic outcomes in CD including its patchiness, the necessity of capturing submucosal layers and the importance of transmural vs histologic healing
	Determine if treatment escalation can achieve histologic healing or histologic normalisation in both UC and CD.
	Compare outcomes in patients randomised to the following treatment targets: clinical remission vs clinical and endoscopic remission vs clinical and endoscopic and histologic remission
	Determine outcomes of patients who achieve mucosal healing vs histologic healing vs transmural healing
	Determine if patients who achieve histologic normalisation or quiescence can have less frequent monitoring or benefit from treatment de-escalation
	Since endoscopic and histologic assessment is poorly tolerated by the patient and lacks practicality, determine: If novel non-invasive treatment targets and endpoints including calprotectin and intestinal ultrasound normalisation can replace or reduce reliance on endoscopic mucosal and histologic endpoints Whether the treat-to-target and tight-control protocols (e.g., frequent monitoring with calprotectin and C-reactive protein) used in the CALM study in newly diagnosed biologic naive patients (73) can relay benefit in the more typical IBD patient in a “real-world” setting

Vedolizumab in IBD and PSC	Explore the efficacy of vedolizumab in treating the extra-intestinal manifestations of IBD including joint inflammation and perianal disease
	Explore the role of therapeutic drug monitoring (TDM) with vedolizumab: Does prospective TDM with vedolizumab (and other newer biologics like ustekinumab) improve clinical outcomes?
	Explore further treatment options for the liver inflammation and eventual bile duct fibrosis and stricture development in IBD-PSC: there are currently multiple clinical trials exploring this space
	Explore whether a prospective treat-to-target strategy in patients with IBD-PSC can improve bowel histologic healing rates and whether this decreases colonic cancer risk

4.3 CONCLUSION

This thesis has demonstrated that histologic healing in CD and histologic healing or normalisation in UC are associated with improved short- and long-term clinical outcomes. Thus, patients who achieve such histologic goals have longer periods of clinical remission, reduced hospitalizations and surgery and are less likely to develop colorectal neoplasia. With modern therapies, histologic healing is an obtainable goal in many patients. However, there remains a treatment gap. New therapies are required to improve our ability to reach these emerging objective targets. Vedolizumab, an anti-integrin, is effective at inducing mucosal and histologic healing and can be effectively combined with calcineurin inhibitors to rapidly induce and maintain remission in patients with severe disease. However, there are still a significantly proportion of patients who will not respond to this therapy and patients with PSC do not gain additional benefit in regard to their liver disease. Despite this, a "treat to objective target" strategy should be embraced when treating patients with IBD to decrease the risk of permanent bowel damage, recognizing that the specific target in individual patients may vary. In order to treat to achieve a target, it is necessary to establish a therapeutic alliance with patients, discuss targets of disease activity that are realistic, but incorporate objective evidence of effectiveness, and adopt the best available therapies to achieve sustained disease control and modify the natural history of disease. The development of new treatment options and reliable surrogate markers of disease activity will enable more refined "tight control" and improve long term outcomes.

Part 5: References

References from non-published chapters:

1. Torres J, Billioud V, Sachar DB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis as a progressive disease: the forgotten evidence. Inflamm Bowel Dis. 2012;18(7):1356-63.
2. Riley SA, Mani V, Goodman MJ, Dutt S, Herd ME. Microscopic activity in ulcerative colitis: what does it mean? Gut. 1991;32(2):174-8.
3. Peyrin-Biroulet L, Ferrante M, Magro F, Campbell S, Franchimont D, Fidder H, et al. Results from the 2nd Scientific Workshop of the ECCO. I: Impact of mucosal healing on the course of inflammatory bowel disease. J Crohns Colitis. 2011;5(5):477-83.
4. Lichtenstein GR, Rutgeerts P. Importance of mucosal healing in ulcerative colitis. Inflamm Bowel Dis. 2010;16(2):338-46.
5. Iacucci M, Ghosh S. Looking beyond symptom relief: evolution of mucosal healing in inflammatory bowel disease. Therap Adv Gastroenterol. 2011;4(2):129-43.
6. Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. Gut. 2012;61(11):1619-35.
7. Truelove SC, Richards WC. Biopsy studies in ulcerative colitis. Br Med J. 1956;1(4979):1315-8.
8. Bouguen G, Peyrin-Biroulet L. Surgery for adult Crohn's disease: what is the actual risk? Gut. 2011;60(9):1178-81.
9. Filippi J, Allen PB, Hebuterne X, Peyrin-Biroulet L. Does anti-TNF therapy reduce the requirement for surgery in ulcerative colitis? A systematic review. Curr Drug Targets. 2011;12(10):1440-7.
10. D'Haens G, Sandborn WJ, Feagan BG, Geboes K, Hanauer SB, Irvine EJ, et al. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. Gastroenterology. 2007;132(2):763-86.
11. Sandborn WJ, Rutgeerts P, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. Gastroenterology. 2009;137(4):1250-60.
12. Froslie KF, Jahnsen J, Moum BA, Vatn MH, Group I. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. Gastroenterology. 2007;133(2):412-22.
13. Colombel JF, Rutgeerts P, Reinisch W, Esser D, Wang Y, Lang Y, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology. 2011;141(4):1194-201.
14. Feagan BG, Reinisch W, Rutgeerts P, Sandborn WJ, Yan S, Eisenberg D, et al. The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients. Am J Gastroenterol. 2007;102(4):794-802.

15. Rubin DT, Huo D, Hetzel JT, Bunnag AP, Sedrak M, Hart JA, et al. Increased degree of histological inflammation predicts colectomy and hospitalization in patients with ulcerative colitis. Gastroenterology. 2007;132(4):A19-A.

16. Feagins LA, Melton SD, Iqbal R, Dunbar KB, Spechler SJ. Clinical implications of histologic abnormalities in colonic biopsy specimens from patients with ulcerative colitis in clinical remission. Inflamm Bowel Dis. 2013;19(7):1477-82.

17. Kiesslich R, Duckworth CA, Moussata D, Gloeckner A, Lim LG, Goetz M, et al. Local barrier dysfunction identified by confocal laser endomicroscopy predicts relapse in inflammatory bowel disease. Gut. 2012;61(8):1146-53.

18. Baars JE, Nuij VJ, Oldenburg B, Kuipers EJ, van der Woude CJ. Majority of patients with inflammatory bowel disease in clinical remission have mucosal inflammation. Inflamm Bowel Dis. 2012;18(9):1634-40.

19. Rosenberg L, Nanda KS, Zenlea T, Gifford A, Lawlor GO, Falchuk KR, et al. Histologic markers of inflammation in patients with ulcerative colitis in clinical remission. Clinical Gastroenterology and Hepatology. 2013;11(8):991-6.

20. Korelitz BI, Sommers SC. Response to drug therapy in Crohn's disease: evaluation by rectal biopsy and mucosal cell counts. J Clin Gastroenterol. 1984;6(2):123-7.

21. Rubin DT, Siegel CA, Kane SV, Binion DG, Panaccione R, Dubinsky MC, et al. Impact of ulcerative colitis from patients' and physicians' perspectives: Results from the UC: NORMAL survey. Inflamm Bowel Dis. 2009;15(4):581-8.

22. Modigliani R, Mary JY, Simon JF, Cortot A, Soule JC, Gendre JP, et al. Clinical, biological, and endoscopic picture of attacks of Crohn's disease. Evolution on prednisolone. Groupe d'Etude Therapeutique des Affections Inflammatoires Digestives. Gastroenterology. 1990;98(4):811-8.

23. Geboes K, Rutgeerts P, Opdenakker G, Olson A, Patel K, Wagner CL, et al. Endoscopic and histologic evidence of persistent mucosal healing and correlation with clinical improvement following sustained infliximab treatment for Crohn's disease. Curr Med Res Opin. 2005;21(11):1741-54.

24. Gomes P, du Boulay C, Smith CL, Holdstock G. Relationship between disease activity indices and colonoscopic findings in patients with colonic inflammatory bowel disease. Gut. 1986;27(1):92-5.

25. Solberg IC, Lygren I, Jahnsen J, Aadland E, Høie O, Cvancarova M, et al. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). Scandinavian journal of gastroenterology. 2009;44(4):431-40.

26. Munkholm P, Langholz E, Davidsen M, Binder V. Disease activity courses in a regional cohort of Crohn's disease patients. Scand J Gastroenterol. 1995;30(7):699-706.

27. Bitton A, Peppercorn MA, Antonioli DA, Niles JL, Shah S, Bousvaros A, et al. Clinical, biological, and histologic parameters as predictors of relapse in ulcerative colitis. Gastroenterology. 2001;120(1):13-20.

28. Rutter M, Saunders B, Wilkinson K, Rumbles S, Schofield G, Kamm M, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology. 2004;126(2):451-9.

29. Gupta RB, Harpaz N, Itzkowitz S, Hossain S, Matula S, Kornbluth A, et al. Histologic inflammation is a risk factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. Gastroenterology. 2007;133(4):1099-105.

30. Hefti MM, Chessin DB, Harpaz NH, Steinhagen RM, Ullman TA. Severity of inflammation as a predictor of colectomy in patients with chronic ulcerative colitis. Dis Colon Rectum. 2009;52(2):193-7.

31. D'Haens G, Geboes K, Rutgeerts P. Endoscopic and histologic healing of Crohn's (ileo-) colitis with azathioprine. Gastrointest Endosc. 1999;50(5):667-71.

32. D'Haens G, Van Deventer S, Van Hogezand R, Chalmers D, Kothe C, Baert F, et al. Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: A European multicenter trial. Gastroenterology. 1999;116(5):1029-34.

33. Geboes K, Riddell R, Öst A, Jensfelt B, Persson T, Löfberg R. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. Gut. 2000;47(3):404-9.

34. Gheorghe C, Cotruta B, Iacob R, Becheanu G, Dumbrava M, Gheorghe L. Endomicroscopy for assessing mucosal healing in patients with ulcerative colitis. J Gastrointestin Liver Dis. 2011;20(4):423-6.

35. Bryant R, Winer S, SPL T, Riddell R. Systematic review: histological remission in inflammatory bowel disease. Is ‘complete’remission the new treatment paradigm? An IOIBD initiative. Journal of Crohn's and Colitis. 2014;8(12):1582-97.

36. Mosli MH, Parker CE, Nelson SA, Baker KA, MacDonald JK, Zou GY, et al. Histologic scoring indices for evaluation of disease activity in ulcerative colitis. Cochrane Database Syst Rev. 2017;5:CD011256.

37. Mosli MH, Feagan BG, Zou G, Sandborn WJ, D'Haens G, Khanna R, et al. Development and validation of a histological index for UC. Gut. 2017;66(1):50-8.

38. Marchal-Bressenot A, Salleron J, Boulagnon-Rombi C, Bastien C, Cahn V, Cadiot G, et al. Development and validation of the Nancy histological index for UC. Gut. 2017;66(1):43-9.

39. Magro F, Lopes J, Borralho P, Lopes S, Coelho R, Cotter J, et al. Comparison of different histological indexes in the assessment of UC activity and their accuracy regarding endoscopic outcomes and faecal calprotectin levels. Gut. 2019;68(4):594-603.

40. Bryant RV, Winer S, Travis SP, Riddell RH. Systematic review: histological remission in inflammatory bowel disease. Is 'complete' remission the new treatment paradigm? An IOIBD initiative. J Crohns Colitis. 2014;8(12):1582-97.

41. Peyrin-Biroulet L, Sandborn W, Sands BE, Reinisch W, Bemelman W, Bryant RV, et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. Am J Gastroenterol. 2015;110(9):1324-38.

42. D'Haens GR, Geboes K, Peeters M, Baert F, Penninckx F, Rutgeerts P. Early lesions of recurrent Crohn's disease caused by infusion of intestinal contents in excluded ileum. Gastroenterology. 1998;114(2):262-7.

43. Christensen B, Rubin DT. Objective assessment of endoscopic disease activity and mucosal healing. Crohn's Disease and Ulcerative Colitis: Springer; 2017. p. 267-77.

44. Vermeire S, Van Assche G, Rutgeerts P. C-reactive protein as a marker for inflammatory bowel disease. Inflamm Bowel Dis. 2004;10(5):661-5.

45. Daperno M, Castiglione F, de Ridder L, Dotan I, Farkkila M, Florholmen J, et al. Results of the 2nd part Scientific Workshop of the ECCO. II: Measures and markers of prediction to achieve, detect, and monitor intestinal healing in inflammatory bowel disease. J Crohns Colitis. 2011;5(5):484-98.

46. Langhorst J, Elsenbruch S, Koelzer J, Rueffer A, Michalsen A, Dobos GJ. Noninvasive markers in the assessment of intestinal inflammation in inflammatory bowel diseases: performance of fecal lactoferrin, calprotectin, and PMN-elastase, CRP, and clinical indices. Am J Gastroenterol. 2008;103(1):162-9.

47. De Cruz P, Kamm MA, Prideaux L, Allen PB, Moore G. Mucosal healing in Crohn's disease: a systematic review. Inflamm Bowel Dis. 2013;19(2):429-44.

48. Rodgers AD, Cummins AG. CRP correlates with clinical score in ulcerative colitis but not in Crohn's disease. Dig Dis Sci. 2007;52(9):2063-8.

49. Solem CA, Loftus EV, Jr., Tremaine WJ, Harmsen WS, Zinsmeister AR, Sandborn WJ. Correlation of C-reactive protein with clinical, endoscopic, histologic, and radiographic activity in inflammatory bowel disease. Inflamm Bowel Dis. 2005;11(8):707-12.

50. Boirivant M, Leoni M, Tariciotti D, Fais S, Squarcia O, Pallone F. The clinical significance of serum C reactive protein levels in Crohn's disease. Results of a prospective longitudinal study. J Clin Gastroenterol. 1988;10(4):401-5.

51. Louis E, Mary JY, Vernier-Massouille G, Grimaud JC, Bouhnik Y, Laharie D, et al. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. Gastroenterology. 2012;142(1):63-70 e5; quiz e31.

52. Schnitzler F, Fidder H, Ferrante M, Noman M, Arijs I, Van Assche G, et al. Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. Gut. 2009;58(4):492-500.

53. Jones J, Loftus EV, Jr., Panaccione R, Chen LS, Peterson S, McConnell J, et al. Relationships between disease activity and serum and fecal biomarkers in patients with Crohn's disease. Clin Gastroenterol Hepatol. 2008;6(11):1218-24.

54. Henriksen M, Jahnsen J, Lygren I, Stray N, Sauar J, Vatn MH, et al. C-reactive protein: a predictive factor and marker of inflammation in inflammatory bowel disease. Results from a prospective population-based study. Gut. 2008;57(11):1518-23.

55. Schoepfer AM, Beglinger C, Straumann A, Trummler M, Renzulli P, Seibold F. Ulcerative colitis: correlation of the Rachmilewitz endoscopic activity index with

fecal calprotectin, clinical activity, C-reactive protein, and blood leukocytes. Inflamm Bowel Dis. 2009;15(12):1851-8.

56. Denis MA, Reenaers C, Fontaine F, Belaiche J, Louis E. Assessment of endoscopic activity index and biological inflammatory markers in clinically active Crohn's disease with normal C-reactive protein serum level. Inflamm Bowel Dis. 2007;13(9):1100-5.

57. Wright EK, Kamm MA, De Cruz P, Hamilton AL, Ritchie KJ, Keenan JI, et al. Comparison of Fecal Inflammatory Markers in Crohn's Disease. Inflamm Bowel Dis. 2016;22(5):1086-94.

58. Roseth AG, Fagerhol MK, Aadland E, Schjonsby H. Assessment of the neutrophil dominating protein calprotectin in feces. A methodologic study. Scand J Gastroenterol. 1992;27(9):793-8.

59. Lobaton T, Rodriguez-Moranta F, Lopez A, Sanchez E, Rodriguez-Alonso L, Guardiola J. A new rapid quantitative test for fecal calprotectin predicts endoscopic activity in ulcerative colitis. Inflamm Bowel Dis. 2013;19(5):1034-42.

60. D'Haens G, Ferrante M, Vermeire S, Baert F, Noman M, Moortgat L, et al. Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. Inflamm Bowel Dis. 2012;18(12):2218-24.

61. D'Inca R, Dal Pont E, Di Leo V, Benazzato L, Martinato M, Lamboglia F, et al. Can calprotectin predict relapse risk in inflammatory bowel disease? Am J Gastroenterol. 2008;103(8):2007-14.

62. Gisbert JP, Bermejo F, Perez-Calle JL, Taxonera C, Vera I, McNicholl AG, et al. Fecal calprotectin and lactoferrin for the prediction of inflammatory bowel disease relapse. Inflamm Bowel Dis. 2009;15(8):1190-8.

63. De Vos M, Dewit O, D'Haens G, Baert F, Fontaine F, Vermeire S, et al. Fast and sharp decrease in calprotectin predicts remission by infliximab in anti-TNF naive patients with ulcerative colitis. J Crohns Colitis. 2012;6(5):557-62.

64. De Vos M, Louis EJ, Jahnsen J, Vandervoort JG, Noman M, Dewit O, et al. Consecutive fecal calprotectin measurements to predict relapse in patients with ulcerative colitis receiving infliximab maintenance therapy. Inflamm Bowel Dis. 2013;19(10):2111-7.

65. Hanai H, Takeuchi K, Iida T, Kashiwagi N, Saniabadi AR, Matsushita I, et al. Relationship between fecal calprotectin, intestinal inflammation, and peripheral blood neutrophils in patients with active ulcerative colitis. Dig Dis Sci. 2004;49(9):1438-43.

66. Sipponen T, Savilahti E, Karkkainen P, Kolho KL, Nuutinen H, Turunen U, et al. Fecal calprotectin, lactoferrin, and endoscopic disease activity in monitoring anti-TNF-alpha therapy for Crohn's disease. Inflamm Bowel Dis. 2008;14(10):1392-8.

67. Sipponen T, Savilahti E, Kolho KL, Nuutinen H, Turunen U, Farkkila M. Crohn's disease activity assessed by fecal calprotectin and lactoferrin: correlation with Crohn's disease activity index and endoscopic findings. Inflamm Bowel Dis. 2008;14(1):40-6.

68. Sorrentino D, Paviotti A, Terrosu G, Avellini C, Geraci M, Zarifi D. Low-dose maintenance therapy with infliximab prevents postsurgical recurrence of Crohn's disease. Clin Gastroenterol Hepatol. 2010;8(7):591-9 e1; quiz e78-9.

69. Molander P, af Bjorkesten CG, Mustonen H, Haapamaki J, Vauhkonen M, Kolho KL, et al. Fecal calprotectin concentration predicts outcome in inflammatory bowel disease after induction therapy with TNFalpha blocking agents. Inflamm Bowel Dis. 2012;18(11):2011-7.

70. Guardiola J, Lobaton T, Rodriguez-Alonso L, Ruiz-Cerulla A, Arajol C, Loayza C, et al. Fecal level of calprotectin identifies histologic inflammation in patients with ulcerative colitis in clinical and endoscopic remission. Clin Gastroenterol Hepatol. 2014;12(11):1865-70.

71. Mooiweer E, Severs M, Schipper ME, Fidder HH, Siersema PD, Laheij RJ, et al. Low fecal calprotectin predicts sustained clinical remission in inflammatory bowel disease patients: a plea for deep remission. J Crohns Colitis. 2015;9(1):50-5.

72. Mumolo MG, Bertani L, Ceccarelli L, Laino G, Di Fluri G, Albano E, et al. From bench to bedside: Fecal calprotectin in inflammatory bowel diseases clinical setting. World J Gastroenterol. 2018;24(33):3681-94.

73. Colombel JF, Panaccione R, Bossuyt P, Lukas M, Baert F, Vanasek T, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. Lancet. 2018;390(10114):2779-89.

74. Ordas I, Rimola J, Rodriguez S, Paredes JM, Martinez-Perez MJ, Blanc E, et al. Accuracy of magnetic resonance enterography in assessing response to therapy and mucosal healing in patients with Crohn's disease. Gastroenterology. 2014;146(2):374-82 e1.

75. Ordas I, Rimola J, Garcia-Bosch O, Rodriguez S, Gallego M, Etchevers MJ, et al. Diagnostic accuracy of magnetic resonance colonography for the evaluation of disease activity and severity in ulcerative colitis: a prospective study. Gut. 2013;62(11):1566-72.

76. Fiorino G, Peyrin-Biroulet L, Danese S. Bowel damage assessment in Crohn's disease by magnetic resonance imaging. Curr Drug Targets. 2012;13(10):1300-7.

77. Rimola J, Rodriguez S, Garcia-Bosch O, Ordas I, Ayala E, Aceituno M, et al. Magnetic resonance for assessment of disease activity and severity in ileocolonic Crohn's disease. Gut. 2009;58(8):1113-20.

78. Panes J, Bouzas R, Chaparro M, Garcia-Sanchez V, Gisbert JP, Martinez de Guerenu B, et al. Systematic review: the use of ultrasonography, computed tomography and magnetic resonance imaging for the diagnosis, assessment of activity and abdominal complications of Crohn's disease. Aliment Pharmacol Ther. 2011;34(2):125-45.

79. Parente F, Molteni M, Marino B, Colli A, Ardizzone S, Greco S, et al. Are colonoscopy and bowel ultrasound useful for assessing response to short-term therapy and predicting disease outcome of moderate-to-severe forms of ulcerative colitis?: a prospective study. Am J Gastroenterol. 2010;105(5):1150-7.

80. Maconi G, Parente F, Bollani S, Cesana B, Bianchi Porro G. Abdominal ultrasound in the assessment of extent and activity of Crohn's disease: clinical significance

and implication of bowel wall thickening. Am J Gastroenterol. 1996;91(8):1604-9.

81. Pascu M, Roznowski AB, Muller HP, Adler A, Wiedenmann B, Dignass AU. Clinical relevance of transabdominal ultrasonography and magnetic resonance imaging in patients with inflammatory bowel disease of the terminal ileum and large bowel. Inflamm Bowel Dis. 2004;10(4):373-82.

82. Bryant RV, Friedman AB, Wright EK, Taylor KM, Begun J, Maconi G, et al. Gastrointestinal ultrasound in inflammatory bowel disease: an underused resource with potential paradigm-changing application. Gut. 2018;67(5):973-85.

83. Ripolles T, Martinez MJ, Paredes JM, Blanc E, Flors L, Delgado F. Crohn disease: correlation of findings at contrast-enhanced US with severity at endoscopy. Radiology. 2009;253(1):241-8.

84. Maaser C, Petersen F, Helwig U, Fischer I, Roessler A, Rath S, et al. Intestinal ultrasound for monitoring therapeutic response in patients with ulcerative colitis: results from the TRUST&UC study. Gut. 2020;69(9):1629-36.

85. Smith RL, Taylor KM, Friedman AB, Gibson RN, Gibson PR. Systematic Review: Clinical Utility of Gastrointestinal Ultrasound in the Diagnosis, Assessment and Management of Patients With Ulcerative Colitis. J Crohns Colitis. 2020;14(4):465-79.

86. Rubin DT, Surma BL, Gavzy SJ, Schnell KM, Bunnag AP, Huo D, et al. Positron emission tomography (PET) used to image subclinical inflammation associated with ulcerative colitis (UC) in remission. Inflammatory Bowel Diseases. 2009;15(5):750-5.

87. Spier BJ, Perlman SB, Jaskowiak CJ, Reichelderfer M. PET/CT in the evaluation of inflammatory bowel disease: studies in patients before and after treatment. Mol Imaging Biol. 2010;12(1):85-8.

88. Sutherland L, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2003(3):Cd000543.

89. Romkens TE, Kampschreur MT, Drenth JP, van Oijen MG, de Jong DJ. High mucosal healing rates in 5-ASA-treated ulcerative colitis patients: results of a meta-analysis of clinical trials. Inflamm Bowel Dis. 2012;18(11):2190-8.

90. Lichtenstein GR, Ramsey D, Rubin DT. Randomised clinical trial: delayed-release oral mesalazine 4.8 g/day vs. 2.4 g/day in endoscopic mucosal healing--ASCEND I and II combined analysis. Aliment Pharmacol Ther. 2011;33(6):672-8.

91. Kruis W, Kiudelis G, Racz I, Gorelov IA, Pokrotnieks J, Horynski M, et al. Once daily versus three times daily mesalazine granules in active ulcerative colitis: a double-blind, double-dummy, randomised, non-inferiority trial. Gut. 2009;58(2):233-40.

92. Hartmann F, Stein J, BudMesa-Study G. Clinical trial: controlled, open, randomized multicentre study comparing the effects of treatment on quality of life, safety and efficacy of budesonide or mesalazine enemas in active left-sided ulcerative colitis. Aliment Pharmacol Ther. 2010;32(3):368-76.

93. Marshall JK, Thabane M, Steinhart AH, Newman JR, Anand A, Irvine EJ. Rectal 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2010(1):CD004115.

94. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J. 1955;2(4947):1041-8.

95. Ardizzone S, Cassinotti A, Duca P, Mazzali C, Penati C, Manes G, et al. Mucosal healing predicts late outcomes after the first course of corticosteroids for newly diagnosed ulcerative colitis. Clin Gastroenterol Hepatol. 2011;9(6):483-9 e3.

96. Sherlock ME, Seow CH, Steinhart AH, Griffiths AM. Oral budesonide for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2010(10):CD007698.

97. Gross V, Bunganic I, Belousova EA, Mikhailova TL, Kupcinskas L, Kiudelis G, et al. 3g mesalazine granules are superior to 9mg budesonide for achieving remission in active ulcerative colitis: a double-blind, double-dummy, randomised trial. J Crohns Colitis. 2011;5(2):129-38.

98. Sandborn WJ, Danese S, D'Haens G, Moro L, Jones R, Bagin R, et al. Induction of clinical and colonoscopic remission of mild-to-moderate ulcerative colitis with budesonide MMX 9 mg: pooled analysis of two phase 3 studies. Aliment Pharmacol Ther. 2015;41(5):409-18.

99. Olaison G, Sjodahl R, Tagesson C. Glucocorticoid treatment in ileal Crohn's disease: relief of symptoms but not of endoscopically viewed inflammation. Gut. 1990;31(3):325-8.

100. Panaccione R, Ghosh S, Middleton S, Marquez JR, Scott BB, Flint L, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Gastroenterology. 2014;146(2):392-400.e3.

101. Wang Y, MacDonald JK, Vandermeer B, Griffiths AM, El-Matary W. Methotrexate for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2015(8):CD007560.

102. Carbonnel F, Colombel JF, Filippi J, Katsanos KH, Peyrin-Biroulet L, Allez M, et al. Methotrexate Is Not Superior to Placebo for Inducing Steroid-Free Remission, but Induces Steroid-Free Clinical Remission in a Larger Proportion of Patients With Ulcerative Colitis. Gastroenterology. 2016;150(2):380-8 e4.

103. Paoluzi OA, Pica R, Marcheggiano A, Crispino P, Iacopini F, Iannoni C, et al. Azathioprine or methotrexate in the treatment of patients with steroid-dependent or steroid-resistant ulcerative colitis: results of an open-label study on efficacy and tolerability in inducing and maintaining remission. Aliment Pharmacol Ther. 2002;16(10):1751-9.

104. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010;362(15):1383-95.

105. Kozarek RA, Patterson DJ, Gelfand MD, Botoman VA, Ball TJ, Wilske KR. Methotrexate induces clinical and histologic remission in patients with refractory inflammatory bowel disease. Ann Intern Med. 1989;110(5):353-6.

106. Laharie D, Reffet A, Belleannee G, Chabrun E, Subtil C, Razaire S, et al. Mucosal healing with methotrexate in Crohn's disease: a prospective comparative study with azathioprine and infliximab. Aliment Pharmacol Ther. 2011;33(6):714-21.

107. Laharie D, Bourreille A, Branche J, Allez M, Bouhnik Y, Filippi J, et al. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. Lancet. 2012;380(9857):1909-15.

108. Ogata H, Kato J, Hirai F, Hida N, Matsui T, Matsumoto T, et al. Double-blind, placebo-controlled trial of oral tacrolimus (FK506) in the management of hospitalized patients with steroid-refractory ulcerative colitis. Inflamm Bowel Dis. 2012;18(5):803-8.

109. D'Haens G, Lemmens L, Geboes K, Vandeputte L, Van Acker F, Mortelmans L, et al. Intravenous cyclosporine versus intravenous corticosteroids as single therapy for severe attacks of ulcerative colitis. Gastroenterology. 2001;120(6):1323-9.

110. McSharry K, Dalzell AM, Leiper K, El-Matary W. Systematic review: the role of tacrolimus in the management of Crohn's disease. Alimentary Pharmacology & Therapeutics. 2011;34(11-12):1282-94.

111. Reinisch W, Sandborn WJ, Hommes DW, D'Haens G, Hanauer S, Schreiber S, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut. 2011;60(6):780-7.

112. Sandborn WJ, van Assche G, Reinisch W, Colombel JF, D'Haens G, Wolf DC, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012;142(2):257-65 e1-3.

113. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014;146(1):96-109 e1.

114. Molander P, Sipponen T, Kemppainen H, Jussila A, Blomster T, Koskela R, et al. Achievement of deep remission during scheduled maintenance therapy with TNFalpha-blocking agents in IBD. J Crohns Colitis. 2013;7(9):730-5.

115. Rutgeerts P, Diamond RH, Bala M, Olson A, Lichtenstein GR, Bao W, et al. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. Gastrointest Endosc. 2006;63(3):433-42; quiz 64.

116. Colombel JF, Sandborn WJ, Rutgeerts P, Kamm MA, Yu AP, Wu EQ, et al. Comparison of two adalimumab treatment schedule strategies for moderate-to-severe Crohn's disease: results from the CHARM trial. Am J Gastroenterol. 2009;104(5):1170-9.

117. Baert FJ, D'Haens GR, Peeters M, Hiele MI, Schaible TF, Shealy D, et al. Tumor necrosis factor alpha antibody (infliximab) therapy profoundly down-regulates the inflammation in Crohn's ileocolitis. Gastroenterology. 1999;116(1):22-8.

118. Dick AP, Grayson MJ. Ulcerative colitis. A follow-up investigation with mucosal biopsy studies. Br Med J. 1961;1(5220):160-5.

119. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369(8):699-710.

120. Arijs I, De Hertogh G, Lemmens B, Van Lommel L, de Bruyn M, Vanhove W, et al. Effect of vedolizumab (anti-alpha4beta7-integrin) therapy on histological healing and mucosal gene expression in patients with UC. Gut. 2018;67(1):43-52.

121. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2013;369(8):711-21.

122. Dulai PS, Singh S, Jiang X, Peerani F, Narula N, Chaudrey K, et al. The Real-World Effectiveness and Safety of Vedolizumab for Moderate-Severe Crohn's Disease: Results From the US VICTORY Consortium. Am J Gastroenterol. 2016;111(8):1147-55.

123. Danese S, Sandborn WJ, Colombel JF, Vermeire S, Glover SC, Rimola J, et al. Endoscopic, Radiologic, and Histologic Healing With Vedolizumab in Patients With Active Crohn's Disease. Gastroenterology. 2019;157(4):1007-18 e7.

124. Sands BE, Sandborn WJ, Panaccione R, O'Brien CD, Zhang H, Johanns J, et al. Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2019;381(13):1201-14.

125. Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med. 2016;375(20):1946-60.

126. Rutgeerts P, Gasink C, Chan D, Lang Y, Pollack P, Colombel JF, et al. Efficacy of Ustekinumab for Inducing Endoscopic Healing in Patients With Crohn's Disease. Gastroenterology. 2018;155(4):1045-58.

127. Li K, Friedman JR, Chan D, Pollack P, Yang F, Jacobstein D, et al. Effects of Ustekinumab on Histologic Disease Activity in Patients With Crohn's Disease. Gastroenterology. 2019;157(4):1019-31 e7.

128. Wiesner RH, LaRusso NF. Clinicopathologic features of the syndrome of primary sclerosing cholangitis. Gastroenterology. 1980;79(2):200-6.

129. Rosen CB, Nagorney DM, Wiesner RH, Coffey RJ, Jr., LaRusso NF. Cholangiocarcinoma complicating primary sclerosing cholangitis. Ann Surg. 1991;213(1):21-5.

130. Loftus EV, Jr., Harewood GC, Loftus CG, Tremaine WJ, Harmsen WS, Zinsmeister AR, et al. PSC-IBD: a unique form of inflammatory bowel disease associated with primary sclerosing cholangitis. Gut. 2005;54(1):91-6.

131. Lunder AK, Hov JR, Borthne A, Gleditsch J, Johannesen G, Tveit K, et al. Prevalence of Sclerosing Cholangitis Detected by Magnetic Resonance Cholangiography in Patients With Long-term Inflammatory Bowel Disease. Gastroenterology. 2016;151(4):660-9 e4.

132. Jørgensen KK, Grzyb K, Lundin KE, Clausen OP, Aamodt G, Schrumpf E, et al. Inflammatory bowel disease in patients with primary sclerosing cholangitis: clinical characterization in liver transplanted and nontransplanted patients. Inflamm Bowel Dis. 2012;18(3):536-45.

133. Ricciuto A, Hansen BE, Ngo B, Aloi M, Walters TD, Church PC, et al. Primary Sclerosing Cholangitis in Children With Inflammatory Bowel Diseases Is Associated With Milder Clinical Activity But More Frequent Subclinical Inflammation and Growth Impairment. Clin Gastroenterol Hepatol. 2020;18(7):1509-17.e7.

134. Chapman R, Fevery J, Kalloo A, Nagorney DM, Boberg KM, Shneider B, et al. Diagnosis and management of primary sclerosing cholangitis. Hepatology. 2010;51(2):660-78.

135. Eksteen B, Grant AJ, Miles A, Curbishley SM, Lalor PF, Hubscher SG, et al. Hepatic endothelial CCL25 mediates the recruitment of CCR9+ gut-homing lymphocytes to the liver in primary sclerosing cholangitis. J Exp Med. 2004;200(11):1511-7.

136. Hillan KJ, Hagler KE, MacSween RN, Ryan AM, Renz ME, Chiu HH, et al. Expression of the mucosal vascular addressin, MAdCAM-1, in inflammatory liver disease. Liver. 1999;19(6):509-18.

137. Eaton JE, Talwalkar JA, Lazaridis KN, Gores GJ, Lindor KD. Pathogenesis of primary sclerosing cholangitis and advances in diagnosis and management. Gastroenterology. 2013;145(3):521-36.

138. Bo X, Broome U, Remberger M, Sumitran-Holgersson S. Tumour necrosis factor α impairs function of liver derived T lymphocytes and natural killer cells in patients with primary sclerosing cholangitis. Gut. 2001;49(1):131-41.

139. Singh S, George J, Boland BS, Vande Casteele N, Sandborn WJ. Primary Non-Response to Tumor Necrosis Factor Antagonists is Associated with Inferior Response to Second-line Biologics in Patients with Inflammatory Bowel Diseases: A Systematic Review and Meta-analysis. J Crohns Colitis. 2018;12(6):635-43.

140. Pai RK, Jairath V, Vande Casteele N, Rieder F, Parker CE, Lauwers GY. The emerging role of histologic disease activity assessment in ulcerative colitis. Gastrointest Endosc. 2018;88(6):887-98.

141. Villanacci V, Antonelli E, Geboes K, Casella G, Bassotti G. Histological healing in inflammatory bowel disease: a still unfulfilled promise. World J Gastroenterol. 2013;19(7):968-78.

142. US Department of Health and Human Services. Ulcerative Colitis: Clinical Trial Endpoints Guidance for Industry. [Sept 18th, 2020]. Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM515143.pdf. .

143. Christensen B, Colman RJ, Micic D, Gibson PR, Goeppinger SR, Yarur A, et al. Vedolizumab as induction and maintenance for inflammatory bowel disease: 12-month effectivenes and safety. Inflamm Bowel Dis. 2018;IN PRESS.

144. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369(8):699-710.

145. Vivio EE, Kanuri N, Gilbertsen JJ, Monroe K, Dey N, Chen CH, et al. Vedolizumab Effectiveness and Safety Over the First Year of Use in an IBD Clinical Practice. J Crohns Colitis. 2015.

146. Pouillon L, Rousseau H, Busby-Venner H, De Carvalho Bittencourt M, Choukour M, Gauchotte G, et al. Vedolizumab Trough Levels and Histological Healing During Maintenance Therapy in Ulcerative Colitis. J Crohns Colitis. 2019;13(8):970-5.

147. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2013;369(8):711-21.

148. Sands BE, Feagan BG, Rutgeerts P, Colombel JF, Sandborn WJ, Sy R, et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. Gastroenterology. 2014;147(3):618-27 e3.

149. Christensen B, Gibson PR, Micic D, Colman RJ, Goeppinger SR, Kassim O, et al. Safety and Efficacy of Combination Treatment With Calcineurin Inhibitors and Vedolizumab in Patients With Refractory Inflammatory Bowel Disease. Clin Gastroenterol Hepatol. 2019;17(3):486-93.

150. Pellet G, Stefanescu C, Carbonnel F, Peyrin-Biroulet L, Roblin X, Allimant C, et al. Efficacy and Safety of Induction Therapy With Calcineurin Inhibitors in Combination With Vedolizumab in Patients With Refractory Ulcerative Colitis. Clin Gastroenterol Hepatol. 2019;17(3):494-501.

151. Szanto K, Molnar T, Farkas K. New Promising Combo Therapy in Inflammatory Bowel Diseases Refractory to Anti-TNF Agents: Cyclosporine Plus Vedolizumab. J Crohns Colitis. 2018;12(5):629.

152. Ollech JE, Dwadasi S, Rai V, Peleg N, Normatov I, Israel A, et al. Efficacy and safety of induction therapy with calcineurin inhibitors followed by vedolizumab maintenance in 71 patients with severe steroid-refractory ulcerative colitis. Aliment Pharmacol Ther. 2020;51(6):637-43.

153. Krugliak Cleveland N, Rubin DT, Hart J, Weber CR, Meckel K, Tran AL, et al. Patients With Ulcerative Colitis and Primary Sclerosing Cholangitis Frequently Have Subclinical Inflammation in the Proximal Colon. Clin Gastroenterol Hepatol. 2018;16(1):68-74.

154. Christensen B, Gibson PR, Rubin DT. Letter: vedolizumab for autoimmune liver disease associated inflammatory bowel disease-Authors' reply. Aliment Pharmacol Ther. 2018;47(10):1423-4.

155. Ungaro R, Colombel JF, Lissoos T, Peyrin-Biroulet L. A Treat-to-Target Update in Ulcerative Colitis: A Systematic Review. Am J Gastroenterol. 2019;114(6):874-83.

156. Bryant RV, Burger DC, Delo J, Walsh AJ, Thomas S, von Herbay A, et al. Beyond endoscopic mucosal healing in UC: histological remission better predicts corticosteroid use and hospitalisation over 6 years of follow-up. Gut. 2016;65(3):408-14.

157. Bouguen G, Levesque BG, Pola S, Evans E, Sandborn WJ. Endoscopic assessment and treating to target increase the likelihood of mucosal healing in patients with Crohn's disease. Clin Gastroenterol Hepatol. 2014;12(6):978-85.

158. De Cruz P, Kamm MA, Hamilton AL, Ritchie KJ, Krejany EO, Gorelik A, et al. Crohn's disease management after intestinal resection: a randomised trial. Lancet. 2015;385(9976):1406-17.

159. Bouguen G, Levesque BG, Pola S, Evans E, Sandborn WJ. Feasibility of endoscopic assessment and treating to target to achieve mucosal healing in ulcerative colitis. Inflamm Bowel Dis. 2014;20(2):231-9.

160. Peyrin-Biroulet L, Reinisch W, Colombel JF, Mantzaris GJ, Kornbluth A, Diamond R, et al. Clinical disease activity, C-reactive protein normalisation and mucosal healing in Crohn's disease in the SONIC trial. Gut. 2014;63(1):88-95.

161. Halpin SJ, Ford AC. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol. 2012;107(10):1474-82.

162. Kane SV, Cohen RD, Aikens JE, Hanauer SB. Prevalence of nonadherence with maintenance mesalamine in quiescent ulcerative colitis. Am J Gastroenterol. 2001;96(10):2929-33.

163. Kane S, Huo D, Aikens J, Hanauer S. Medication nonadherence and the outcomes of patients with quiescent ulcerative colitis. Am J Med. 2003;114(1):39-43.

164. Greenley RN, Kunz JH, Walter J, Hommel KA. Practical strategies for enhancing adherence to treatment regimen in inflammatory bowel disease. Inflamm Bowel Dis. 2013;19(7):1534-45.

165. Haines ML, Ajlouni Y, Irving PM, Sparrow MP, Rose R, Gearry RB, et al. Clinical usefulness of therapeutic drug monitoring of thiopurines in patients with inadequately controlled inflammatory bowel disease. Inflamm Bowel Dis. 2011;17(6):1301-7.

166. Kennedy NA, Asser TL, Mountifield RE, Doogue MP, Andrews JM, Bampton PA. Thiopurine metabolite measurement leads to changes in management of inflammatory bowel disease. Intern Med J. 2013;43(3):278-86.

167. Bouguen G, Levesque BG, Feagan BG, Kavanaugh A, Peyrin-Biroulet L, Colombel JF, et al. Treat to Target: A Proposed New Paradigm for the Management of Crohn's Disease. Clin Gastroenterol Hepatol. 2013.

168. Hirten RP, Iacucci M, Shah S, Ghosh S, Colombel JF. Combining Biologics in Inflammatory Bowel Disease and Other Immune Mediated Inflammatory Disorders. Clin Gastroenterol Hepatol. 2018;16(9):1374-84.

169. Yamamoto T, Nakahigashi M, Saniabadi AR. Review article: diet and inflammatory bowel disease--epidemiology and treatment. Aliment Pharmacol Ther. 2009;30(2):99-112.

170. Cheifetz AS, Gianotti R, Luber R, Gibson PR. Complementary and Alternative Medicines Used by Patients With Inflammatory Bowel Diseases. Gastroenterology. 2017;152(2):415-29 e15.

171. Christensen B, Hanauer SB, Erlich J, Kassim O, Gibson PR, Turner JR, et al. Histologic Normalization Occurs in Ulcerative Colitis and Is Associated With Improved Clinical Outcomes. Clin Gastroenterol Hepatol. 2017;15(10):1557-64 e1.

172. Christensen B, Erlich J, Gibson PR, Turner JR, Hart J, Rubin DT. Histologic Healing Is More Strongly Associated with Clinical Outcomes in Ileal Crohn's Disease than Endoscopic Healing. Clin Gastroenterol Hepatol. 2020;18(11):2518-25 e1.

173. Christensen B, Rubin DT. Objective Assessment of Endoscopic Disease Activity and Mucosal Healing. In: Baumgart DC, editor. Crohn's Disease and Ulcerative Colitis: From Epidemiology and Immunobiology to a Rational Diagnostic and Therapeutic Approach. Cham: Springer International Publishing; 2017. p. 267-77.

174. Colombel JF, Keir ME, Scherl A, Zhao R, de Hertogh G, Faubion WA, et al. Discrepancies between patient-reported outcomes, and endoscopic and histological appearance in UC. Gut. 2017;66(12):2063-8.

175. Colombel JF, Shin A, Gibson PR. AGA Clinical Practice Update on Functional Gastrointestinal Symptoms in Patients With Inflammatory Bowel Disease: Expert Review. Clin Gastroenterol Hepatol. 2019;17(3):380-90 e1.

176. Sands BE, Peyrin-Biroulet L, Loftus EV, Jr., Danese S, Colombel JF, Toruner M, et al. Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis. N Engl J Med. 2019;381(13):1215-26.

177. Singh S, Fumery M, Sandborn WJ, Murad MH. Systematic review with network meta-analysis: first- and second-line pharmacotherapy for moderate-severe ulcerative colitis. Aliment Pharmacol Ther. 2018;47(2):162-75.

178. Singh S, Murad MH, Fumery M, Dulai PS, Sandborn WJ. First- and Second-Line Pharmacotherapies for Patients With Moderate to Severely Active Ulcerative Colitis: An Updated Network Meta-Analysis. Clin Gastroenterol Hepatol. 2020;18(10):2179-91.e6.

179. Singh S, Fumery M, Sandborn WJ, Murad MH. Systematic review and network meta-analysis: first- and second-line biologic therapies for moderate-severe Crohn's disease. Aliment Pharmacol Ther. 2018;48(4):394-409.

180. Vickers AD, Ainsworth C, Mody R, Bergman A, Ling CS, Medjedovic J, et al. Systematic Review with Network Meta-Analysis: Comparative Efficacy of Biologics in the Treatment of Moderately to Severely Active Ulcerative Colitis. PLoS One. 2016;11(10):e0165435.

181. Allamneni C, Venkata K, Yun H, Xie F, DeLoach L, Malik TA. Comparative Effectiveness of Vedolizumab vs. Infliximab Induction Therapy in Ulcerative Colitis: Experience of a Real-World Cohort at a Tertiary Inflammatory Bowel Disease Center. Gastroenterology Res. 2018;11(1):41-5.

182. Hupe M, Riviere P, Nancey S, Roblin X, Altwegg R, Filippi J, et al. Comparative efficacy and safety of vedolizumab and infliximab in ulcerative colitis after failure of a first subcutaneous anti-TNF agent: a multicentre cohort study. Aliment Pharmacol Ther. 2020;51(9):852-60.

183. Danese S, Fiorino G, Peyrin-Biroulet L. Positioning Therapies in Ulcerative Colitis. Clin Gastroenterol Hepatol. 2020;18(6):1280-90 e1.

184. Mayberry H, Moshkovska T, Mayberry JF. Co-prescribing azathiopurine or 6-mercaptopurine and 5-aminosalicylate compounds in ulcerative colitis. Inflamm Bowel Dis. 2009;15(2):190-2.

185. Singh S, Kim J, Zhu W, Dulai PS, Sandborn WJ, Jairath V. No benefit of continuing vs stopping 5-aminosalicylates in patients with ulcerative colitis escalated to anti-metabolite therapy. Aliment Pharmacol Ther. 2020;52(3):481-91.

186. van Schaik T, Maljaars JP, Roopram RK, Verwey MH, Ipenburg N, Hardwick JC, et al. Influence of combination therapy with immune modulators on anti-TNF trough levels and antibodies in patients with IBD. Inflamm Bowel Dis. 2014;20(12):2292-8.

187. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010;362(15):1383-95.

188. Mao EJ, Lewin S, Terdiman JP, Beck K. Safety of dual biological therapy in Crohn's disease: a case series of vedolizumab in combination with other biologics. BMJ Open Gastroenterol. 2018;5(1):e000243.

189. Christensen B, Micic D, Gibson PR, Yarur A, Bellaguarda E, Corsello P, et al. Vedolizumab in patients with concurrent primary sclerosing cholangitis and inflammatory bowel disease does not improve liver biochemistry but is safe and effective for the bowel disease. Aliment Pharmacol Ther. 2018;47(6):753-62.

190. Wagner M, Fickert P. Drug Therapies for Chronic Cholestatic Liver Diseases. Annu Rev Pharmacol Toxicol. 2020;60:503-27.

191. Vesterhus M, Melum E. Prognostic biomarkers and surrogate end points in PSC. Liver Int. 2016;36(12):1748-51.

192. de Vries EM, Wang J, Leeflang MM, Boonstra K, Weersma RK, Beuers UH, et al. Alkaline phosphatase at diagnosis of primary sclerosing cholangitis and 1 year later: evaluation of prognostic value. Liver Int. 2016;36(12):1867-75.

193. Ponsioen CY, Chapman RW, Chazouilleres O, Hirschfield GM, Karlsen TH, Lohse AW, et al. Surrogate endpoints for clinical trials in primary sclerosing cholangitis: Review and results from an International PSC Study Group consensus process. Hepatology. 2016;63(4):1357-67.

Part 6: Supplementary Material

6.1 Introduction to Supplementary Material

There are three supplementary articles that accompany this thesis:

Supplementary I: Supplementary I contains' a follow-up study of Chapter 2.2 on long-term outcomes in patients who achieve histological normalisation. It reports that these patients often have findings of architectural change on subsequent endoscopy but still have improved clinical long-term outcomes.

Supplementary II: Supplementary II contains a follow-up study on Chapter 3.3 following a larger cohort of severe UC patients treated with combination therapy vedolizumab and calcineurin inhibitors. Efficacy and safety were again demonstrated.

Supplementary III: Supplementary III contains the accompanying reply from the candidate and co-authors to a letter regarding the paper in Chapter 3.4.

6.2 Supplementary I: Follow-Up of Patients with Ulcerative Colitis and Histological Normalization

Sandborn WJ, van Assche G, Reinisch W, Colombel JF, D'Haens G, Wolf DC, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012;142(2):257-65 e1-3.

Clinical Gastroenterology and Hepatology 2020;18:987–988

Follow-Up of Patients With Ulcerative Colitis and Histological Normalization

Amanda Israel,[*] Britt Christensen,[‡,§] Katia El Jurdi,[*] Victoria Rai,[*] Jacob E. Ollech,[*] Russell D. Cohen,[*] Atsushi Sakuraba,[*] Sushila R. Dalal,[*] and David T. Rubin[*]

[*]Inflammatory Bowel Disease Center, University of Chicago Medicine, Chicago, Illinois; [‡]Department of Gastroenterology, Alfred Hospital and Monash University, Melbourne, Australia; and [§]Department of Gastroenterology, Royal Melbourne Hospital, Melbourne, Australia

The natural history of ulcerative colitis (UC) follows a relapsing and remitting course of inflammation and is accompanied by associated mucosal injury and historically, microscopic features of chronicity that were the sine qua non for the diagnosis.[1] As goals for the management of UC have evolved to include objectively measured endoscopic improvement of the mucosa, there also has been a move to include histological endpoints in assessment of disease activity.[2,3] However, there remain a number of unanswered questions about histology in UC and this is not yet a specific treatment goal.[4]

We recently reported the association of histological activity and both clinical and endoscopic activity in patients with UC, as well as the clinical outcomes of these patients.[2] In this study of 646 patients with confirmed UC, we included a previously undescribed histologic endpoint of "normalization" (Hn), in which there were no features of acute or chronic inflammation. Importantly, with median 22 months of clinical follow-up, the patients with Hn were less likely to suffer a clinical relapse than patients with histological inflammation or even histological quiescence. Here, we report the subsequent longer term follow-up of the subset of UC patients who achieved Hn and describe their clinical and histologic progression.

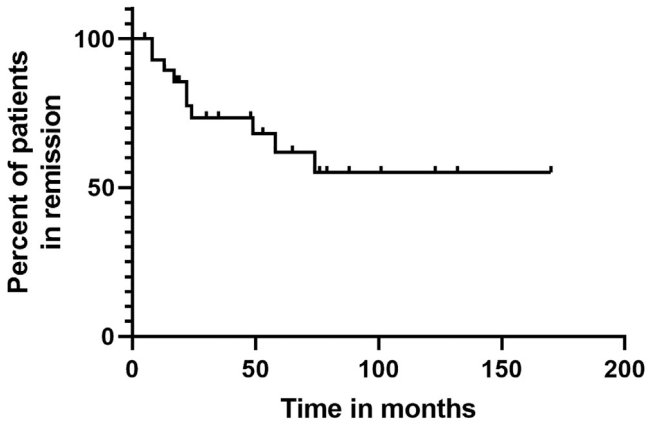


Figure 1. Kaplan-Meyer curve for relapse in UC patients subsequent to demonstrating colonic Hn. The line represents the proportion of patients not experiencing clinical relapse among patients with Hn at the end of follow-up.

Materials and Methods

This is an Institutional Review Board–approved retrospective review from our tertiary inflammatory bowel disease center of adult patients with confirmed UC who had Hn on endoscopic colon biopsies taken between August 2005 and October 2013. These patients were followed to October 2018. Demographic and disease-related information was collected from our institutional database. We assessed prior and subsequent reports from pathology using our previously described 6-point scoring system and categorized tissue as normal (score = 0), quiescent (score=1) or active (score $\geq 1 = 2$).[5] We also reviewed all subsequent clinical notes to evaluate for clinical relapse.

Results

We identified 30 UC patients (13 men [40%]) with Hn of the colorectum who had at least 1 subsequent clinical or histological assessment. The median age at UC diagnosis was 25 $\pm$ 15.3 years and the median age at Hn index was 41.5 $\pm$ 15.4 years. The disease distribution by Montreal classification was 6 (20%) E1, 5 (17%) E2, and 19 (63%) E3. Median follow-up time was 5.16 (range, 1.13–14.19) years.

Of the 29 of 30 patients who had clinical follow-up, 19 (66%) remained inactive and 10 (33%) had a clinical relapse (median 4.9 [range, 1.13–14.19] years). The percent of patients without relapse noted on the Kaplan-Meyer curve was <50% over the entire duration of follow-up and over 90% in the first 1 year (Figure 1).

Most current article

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2019.06.025

After normalization, 10 of these 29 patients underwent medical de-escalation of therapy, 1 had change within class, and 3 had medical escalation. Of the 18 of 30 patients who had histological follow-up, 6 (33%) maintained Hn for median 6 ± 2.8 year follow-up, 9 (50%) became quiescent then reverted back to Hn, 2 (11%) became quiescent and remained quiescent, and 1 (5.5%) became histologically active (Supplementary Figure 1). Six of these 18 patients underwent medical de-escalation of therapy, 1 had change within class, and 3 had medical escalation. Two (33%) maintained Hn, 2 (33%) became quiescent then reverted back to Hn, 1 (17%) became quiescent and remained quiescent, and 1 (17%) became histologically active.

Discussion

In recent years, histological healing has been increasingly discussed as a possible target in achieving remission with the notion that healing the bowel beyond what is seen on endoscopy may provide additional benefit. While there has been evidence demonstrating that histologic inflammation is associated with increased risk of clinical relapse, hospitalization, surgery, and colorectal cancer,[6,7] the characteristics and natural history of UC patients who achieve normalization has not been previously described. In this small observational cohort of patients with UC who have achieved Hn, one-third appear to have stable disease, but in follow-up, a majority had subsequently identified histological findings of classical quiescence, suggesting that the prior normalization finding is either transient or may have been a sampling or interpretation error. The variation in number of endoscopies per patients in study may have contributed to this finding. Histologically active inflammation and clinical relapse were rare but did occur. Although the small number and retrospective nature were limitations, this is the first long-term follow-up of Hn patients to exist in the literature. These findings demonstrate that a single finding of Hn is associated with favorable prognosis, but that Hn does not represent cure. Further research in this endpoint and in therapeutic de-escalation and monitoring of these patients is warranted.

Supplementary Material

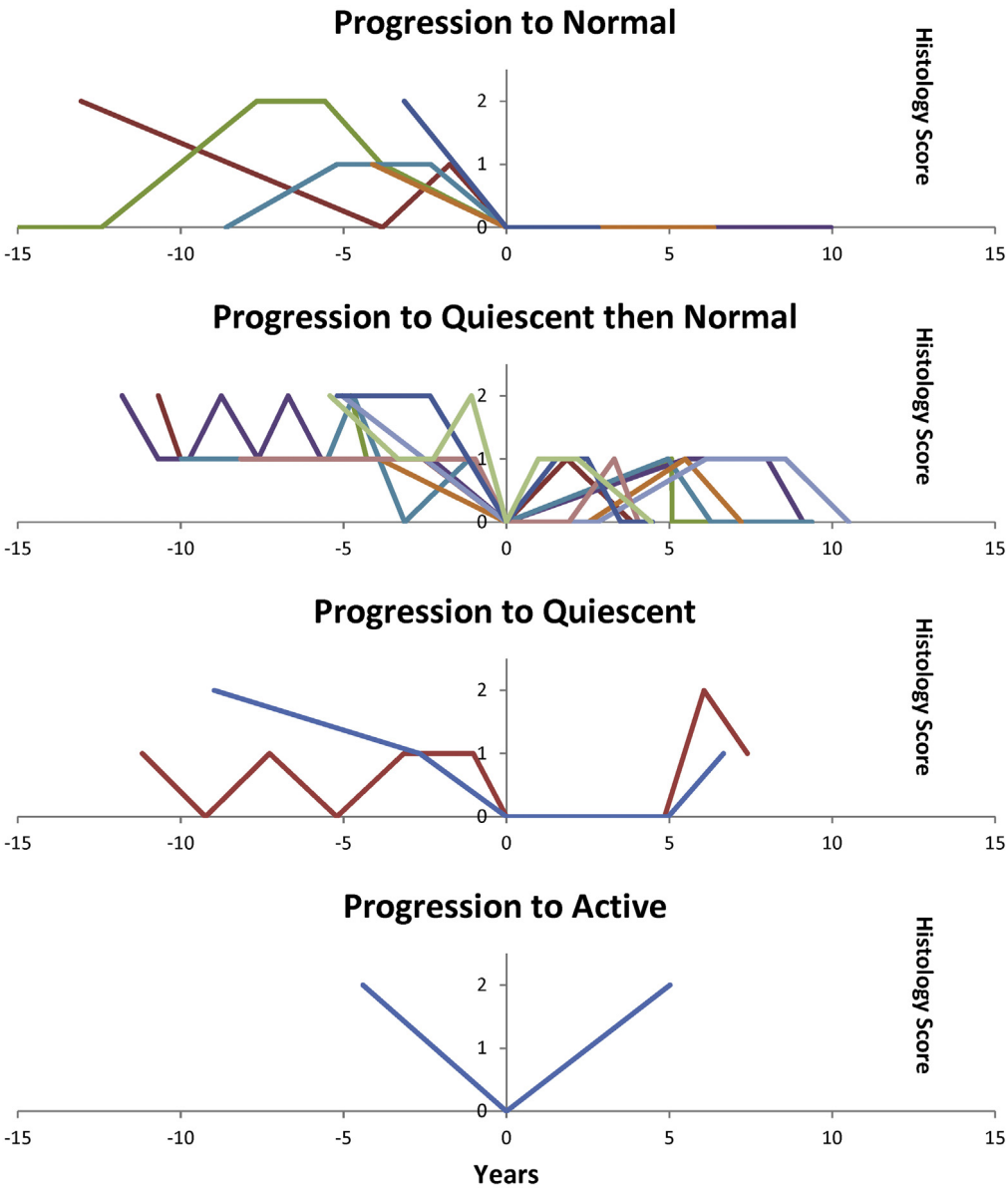
Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2019.06.025.

References

1. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG clinical guideline: ulcerative colitis in adults. Am J Gastroenterol 2019; 114:384–413.
2. Christensen B, Hanauer S, Erlich J, et al. Histologic normalization occurs in ulcerative colitis and is associated with improved clinical outcomes. Clin Gastroenterol Hepatol 2017; 15:1557–1564.
3. Peyrin-Biroulet L, Bressenot A, Kampman W. Histologic remission: the ultimate therapeutic goal in ulcerative colitis? Clin Gastroenterol Hepatol 2014;12:929–934.
4. Long MD, Rubin DT. Histologic remission in ulcerative colitis – are we there yet? Am J Gastroenterol 2019;114:713–715.
5. Rubin DT, Huo D, Kinnucan JA, et al. Inflammation is an independent risk factor for colonic neoplasia in patients with ulcerative colitis: a case-control study. Clin Gastroenterol Hepatol 2013;11:1601–1608.
6. Bitton A, Peppercorn MA, Antonioli DA, et al. Clinical, biological, and histologic predictors of relapse in ulcerative colitis. Gastroenterol 2001;120:13–20.
7. Riley SA, Mani V, Goodman MJ, et al. Microscopic activity in ulcerative colitis: what does it mean? Gut 1991;32:174–178.

Reprint requests
Address requests for reprints to: David T. Rubin, MD, Inflammatory Bowel Disease Center, University of Chicago Medicine, 5841 South Maryland Avenue, MC 4076, Chicago, Illinois 60637. e-mail: drubin@uchicago.edu; fax: (773) 702-2182.

Conflicts of interest
These authors disclose the following: Russell D. Cohen is a consultant at Abbvie, Celgene, Janssen, Pfizer, Takeda, and UCB Pharma. Atsushi Sakuraba has received funding from AbbVie, Celltrion, and Takeda. David T. Rubin is a consultant and has received grant support from Abbvie, Merck & Co., Janssen, Takeda, and Pfizer. No funding or sponsorship was received for this study or publication of this article. The remaining authors disclose no conflicts.



Supplementary Figure 1. Follow-up of histological disease activity in UC patients who have achieved histologic normalization. Year 0 is time of indexed normalization date. Histology scores: 0, normal; 1, quiescent; 2, active.

6.3 Supplementary II: Efficacy and safety of induction therapy with calcineurin inhibitors followed by vedolizumab maintenance in 71 patients with severe steroid-refractory ulcerative colitis

Ollech JE, Dwadasi S, Rai V, Peleg N, Normatov I, Israel A, et al. Efficacy and safety of induction therapy with calcineurin inhibitors followed by vedolizumab maintenance in 71 patients with severe steroid-refractory ulcerative colitis. Aliment Pharmacol Ther. 2020;51(6):637-43.

Received: 9 July 2019 | First decision: 14 August 2019 | Accepted: 26 November 2019

DOI: 10.1111/apt.15616

AP&T Alimentary Pharmacology & Therapeutics WILEY

Efficacy and safety of induction therapy with calcineurin inhibitors followed by vedolizumab maintenance in 71 patients with severe steroid-refractory ulcerative colitis

Jacob E. Ollech[1] | Sujaata Dwadasi[1] | Victoria Rai[1] | Noam Peleg[2,3] | Inessa Normatov[1] | Amanda Israel[1] | Philip H. Sossenheimer[1] | Britt Christensen[4] | Joel Pekow[1] | Sushila R. Dalal[1] | Atsushi Sakuraba[1] | Russell D. Cohen[1] | David T. Rubin[1]

[1]Inflammatory Bowel Disease Center, University of Chicago Medicine, Chicago, IL, USA

[2]Inflammatory Bowel Disease Center, Rabin Medical Center, Petah Tikva, Israel

[3]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[4]Department of Gastroenterology, The Royal Melbourne Hospital, Melbourne, Australia

Correspondence
David T. Rubin, Inflammatory Bowel Disease Center, University of Chicago Medicine, 5841 S. Maryland Ave, MC 4076, Chicago, IL 60637, USA.
Email: drubin@uchicago.edu

Summary

Background: Following induction therapy with a calcineurin inhibitor (CNI) in severe ulcerative colitis, transitioning to vedolizumab as maintenance therapy could be an option.

Aim: To report on the largest cohort of patients successfully induced with CNIs who were transitioned to vedolizumab maintenance therapy.

Methods: This is a retrospective observational study of adult patients with severe steroid-refractory ulcerative colitis. Patients were included if they were induced with a CNI followed by maintenance therapy with vedolizumab between January 2014 and December 2018. The primary endpoint was colectomy-free survival. Secondary endpoints included survival without vedolizumab discontinuation as well as clinical, steroid-free and biochemical remission at week 14.

Results: A total of 71 patients (59% male) were treated with vedolizumab after induction therapy with CNIs for severe steroid-refractory colitis. Patients were followed for a median time of 25 months (IQR 16-36). Colectomy-free survival rates from vedolizumab initiation were 93% at 3 months, 67% at 1 year and 55% at 2 years. At the end of induction with vedolizumab at week 14, 50% of patients were in clinical remission, and 62% of patients had a normal CRP. At 1 and 2 years following vedolizumab initiation, 43% and 28% of patients were still on vedolizumab respectively. Vedolizumab was dose escalated to infusions every 4 weeks in 44% of patients. The median time to dose escalation was 5.6 months (IQR 4.1-8.2). No serious adverse events were recorded in our patient cohort.

Conclusions: Transitioning to vedolizumab following induction of remission with CNIs is effective and safe.

The Handling Editor for this article was Dr Nicholas Kennedy, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

Ulcerative colitis is a chronic inflammatory disease of the colon with varying degrees of disease severity as defined by several clinical, biochemical and endoscopic parameters.[1,2]

The options for the medical management of patients with severe steroid-refractory ulcerative colitis are limited and include calcineurin inhibitors (CNIs) or infliximab,[1-6] with infliximab being the predominant agent used in such a setting, due to its ease of administration and familiarity with its use by prescribing physicians.[7] Patients who are successfully induced with infliximab continue to maintenance therapy with this drug. Secondary to its increased use in ulcerative colitis, patients failing infliximab are becoming more prevalent.[8]

While highly effective at inducing remission in patients with ulcerative colitis,[3,5] protracted use of CNIs is limited by adverse events, including infection, nephrotoxicity, hypercholesterolaemia and hypertension. Consequently, their use in inflammatory bowel disease has been limited to induction therapy. Patients who are successfully induced with CNIs in the setting of severe steroid-refractory ulcerative colitis are bridged to azathioprine for maintenance therapy.[1,2] Previously, patients who had failed or were intolerant to thiopurines were not considered candidates for calcineurin therapy due to the absence of effective maintenance therapy.

Vedolizumab is an effective and safe medication approved for induction and maintenance therapy in ulcerative colitis.[9,10] Vedolizumab's impressive safety data[10] makes it an ideal candidate agent for use as maintenance therapy in combination with the fast-acting CNIs as induction therapy. Our group previously reported our preliminary data on the potential safety and efficacy of this sequential combination regimen.[11] That study, however, was limited by the small number of patients and heterogeneous population included (11 patients with ulcerative colitis and nine patients with Crohn's disease) and as such encouraged further larger observational cohorts using this treatment strategy. In this study, by enrolling a significant number of subsequent patients with steroid-refractory ulcerative colitis, we are now able to cumulatively report on long-term safety and efficacy in a more homogenous population.

We describe the largest cohort of patients with steroid-refractory ulcerative colitis successfully induced with CNIs who were then transitioned to vedolizumab maintenance therapy and show that such a management strategy is effective and safe over a long follow-up period.

2 | METHODS

2.1 | Study design and patients

We performed a retrospective single-centre observational study of adult ulcerative colitis patients followed at the University of Chicago Inflammatory Bowel Disease Center, a large tertiary referral centre. All patients with severe steroid-refractory ulcerative colitis who received a CNI (ciclosporin or tacrolimus) as induction therapy followed by maintenance therapy with vedolizumab between January 2014 and December 2018 were included. All patients responded to IV ciclosporin or oral tacrolimus and received at least one vedolizumab infusion while on calcineurin therapy.

2.2 | Medications

All patients were treated with either IV ciclosporin or oral tacrolimus.

Ciclosporin was given as a continuous infusion at an initial dose of 2-4 mg/kg/d, aiming for serum trough levels of 300-400 ng/mL. In case of response (decrease of bowel movement frequency by 50% with the absence of haematochezia), a switch to an oral formulation was performed using a total daily dose equivalent to twice the 24 hour intravenous dose.

Tacrolimus was started orally at 0.1 to 0.2 mg/kg/d, targeting a blood concentration of 10-15 ng/g. The choice of the CNI used, ciclosporin or tacrolimus, was made according to the attending physician discretion.

In patients who responded to calcineurin induction, vedolizumab was administered as 300 mg infusions with standard loading doses; weeks 0, 2 and 6, and then every 8 weeks. In case of continued clinical activity or objective evidence of continued inflammation (laboratory or endoscopic), vedolizumab could be prescribed every 4 weeks following induction. Following the induction infusions of vedolizumab the CNI was tapered off. In the case of vedolizumab failure, subsequent treatments were documented, as well.

2.3 | Data collection

At inclusion, the following characteristics were recorded for each patient: sex, age, disease duration, smoking status, disease extent according to the Montreal classification, prior received treatments (steroids, thiopurine, methotrexate, infliximab, adalimumab, golimumab), endoscopic activity measured with the endoscopic Mayo subscore, C-reactive protein (CRP), haemoglobin and albumin levels. All patients included had a clinic follow-up of at least 3 months.

2.4 | Endpoints

The primary endpoint was colectomy-free survival. Secondary endpoints included survival without vedolizumab discontinuation as well as clinical, steroid-free, biochemical remission at week 14 as well as time to endoscopic remission and rate of endoscopic remission at 12 months. Clinical remission was defined as the absence of blood in the stools and <3 stools per day with the lack of abdominal pain. Biochemical remission was defined by a normal CRP level (<5 mg/L). Endoscopic remission was defined as an Mayo endoscopic score of 0 or 1. In addition, all adverse events were described. The study was approved by the University of Chicago Institutional Review Board.

2.5 | Statistical analysis

Descriptive statistics for demographic and clinical characteristics include median (IQR) for continuous variables and frequency distributions for categorical data. Kaplan-Meier curves were generated for time-to-event data, that is, time from first vedolizumab infusion until colectomy or cessation of vedolizumab treatment. Patients who did not have a colectomy or who were still on vedolizumab were censored as of the date of the last follow-up. Cox regression models were fit to examine the effects of different covariates on time to colectomy and vedolizumab cessation. Covariates analysed included age, sex, smoking status, disease extent, pre-vedolizumab treatments, clinical and biochemical remission at week 14, as well as haemoglobin, CRP and albumin. Due to the limited number of events, models for time to colectomy or vedolizumab cessation included only one covariate at a time to avoid overfitting.

3 | RESULTS

3.1 | Patients

A total of 71 patients (59% male) were treated with vedolizumab after induction therapy with CNIs for severe steroid-refractory ulcerative colitis. Eighty-five per cent (n = 60) of patients had previously been exposed to TNF antagonists' medications. Most had extensive disease (72%); the median disease duration was 44.1 months (IQR 15.2-115). Truelove and Witts criteria for acute severe ulcerative colitis (ASUC) were present in 76% (n = 54) of patients. Moderate to severe endoscopic disease was present in 97% of patients. Patients were followed for a median time of 25 months (IQR 16-36).

3.2 | Study medications

Sixty-eight per cent of patients (n = 48) received ciclosporin, and 32% (n = 23) of patients received tacrolimus. The CNI was continued for a median duration of 3.5 months (IQR 2.4-5.4). The majority (79%, n = 55) were induced with CNIs as inpatients, with ciclosporin being the drug of choice in most inpatients (88%, n = 48). Vedolizumab was started after a median of 29 days (IQR 16-44) from the initiation of the CNI. Vedolizumab was dose escalated to infusions every 4 weeks in 44% of patients. The median time to dose escalation was 5.7 months (IQR 4.1-8.2). Table 1 describes the baseline characteristics of the study cohort allocated according to the CNI used.

3.3 | Efficacy

Thirty patients (42%) underwent colectomy during the follow-up period. Colectomy-free survival rates from vedolizumab initiation were 93% at 3 months, 67% at 1 year and 55% at 2 years (Figure 1A). Only lack of clinical remission at week 14 was associated with colectomy (P = 0.023). There was no significant difference in colectomy rates between anti-TNF naïve patients and

TABLE 1 Baseline characteristics: allocation according to CNI type—ciclosporin and tacrolimus

Characteristic	Ciclosporin (N = 48)	Tacrolimus (N = 23)	*P*
Median age, y (IQR)	29.2 (22.8-39.4)	29.8 (20.1-38.2)	0.59
Male sex	34 (70.8%)	8 (34.8%)	0.004
Disease duration, y (IQR)	5 (1.1-10.6)	2.5 (1.6-7.5)	0.22
Smoker	13 (27.1%)	5 (21.7%)	0.63
Montreal classification			
1	1 (2.1%)	1 (4.3%)	0.66
2	10 (20.58%)	6 (26.1%)	
3	33 (68.8%)	13 (56.5%)	
Prior treatment			
Steroids	48 (100%)	23 (100%)	—
Thiopurines	27 (56.3%)	11 (47.8%)	0.51
Anti-TNFs	41 (85.4%)	19 (82.6%)	0.67
Methotrexate	9 (18.8%)	4 (17.4%)	0.89
Median CRP, mg/L (IQR)	13 (4-46)	18 (3.2-50)	0.99
Median haemoglobin, g/dL (IQR)	11.5 (9.9-13.3)	11.7 (9.7-13.3)	0.86
Median albumin, g/dL (IQR)	3.4 (3.1-3.9)	3.6 (3.2-4.1)	0.35
Endoscopic Mayo Score			
1	1 (2.1%)	1 (4.3%)	0.13
2	11 (22.9%)	5 (21.7%)	
3	36 (75%)	7 (30.4%)	

anti-TNF experienced patients, (P = 0.79) (Figure 1B). Likewise, choice of the CNI used to induce remission was not associated with colectomy rates (P = 0.91). Patients meeting Truelove and Witts criteria for ASUC had numerically higher colectomy rates at 3 months and 1 year when compared to patients not meeting these criteria (9.5% and 37.1% vs 6.25% and 19.65% respectively), but this difference was not statistically significant (P = 0.8). Table 2 describes the baseline characteristics of patients with and without ASUC.

At the end of induction with vedolizumab at week 14, 50% of patients were in clinical remission, and 62% of patients were in biochemical remission with a normal CRP. Steroid-free remission rates were 27%, 43% and 76% at 3 months, 12 months and 24 months respectively.

Sixty-three per cent of patients were still on vedolizumab 6 months after induction. After 1 and 2 years, 43% and 28% of patients were still on vedolizumab respectively (Figure 1C). Both lack of clinical and biologic remission at week 14 were associated with vedolizumab discontinuation (P = 0.0003 and P = 0.003 respectively). Previous TNF antagonist therapy was not associated with an increased rate of vedolizumab discontinuation (P = 0.86). Data regarding endoscopic remission were available for 44 participants (61.9% of the study cohort), twenty-one patients (48%) reached the endpoint of endoscopic remission during follow-up. The cumulative rate of endoscopic remission at 12 months was 20.9%.

3.4 | Drug therapy following discontinuation of vedolizumab

Thirty-one patients (44%) were transitioned to another drug after failing vedolizumab maintenance therapy. Seventeen patients were transitioned to an anti-TNF (71% infliximab); of these 17 patients, 15 (88%) had previously been on anti-TNF therapy, and 12 (71%) of these patients averted colectomy at the end of follow-up. Eleven patients were transitioned to tofacitinib. Eight (73%) of these patients had previously been on anti-TNF therapy, and six (55%) averted colectomy at the end of follow-up. Three patients were transitioned to ustekinumab. Two of these patients were previously on anti-TNF therapy, and two patients averted colectomy at the end of follow-up. Of these 31 patients who failed vedolizumab and transitioned to another drug, 20 (65%) averted colectomy at the end of follow-up. Colectomy-free survival times were similar after excluding patients who received other biologics after vedolizumab failure (Figure 1A). The median time to switch in therapy was 7.1 months (IQR 3.7-14.3) from vedolizumab initiation.

3.5 | Adverse events

Eighteen patients (25.4%) experienced adverse events. No mortality events were recorded during the follow-up period. In addition, all adverse events documented occurred while on CNIs, with none of the adverse events leading to discontinuation of the drug. The most common adverse event was acute kidney injury in eight patients (11.3%) (Table 3).

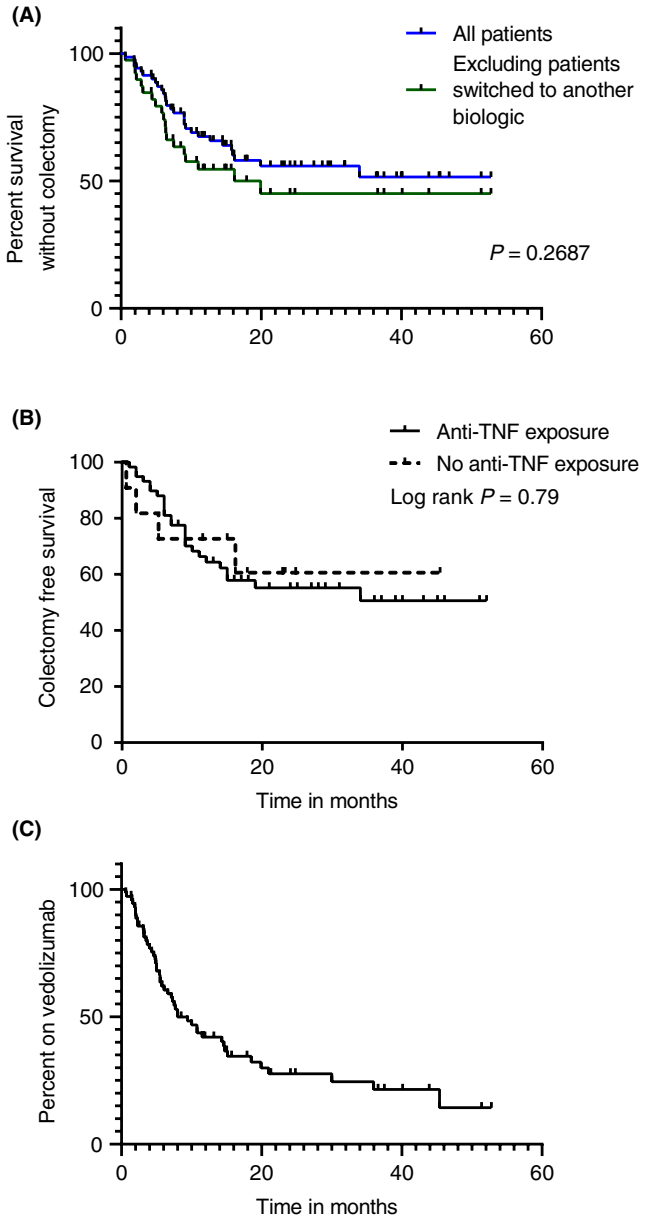


FIGURE 1 A, Kaplan Meier curve of colectomy free survival for all patients and after excluding patients who received other biologics after vedolizumab failure. B, Kaplan Meier of colectomy free survival for patients exposed and not exposed to TNF antagonists. C, Kaplan Meier curve of time to vedolizumab discontinuation

4 | DISCUSSION

In this study, we have shown that patients with severe steroid-refractory ulcerative colitis induced with CNIs and then transitioned to maintenance therapy with vedolizumab avoided colectomy in 67% of cases after 12 months and in 55% of cases after 2 years. Such a

TABLE 2 Baseline characteristics of patients with and without ASUC

Characteristic	Acute severe UC (N = 54)	No acute severe UC (N = 17)	*P*
Median age, y (IQR)	29.2 (22.2-38.2)	36.2 (23.6-38.8)	0.48
Male sex	34 (63%)	7 (41.1%)	0.17
Disease duration, y (IQR)	3.8 (1.2-10.7)	3.1 (1.1- 5.9)	0.73
Smoker	15 (27.8)	3 (17.6%)	0.47
Montreal classification			
1	0 (0%)	2 (11.7%)	0.03
2	12 (22.2%)	4 (23.5%)	
3	36 (66.7%)	9 (52.9%)	
Prior treatment			
Steroids	54 (100.0%)	17 (100%)	–
Thiopurines	30 (55.6%)	8 (47.0%)	0.69
Anti-TNFs	46 (85.2%)	14 (82.3%)	0.81
Methotrexate	7 (13.0%)	6 (35.3%)	0.03
Median CRP, mg/L (IQR)	22.5 (8.7-51.2)	7 (3-9.2)	<0.001
Median haemoglobin, g/dL (IQR)	10.9 (9.3-12.1)	13.5 (12.7-14.5)	<0.001
Median albumin, g/dL (IQR)	3.3 (2.9-3.7)	3.8 (3.7-3.9)	<0.001
Endoscopic Mayo Score			
1	0 (0)	2 (11.7%)	<0.001
2	6 (11.1%)	10 (58.8%)	
3	39 (72.2%)	3 (17.6%)	
CNI type			
Ciclosporin	38 (70.4%)	10 (58.8%)	0.29
Tacrolimus	16 (29.6%)	7 (41.1%)	

strategy was well tolerated in our cohort, with relatively few adverse events.

The strength of this study includes its large cohort of patients, larger than all previously reported studies combined, as well as the long median follow-up of over 2 years.

There have been two previous studies[11,12] and a case series of two patients[13] that demonstrated the feasibility of inducing remission with ciclosporin followed by maintenance of remission with vedolizumab. However, both studies had limitations, including small patient numbers and limited follow-up time. The earlier study from our group by Christensen et al[11] reported on nine patients with Crohn's disease and 11 patients with ulcerative colitis treated with combination therapy of vedolizumab with either ciclosporin or tacrolimus, and found that by week 14 of treatment, four (44%) patients with Crohn's disease and six (55%) patients with ulcerative colitis were in clinical remission.

The second study by Pellet G et al[12] was a multicentre retrospective study from France. In this study, information was collected on 39 patients with steroid-refractory UC. The authors reported that after a median follow-up period of 11 months, 11 patients (28%) underwent colectomy and that patients meeting Truelove and Witts criteria for ASUC had higher colectomy rates when compared to patients who did not meet these criteria. While both studies reported on the feasibility of combination treatment with CNIs and vedolizumab to induce and maintain remission, larger observational studies are needed to better explore the efficacy and safety of such a strategy before advocating for its use in everyday practice.

In our large patient cohort with prolonged follow-up time, we have shown the safety and efficacy of such a treatment strategy. We chose colectomy-free survival as our primary endpoint as colectomy is an unambiguous event in a retrospective cohort series. Indeed, our study showed that in this very sick cohort of patients, a substantial proportion of patients were able to avoid colectomy in the short and long term by inducing patients with CNIs and transitioning to vedolizumab as maintenance therapy. Unlike the study by Pellet G et al[12] in our patient cohort, there was no significant difference between patients who met Truelove and Witts criteria for ASUC and those that did not in regards to colectomy free survival ($P = 0.8$). However, patients with ASUC did have numerically higher colectomy rates at 3 months and 1 year when compared to those without ASUC (9.5% and 37.1% vs 6.25% and 19.65% respectively). The study was likely underpowered to detect a difference, especially as the group without ASUC was relatively small at only 17 patients. It is also possible that as this study only included patients who had already responded to ciclosporin induction that colectomy rates between groups might have been attenuated.

We also looked at the time to vedolizumab discontinuation, and we have shown that despite a significant number of patients failing

TABLE 3 Adverse events

Event	Treatments given at the time of event (N)	N (%)
Acute kidney injury	Tacrolimus (1)	8 (11.3)
	Ciclosporin (2)	
	Tacrolimus + Vedolizumab (2)	
	Ciclosporin + Vedolizumab (3)	
Paraesthesia	Ciclosporin (1)	2 (2.8)
	Ciclosporin + Vedolizumab (1)	
Muscle weakness	Ciclosporin	1 (1.4)
Hirsutism	Ciclosporin	1 (1.4)
Gingival hypersensitivity	Tacrolimus	1 (1.4)
Myositis	Ciclosporin	1 (1.4)
Headaches	Tacrolimus + Vedolizumab	1 (1.4)
Pruritus	Ciclosporin + Vedolizumab	1 (1.4)
Tremor	Ciclosporin	1 (1.4)
Hand and feet swelling	Tacrolimus + Vedolizumab	1 (1.4)

vedolizumab over time, patients were able to avoid colectomy in the short and long term. In our cohort, after 2 years of therapy, 72% of patients had stopped vedolizumab therapy. Of note, in the pivotal GEMINI-1 clinical trial,[9] in patients who responded to vedolizumab induction, mucosal healing at 1 year was 50%, and steroid-free remission was 31% at 1 year. Likewise, in the recently published VARSITY trial,[14] steroid-free remission at 1 year was 12.6%. Similar data for other biologic therapy over time exists as well; for example, in the ACT-1 study of infliximab for moderate to severe UC,[15] remission rates at 1 year were only 20%.

At the University of Chicago, patients were treated in a 'treat to target' management strategy consistent with the 'Selecting Therapeutic Targets in Inflammatory Bowel Disease' Consensus statement.[16] Over time, even if patients averted colectomy, patients who still had clinical disease with endoscopic activity or were corticosteroid dependent were switched to other therapies. It is plausible that over a long follow-up period, a substantial number of patients will not reach management targets and will be switched to other therapies as these become available and treatment targets become more stringent. Patients who discontinued vedolizumab were able to successfully transition and regain response with other therapies, mainly tofacitinib and infliximab.

Interestingly, many patients transitioned to anti-TNFs after failing vedolizumab maintenance therapy were previously treated with an anti-TNF. Due to the retrospective nature of our study, we were unable to document the reason why anti-TNF therapy was stopped for a large proportion of these patients. Some patients had a distant history of anti-TNF use, and, as many of these patients were referred from outside institutions, no further data were available to us in order to clarify the reason behind anti-TNF discontinuation. Likewise, due to the small number of patients who transitioned to further therapy with anti-TNFs and the lack of historical data for many of these patients, these results, while interesting, should be exploratory. Further studies should be performed looking into the possibility of 'circling back' to prior therapies in order to establish the efficacy of such a treatment strategy.

Inducing remission with CNIs and transitioning to vedolizumab maintenance therapy is becoming more relevant as more patients with ulcerative colitis now have a history of previous exposure and failure to anti-TNFs and azathioprine.[8] Likewise, since the publication of the CYSIF and CONSTRUCT trials,[17,18] which demonstrated similar short-term response rates between infliximab and ciclosporin in the setting of acute severe ulcerative colitis, infliximab has emerged as the predominant agent used in such patients,[7] and more patients are presenting to tertiary care centres after failing infliximab.[8] A potential reason for nonresponse to infliximab is secondary loss of serum proteins due to monoclonal antibodies loss through an inflamed gut[19] and in such patients, the use of a nonprotein-based therapy for induction of remission, such as a CNI, could be useful.

The current study adds confidence to using the approach of inducing remission with CNIs—which are potent and fast-acting drugs with proven efficacy in treating patients with severe ulcerative colitis[3,5-8,17,18,20] and then transitioning to the slower acting steroid-sparing agent, vedolizumab, for maintenance therapy.[9,10] We have shown that overlapping these two drugs is effective and safe. This study adds to the armamentarium of therapeutic interventions available to physicians treating patients with severe steroid-refractory ulcerative colitis.

There are several limitations to our study, mainly linked to its retrospective single-centre setting with the inherent risk of bias, and incomplete data for some patients. Treatments were not standardised, and the side effects of drugs may have been underestimated. It should also be emphasised that patients were treated by expert physicians in a large referral centre.

In conclusion, induction of remission with CNIs with a transition to vedolizumab is effective and safe and leads to avoidance of colectomy in a substantial subgroup of patients over a long follow-up period. Such a treatment strategy might be considered in patients with steroid-refractory colitis, especially if they had previously failed either anti-TNFs or thiopurines. Such a strategy enables the introduction of safe protein-based therapies such as vedolizumab following stabilisation and induction of remission with CNIs.

ACKNOWLEDGEMENTS

Declaration of personal interests: None.

AUTHORSHIP

Guarantor of the article: David T Rubin.

Consultant: AbbVie, Janssen, Pfizer, Takeda.

Grant Support: Takeda.

Author contributions: JEO and DTR conceived and designed the study. JEO, AI, JP, SRD, RDC, NP, and DTR drafted the manuscript

with critical revisions by SD, IN, BC, and AS. All authors contributed to the acquisition of the data. JEO, VR, PHS, RDC, NP, and DTR contributed to the analysis and interpretation of data.

All authors approved the final version of the manuscript.

LINKED CONTENT

This article is linked to Battat et al paper. To view this article, visit https://doi.org/10.1111/apt.15632.

ORCID

Britt Christensen https://orcid.org/0000-0002-8746-4275
Atsushi Sakuraba https://orcid.org/0000-0003-2519-6129
David T. Rubin https://orcid.org/0000-0001-5647-1723

REFERENCES

1. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol*. 2019;114:384-413.
2. Harbord M, Eliakim R, Bettenworth D, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: current management. *J Crohns Colitis*. 2017;11:769-784.
3. Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med*. 1994;330:1841-1845.
4. Järnerot G, Hertervig E, Friis-Liby I, et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. *Gastroenterology*. 2005;128:1805-1811.
5. Wu B, Tong J, Ran Z. Tacrolimus therapy in steroid-refractory ulcerative colitis: a review. *Inflamm Bowel Dis*. 2019. https://doi.org/10.1093/ibd/izz068 [Epub ahead of print].
6. Hoffmann P, Wehling C, Krisam J, Pfeiffenberger J, Belling N, Gauss A. Performance of tacrolimus in hospitalized patients with steroid-refractory acute severe ulcerative colitis. *World J Gastroenterol*. 2019;25:1603-1617.
7. Sjöberg M, Walch A, Meshkat M, et al. Infliximab or cyclosporine as rescue therapy in hospitalized patients with steroid-refractory ulcerative colitis: a retrospective observational study. *Inflamm Bowel Dis*. 2012;18:212-218.
8. Weisshof R, Ollech JE, El Jurdi K, et al. Ciclosporin therapy after infliximab failure in hospitalized patients with acute severe colitis is effective and safe. *J Crohns Colitis*. 2019;13:1105-1110.
9. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2013;369:699-710.
10. Colombel J-F, Sands BE, Rutgeerts P, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. *Gut*. 2017;66:839-851.
11. Christensen B, Gibson PR, Micic D, et al. Safety and efficacy of combination treatment with calcineurin inhibitors and vedolizumab in patients with refractory inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2019;17:486-493.
12. Pellet G, Stefanescu C, Carbonnel F, et al. Efficacy and safety of induction therapy with calcineurin inhibitors in combination with vedolizumab in patients with refractory ulcerative colitis. *Clin Gastroenterol Hepatol*. 2019;17:494-501.
13. Szanto K, Molnar T, Farkas K. New promising combo therapy in inflammatory bowel diseases refractory to anti-TNF agents: cyclosporine plus vedolizumab. *J Crohns Colitis*. 2018;12:629.
14. Sands BE, Peyrin-Biroulet L, Loftus EV, et al. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. *N Engl J Med*. 2019;381:1215-1226.
15. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2005;353:2462-2476.
16. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. *Am J Gastroenterol*. 2015;110:1324-1338.
17. Williams JG, Alam MF, Alrubaiy L, et al. Infliximab versus ciclosporin for steroid-resistant acute severe ulcerative colitis (CONSTRUCT): a mixed methods, open-label, pragmatic randomised trial. *Lancet Gastroenterol Hepatol*. 2016;1:15-24.
18. Laharie D, Bourreille A, Branche J, et al. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. *Lancet*. 2012;380:1909-1915.
19. Brandse JF, van den Brink GR, Wildenberg ME, et al. Loss of infliximab into feces is associated with lack of response to therapy in patients with severe ulcerative colitis. *Gastroenterology*. 2015;149:350-355; e2.
20. Ordás I, Domènech E, Mañosa M, et al. Long-term efficacy and safety of cyclosporine in a cohort of steroid-refractory acute severe ulcerative colitis patients from the ENEIDA registry (1989–2013): a Nationwide Multicenter Study. *Am J Gastroenterol*. 2017;112:1709-1718.

How to cite this article: Ollech JE, Dwadasi S, Rai V, et al. Efficacy and safety of induction therapy with calcineurin inhibitors followed by vedolizumab maintenance in 71 patients with severe steroid-refractory ulcerative colitis. *Aliment Pharmacol Ther*. 2020;51:637–643. https://doi.org/10.1111/apt.15616

6.4 Supplementary III: Letter: vedolizumab for autoimmune liver disease associated inflammatory bowel disease—Authors' reply

Christensen B, Gibson PR, Rubin DT. Letter: vedolizumab for autoimmune liver disease associated inflammatory bowel disease-Authors' reply. Aliment Pharmacol Ther. 2018;47(10):1423-4.

M. Mañosa
E. Domènech
IBD Unit, Gastroenterology Department, Hospital Universitari Germans Trias i Pujol, Badalona, Spain
Email: mmanosa.germanstrias@gencat.cat

REFERENCES

1. Everhov AH, Ludvigsson JF, Olén O. Letter: phenotype and natural history of elderly onset inflammatory bowel disease. *Aliment Pharmacol Ther*. 2018;47:1420-1421.
2. Mañosa M, Calafat M, de Francisco R, et al. Phenotype and natural history of elderly onset inflammatory bowel disease: a multicentre, case-control study. *Aliment Pharmacol Ther*. 2018;47:605-614.
3. Everhov AH, Halfvarson J, Myrelid P, et al. Incidence and treatment of patients diagnosed with inflammatory bowel diseases at 60 years or older in Sweden. *Gastroenterology*. 2017;154:518-528.
4. Lobatón T, Ferrante M, Rutgeerts P, Ballet V, van Assche G, Vermeire S. Efficacy and safety of anti-TNF therapy in elderly patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2015;42:441-445.
5. Cottone M, Kohn A, Daperno M, et al. Advanced age is an independent risk factor for severe infections and mortality in patients given anti-tumor necrosis factor therapy for inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2011;9:30-35.
6. Calafat M, Mañosa M, Cañete F, et al. The initiation of thiopurines in elderly patients with inflammatory bowel disease is associated with an increased risk of adverse effects: a case–control study of the ENEIDA registry. *J Crohn's Colitis*. 2018;12:S023-S025.
7. Charpentier C, Salleron J, Savoye G, et al. Natural history of elderly onset inflammatory bowel disease: a population-based cohort study. *Gut*. 2014;63:423.
8. Lakatos PL, David G, Pandur T, et al. IBD in the elderly population: results from a population-based study in Western Hungary, 1977-2008. *J Crohn's Colitis*. 2011;5:5-13.
9. Jeuring SF, van den Heuvel TR, Zeegers MP, et al. Epidemiology and long-term outcome of inflammatory bowel disease diagnosed at elderly age-an increasing distinct entity? *Inflamm Bowel Dis*. 2016;22:1425-1434.
10. Fries W, Viola A, Manetti N, et al. Disease patterns in late-onset ulcerative colitis: results from the IG-IBD "AGED study". *Dig Liver Dis*. 2017;49:17-23.

DOI: 10.1111/apt.14603

Letter: vedolizumab for autoimmune liver disease associated inflammatory bowel disease

EDITORS,

We read with great interest the manuscript by Christensen et al summarising their multicentre experience of treating 34 PSC-IBD patients with vedolizumab (VDZ).[1] The authors provide subjective and objective evidence of improvement in the activity of IBD. Disappointingly, no improvement was seen in the activity of PSC based on liver biochemistry or Mayo score.

Since our first report on VDZ use in autoimmune liver disease (AILD) associated IBD[2] we have treated in total 17 patients with active IBD (nine with recurrence post liver transplantation, treatment duration: 18 patient/years). Prior to VDZ commencement a loss of response to anti-TNF and/or a thiopurine was seen in 8 (48%) patients while nine were on a combination of tacrolimus, mycophenolate mofetil and prednisolone (post-transplant immunosuppression). An improvement in IBD activity as assessed by the attending physician based on clinical scoring and endoscopy or faecal calprotectin (fcal) was seen in 11/17 (65%) in the first 6 months after drug initiation. At 12 months of follow-up 9/17 (53%) remained on the drug. At the end of follow-up 11/17 (65%) had stopped treatment due to lack of efficacy (9/11, 81%), one in preparation for liver transplantation and two who required colectomy due to the development of colonic malignancy (one with high grade dysplasia and one with post-transplant lymphoproliferative disorder-PTLD). Both these patients had a long history of PSC-IBD (>10 years, on VDZ for 11 and 18 months respectively) and underwent colonic surveillance annually. Notwithstanding the observed clinical and endoscopic response to VDZ (treated for 11 and 18 months) residual pseudopolyps were found in both patients and fcal never normalised (>50 ug/g, Bulhmann ELISA assay). In this high-risk population for colorectal malignancies, currently at our centre we follow a strict endoscopic review annually and even biannually for those with additional risk factors (ie pseudopolyps, ongoing inflammation: fcal > 150 ug/g, EBV viraemia for transplant patients). We feel that this is the safest approach especially while long-term data on the effects of anti-trafficking therapies on IBD related colorectal cancer are still being collected.

We also did not identify any change in the liver biochemistry before and after 12 months of VDZ therapy (n = 17, AST: median 42 IU/L [IQR: 27-66] vs 41 [IQR: 28-56], $P = 0.80$, ALP: 174 IU/L [IQR: 92-570] vs 225 [IQR: 76-501], $P = 0.46$, GGT: 100 IU/L [IQR: 61-633] vs 175 [IQR: 73-637], $P = 0.79$, respectively). As the authors point out though, it is well accepted that these tests are only surrogate markers of the cholangiopathy seen with PSC, with limited prognostic value. One could argue that episodes of cholangitis, the need for biliary duct drainage or stricture dilatation are more robust outcomes of PSC activity. However, there were no such events seen in our non-transplant patients in the year before or after VDZ commencement. It

would be very informative if the authors could identify and report these events interrogating their larger cohort.

ACKNOWLEDGEMENTS

Declaration of personal interests: PP, JG, SG, DJ, MH: none to declare. PD: has received travel grant to ECCO 2018 by Takeda Pharmaceuticals. BH: has served as a speaker and has received research grant from Takeda Pharmaceuticals.

FUNDING INFORMATION

None.

ORCID

P. Pavlidis http://orcid.org/0000-0003-4864-2208

LINKED CONTENT

This article is linked to Christensen et al papers. To view these articles visit https://doi.org/10.1111/apt.14525 and https://doi.org/10.1111/apt.14638.

P. Pavlidis[1]
J. Graham[2]
S. Gulati[1]
P. Dubois[1]
M. Heneghan[2]
D. Joshi[2]
B. Hayee[1]

[1]*Department of Gastroenterology, King's College Hospital, London, UK*
[2]*Institute of Liver Studies, King's College Hospital, London, UK*
Email: ppavlidis@nhs.net

REFERENCES

1. Christensen B, Micic D, Gibson PR, et al. Vedolizumab in patients with concurrent primary sclerosing cholangitis and inflammatory bowel disease does not improve liver biochemistry but is safe and effective for the bowel disease. *Aliment Pharmacol Ther*. 2018;47:753-762.
2. Lim TY, Pavlidis P, Gulati S, et al. Vedolizumab in inflammatory bowel disease associated with autoimmune liver disease pre- and post liver transplantation: a case series. *Inflamm Bowel Dis*. 2016;22:E39-E40.

DOI: 10.1111/apt.14638

Letter: vedolizumab for autoimmune liver disease associated inflammatory bowel disease—Authors' reply

EDITORS,

We thank Pavlidis and colleagues[1] for their interest in our article, and the excellent addition of their own experience in primary sclerosing cholangitis (PSC) patients treated with vedolizumab. Similar to our study, they have demonstrated that patients with IBD-PSC have improvement in IBD clinical activity but no improvement in liver enzymes after 12 months of therapy.

In regards to more rigorous measure of PSC activity, we describe two patients who did develop cholangitis in the first 6 months of treatment with vedolizumab, one who required liver transplant for progressive PSC and one who required dilation of a dominant stricture. Both continued on vedolizumab. In addition, one patient ceased vedolizumab due to a drug reaction in the liver that was unrelated to PSC. Unfortunately, despite these observations, it is still difficult to determine if vedolizumab may be of benefit in the long term in patients with PSC. This is why long-term registry studies are required to determine if this medication can change the natural progression of PSC on negative liver outcomes.

We also note with interest the two cases of malignancy following initiation of vedolizumab in Pavlidis' cohort.[1] In our series, there were no cases of high grade dysplasia or malignancy. However, as identified by Pavlidis et al[1] and commented in our own study,[2] strict endoscopic surveillance of these patients is required, particularly given the lack of long-term data on the effects of anti-integrin therapies on dysplasia and colorectal cancer rates.

ACKNOWLEDGEMENTS

The authors' declarations of personal and financial interests are unchanged from those in the original article.[2]

ORCID

B. Christensen http://orcid.org/0000-0002-8746-4275

LINKED CONTENT

This article is linked to Christensen et al and Pavlidis et al papers. To view these articles visit https://doi.org/10.1111/apt.14525 and https://doi.org/10.1111/apt.14603.