Medication adherence in patients with rheumatoid arthritis in Iran; focusing on the effect of medication out-of-pocket costs on medication adherence

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Abstract

Background:

Patients with rheumatoid arthritis (RA) often require long term treatment with multiple medications. Synthetic disease-modifying antirheumatic drugs (sDMARDs) and newer biologic DMARDs (bDMARDs) are the main pharmaceutical treatments for RA. Early and aggressive intervention with these medications has been shown to improve clinical outcomes, induce remission and prevent joint erosion progress. Medication adherence is essential to encourage the best health results in RA; however, adherence has found to be sub-optimal. With the introduction of expensive bDMARDs, patients with RA are likely to experience cost-related medication non-adherence (CRN). In 2014, the Iran government launched a Health Sector Evolution Plan to reduce healthcare costs for patients and provide equal access to healthcare. The outcome of this Plan has not been investigated for patients with RA.

Aims:

This thesis assessed medication adherence to oral RA medications in patients with RA in Iran and examined determinants of adherence with a specific focus on the effect of medication OOP costs.

Methods:

Guided by Andersen's Behavioral Model of Health Services Use, a concurrent mixed methods study was designed. The study was conducted in Shiraz, Iran and had two components. In Component One, a cross-sectional survey of 308 patients with RA was conducted to assess medication adherence to oral RA medications and its determinants with a focus on the effect of OOP costs on medication adherence. In Component Two, 10 semi-structured interviews were conducted with rheumatologists to explore their

insights regarding medication adherence and its determinants with a focus on the effect of OOP costs on medication adherence of patients with RA.

Results:

The survey found 121 out of 308 (40.3%) participants were adherent to their oral RA medications. Sixty-one out of 308 participants (just under 20%) were bDMARDs users, and these bDMARDs users were 0.82 times less likely to be adherent to oral medications compared to non-bDMARDs users ($p<0.05$). There was no statistically significant association between OOP costs and adherence to oral RA medications ($p>0.05$). However, 28.7% of participants reported not refilling, delayed refilling, skipped doses or took smaller doses due to cost. In the findings of the open-ended question of the survey, medication costs and affordability were the most commonly reported barriers to medication adherence. In the results of the survey, using bDMARDs was the only statistically significant determinant of adherence to oral RA medications. Rheumatologists identified 16 adherence determinants that were mapped into the Andersen's Behavioral Model of Health Services Use and divided into three related determinant groups: patient (n=9), rheumatologist (n=3) and healthcare organisation (n=4). Rheumatologists reported financial difficulties mostly affected medication adherence to the more costly bDMARDs rather than sDMARDs. Although, for patients with low socioeconomic status, even small costs were a burden for purchasing sDMARDs.

Conclusion:

Medication non-adherence is prevalent among Iranian patients with RA necessitating the development of interventions that will consider all identified determinants. Patients with RA experience cost-related medication non-adherence as the majority of them

belong to the low socio-economic level. Besides, the identified determinants of adherence can be used to develop interventions to improve medication adherence in patients with RA.

Keywords:

Medication adherence, medication non-adherence, rheumatoid arthritis, out-of-pocket costs, out-of-pocket payments.

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Publications, Conferences and Awards during enrolment

Refereed Journal Articles

1. **Heidari, P**., Cross, W., & Crawford, K. (2018). Do out-of-pocket costs affect medication adherence in adults with rheumatoid arthritis? A systematic review. *Seminars in Arthritis and Rheumatism*, 48(1), 12-21. doi:https://doi.org/10.1016/j.semarthrit.2017.12.010

2. **Heidari, P**., Cross, W., Weller, C., Nazarinia, M., & Crawford, K. (2019). Medication adherence and cost-related medication non-adherence in patients with rheumatoid arthritis: A cross-sectional study. *International Journal of Rheumatic Diseases*, 22(4), 555-566. doi:10.1111/1756-185x.13

3. **Heidari, P**., Cross, W., Weller, C., Team, V., Nazarinia, M., & Crawford, K. (2019). Rheumatologists' insight into medication adherence in patients with rheumatoid arthritis: a qualitative study. *International Journal of Rheumatic Diseases*. doi: 10.1111/1756-185X.13660

Fully refereed conference proceedings

1. **Heidari-Orojloo, P**., Cross, W., & Crawford, K. (2017). Do out-of-pocket costs affect medication adherence in adults with rheumatoid arthritis? A systematic review. Internal Medicine Journal 47 (Suppl. 2), 34. doi:10.1111/imj.13426. Australian Rheumatology Association and New Zealand Rheumatology Association Annual Scientific Meeting Auckland Convention Centre, Auckland, New Zealand. May 20-23

2. **Heidari, P**., Cross, W., Nazarinia, M., & Crawford, K. (2018). THU0123 Medication adherence and cost-related medication non-adherence in patients with rheumatoid arthritis, a mixed methods study in Iran. Annals of the Rheumatic Diseases,

77 (Suppl 2), 283-283. doi:10.1136/annrheumdis-2018-eular.3165. Annual European Congress of Rheumatology (EULAR), Amsterdam, The Netherlands. June 13-16

3. **Heidari, P**., Cross, W., Nazarinia, M., & Crawford, K. (2018). Medication adherence in patients with rheumatoid arthritis, a cross-sectional study in Iran. Internal Medicine Journal, 48(4), 18-18. Australian Rheumatology Association Annual Scientific Meeting, Melbourne, Australia. May 5-8

Awards

1. Winner of the Monash Graduate Scholarship Co-funded (MGS-Co) and Faculty Graduate Research International Scholarship (FGRIS). These scholarships included the living allowances and the tuition fee for the duration of PhD (2015).
2. Winner of the Postgraduate Publications Award from Monash Graduate Research Office (2019).
3. Winner of the Travel Grant from Monash University valued at 2000 AUD that covered the travel expenses of attending the Australian Rheumatology Association and New Zealand Rheumatology Association Annual Scientific Meeting in Auckland, New Zealand (2017).
4. Winner of the People's Choice award in the 3-Minute Thesis competition for the School of Nursing and Midwifery, Monash University (2017).
5. Awarded Runner-up place in the 3-Minute Thesis competition for the School of Nursing and Midwifery, Monash University (2017).
6. Winner of the photo competition, Communities and Connections, Diversity and Inclusion week in Faculty of Medicine, Nursing and Health Sciences, Monash University (2017).

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 two papers published in peer reviewed journals and one accepted publication. The core theme of the thesis is "medication adherence in Iranian people with rheumatoid arthritis". The ideas, development and writing up of all the publications in this thesis were the principal responsibility of myself, the student, working within the School of Nursing and Midwifery under the supervision of Professor Carolina Weller, Dr Kimberley Crawford and Professor Wendy Cross. 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, 4 and 5 my contribution to the work involved the following:

Thesis Chapter	**Publication Title**	**Status**	**Nature and % of student contribution**	**Co-author names Nature and % of Co-author's contribution***	**Co-author(s), Monash student**
2	Do out-of-pocket costs affect medication adherence in adults with rheumatoid arthritis? A systematic review	Published	85%. Concept and collecting data and writing first draft	Kimberley Crawford, input into manuscript 10% Wendy Cross, input into manuscript 5%	No

4	Medication adherence and cost-related medication non-adherence in patients with rheumatoid arthritis: a cross-sectional study	Published	80%. Concept and collecting data and writing first draft	Kimberley Crawford, input 8% Wendy Cross, input 6% Carolina Weller, input 4% Mohammadali Nazarinia, input 2%	No
5	Rheumatologists' insight into medication adherence in patients with rheumatoid arthritis: a qualitative study.	Published	75%. Concept and collecting data and writing first draft	Kimberley Crawford, input 8% Wendy Cross, input 6% Carolina Weller, input 4% Victoria Team, input 2% Mohammadali Nazarinia, input 2%	No

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

Student name: *Parvaneh Heidari* **Date:** 1/08/2019

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.

Main Supervisor name: *Professor Carolina Weller* **Date:** 1/08/2019

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List of abbreviations

ACR	American College of Rheumatology
BDMARDs	biologic DMARDs
BoDMARDs	biological original DMARDs
BsDMARDs	biosimilar DMARDs
CBC	complete blood count
COPD	chronic obstructive pulmonary disease
Cr	Creatinine
CRN	cost-related medication non-adherence
CRP	C reactive protein
CQR	Compliance Questionnaire Rheumatology
CsDMARDs	conventional synthetic DMARDs

DALYs	disability-adjusted life years
DMARDs	disease-modifying antirheumatic drugs
EULAR	European League Against Rheumatism
ESR	erythrocyte sedimentation rate
HCQ	Hydroxychloroquine
HR-QOL	health-related quality of life
IQR	inter-quartile range
JAKs	Janus kinases
LFTs	Liver function tests
MTX	Methotrexate
NSAIDs	Nonsteroidal anti-inflammatory drugs
OOP	out-of-pocket

QOL	Quality of life
RA	rheumatoid arthritis
SUMS	Shiraz University of Medical Sciences
TsDMARDs	targeted synthetic DMARDs
WHO	World Health Organisation
YLDs	years of life lived with disability
YLLs	years of life lost due to premature mortality
PedsQL	Pediatric Quality of Life Inventory
MMAS	Morisky’s Medication adherence scale

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Definitions

Out-of-pocket (OOP) costs	OOP costs comprise the portion of total costs that patients pay to receive healthcare services.
Medication adherence	The degree to which patients follow treatment recommendations using medications, pertaining to the dosage, frequency and timing of medication taking for the prescribed course.

Chapter 1

Introduction

1. Chapter 1

1.1. Chapter overview

This chapter introduces the thesis, addresses the research problem and provides an overview of the significance of the study. The specific aims and a summary of the project are also presented. Finally, an outline of the thesis is described to inform the reader of its overall structure.

1.2. Introducing the study

The term arthritis refers to joint diseases; there are many different types of arthritis (Shmerling, 2017). Osteoarthritis and rheumatoid arthritis (RA) are the two most common types of arthritis respectively (McHugh, 2018). RA is a systemic autoimmune inflammatory condition which results in severe articular and extra-articular morbidity and increased mortality from accelerated cardiovascular disease (Smolen et al., 2018). RA has a negative effect on the ability to do daily activities, including household duties such as preparing meals or cleaning and work related tasks (Pincus et al., 1984). RA also impacts health-related quality of life (HR-QOL) (Salaffi et al., 2009) and increases mortality (Pincus et al., 1984); in a cohort study of 1222 patients with RA during 15 years, approximately one life-year was lost due to RA and the risk of mortality in patients with RA was 54% higher than the healthy population (van den Hoek et al., 2017). Although strategies such as psychosocial consultation and physical activity may support patients in coping with the symptoms of RA (Christie et al., 2007; Cramp et al., 2013), medication plays the main role in RA treatment (Aletaha et al., 2010).

Current treatment strategies focus on early diagnosis and early pharmaceutical treatment which aims to prevent the progression of joint damage to decrease disease severity and optimising remission (Smolen et al., 2018). Synthetic disease-modifying antirheumatic drugs (sDMARDs) and biologic DMARDs (bDMARDs) are the main RA medications prescribed to patients (Benjamin et al., 2018). Patients are required to take RA medications long term and, medication adherence is essential to prevent structural damage in joints and to reach optimal health outcomes in patients (Ragab et al., 2017). However, non-adherence is found to be prevalent among patients with RA (Blum et al., 2011; Fidder et al., 2013; Harrold et al., 2009). Many factors affect medication adherence in chronic diseases like RA (Jimmy et al., 2011). According to the 2003 World Health Organisation (WHO) report, adherence determinants are comprised of five dimensions including factors that are patient related, socioeconomic related, therapy related, disease related and healthcare system and team situation related (Sabaté, 2003). Among healthcare system-related determinants, medication out-of-pocket (OOP) costs have been reported as one of the barriers to medication adherence (Hennessy et al., 2016). In addition, the production of bDMARDs is a complex process, so, they are more expensive than sDMARDs, which may limit medication utilisation (Hresko et al., 2018; Kalkan et al., 2014) and may contribute to medication non-adherence (Curkendall et al., 2008; Harrold et al., 2013).

In 2014, the Iran government launched a Health Sector Evolution Plan for hospitals to reduce healthcare costs for patients, improve the quality of healthcare services and provide equal access to inpatient care (Moradi-Lakeh et al., 2015). The outcomes of this reform have not been reported. For the first time in Iran, this study investigated medication adherence, and adherence determinants with the focus on the effect of OOP costs on medication adherence in patients with RA. A mixed methods approach was

employed; interviews were conducted with rheumatologists who provide routine follow-up care for patients with RA and surveys were undertaken with patients with RA visiting rheumatologists, in public and private centres of Shiraz University of Medical Sciences (SUMS).

1.3. Significance of the thesis

WHO recognises medication adherence improvement is even more important than any improvement in specific medical treatment (Sabaté, 2003). Adherence to RA medications induces a state of remission and improves quality of life (QOL) in patients with RA (Ragab et al., 2017; Salt et al., 2012; Uckun et al., 2017). For the health service, when patients are adherent, there is a reduction in long term healthcare costs such as hospitalisation and other healthcare services utilisation costs (Iuga et al., 2014). Therefore, to improve patients' health outcomes and manage healthcare costs, it is important to detect medication non-adherence in order to initiate interventions (Brown et al., 2018). Two systematic reviews were conducted regarding studies that assessed adherence to RA medications such as bDMARDs and methotrexate (MTX) in patients with RA. They reported most studies were conducted in the United States of America (USA) or European countries (Blum et al., 2011; Curtis et al., 2016) and adherence to RA medications was sub-optimal (Blum et al., 2011; Fidder et al., 2013; Harrold et al., 2009). However, these review findings highlight the lack of studies related to medication adherence in developing countries.

In a systematic review and meta-analysis of studies investigating OOP costs in Iran's healthcare system, seven studies were identified. The included studies were conducted in the years between 2002 and 2014, in five provinces of Iran including Tehran, Qazvin,

Kurdistan, Gorgan and Tabriz. They reported the rate of OOP costs was 50% of the total healthcare costs (95% CI: 45-57%) (Mirabedini et al., 2017) which was higher in comparison to the world's average of 24% (World Health Organisation, 2004). To combat these costs, in 2014, Iran's government launched a Health Sector Evolution Plan for hospitals (Moradi-Lakeh et al., 2015). The main goals were to reduce patient healthcare costs, improve the quality of healthcare services and provide equal access to inpatient care (Moradi-Lakeh et al., 2015). Although OOP costs decreased for inpatients at the time of this initiative, the outcomes of this reform are still unknown on outpatients and require further investigation.

The use of bDMARDs in the treatment of RA has expanded due to their efficacy. However, the economic aspect of treatment has become one of the dominant factors in the treatment plan of patients with RA because bDMARDs are more expensive compared to sDMARDs (van Vollenhoven, 2016). Consequently, economic factors became important determinants of adherence to bDMARDs. Therefore, there is a need to understand the effect of OOP costs on medication adherence. Studies considering OOP payments and its relationship with medication adherence are very beneficial for the decision-making process for policy makers (De Vera et al., 2014; Erkan et al., 2002), particularly across different populations due to different financial burden implications that OOP costs may have on access to and use of healthcare (Machlin, 2006).

Therefore, this study aimed to assess medication adherence in Iranian people with RA and explore adherence determinants with the focus on the effect of OOP costs on medication adherence. The findings will provide vital information regarding medication adherence status in Iran. In addition, results will provide information for healthcare providers and policymakers to inform strategies to enhance medication adherence in

patients with RA. To our knowledge, there has been no study investigating the effect of OOP costs on medication adherence in Iran.

1.4. Aims

The overarching aim of this study was to assess adherence to oral RA medications in patients with RA in Shiraz, Iran and to explore determinants of adherence with a focus on the effect of OOP costs on medication adherence.

Two research strategies were used. One involved a survey of patients and the other involved in-depth interviews with rheumatologists.

1.4.1. Objectives of the survey

1. To examine demographic and clinical characteristics of patients with RA in Shiraz, Iran.

2. To assess adherence to oral RA medications in patients with RA in Shiraz, Iran.

3. To examine the relationship between medication adherence and OOP costs in patients with RA in Shiraz, Iran.

1.4.2. Objectives of the interviews

1. To explore how rheumatologists assess medication adherence in patients with RA.

2. To explore medication adherence determinants in patients with RA from the perspective of rheumatologists.

3. To explore whether medication OOP costs affect medication adherence from the perspective of rheumatologists.

1.5. Overview of the approach

This thesis utilised a concurrent mixed methods approach (Creswell et al., 2018; Creswell et al., 2003) investigating the aims of the study from the perspective of patients with RA and rheumatologists, to gain a deeper understanding of the issues of medication adherence. The study recruited patients visiting the main rheumatology clinics of SUMS and rheumatologists who work at SUMS, the main medical university and healthcare provider in south of Iran. The overarching aim of this study was to assess adherence to oral RA medications in patients with RA in Shiraz, Iran and to explore determinants of adherence with a focus on the effect of OOP costs on medication adherence. The project outline is summarised in Figure 1.3. As outlined, a systematic review was conducted to provide the current evidence on the relationship between OOP costs and medication adherence in patients with RA. The results of the systematic review assisted with the design of the concurrent mixed methods study. The study involved surveys with patients to assess medication adherence and to explore adherence determinants and, interviews with rheumatologists to explore their experiences regarding medication adherence and its determinants. Data were collected concurrently (Creswell et al., 2003). Finally, the two sets of data were analysed separately and the results were aggregated. Andersen's Behavioral Model of Health Services Use (Andersen, 2008) was employed to guide the study design and data analysis.

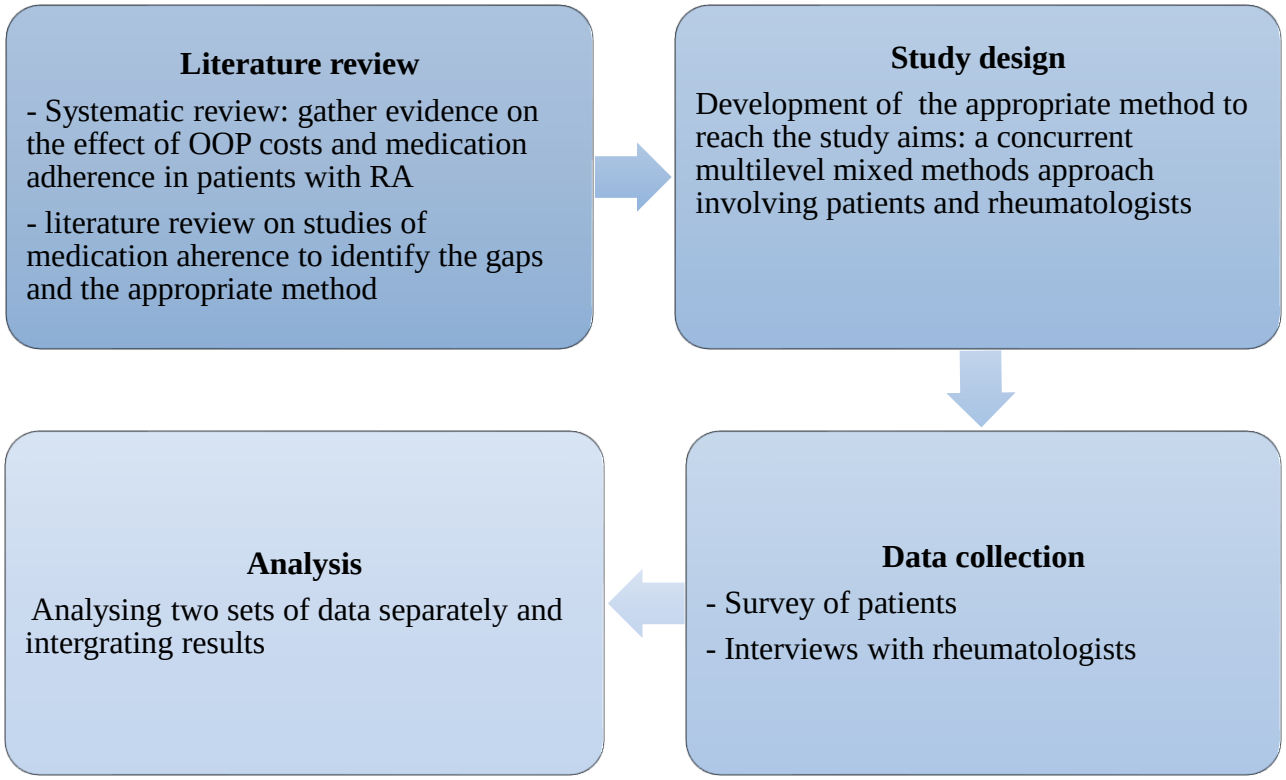


Figure 1.1. The thesis sequential steps

1.6. Outline of the thesis

This thesis, with publications, is presented in seven chapters and is organised according to Monash University's Guidelines for submission. The position where each step of the research is placed within the thesis is shown in Table 1.1. Three of the chapters (Chapters 2, 4 and 5) included peer-reviewed publications which has been shown in boxes. A brief description of each chapter in the thesis is outlined in the following paragraphs.

Chapter 1 provides the introduction and significance of the study, explains the research problem, aims and provides an overview of the study.

In **Chapter 2**, a review of RA mechanisms, RA medications, determinants of medication adherence, and different methods of adherence measurement is presented.

Table 1.1. Thesis structure

Chapters	Content
❖ Chapter **1**	Introduction and aims
❖ Chapter **2**	Background and literature review Publication 1
❖ Chapter **3**	Research methodology
❖ Chapter **4**	Results of the survey Publication 2
❖ Chapter **5**	Results of the interviews Publication 3
❖ Chapter **6**	Integration of results and discussion
❖ Chapter **7**	Conclusion, recommendations, limitations and strength

Chapter 2 also includes a manuscript entitled ‘Do out-of-pocket costs affect medication adherence in adults with rheumatoid arthritis? A systematic review’. This manuscript

was published in Seminars in Arthritis and Rheumatism with the impact factor of 4.356 and explored the relationship between OOP costs and medication adherence in patients with RA.

Chapter 3 outlines the research methodology with particular reference to the use of a mixed methods design and the conceptual model that was employed to guide the study and the integration of the results.

Chapter 4 presents the manuscript that includes the results of the survey that is published in the International Journal of Rheumatic Diseases with the impact factor of 2.423. It is entitled 'Medication adherence and cost-related medication non-adherence in patients with rheumatoid arthritis: a cross-sectional study'. The publication explores the demographic and clinical characteristics of patients with RA as well as medication adherence status. It also explores medication adherence determinants with the focus on the effect of OOP costs on medication adherence.

Chapter 5 presents the manuscript that includes the results of the interviews. The manuscript explores medication adherence determinants from the perspective of rheumatologists. This chapter also presents the findings on how rheumatologists assess medication adherence in patients with RA. This manuscript is accepted in the International Journal of Rheumatic Diseases with the impact factor of 2.423.

In **Chapter 6** the results of both interviews and survey are integrated, and discussed in detail.

Chapter 7 includes the conclusion of the findings, recommendations for healthcare providers, insurers and policymakers, recommendations for future studies, strengths and, limitations of the study.

According to Monash University's guidelines for a thesis including published works, all included papers are presented in the original publication format. Furthermore, additional framing texts, which are provided as explanations, link the publications with other sections of the thesis.

This thesis has been structured to allow the reader to follow the various steps involved in conducting this study. As a result of the requirements for publication, it is acknowledged that there may be some repetition in the journal articles and the thesis, especially the definition of terms and the methods.

Chapter 2

Background

and

Literature Review

2. Chapter 2

This chapter provides the background to the development, aetiology and the current treatment strategies for RA. The literature regarding RA medications, medication adherence and determinants of adherence are also outlined in this chapter. To explore the effect of OOP costs on medication adherence in patients with RA, a systematic review was conducted to consolidate the literature. Finally, a review of adherence measurement methods is also presented.

2.1. Rheumatoid arthritis (RA) development

RA is a systemic autoimmune inflammatory disease which results in severe articular and extra-articular morbidity (Choy, 2012). Articular morbidity occurs in joints in the fingers, thumbs, wrists, elbows, shoulders, knees, feet, and ankles (Fox, 2016). Generally, RA is characterised by joint swelling, joint tenderness, and destruction of synovial joints, leading to severe disability and premature mortality (Aletaha et al., 2010; Mitchell et al., 1986; Scott et al., 1987). RA develops in several phases (Figure 2.1). RA begins with genetic risk factors (60% of risk) and non-genetic risk factors (40% of risk) (Deane, 2012; Smolen et al., 2018). Disease initiation involves the spreading of autoimmunity against modified self-proteins (Smolen et al., 2018). The abnormalities of RA-related autoantibodies and biomarkers of inflammation can continue for years without inflammatory arthritis signs and symptoms. This phase is known as preclinical RA (Deane, 2012).

The next phase is known as early RA in which the inflammatory process occurs. The synovium (synovial membrane) is a central player and the primary site of the inflammatory process that is characterised by an increase in lining layer thickness and

infiltration of inflammatory cells into the sub-lining area (Cooles et al., 2011; Guo et al., 2018). In the last phase known as established RA, the inflammatory cells of the immune system in the lining of the joint, form a fibrous layer of tissue, the pannus. The pannus releases substances that erode bone, destruct cartilage and damage the surrounding ligaments resulting in deformities (Mann, 2015). RA develops progressively in which the disease begins with minimal joint involvement, and over the years it progresses slowly to multiple joints (Guo et al., 2018).

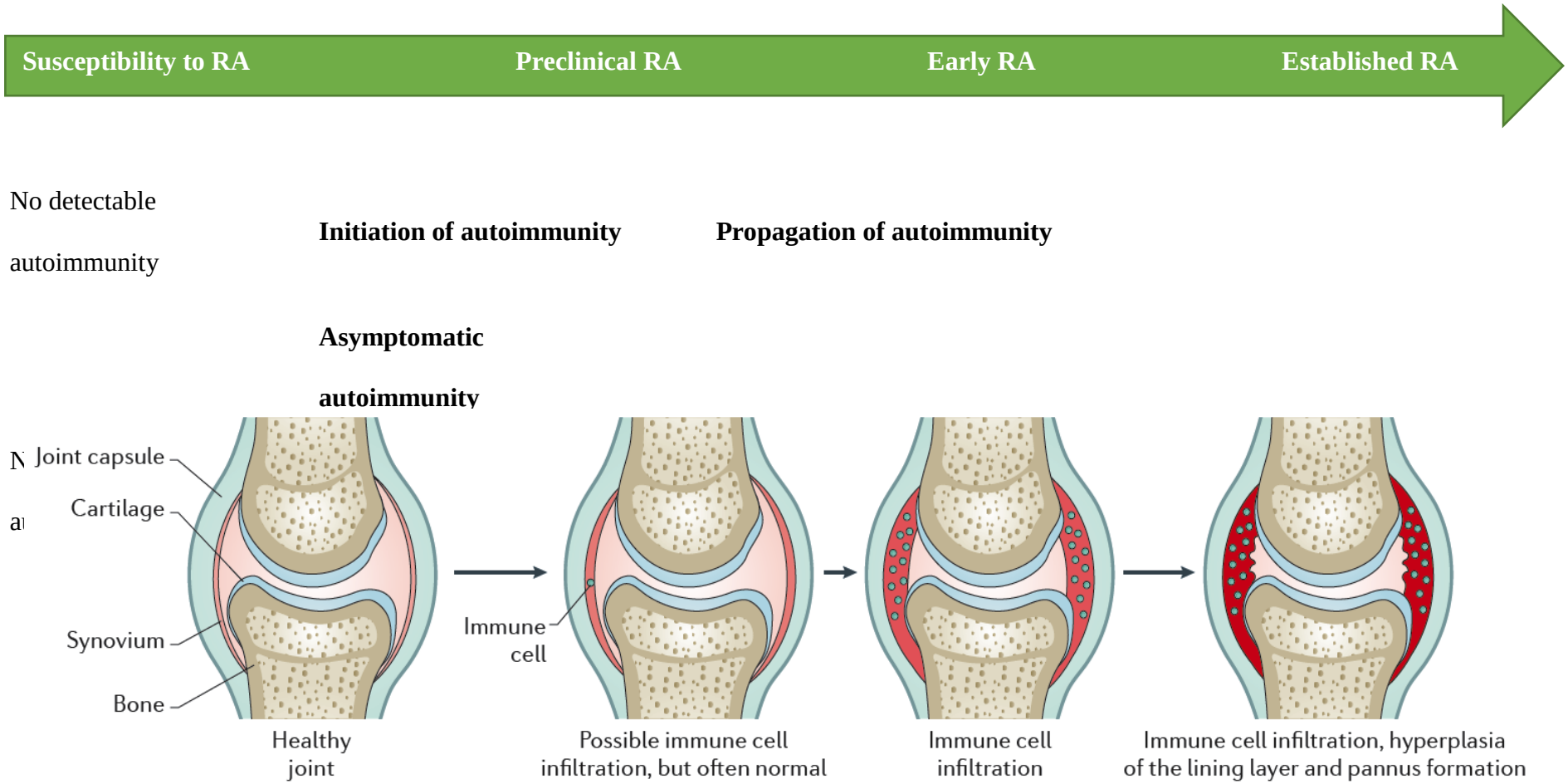


Figure 2.1. Development and progression of RA. This photo is extracted from Smolen, (2018, p.3). Copyright (2018) by Springer Nature - Macmillan Publishers Limited.

2.2. Aetiology and risk factors

Rheumatoid arthritis (RA) is most likely to develop in people who have a genetic predisposition to the disorder and have been exposed to certain environmental factors although the underlying cause of RA remains unknown (Fox, 2016). The genes responsible for RA development are the genes essential for producing the proteins for immune responses. Among the environmental factors that can lead to the development of RA, smoking is the only well-established risk factor for RA (Aletaha, 2015; Fox, 2016). Besides smoking, there are other environmental factors that are not well-established as RA risk factors (Table 2.1). Dust exposure is one of these risk factors (Aletaha, 2015). A study was conducted on fire fighters and other emergency service workers exposed to dust at the site of the 2001 World Trade Centre collapse in New York. It reported prolonged work at a dusty site is a risk factor of autoimmune diseases including RA (Webber et al., 2015). Another study of Malaysian women who had exposure to textile dust at work reported an increased risk of developing RA (Too et al., 2016). Bacterial and viral infections are other unestablished RA risk factors, although direct infection of joints has not been demonstrated (Fox, 2016). In addition, epidemiologic and clinical studies have suggested there is an association between RA and periodontal disease. The presence of circulating antibodies against periodontopathic bacteria and associated inflammatory response has been reported in both patients with RA and individuals at risk for disease development (Bingham et al., 2013; Fox, 2016). In addition, female gender is also known as a RA risk factor (Smolen et al., 2018). Regarding unestablished RA risk factors, some studies have reported a reduced risk of RA in women who had breastfeed for a long time (Pikwer et al., 2009) or used the contraceptive pill (Doran et al., 2004). Table 2.1 shows the environmental risk factors for RA.

Table 2.1. Environmental risk factors of RA that are not well established. (Aletaha, 2015; Smolen et al., 2018)

Risk factor	Association
Dust exposure	Positive
Infections	Positive
Coffee	Positive and negative
Alcohol	Negative
Parous	Negative
Breastfeeding	Negative
Hormone replacement therapy/ Oral contraceptives	Negative
Obesity	Positive
Vitamin D deficiency	Positive

2.3. RA diagnosis

Although the prevalence of RA increases in older age, RA can occur at any age, and often develops gradually with increasing signs and symptoms (Goemaere et al., 1990; Villa-Blanco et al., 2009). Early diagnosis is important to prevent joint destruction by using DMARDs at the early onset of the disease (Espinoza et al., 2016). There have been some advances in early RA diagnosis including the RA classification criteria and new biomarkers that assist with the identification of RA (Aletaha et al., 2010; Nakken et al., 2017; Zhao et al., 2014). The 1987 American College of Rheumatology (ACR) classification criteria (Arnett et al., 1988) had been widely used for RA diagnosis for many years. However, it lacked the sensitivity to identify early RA (van Der Linden et al., 2011). To improve the sensitivity, ACR and European League Against Rheumatism

(EULAR) introduced another RA classification criteria in 2010 (Aletaha et al., 2010), which is today the most widely tested guideline to aid rheumatologists to diagnose RA (Radner et al., 2013). In this classification, individuals are scored across four areas including joint involvement, serology, acute-phase reactants and duration of symptoms (Table 2.2). A score of 6 or above would indicate a diagnosis of RA (Aletaha et al., 2010). People usually refer to a doctor with symptoms of joint stiffness and inflammation. Rapid referral to a rheumatologist is recommended if any of the following symptoms are present: three or more swollen joints, metatarsophalangeal or metacarpophalangeal involvement, and morning stiffness of more than 30 minutes (Emery et al., 2002). A rheumatologist will confirm the final diagnosis with a physical examination and blood tests according to the 2010 ACR/EULAR guidelines (Table 2.2).

Table 2.2. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis (Aletaha et al., 2010, p. 2574).

	Score
Target population (Who should be tested?): Patients who	
1) have at least 1 joint with definite clinical synovitis (swelling)*	
2) with the synovitis not better explained by another disease†	
Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of ≥6/10 is needed for classification of a patient as having definite RA)‡	
A. **Joint involvement§**	
1 large joint¶	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)#	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)**	5
B. **Serology (at least 1 test result is needed for classification)††**	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. **Acute-phase reactants (at least 1 test result is needed for classification)‡‡**	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. **Duration of symptoms§§**	
<6 weeks	0
≥6 weeks	1
*** The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of rheumatoid arthritis (RA) with a history compatible with prior fulfilment of the 2010 criteria should be classified as having RA. Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have**	

previously fulfilled the 2010 criteria should be classified as having RA.

† Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted.

‡ Although patients with a score of <6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time.

§ Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are excluded from assessment. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.

¶ "Large joints" refers to shoulders, elbows, hips, knees, and ankles.

 # "Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

**** In this category, at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular, etc.).**

†† Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay. Where rheumatoid factor (RF) information is only available as positive or negative, a positive result should be scored as low-positive for RF. ACPA= anti-citrullinated protein antibody.

‡‡ Normal/abnormal is determined by local laboratory standards. CRP=C-reactive protein; ESR= erythrocyte sedimentation rate.

§§ Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

2.4. Burden of RA

A systematic review was conducted to find population-based studies that reported the prevalence of RA in low and middle-income countries according to the WHO regions

(Rudan et al., 2015). The review reported RA prevalence was 0.40% for Southeast Asian, 0.37% for Eastern Mediterranean, 0.62% for European, 1.25% for American and 0.42% for Western Pacific regions (Rudan et al., 2015). Due to a growth in population and increase in aging, disability-adjusted life years (DALYs) of RA increased from 3.3 million years (95% CI 2.6 to 4.1) in 1990 to 4.8 million years (95% CI 3.7 to 6.1) in 2010. DALYs is the sum of years of life lived with disability (YLDs) and the years of life lost due to premature mortality (YLLs). Of the 291 diseases studied, RA was the 42nd highest contributor to global disability (Cross et al., 2014). Although the activity and damaging effects of RA have decreased over time due to the improvements in medication and improvement in patient diagnosis, there was no decrease in the frequency or mortality of RA (Minichiello et al., 2016).

RA carries a substantial burden for both the individual and society (Cross et al., 2014). The individual burden includes physical and psychological challenges (Poh et al., 2015). All aspects of everyday life are affected by RA including activities engaging with self-care, domestic lifestyle, interpersonal interactions and community life (Sverker et al., 2015). Self-care and domestic activities include bathing, toileting, dressing, eating, drinking and a variety of household activities such as gardening, sewing, cleaning, and shopping in which RA sufferers have to walk, carry or lift objects and use their hands and arms (Rkain et al., 2006; Sverker et al., 2015). Limited physical ability in activities of self-care and domestic life, affects patients' interactions and relationship with their family members including children and grandchildren (Sverker et al., 2015). RA also affects the intimate relationships including physical relationship like hugging and sexual relationships due to pain, fatigue and feeling unsexy (Bird et al., 2003; Rkain et al., 2006; Sverker et al., 2015). In an Egyptian study of patients with RA, 46% of females and 54% of males reported sexual dysfunction (El Miedany et al., 2012). With

regard to community and social activities, RA limits patients' choice in leisure activities such as sports like fishing, gymnastics, dancing, skiing or riding a horse mostly due to the pain and fatigue they cause and their need for a high level of physical activity (Sverker et al., 2015). In addition, a systematic review and meta-analysis reported 16% of patients with RA have depression (Matcham et al., 2013), and these patients exhibit levels of anxiety that are higher than a normative group of age-equivalent adults (VanDyke et al., 2004).

Regarding socioeconomic burden, work disability is the major consequence of RA resulting in lost income for the patient and less productivity for society (Puolakka et al., 2005). Patients with RA have a lower employment rate due to their reduced work capacity due to pain, fatigue and poor physical function (Kwon et al., 2012). Initially, RA affects the quality of patients' presence at work (low work productivity), later it increases work absenteeism and, if not treated, it may eventually result in permanent work disability (Martikainen et al., 2016). A study in England on 353 patients with RA reported 29% of patients stopped their work due to RA during the period of five years and the work disability was more likely in patients working in physically demanding jobs (Young et al., 2002). A Swedish study reported the costs related to hospital care, medications and work loss in patients with RA were two to three times higher than the costs in the general population (Eriksson et al., 2015). In addition, medical costs for patients with RA is substantial. A meta-analysis on medical costs of RA in the USA reported that total direct medical costs were estimated at US$12,509 for all patients with RA using any medication regimen and US$36,053 for bDMARDs users (Hresko et al., 2018). Moreover, societal participation in people with RA is lower compared with people without RA due to pain and fatigue (Schneider et al., 2008).

High prevalence rates of cardiovascular risk factors are reported in patients with RA including hypertension (18.6%), diabetes mellitus (6.0%), hyperlipidaemia (9.9%), and obesity (4.4%) (Radner et al., 2017). A case-control study reported patients with RA had a higher risk of cardiovascular diseases, particularly in patients who smoke, are obese, have high triglycerides and have extra-articular disease severity (Sliem et al., 2010). Also, due to the inflammation in joints and decreased physical exercise in patients with RA, they have a higher risk of osteoporosis (Rangel-Botello et al., 2017; Shibuya et al., 2002). Although RA mortality rate decreased due to the improvement and availability of RA medications, cardiovascular disease is the most common cause of premature death in patients with RA (Radner et al., 2017). Women with RA have a higher risk of total mortality compared with those without RA; in particular, cardiovascular disease mortality and respiratory disease mortality (Sparks et al., 2016).

2.4.1. Burden of RA in Iran

In Iran, in 2016, a study by WHO that included three urban areas and one rural area reported the prevalence of RA was 0.37% in the 19,786 population studied (Davatchi et al., 2016). RA prevalence was six times more likely in Iranian women than men, and the mean age (± SD) of patients with RA was 52.3 (± 17.6) years. Approximately 46% of Iranian patients with RA had difficulty performing daily activities including stair climbing (43%), lifting (40%), walking (37%), squatting (37%), carrying items (31%), dressing (17%), showering (9%) and hair combing (9%) (Jamshidi et al., 2014). A survey in Iran (n=197) using the Pediatric Quality of Life Inventory (PedsQL) reported lower QOL in patients with RA (64%) compared to healthy participants (76%) (Pakpour et al., 2013). Karimi et al. (2013) conducted a systematic review of studies on

Iranian people with RA to examine the QOL in this group of patients. They identified 11 studies; five studies used the short form 36 item (SF-36) questionnaire and two studies used the Medical Outcome Survey Short Form 20 (MOS-SF-20). The data were combined into eight dimensions of QOL including physical functioning, role–physical, bodily pain, general health, vitality, social functioning, role–emotional and mental health. Among the eight components of QOL, the highest score was social functioning with a mean score of 63.4 and the lowest was physical functioning with a mean score of 43. The overall score of eight dimensions was 52.47 out of 100 (higher score indicates higher QOL), and they reported the QOL determinants were, depression, income, education, employment status, marital status, fatigue, anxiety, disease severity and pain. They reported empowering patients in self-care by educating them and, encouraging participation in decision making may improve QOL (Karimi et al., 2013). The findings from this study in Iran and other studies that examined QOL in patients with RA (Matcham., 2014) indicate that RA has a substantial influence on QOL necessitating the appropriate treatment.

2.5. Comorbidities in adults with RA

Comorbidities can either exist prior to RA or, the chronic autoimmunity that occurs in RA may lead to comorbidity and premature ageing (van Onna et al., 2016). RA medications targeting inflammatory conditions including sDMARDs, bDMARDs and glucocorticoids may also increase or decrease the probability of comorbidities (Roubille et al., 2015). Several diseases occur more frequently in RA patients when compared to the general population (van Onna et al., 2016). An international cross-sectional study, including 3920 patients with RA from 17 participating countries

reported the most prevalent comorbidities were depression (15%), asthma (6.6%), cardiovascular disease (CVD) (6%), solid malignancies (4.5%) and chronic obstructive pulmonary disease (COPD) (3.5%) (Dougados et al., 2014). In a systematic review of 17 studies reporting cardiovascular mortality risk, RA was associated with a 60% increase in risk of cardiovascular death compared with the general population (Meune et al., 2009) and CVD is increased in patients with RA (Jagpal et al., 2018). CVD risk factors such as hypertension, hyperlipidaemia and diabetes mellitus are also highly prevalent among patients with RA and contribute to the CVD risk (Jagpal et al., 2018). Systematic reviews and meta-analysis reported that patients with RA had a higher risk of COPD (Ungprasert et al., 2016) and fractures (Jin et al., 2018) compared to the general population. Comorbidities and the complexity they add in RA treatment influence therapeutic decisions. High-risk comorbidities like malignancy, CVD, and infection limit the treatment options available to people with RA and consequently may adversely affect disease outcomes (Gopalarathinam et al., 2017). On the other hand, comorbidities such as osteoporosis require the addition of new therapies to prevent fractures such as calcium supplementation and bisphosphonates (Hoes et al., 2015).

2.6. RA treatment

There is no ultimate cure for RA (Aletaha, 2015). However, a state of remission is achievable with early intervention before structural impairment occurs (Aletaha, 2015). Non-pharmaceutical interventions may support patients in coping with the disease consequences (Christie et al., 2007). For example, interventions such as psychosocial consultation and physical activity may reduce fatigue (Cramp et al., 2013). However, pharmaceutical treatment plays the main role in RA management (Aletaha et al., 2010).

RA management has significantly improved over the last two decades (Smolen et al., 2018). Until the 1990s, patients with RA would usually have to live with progressive joint deformity and considerable disability (Sokka et al., 2009) and the pharmaceutical treatment was not generally administered in the initial stages of the disease (Fries, 2000).

In the past, a "pyramid" approach, encouraged the administration of non-pharmaceutical interventions such as physiotherapy, occupational therapy, rest and rehabilitation and, pharmaceutical treatments such as analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs were the first-line treatment and DMARDs were prescribed relatively late in the disease (Fries, 2000). The only DMARDs at that time were gold salts and D-penicillamine (Lipsky, 2008). This approach was not optimal as it was not able to prevent severe disabilities and morbidity due to cardiovascular diseases (Sokka et al., 1999). Further research revealed that increased consequences of RA were due to misdirected and inadequately controlled inflammation that caused joint destruction and loss of function (Moreland et al., 2001).

RA management evolved due to several reasons. First, due to the improvement in RA diagnosis (as explained in section 2.3). Second, the need for early treatment was well established and a "window of opportunity" was introduced; which recommended initiating DMARDs as soon as possible after diagnosis (Figure 2.2) (Emery, 2002).

The development of RA will often damage bone and cartilage, which results in erosions and joint space narrowing (van der Linden et al., 2010). In most cases this damage is irreversible (van der Linden et al., 2010). Figure 2.3 shows the significance of early treatment. Thirdly, the concept of "treat to target" was introduced in which pharmaceutical adjustments must be based on disease activity that is measured by a

validated tool (Smolen et al., 2010). Treat-to-target is defined as a treatment strategy in which the clinician begins the treatment aggressively to reach and maintain specified goals, such as remission or low disease activity (Solomon et al., 2014). In the last 20 years, several measures have been developed such as the Disease Activity Score 28 (DAS-28) (Prevoo et al., 1995), the Simplified Disease Activity Index (Smolen et al., 2003) and the Clinical Disease Activity Index (CDAI) (Aletaha et al., 2005) to classify the disease activity status into remission, low, moderate and high categories. These categories are used to adjust medications to achieve a tight RA control and attain the target, which is remission or at least low disease activity (Felson et al., 2011). Finally, the substantial increase in the number of sDMARDs and the introduction of bDMARDs was able to modify the natural evolution of RA (Fautrel et al., 2018; Takeuchi, 2011). The introduction of bDMARDs in the 1990s (Benjamin et al., 2018) was regarded as a major advancement in RA treatment as they are faster in action and work in patients who had an inadequate response to treatment with sDMARDs (Klippel, 2000). However, they are more expensive than sDMARDs, which may limit their utilisation (Kalkan et al., 2014).

RA treatment has two targets: first, relieve the pain and second to prevent the destruction of joints' structure. Reaching these two goals requires two types of pharmaceutical interventions (van Vollenhoven, 2016). While analgesics and NSAIDs may provide a degree of symptomatic relief, anti-inflammatory medications are used to prevent structural damage (van Vollenhoven, 2016). The ACR and EULAR Guidelines that are the treatment guidelines that are used for RA (Singh et al., 2016) recommend the use of sDMARDs, bDMARDs, tofacitinib, and glucocorticoids for patients with early diagnosis and established RA (Singh et al., 2016; Smolen et al., 2017). These

ACR and EULAR guidelines are the most widely used resources for RA treatment; both emphasising the treat-to-target approach (Singh et al., 2016; Smolen et al., 2017).

Further details on each medication is presented in the following section (section 2.6). Early and aggressive intervention with sDMARDs and bDMARDs has been shown to improve clinical outcomes, induce remission and prevent joint erosion progress (Nam, 2016). Therefore, it improves patients' functional status, HR-QOL, and reduces fatigue (Breedveld, 2011).

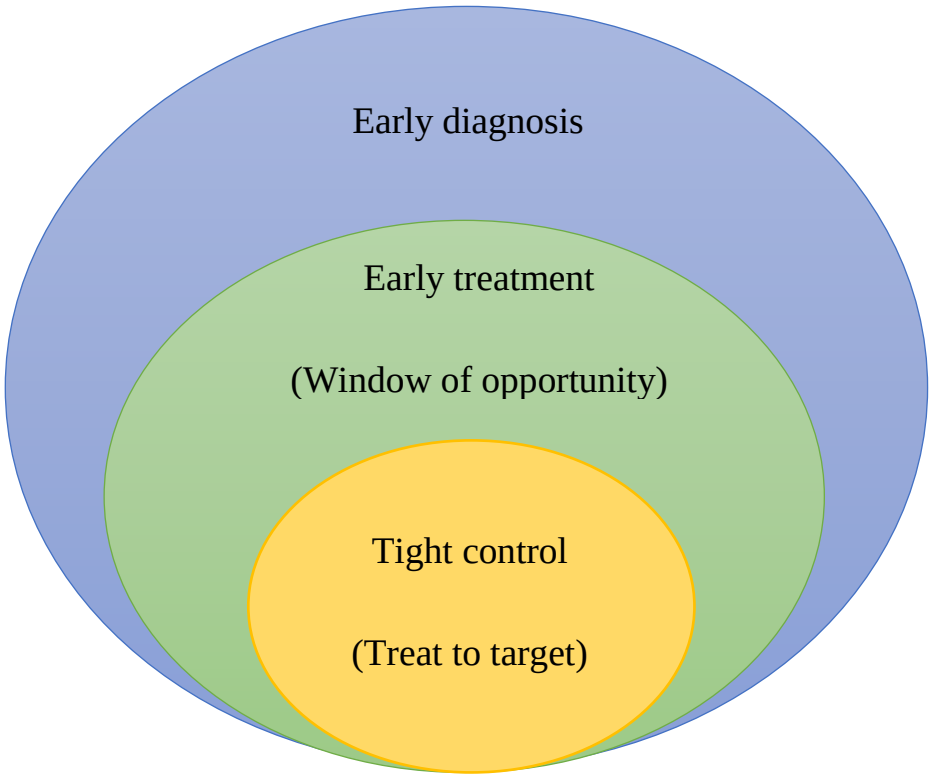


Figure 2.2. Standards of RA treatment. Extracted from (Fautrel et al., 2018, p. 213). Copyright (2018) by the BMJ.

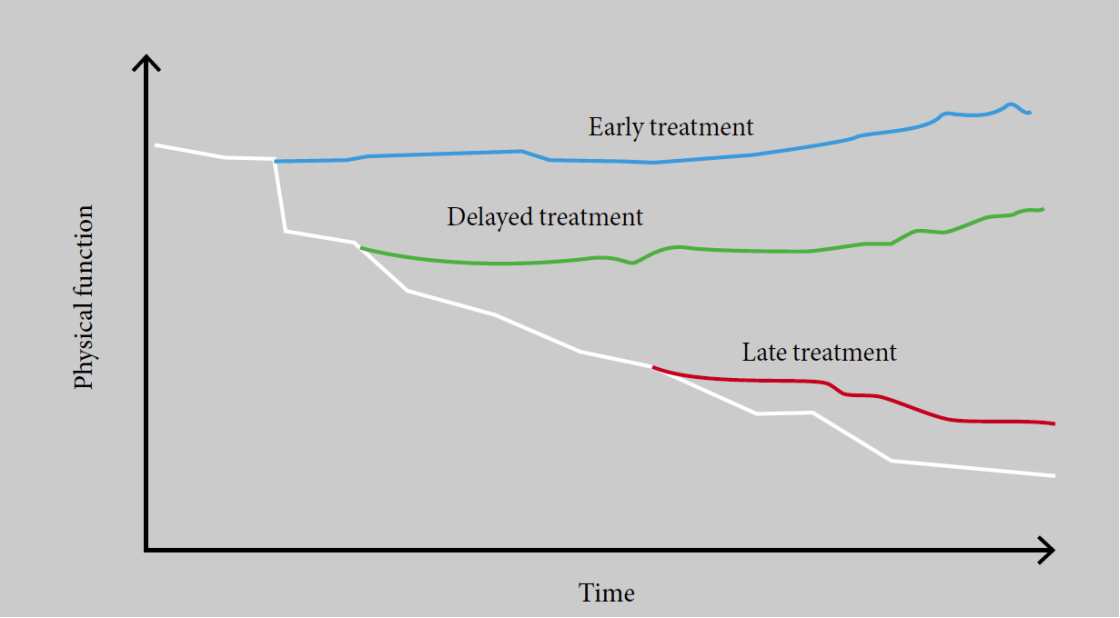


Figure 2.3. Significance of early treatment for patients with rheumatoid arthritis. Extracted from (Aletaha, 2015) from the results of (Nell et al., 2004). Copyright (2015) by Springer Healthcare.

2.7. RA medications

Currently recommended medications include glucocorticoids and DMARDs (biological or synthetic) (Burmester et al., 2017), which are presented in Figure 2.4.

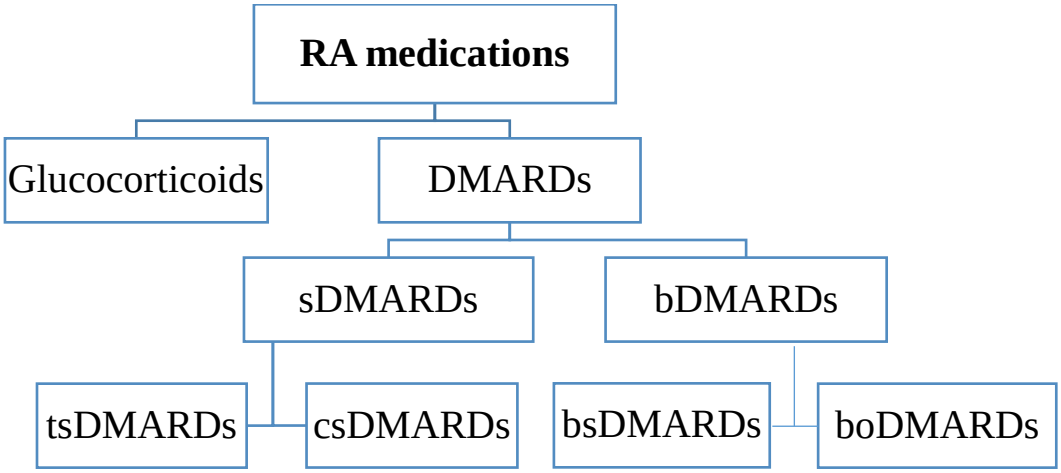
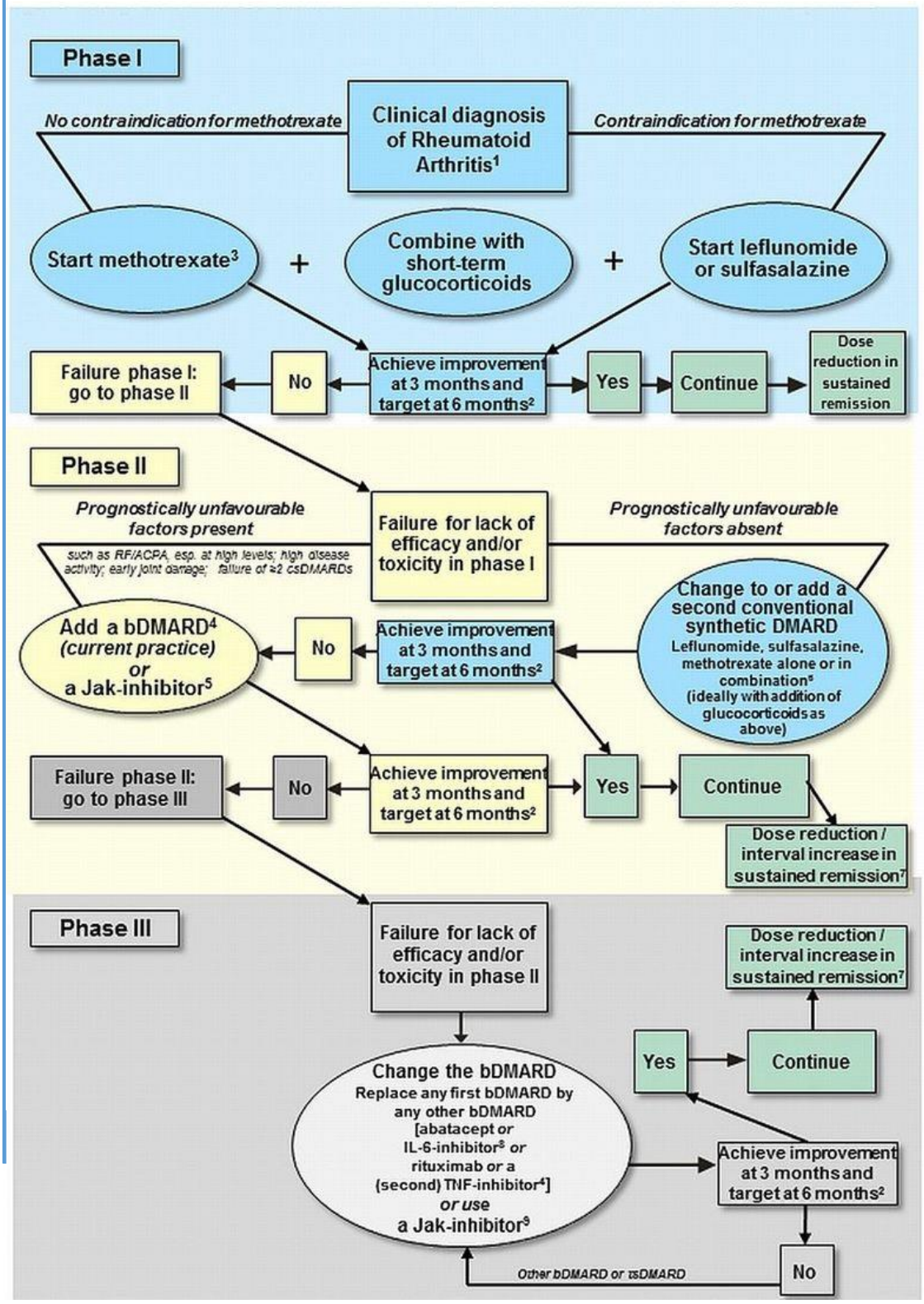


Figure 2.4. Categories of RA medications.

RA: rheumatoid arthritis, DMARDs: disease-modifying antirheumatic drugs, sDMARDs: synthetic disease-modifying antirheumatic drugs, bDMARDs: biologic disease-modifying antirheumatic drugs, tsDMARDs: targeted disease-modifying antirheumatic drugs, csDMARDs: conventional synthetic disease-modifying antirheumatic drugs, boDMARDs: biological original disease-modifying antirheumatic drugs, bsDMARDs: biosimilar disease-modifying antirheumatic drugs

The pathway developed by EULAR is the most widely used guideline for RA treatment (Figure 2.5). In this guideline, treatment starts with methotrexate (MTX) as the first and main treatment strategy combined with glucocorticoids. In the case of intolerance with MTX, leflunomide or sulfasalazine is substituted, and the glucocorticoids dosage should be tapered when clinically feasible. If progress is not observed within three to six months, other csDMARDs should be added. In the case of high disease activity, tsDMARDs and bDMARDs are added to the csDMARD therapy (Burmester et al., 2017). Glucocorticoids are not recommended for long-term use due to their side effects (Burmester et al., 2017).

Figure 2.5. Algorithm based on the 2016 European League Against Rheumatism (EULAR) recommendations on RA management. This figure is extracted from (Smolen et al., 2017, p. 968). Copyright (201) by the BMJ.



"[1] ACR-EULAR classification criteria can support early diagnosis. [2] The treatment target is clinical remission according to ACR-EULAR definition or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed in no sufficient improvement is seen after 3 months. [3] "MTX should be part of the first treatment strategy"; while combination therapy of csDMARDs is not preferred by the Task Force, starting with MTX does not exclude its use in combination with other csDMARDs. [4] TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA approved bsDMARDs), abatacept, IL-6-inhibitors, or rituximab; in patients who cannot use csDMARDs as comedication, IL6-inhibitors and tsDMARDS have some advantages. [5] Current practice would be to start with a bDMARDs (in combination with MTX or other csDMARDs) because of the long-term experience compared with tsDMARDs (Jak-inhibitors). [6] The most frequently used combination comprises MTX, sulfasalazine and hydroxychloroquine. [7] Dose reduction or interval increase can be safely done with all bDMARDs with little risk of flares; stopping is associated with flare rates; most but not all patients can recapture their good state upon re-institution of the same bDMARD. [8] Efficacy and safety of bDMARDs after Jak-inhibitor failure is unknown; also, efficacy and safety of an IL-6 pathway inhibitor after another one has failed is currently unknown. [9] Efficacy and safety of a Jak-inhibitor after insufficient response to a previous Jak-inhibitor is unknown." (Smolen et al., 2017)

ACPA, anticitrullinated protein antibody; bDMARD, biological DMARD; bsDMARD, biosimilar DMARDs; csDMARDs, conventional synthetic DMARDs; EMA, European Medicines Agency; FDA, Food and Drug

Administration; IL, interleukin; MTX, methotrexate; RF, rheumatoid factor; TNF, tumour necrosis factor; tsDMARDs, targeted synthetic DMARDs.

2.7.1. Disease-modifying anti-rheumatic drugs (DMARDs)

DMARDs are the mainstay of RA treatment. These medications are immunosuppressive that act by slowing structural damage in the joints, they can induce or maintain remission and reduce the frequency of flare-ups (Benjamin et al., 2018). DMARDs are divided into two categories: synthetic and biologic.

2.7.1.1. Synthetic DMARDs

This group of medications include conventional synthetic DMARDs (csDMARDs) and targeted synthetic DMARDs (tsDMARDs). While csDMARDs were used for many years for RA treatment, tsDMARDs were introduced in the market in 2012 (van Vollenhoven, 2016). TsDMARDs are small-molecule agents that target the Janus kinases (JAKs). Whilst not biologic agents, similar to biologic agents they have a target, and their efficacy is comparable to biologic agents (van Vollenhoven, 2016).

Tofacitinib was the first introduced JAK inhibitor for RA treatment (Felice et al., 2018). It received the first marketing authorisation in the USA in November 2012 (Cohen et al., 2018). The usual oral dose is 5 mg twice daily. Tofacitinib monotherapy or in combination with a csDMARD is effective in reducing RA symptoms and improving health-related quality of life (HR-QOL) (Dhillon, 2017). Other JAK inhibitors such as Baricitinib were recently introduced. However, the safety data for Baricitinib is still limited, and further research is needed to evaluate their use (Felice et al., 2018).

The csDMARDs have two functions in RA treatment; symptom relief and joint protection. Their onset of action is slow; six weeks to four months, and there is a high risk of toxicity that requires monitoring through regular blood tests. The most important csDMARDs include MTX, leflunomide, hydroxychloroquine (HCQ), and sulfasalazine (Benjamin et al., 2018).

Methotrexate (MTX) is the most effective and commonly used medication for RA. It is effective in long term treatment, its mechanism of action is slightly faster than other csDMARDs and it has lower toxicity. The onset of action is about four to eight weeks and usually the clinical efficacy is obtained during the first six months. It can be administered orally, subcutaneously, and intramuscularly (Kremer, 2018). The bioavailability of the subcutaneous and intramuscular administrations are higher than the oral administration (Schiff et al., 2014). However, the oral form is more common and patients have a positive perception of it (Nash et al., 2013). The usual dose is 25 mg once weekly (Smolen et al., 2016) and it is prescribed as a monotherapy or in combination with other medications. Nausea, diarrhoea, liver toxicity, lymphoma, infections and pneumonitis are the potential side effects (Kahlenberg et al., 2011). Monitoring of liver function tests (LFTs), creatinine (Cr) and complete blood count (CBC) is essential every four to eight weeks (Kahlenberg et al., 2011).

Sulfasalazine is generally considered a less potent DMARD; its combination with other sDMARDs has been shown to improve RA treatment with relatively low toxicity (Kahlenberg et al., 2011). It is generally well-tolerated. However, 20% to 25% of patients are intolerant to side effects including nausea, diarrhoea and headache. Allergic reactions, rashes and leukopenia are rare side effects (Kahlenberg et al., 2011). Sulfasalazine is one of the few DMARDs that are relatively safe in pregnancy (Krause

et al., 2016). CBC monitoring is essential every four to eight weeks during the first year of treatment (Kahlenberg et al., 2011). The usual dose is 2-3 g daily taken orally in two divided doses (twice a day) and it is recommended that it starts with the low dose and gradually increases by the maximum dose of 500 mg a week to minimise the potential toxicity (Smolen et al., 2016).

Leflunomide is observed as efficacious as MTX (Cohen et al., 2001). It is used alongside sulfasalazine in patients where MTX is contraindicated or limited by side-effects. The route of administration is oral and leflunomide is available in tablets of 10, 20 and 100 mg. The initial administration dose is 100 mg daily for three days followed by a maintenance dose of 10 to 20 mg daily (Mehta et al., 2009). The main side effects of leflunomide are gastrointestinal and liver problems, minor allergic reactions such as rash and itch, alopecia, infections and hypertension (Murphy et al., 2018). Similar to MTX, monitoring of LFTs, Cr and CBC is essential every four to eight weeks (Kahlenberg et al., 2011). Similar to other csDMARDs, it may take several weeks to begin taking effect, and complete benefits may not be experienced until 6 to 12 weeks after medication initiation (Paz, 2018).

Hydroxychloroquine (HCQ) is a mild DMARD that its monotherapy did not demonstrate significant efficacy in joint damage prevention (Van Der Heijde et al., 1990). Therefore, it is recommended in combination with other DMARDs in particular with MTX (Kahlenberg et al., 2011). Like other DMARDs, the onset of effectiveness is slow (two to four months). HCQ users may be protected from the subsequent development of cardiovascular diseases and diabetes (Hage et al., 2014). Retinal toxicity and nausea are common side effects and an ophthalmologic exam (eye examination) is essential every year (Kahlenberg et al., 2011). The administration mode

is oral and the usual dose is 400 mg daily in two divided doses (twice daily) (Smolen et al., 2016).

2.7.1.2. Biologic disease-modifying anti-rheumatic drugs (BDMARDs)

BDMARDs are divided into two categories: biological original DMARDs (boDMARDs) and biosimilar DMARDs (bsDMARDs). These bDMARDs target specific cells in the body. The most commonly used bDMARDs, the route of administration, their usual dose and the frequency of administration are outlined in Table 2.3. BoDMARDs were introduced to the market in the early 1990s (Benjamin et al., 2018). They were regarded as a major advance in RA treatment (Klippel, 2000) as they are efficacious in the treatment of patients with an inadequate response to sDMARDs (Agarwal, 2011). In addition, bDMARDs can postpone radiographic progression, showing the potential benefits in preventing long-term disability from joint destruction in addition to the short-term disability from symptoms of inflammatory arthritis (Agarwal, 2011). The manufacturing of bDMARDs is a complex process that uses recombinant DNA technology (Conner et al., 2014). BsDMARDs are a copy of boDMARDs and highly similar in all essential aspects to boDMARDs including efficacy and safety (Dörner et al., 2013).

Table 2.3. Common bDMARDs for RA treatment.

Target cell	Generic name	Route of administration	Usual dose	Usual starting frequency of administration
TNF agents	Etanercept	Subcutaneous	50 mg	Once a week
	Infliximab	Intravenous	3 mg/kg	Every 8 weeks
	Adalimumab	Subcutaneous	40 mg	Every other week
	Certolizumab	Subcutaneous	200 mg	Every other week
	Golimumab	Subcutaneous	50 mg	Once a month
IL1	Anakinra	Subcutaneous	100 mg	Daily
B-cell	Rituximab	Intravenous	500– 1000 mg	Two infusions every 6 months
T-cell	Abatacept	Intravenous	500– 1000 mg	Every 4 weeks
		Subcutaneous	125 mg	Once a week
IL6	Tocilizumab	Intravenous	4–8 mg/kg	Every 4 weeks
		Subcutaneous	162 mg	Once a week

BDMARDs: biologic DMARDs, TNF: anti-tumor necrosis factor, IL: interleukin.

Tumor necrosis factor (TNF)-α antagonists, such as infliximab, etanercept, adalimumab, golimumab and certolizumab are the most widely used bDMARDs for the treatment of RA. **Infliximab** is used in patients with high disease activity that has not responded adequately to at least two DMARDs including MTX (Chen et al., 2006). The efficacy of infliximab in combination with MTX was higher than MTX monotherapy or combined DMARDs. The usual dose of infliximab is 3 mg/kg every eight weeks, following an induction period of six weeks. An increase of up to 10 mg/kg in dosage or

a decrease of the dosing intervals to 4 weeks is recommended in case of insufficient response (Eng et al., 2013). Dose increase more than the recommended dosage are related to an increased incidence of infections (Costa et al., 2015). Infliximab represents approximately 40% of bDMARDs prescribed (Costa et al., 2015). **Etanercept** is another widely used bDMARDs that has been shown to be safe and effective in rapid reduction of disease activity in patients with RA and in sustaining that improvement (Bathon et al., 2000; Moreland et al., 2001). It is used as monotherapy or in combination therapy with MTX. A clinical trial comparing etanercept monotherapy with MTX monotherapy reported that etanercept as a monotherapy was superior to MTX monotherapy in reducing disease activity and disability and, having less side effects (Genovese et al., 2002). **Adalimumab**, **certolizumab** and **golimumab** are other TNF-α antagonists that are used for RA treatment. Systematic reviews of clinical trials reported that these medications as a monotherapy or in combination with MTX had high efficacy and decreased radiographic progression (de Ávila Machado et al., 2013; Ruiz Garcia V et al., 2017; Singh et al., 2010). However, patients treated with TNF-α antagonists were at higher risk of serious infections (Bongartz et al., 2006; Curtis et al., 2007). Therefore, monitoring patients for signs of infection, in particular in the first six months the medication is prescribed, is recommended to rheumatologists (Curtis et al., 2007).

Anakinra is the first bDMARDs designed to modify the immune response of interleukin 1 (IL-1) (Mertens et al., 2009). It is used in patients with RA who failed at least one DMARDs (Mertens et al., 2009). Like other bDMARDs, anakirna has shown a high efficacy with several side effects such as injection site reaction and infections (Nikfar et al., 2018). **Rituximab** is a monoclonal antibody that depletes B cells from

the circulation (Randall, 2016). Findings of a systematic review and meta-analysis of clinical trials on rituximab efficacy reported that rituximab is an effective choice for patients with RA, particularly for patients who failed anti-TNF treatment (Lemos et al., 2014). **Abatacept** is a protein that targets T-cells (Moreland et al., 2006). Like rituximab, it is recommended to patients with RA who have had an inadequate or unsustained response to anti-TNF treatment (Genovese et al., 2005). **Tocilizumab** is designed to modify the immune response of IL6 (Oldfield et al., 2009). It is used for patients with RA who have had inadequate response to, or who were intolerant of, prior DMARDs or anti-TNF treatment (Oldfield et al., 2009). Results of a clinical trial also reported that tocilizumab initiation, with or without MTX, in patients who newly diagnosed with RA showed a high efficacy (Bijlsma et al., 2016).

2.7.2. Glucocorticoids

Also referred to as corticosteroids, glucocorticoids are steroidal medications that reduce inflammation and have been used for RA treatment for over 65 years (Bijlsma et al., 2014). Prednisone is the most commonly used glucocorticoid in RA treatment. It is recommended to be used at the lowest possible dose (≤10 mg/day) and for the shortest duration (≤3 months) due to side effects (Singh et al., 2016). Glucocorticoids can be administered in different formats including orally (usually taken once a day), intra-articular (into the joint), intravenous and intramuscular (Freeman, 2018). These medications are beneficial for RA treatment due to their joint protection function (Freeman, 2018) and lower risk of toxicity in comparison to NSAIDs (Chatzidionysiou et al., 2017). The addition of glucocorticoids to sDMARDs can benefit patients (Chatzidionysiou et al., 2017), in particular, during periods of flare-ups where

severe symptoms are experienced (Freeman, 2018). The common side effects that make this medication unfavourable for long-term use are weight gain, skin thinning, sleep disturbance and neuropsychiatric disorders (McDonough et al., 2008).

2.8. Medication adherence

Adherence is defined as "the extent to which patients follow the instructions they are given for prescribed treatments. The term, adherence, is intended to be non-judgmental, a statement of fact rather than of blame of the patient, prescriber, or treatment" (Haynes et al., 2008). The terms adherence, compliance and persistence are used in adherence-related studies. Although they are different, in the literature they may be used interchangeably (Ahmed et al., 2014). The term persistence defines the duration of time from initiation to discontinuation of treatment (Cramer et al., 2008). Compliance refers to the extent to which the patient follows the prescribed regimen the physician decides for the patient. This concept reflects a degree of paternalistic approach to the patient-physician relationship (Marengo et al., 2015). Currently, adherence is the most recent word that is used to describe the extent to which patients follow the prescriber recommendation about medicine taking behaviour (Horne et al., 2005). Understanding medication adherence across different diseases is essential due to the negative consequences associated with medication non-adherence. Medication non-adherence results in poor clinical outcomes, increased disease severity, low quality of health, increased morbidity and mortality rates, and high economic costs on the healthcare system (Osterberg et al., 2005; Sokol et al., 2005). Although adherence to medications is necessary, WHO reported medication adherence in patients with chronic diseases

was found to be 50% in developed countries and less than 50% in developing countries (Sabaté, 2003).

In the past, the common belief was that the patient was responsible for non-adherence (Brown et al., 2011). A 2003 WHO report defined adherence as a multidimensional phenomenon comprising of five dimensions in which the patient is just one dimension (Sabaté, 2003). The other dimensions include factors that relate to socioeconomic, therapy, disease and healthcare system and team situation (Sabaté, 2003).

2.9. Medication adherence in patients with RA

To achieve a target clinical outcome, a certain amount of medication intake or adherence is required. Medication adherence of ≥80% was found to be sufficient in Haynes's early empirical study of patients with hypertension (Haynes et al., 1980). This cut-off was also found as a reasonable cut-off point in schizophrenia, diabetes, hypertension, congestive heart failure, or hyperlipidaemia (Karve et al., 2009). In RA related studies, 80% medication adherence was used as a cut-off to divide patients as adherent or non-adherent and adherence less than 80% was considered sub-optimal (Arshad et al., 2016; Blum et al., 2011; Borah et al., 2009; Cannon et al., 2011; Harley et al., 2003; Rauscher et al., 2015; Richards et al., 2012; van den Hoogen et al., 2009; Xia et al., 2016).

In this section, we report the findings of several systematic reviews that investigated medication adherence among patients with RA (Blum et al., 2011; Fidder et al., 2013; Harrold et al., 2009).

In the systematic review of Harrold and Andrade (2009), investigating medication adherence to NSAIDs and DMARDs in rheumatic conditions, 11 of 20 identified articles were on RA. While adherence in patients with RA varied from 30% to 93%, 10 of 11 studies reported the adherence rate was less than 70% in patients with RA. They also reported that adherence has not been widely examined for most chronic inflammatory rheumatic diseases and the few studies that exist used different definitions limiting the conclusion. Quality of the included studies has not been assessed and due to the variety of rheumatic diseases and adherence measurement methods drawing a definite conclusion is impossible. Authors of this systematic review have not reported the country in which the included studies were conducted. By investigating each individual included study, we found that all studies were conducted in either England, USA or European countries.

Blum et al. (2011) assessed persistence with and adherence to bDMARDs in patients with RA. Of the 52 studies identified, 49 (94%) studies were conducted in Europe and the USA. Fifty-one studies reported measures of persistence and four studies reported on adherence, all of which were conducted in the USA and used administrative claims data for the calculation of medication possession ratio (MPR). Only two of the studies reported mean adherence rates and two reported the proportion of adherent patients (adherence more than 80%). They reported the range of medication continuation in one year was 32% to 90%, and continuation rates were higher with the addition of MTX or other DMARDs to the treatment plan.

Fidder et al. (2013) systematically reviewed studies that assessed adherence to bDMARDs including adalimumab, infliximab and etanercept in patients with Crohn's disease and RA. They identified three studies in RA conducted in the USA (Borah et al.,

2009; Harley et al., 2003; Li et al., 2010). The sample size-weighted mean adherence was 59% in these studies. Adherence was 67%, 59% and 48% for adalimumab, etanercept and infliximab respectively. They reported female gender as a negative determinant of adherence (Borah et al., 2009; Harley et al., 2003; Li et al., 2010).

Scheiman-Elazary et al. (2016) conducted a systematic review of studies reporting medication adherence to DMARDs, steroids, and NSAIDs in patients with RA. Thirty-one studies were identified; 14 of these studies were conducted in the USA, six in the UK, seven in European countries, and one each in Australia, New Zealand, Turkey and Mexico. The mean adherence rate was 66% (95% CI 0.58–0.75). Adherence in the Turkish study was 52% (Tuncay et al., 2007).

According to these above-mentioned systematic reviews, medication adherence is sub-optimal in patients with RA, and the majority of studies in this area were conducted in developed countries.

A few single studies were found in Middle Eastern countries including Saudi Arabia, Turkey, Egypt and Iran (Almazrou et al., 2016; Gadallah et al., 2015; Salehi et al., 2017; Uckun et al., 2017). A study in Saudi Arabia surveyed 126 patients and reported 47.7% were adherent (Almazrou et al., 2016). Another Turkish study surveyed 82 patients and found 50% of participants were highly adherent (Uckun et al., 2017) and the study in Egypt that surveyed 140 patients found 9.4% were classified as moderately adherent and none classified as highly adherent (Gadallah et al., 2015). The Iranian study in Tehran on 252 patients reported 65% were adherent (Salehi et al., 2017). This low quality study had some limitations, including misconduct in adherence measurement. The researchers used the Compliance Questionnaire Rheumatology (CQR) questionnaire to assess adherence, however they did not report adherence according to

the guidelines that the CQR developers provided. This erroneous reporting may have resulted in an inaccurate adherence measurement. Finally, among developing countries, a study in India on 72 patients with RA found the adherence rate was 36% (Doddapaneni et al., 2014). These studies highlight the lack of studies focusing on medication adherence in developing countries and in the Middle East region.

2.10. Significance of medication adherence in patients with RA

Adherence to RA medications is essential in patients with RA to prevent structural damage in joints and to reach optimal health outcomes in patients with RA (Ragab et al., 2017). A systematic review and meta-analysis that was conducted to explore the impact of medication adherence on disease activity in patients with RA reported that RA patients with higher medication adherence tended to have lower disease activity (Li et al., 2017). A total of 1,963 adults with RA were included in the meta-analysis with DAS-28 used as the tool to assess disease activity. DAS-28 is a validated tool that measures disease severity in patients with RA. The results of this systematic review reported disease activity was significantly lower in adherent patients than in non-adherent patients (Mean difference =−0.42, 95% CI [−0.80, −0.03], P=0.03) (Li et al., 2017). Another cohort study of 103 patients with RA in the Netherlands explored the impact of medication adherence on disease activity during the first year after diagnosis. Medication adherence was assessed by a medication event monitoring system (MEMS) device. The EULAR/ACR2010 criteria was used for RA diagnosis and DAS-28 for disease activity assessment. They reported that non-adherent patients have a higher disease activity ($p = 0.01$), especially three months after diagnosis compared with adherent patients (Pasma et al., 2015). Also, they reported non-adherence is an

important determinant of higher disease activity in the first six months of treatment and it needs extra attention in the early stages of disease. As explained in section 2.5, it is important to begin treatment in the early stages of the disease to reach a state of remission as soon as possible to avoid structural damage to joints.

The negative impact of non-adherence is not limited to the patient's disease activity. In a cohort study of 194 patients with rheumatic diseases (74.2% had RA) the association between adherence was assessed by MEMS and healthcare costs were examined over a one year follow up period. They collected information on hospital costs including consultations, emergency department visits, hospitalisation, medical procedures, imaging facilities, medication costs, and laboratory tests. By using a multivariate regression analyses, they reported non-adherence resulted in higher total healthcare costs, higher hospital admissions costs and higher costs made at the rheumatology outpatient clinics (Pasma et al., 2017).

2.11. Medication adherence determinants

As stated in section 2.7, adherence is defined as a multidimensional phenomenon comprising of five dimensions (Sabaté, 2003). These dimensions relate to the person, socioeconomic factors, the disease, the therapy, the healthcare system and team situation (Sabaté, 2003).

2.11.1. Person-related factors

Person-related factors represent the patients' attitudes, perceptions, knowledge and beliefs. Some of these factors are forgetfulness; fear of side-effects; low motivation;

poor knowledge of disease; lack of self-perceived need for treatment; uncertainty about the efficacy of the treatment; denial in the diagnosis; irregular attendance at follow-ups; hopelessness; frustration with healthcare providers and treatment and fear of medication dependence (Sabaté, 2003) . In RA, lack of knowledge about the disease and its treatment and, perception of lack of treatment effectiveness can result in non-adherence to prescribed medications (Koutsogianni, 2017; Neame et al., 2005; Pasma et al., 2015; Uckun et al., 2017). The uncertainty about the efficacy of medications, negative beliefs about medication and the refusal to accept the chronic nature of RA that requires long-term treatments, are all barriers to adherence (Hope et al., 2017; Koutsogianni, 2017; Wohlfahrt et al., 2018).

These negative beliefs influence self-management and self-efficacy skills, consequently affecting patients' ability to follow the prescribed recommendations (Marengo et al., 2015). In addition, people may forget to take their medications (Barbosa et al., 2015; Uckun et al., 2017). Beside the actual side effects of the medications, fear of side effects is also a reported barrier to medication adherence in patients with RA (Barbosa et al., 2015; Garcia Popa-Lisseanu et al., 2005; Koutsogianni, 2017; Wohlfahrt et al., 2018).

2.11.2. Socioeconomic status

Socioeconomic status significantly influences medication adherence in people living in developing countries due to limited resources (Sabaté, 2003). In particular, patients with chronic diseases may skip medication treatment to meet other needs of their family members. Socioeconomic-related factors include poverty, low level of education, unemployment, living in rural areas, high medication cost, lack of effective community

support networks, culture and lay beliefs about disease and treatment (Sabaté, 2003). Previous studies reported socioeconomic factors associated with adherence in patients with RA these were; level of education, income (Xia et al., 2016), employment status (Ghosh et al., 2015), living alone (De Cuyper et al., 2016), out-of-pocket costs (Curkendall et al., 2008; Heidari et al., 2018) and challenges with access to medications (Wohlfahrt et al., 2018). However, the findings have been inconsistent as the association between these factors and medication adherence were not significant in all studies on medication adherence determinants in patients with RA (Marengo et al., 2015; Uckun et al., 2017).

2.11.3. Disease-related factors

Disease-related factors represent disease-related demands faced by the patients. Disease severity and the level of discomfort, pain and disability arisen from the disease are among these factors (Sabaté, 2003). In RA, previous studies report factors associated with adherence were; RA severity (Ghosh et al., 2015; Uckun et al., 2017), depression (Xia et al., 2016), mental health status (De Cuyper et al., 2016), presence of other diseases and the number of other diseases (Calip et al., 2017; De Cuyper et al., 2016). Patients who had shorter disease duration, better mental health and lower disease activity were more likely to adhere to medications than patients with opposite traits (Waimann et al., 2013).

2.11.4. Therapy-related factors

Therapy-related factors that affect adherence mostly reflect the experiences that patients have had with medication and treatment. These factors include a complex

medical regimen, medication side-effects, treatment duration and frequent treatment changes (Sabaté, 2003). Previous studies reported several therapy-related factors associated with adherence in patients with RA. MTX was found as the RA medication that patients are more likely to demonstrate non-adherence due to the side effects such as nausea and hair loss (Barbosa et al., 2015) and the administration frequency (Alten et al., 2016). The usual administration of MTX is every week or every two weeks which makes this medication unfavourable for administration (Alten et al., 2016). The patient's experience of medication also affects adherence; experiencing positive or negative effects improves or deters adherence, respectively (Brandstetter et al., 2016; Koutsogianni, 2017; Pasma et al., 2013).

Regarding adherence to bDMARDs, perceived effectiveness of the medication, injection experiences, injections frequency (Bolge et al., 2015), hospitalisation and emergency department visits affect adherence (Calip et al., 2017). Being hospitalised or attending an emergency department was reported to be associated with lower medication adherence (Calip et al., 2017).

2.11.5. Healthcare system and team factors

Healthcare system and team factors that influence adherence include factors related to insurance, the healthcare system and the healthcare professionals. A good patient-provider relationship and patient education improve adherence. However, inadequate reimbursement by health insurance programs, poor medication availability in the market, low skilled healthcare providers on managing chronic diseases and medication adherence, time limitation and poor patient follow-up are barriers to adherence (Sabaté, 2003). In RA, a relationship regarding trust building and treatment plan explanation

between the rheumatologist and the patient improves adherence (Brandstetter et al., 2016; Koutsogianni, 2017; Pasma et al., 2015). A trustful physician-patient relationship was highly appreciated by patients. Other adherence determinants in this category included access to and availability of rheumatologist and medications and insurance. In a qualitative study, Voshaar et al. (2016) identified barriers and facilitators of adherence to DMARDs. Regarding the environmental context, access to health professionals and availability of medications in the pharmacy were significant adherence determinants. They also reported that medication OOP costs contribute to non-adherence in patients with RA.

2.12. Out-of-pocket (OOP) costs and medication adherence

Since 2000, the use of expensive new medications with chronic conditions has increased healthcare costs (Health Care in America 2006 Survey, 2006) and therefore, individual OOP costs have also increased (Paez et al., 2009). OOP cost is defined as the portion of total healthcare expenditure that is paid by the patient excluding the payments made for health insurance premiums (Machlin, 2006). A study of 7,527 patients with RA in the USA reported the introduction of bDMARDs had increased the total annual cost of treatment three-fold (Michaud et al., 2003). These high prices may limit the utilisation of these medications (Desai et al., 2014). In another study of 8,545 patients with RA in the USA, 43.6% of patients reported difficulty paying OOP costs and of these patients, 9.0% reported they were unable to purchase all medications and pay for the care they needed. They reported that 2.4% to 19.2% of household income was consumed by OOP costs and household income was the main determinant of OOP burden, followed by disease activity, and coverage of health insurance. They reported

patients younger than 65 years of age, encounter substantial OOP burden (Wolfe et al., 2009). A cohort study of 81 patients with RA in Australia reported that OOP burden was higher in younger patients and patients with private health insurance than their older counterparts who were covered by pensions (Lapsley et al., 2002). A study in Mexico investigated catastrophic expenses of 262 patients with RA. Catastrophic expenses referred to health expenses more than 30% of the total household income. They reported that RA caused catastrophic expenses in 47% of households, which were significantly associated with the type of health insurance coverage and disease duration. They also investigated impoverishment, defined as those households that could not afford the Mexican basic food basket. They reported that impoverishment occurred in 67% of households and was associated with catastrophic expenses and low socioeconomic level (Álvarez-Hernández et al., 2012).

Review studies have shown that increasing patient OOP costs decreases medication adherence in a variety of diseases. For example, Eaddy et al. (2012) identified 66 studies in a systematic review that evaluated the relationship between changes in OOP costs and medication adherence in chronic diseases, 85% of those identified studies reported increasing the OOP costs was significantly associated with a decrease in medication adherence. Patients with RA are more vulnerable to cost-related non-adherence because of high prices of the bDMARDs (De Vera et al., 2014). Cost-related medication non-adherence (CRN) is related to the patient delaying or, not refilling prescriptions, skipping doses or taking smaller doses of their medication due to cost (Harrold et al., 2013; Soumerai et al., 2006). Therefore, as part of this thesis, we conducted a systematic review to determine whether OOP costs affect medication adherence in adults with RA. This work is presented in section 2.13.

2.13. A systematic review of medication adherence and OOP costs in patients with RA

Before designing the study, a systematic review was conducted to investigate the literature regarding the relationship between medication adherence and OOP costs in patients with RA. It was important to identify the existing research that had been conducted, to assist with the design of the PhD study effectively. Findings of the systematic review have been published in Seminars in Arthritis and Rheumatism (2018).

Only six studies were identified through a broad search of 12 databases; of which five out of six were conducted in the USA. The population and the methods of the included studies varied widely. However, an inverse relationship between OOP costs and medication adherence was identified. Findings suggest that healthcare providers and health policy makers should be aware that OOP costs can contribute to non-adherence to RA medications. Therefore, health policy makers globally should identify the appropriate OOP amount, so patients do not experience CRN.

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Do out-of-pocket costs affect medication adherence in adults with rheumatoid arthritis? A systematic review

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ABSTRACT

Introduction: For individuals with a chronic condition, long-term management of their medication can be difficult and as a result non-adherence is common among this cohort. In patients with rheumatoid arthritis (RA), the introduction of biologic agents was a revolutionary treatment but the high costs of this medication might limit their utilisation.

Objective: This systematic review aimed to determine whether out-of-pocket (OOP) costs affect adherence to RA medications in adults with a diagnosis of RA.

Methods: Twelve databases were searched to identify primary peer-reviewed articles, written in English from inception to April 2016 that referred to the relationship between adherence to RA medication and OOP costs. The CASP check list was used to assess the quality rating of the included studies.

Results: Six articles were identified in the review and all were considered as high quality studies. Among them, three directly considered the association between OOP costs and medication adherence as their main objective. Although the population and the methods of the studies varied widely, there was an inverse relationship between OOP costs and medication adherence in patients with RA.

Conclusion: The findings of this review suggest that OOP costs can contribute to non-adherence to RA medication in patients with RA. Therefore, health policy makers globally should identify the appropriate OOP amount so these costs do not affect adherence whilst simultaneously ensuring that costs are not an intolerable burden for governments, providers and insurers.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that often requires long-term treatment with multiple medications [1]. Most common pharmaceutical treatments of RA includes symptom relief drugs, disease-modifying antirheumatic drugs (DMARDs) and newer biologic agents [2]. Early and aggressive intervention with DMARDs and biologic agents has been shown to improve clinical outcomes, induce remission and prevent progression of joint erosion [3]. As a consequence, it improves patients' functional status, health-related quality of life, and reduces fatigue [4]. Patient adherence to their treatment protocols is essential to encourage the best health results in RA [5]. Medication adherence refers to "the degree or extent of conformity to the recommendations about day-to-day treatment by the provider with respect to the timing, dosage, and frequency" [6]. There are several different adherence-related terms in the literature [7] and there is no gold standard for measuring medication adherence [8]. A systematic review conducted by Scheiman-Elazary et al. [9] investigated adherence to anti-arthritis medications including DMARDs, steroids, and nonsteroidal anti-inflammatory drugs among patients with RA. The results of the review showed no differences in adherence among the different measurement methods such as questionnaires, pill count, claims databases or interviews.

In most studies investigating medication adherence in different chronic diseases [10], including RA [11–13] 80% was the cut-off used to identify patients as adherent or non-adherent; adherence more than 80% is considered optimal. In a number of systematic review articles assessing medication adherence among RA patients, the majority of studies showed that adherence was suboptimal and non-adherence is a major problem [14–16]. Non-adherence results in negative disease outcomes including higher disease activity, lower physical ability and lower quality of life [17–20] and increased hospital costs [21].

In chronic diseases, many factors affect medication adherence. Determinants of non-adherence include patient, provider and health system factors, with interactions among them [22]. Some barriers of adherence also include fear of side effects, poor

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doctor-patient relationship, poor knowledge about the effectiveness of the medication, multiple prescribed medications with different dosing schedules, access to the medication and cost [22].

Biologic DMARDs were a revolution in RA treatment, decreasing joint erosions and improving patient quality of life [5]. However, high prices may limit their utilisation [23]. A study in 2011 showed that 10 out of 46 European countries had no reimbursement for biologic DMARDs and patients with RA living in lower income European countries had difficulty affording biologics [24]. Using biologic treatments is also challenging in developing countries because of financial constraints. The gross national product (GNP) and average expenditure on health care system is lower in developing countries, which makes it difficult for RA patients to afford biologic medications [25].

A study of patients with RA in the United states of America (USA) noted that the introduction of new biologic medications have increased the total annual cost of treatment three-fold [26] therefore, out-of-pocket (OOP) costs have also increased [27]. OOP costs are defined as the portion of total healthcare expenditure that is paid by the patient, excluding payments made for health insurance premiums [28]. Studies have shown that increasing patient OOP costs decrease medication adherence [19,29,30]. For example, a systematic review conducted by Eaddy et al. [19] identified 66 studies that evaluated the association between changes in OOP costs and adherence in chronic diseases, 85% of those identified studies showed that increasing the patient's share of medication OOP costs was significantly associated with a decrease in adherence. Individuals with RA are more vulnerable to cost-related non-adherence because of high prices of the biologics [31].

In every country, national policies in pharmaceutical financing determine OOP payments. So, policy makers should be aware of the degree of the relationship between medication non-adherence and the costs of medications [32]. Studies considering OOP costs and its relationship with treatment adherence are beneficial for the decision-making process for policy makers [31,33]. This issue specifically has significance in RA management because biologics are a mainstay treatment for RA patients who may not have responded to traditional DMARDs. However, the high prices of the biologics may result in non-adherence, which causes an increase to health care costs including outpatient, inpatient and laboratory services [31,34].

From our knowledge, there is no systematic review of the literature in which the relationship between OOP costs and medication adherence has been assessed in patients with RA. The aim of this review is to consolidate information from a range of studies which have investigated the relationship between medication OOP costs and RA medication adherence in patients with RA.

Materials and methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA statement) was used as a guide to ensure accuracy of the systematic review [35].

Literature search

Twelve databases including PubMed, PsycINFO, ABI/ inform, Business Source, CINAHL, EMBASE, MEDLINE, Ovid MEDLINE, ProQuest, ScienceDirect, Scopus, Web of Science were systematically searched from their inception to April 2016 to identify studies that investigated the relationship between medication OOP costs and medication adherence in patients with RA. In undertaking the broad search the following keywords from MeSH (Medical Subject Heading) [36] were used to retrieve the relevant articles: 'Medication adherence', 'compliance', 'persistence', 'Disease-modifying antirheumatic drugs', 'biologic agents', 'out-of-pocket costs', 'rheumatoid arthritis'. The PICO (Population or Patient, Intervention or Indicator, Comparator or Control, Outcome) strategy was applied for identifying the key terms [37]. The full list of the search terms is provided in Appendix A. In the World Health Organization (WHO) report the terms 'adherence' and 'compliance' do not have the same meaning in the present era of patient-oriented care. This has resulted in the use of words such as persistence to refer to the extent to which the patient follows the treatment regimen [38]. Persistence, adherence and compliance were all used in this search. The search strategy pattern was used across all 12 databases searched. Reference lists of eligible articles and review articles were examined to identify additional sources not identified in the database searches.

Selection criteria

Studies were included if they referred to the relationship of adherence to RA medication and medication OOP costs in patients who were over 18 years of age with RA. Patients had to have a diagnosis of RA assessed through a validated guideline such as ICD-9 disease codes, the revisions of diagnostic criteria for RA (ARA criteria) or the American College of Rheumatology (ACR). All studies had to be written in English and primary research studies that were published in peer reviewed journals. No restrictions were imposed on study design or study duration. With regard to medication adherence, studies that measured medication adherence or mentioned different definitions of adherence were included in the review such as initiation and continuation of medication. Therefore, all definitions of adherence, compliance, persistence and continuation were accepted for review.

Articles were excluded if they discussed total costs without separating OOP costs; did not mention clearly which type of costs they investigated; if they considered juvenile arthritis or other kinds of arthritis; and were non-primary research articles (newspaper articles, editorials, book chapters, conference abstracts and reviews). Titles and abstracts were reviewed by PH, articles that did not meet the inclusion criteria were excluded. Full-text reading was conducted by two reviewers (P.H. and K.C.) who independently assessed the articles for possible inclusion in the review. Differences in assessment were discussed until both reviewers came to a consensus. Information about combining the results, removing duplicates, reading titles, abstracts and full-text were undertaken according to PRISMA [39].

Data extraction

To ensure that all data relevant to the focused question of the review were collected, data were entered into tables that were designed to provide information on each study. Characteristics of the included studies included author, year of the study, country where study was conducted, study design, medication assessed, follow-up times for adherence, data source and subjects' characteristics.

Data synthesis

Due to the small number of studies and different methods and their heterogeneous findings, a meta-analysis was not possible. A qualitative synthesis focussed upon the relationship between medication adherence and OOP costs.

Quality ratings

The quality of all retrieved articles was critically appraised using the Critical Appraisal Skills Programme (CASP) 'Cohort Study' tool. [40]. This appraisal tool has been used previously as an appraisal tool in other published systematic reviews [41–43]. This appraisal tool assesses each study based on the validity of results, study results and helpfulness of the results. The checklist contains twelve questions including nine questions with yes, no, 'cannot tell' responses and three open-ended questions (Q 7, 8 and 12). Each of those nine close-ended questions with a 'yes' response received one point and for those three open-ended questions, if the quality asked in the checklist was found, one point was given. Studies were determined high quality if they gained 9 to 12 points, 6 to 8 points was considered moderate quality and below 6 is judged low quality [42]. Two reviewers (K.C. and P.H.) assessed the quality of the studies independently. Any disagreements were discussed and resolved through a third reviewer (W.C.).

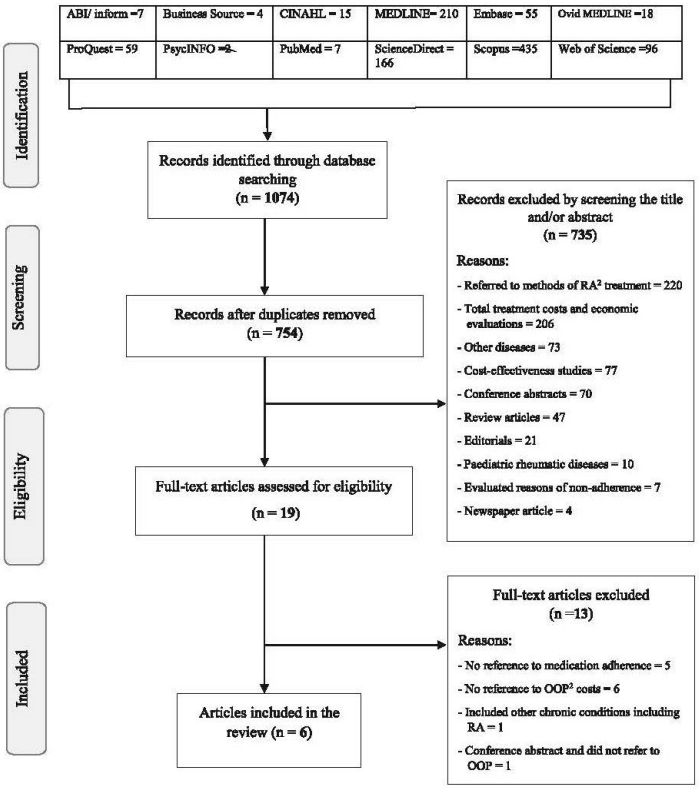
Results

Search results

A total of 1074 articles were retrieved from the initial search. After removing duplicates, 754 articles remained. Following the exclusion of articles based on the title or abstract, 19 were included for full-text reading. After applying the inclusion and exclusion criteria, 6 articles were included in the final review. The PRISMA process of selecting articles is presented in Figure 1. No additional articles were identified through searching the reference lists of included studies or review articles.

Study characteristics

The characteristics of the 6 included articles are presented in Table 1. All included studies were quantitative studies published between 2005 and 2016, 5 of the 6 studies were conducted in the United States of America (USA) [44–48] and 1 in Morocco [49]. Among the included studies, the patient's selection criteria for RA varied. Four studies employed the ICD-9 disease codes for RA [44,46–48], 1 study used the 1987 revision of ARA criteria [45] and 1 utilised the ACR guideline for RA eligibility [49]. Two studies reported the disease duration of RA, which varied from 8.5 years to 12.8 years [45,49]. The majority of participants in the studies were female (on average, 72.7% of the population studied were female), 11.5% of sample populations were living in rural areas and the mean age across all studies was 61.3, ranging from 43.5 to 63.5 years of age. Sample size varied between 100 [49] and 14,804 [46]; the four studies utilising claims databases in the USA [44,45,47,48] that were obtained from employers [44,48], health plans [47,48]



[1] Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
[2] Rheumatoid arthritis
[3] Out-of-pocket

Fig. PRISMA[1] flow diagram.

Table 1
Characteristics of included studies

Author (year), country	Study design	Medication assessed*	Follow-up time for adherence	Data source	RA diagnosis	Population	Sample size	Demographics of patients					
								Gender (female %)	Mean age (years)	Mean age at RA onset	Mean RA duration	Rural residency (%)	Prescribed non-biologic DMARDs (%)
Curkendall et al. (2008), USA [44]	Retrospective cohort study	Etanercept, adalimumab	1 year	MEDSTAT MarketScan database that includes approximately 45 large employers	ICD-9-CM	RA patients who had newly initiated etanercept and adalimumab and had made a claim for these biologics during 2002 to 2004	2285 newly initiated patients	74	54	–	–	25	48
Rkain et al. (2005), Morocco [49]	Cross-sectional	Symptomatic medications, DMARD	_	Survey	ACR	RA patients	100	88	43	31	12.8	75	91
Gibofsky et al. (2015), USA [45]	Prospective cohort study	Etanercept, methotrexate, other DMARDs	5 years	RADIUS 2 database between October 2002 and June 2003	1987 ARA	RA adults listed in RADIUS 2 with moderate to severe RA who had initiated etanercept	3484	77	–	43	8.5	–	72
Hopson et al. (2016), USA [47]	Retrospective cohort study	Biologic DMARDs	July 1, 2007 to December 31, 2012	Medicare Advantage members in Humana's database	ICD-9-CM	Members of MAPD plan with a claim for RA medication	864	77	63	–	–	<50	78
Harrold et al. (2013), USA [46]	Cross-sectional	RA medications	1 year; 5 times from 2004 to 2008	Survey (MCBS)	ICD-9	Older adults with RA	14,498 in 2004, 14,699 in 2005, 14,731 in 2006, 14,804 in 2007 and 13,651 in 2008	76	–	–	–	26	–
Karacamandic et al. (2010), USA [48]	Retrospective	Etanercept, adalimumab, infliximab	5 years; 2000 to 2005	Databases of 35 large private employers and 176 health plans from 2000 to 2005.	ICD-9	RA patients	Newly diagnosed = 8557, existing biologic users = 2066.	70	62	–	–	1	35 (70 for biologic users)

RA: rheumatoid arthritis, DMARD: disease-modifying antirheumatic drug, ACR: American College of Rheumatology, ARA: American Rheumatism Association, RADIUS 2: the rheumatoid arthritis disease-modifying antirheumatic drug intervention and utilization study 2, Humana is a large national health insurance provider, MAPD: Medicare Advantage and Prescription Drug, MCBS: The Medicare Current Beneficiary Survey. For missing data or not reported data "–" was used. *Medication assessed: list of medications were provided otherwise it was not reported in the study

Table 2
Quality rating using Critical Appraisal Skills Programme (CASP) cohort study checklist [26]

	Author (year)					
question number	Curkendall et al. (2008)	Rkain et al. (2005)	Gibofsky et al. (2015)	Hopson et al. (2016)	Harrold et al. (2013)	Karaca-mandic et al. (2010)
1. Did the study address a clearly focused issue?	1	1	1	1	1	1
2. Was the cohort recruited in an acceptable way?	1	1	1	1	1	1
3. Was the exposure accurately measured to minimise bias?	1	1	0	1	1	1
4. Was the outcome accurately measured to minimise bias?	1	0	1	1	1	1
5. Have the authors identified all important confounding factors or have they taken account of the confounding factors in the design and/or analysis?	1	1	0	1	1	1
6. Was the follow-up of subjects complete enough or was the follow-up of subjects long enough?	1	1[a]	1	1	1[a]	1
7. What are the results of this study?	1	1	1	1	1	1
8. How precise are the results?	1	1	0.5	1	1	1
9. Do you believe the results?	1	1	1	1	1	1
10. Can the results be applied to the local population?	1	1	1	1	1	1
11. Do the results of this study fit with other available evidence?	1	1	1	1	1	1
12. What are the implications of this study for practice?	1	1	1	1	1	1
Total score	**12**	**11**	**9.5**	**12**	**12**	**12**

[a] Not applicable: in not applicable cases 1 score is given.

and a registry that collected data on DMARDs utilisation [45] had the largest sample sizes. Another study used information from a large survey of a representative national sample of Medicare beneficiaries in the USA [46] and the last study surveyed 100 RA patients [49]. Five studies reported the percentage of participants prescribed traditional DMARDs, which varied from 35% [48] to 91% [49] and the remaining did not specify which medication was taken by their participant group. None of the studies provided details on the doses or the number of medications participants were taking.

Quality rating

The results of the critical appraisal are presented in Table 2. All included studies were determined as high quality studies; the methodological quality of the studies ranged from 9.5 to 12 points. Four studies [44,46–48] received the total score of 12. The other two studies showed some limitations. Gibofsky et al. [45] scored the lowest of all included studies; although they stated that the most common reason of biologic discontinuation was cost, they did not report the exact OOP costs and the relationship with medication adherence was not assessed statistically. Also, no statistical tests were performed for analysing results and cofounding factors. Rkain et al. [49] had ambiguity in measuring the outcome; whilst they did report medication adherence in their results, they did not explain how medication adherence was assessed in the survey.

Measures of medication adherence

Among the included studies, medication adherence was assessed via multiple methods (Table 3). One study measured medication possession ratio (MPR) [44] which is described as the percentage of days during the retrospective follow-up period for which a patient had medication available and it is calculated by dividing the days' supply of a medication dispensed by the number

Table 3
Medication adherence and out-of-pocket (OOP) costs among rheumatoid arthritis patients

Author (year)	Adherence measurement tool	Mean Adherence[a] (%)	Medication OOP costs	OOP cost and medication adherence
MPR (Medication possession ratio)				
Curkendall et al. (2008) [44]	MPR	52 ± 31 (SD)	33.6 USD[b] ± 60.6 USD monthly from 2002 to 2004	Negative significant relationship was found (p-value < 0.0001)
Self-report tools				
Rkain et al. (2005) [49]	Self-developed questionnaire	61	510 dirhams (≈54 USD) monthly in 2004	Financial problems led to suboptimal adherence in 61% of patients.
Harrold et al. (2013) [46]	Cost-related medication non-adherence (CRN) questionnaire: CRN was defined as skipping or reducing medication doses or not obtaining prescriptions due to cost.	CRN in 2004 = 20.7[a] CRN in 2008 = 18.5[a]	Not reported.	Having RA was associated with a 3.5-fold increase in the risk of CRN as compared to those without a chronic disease.
Initiation and continuation concept				
Gibofsky et al. (2015) [45]	Etanercept continuation assessed in patients who were categorised in to four groups: (1) etanercept monotherapy, (2) etanercept plus methotrexate, (3) etanercept plus methotrexate plus other DMARDs and (4) etanercept plus other DMARDs.	1) Etanercept monotherapy = 84 2) Etanercept plus methotrexate =73.3 3) Etanercept plus methotrexate plus other DMARDs = 72.6 4) 4) Etanercept plus other DMARDs = 73.9	Not reported.	Across these four groups, the most common reason for discontinuing etanercept was OOP costs.
Hopson et al. (2016) [47]	Prescription abandonment rate: defined as a reversed claim for biologics without evidence of a subsequent paid claim in the 180-day period following the initial reversed claim	Percentage of initial abandonment rate in each cost group:[a] $0-$25 = 0, $25-$100 = 4.7, $100-$250 = 12, $250-$400 = 20.9, $400-$550 = 28.9, > $550 = 32.7, overall = 18.2	Number of patients in every cost group: $0-$25 = 30.6, $25-$100 = 2.4, $100-$250 = 2.8, $250-$400 = 18.8, $400-$550 = 26.0, > $550 = 19.0	The overall initial abandonment rate was 18.2% for biologic DMARDs, ranging from 1.3% for the lowest OOP cost group to 32.7% for the highest OOP cost group. The negative association between OOP cost and likelihood of refilling a prescription was highly significant.
Karaca-mandic et al. (2010) [48]	Number of person-years[c] of initiators and continuers (initiation defines as first time use of biologics and continuation defined as using biologics continuously without a gap more than one year)	1629 initiators (8.4), 3257 continuers (70.6)	Monthly in all plans: infliximab: $125 (SD = $174), etanercept and adalimumab: $35 (SD = $53) In non-generous plans: infliximab ≥$353.4, etanercept and adalimumab: $90.4 Patients who never initiated biologics = $53.5 Biologic initiators = $107.7 1 year gap in biologic use = $90.3 Using biologics every year = $114.5 monthly	For both initiation and continuation the negative relationship was found, although this relationship was not significant for continuation.

[a] In Harrold et al. [46] and Hopson et al. [47] studies, the reported figures are non-adherence percentages.
[b] United States Dollar.
[c] Person-year: a measurement combining the number of persons and their time contribution in the study; it is the sum of individual units of time that the person in the study population have been exposed or at the risk to the condition of interest.

of monitored days in the selected time frame, which is usually one year (365 days).

Two studies measured medication adherence through self-report tools; one using the validated cost-related medication non-adherence (CRN) questionnaire [46] that investigated CRN in the previous 12 months and made a comparison between patients with RA and older adults with other chronic diseases. The other study developed their own questionnaire [49]. The questionnaire was divided into four sections, in which the third section included questions in regard to medication OOP costs, RA related financial difficulties which was divided into none, manageable, or unmanageable and then the consequences of these financial difficulties on treatment compliance. Although Rkain et al. [49] reported adherence levels from their survey respondents, they did not explicitly state how they assessed adherence in their survey.

The final three studies considered medication adherence in terms of initiation and continuation of medications [45,47,48]; databases were appraised to determine whether firstly, participants initiated the taking of their medication and then secondly, whether they continued to take the medication according to their

prescription. Gibofsky et al. [45] examined biologic DMARDs continuation and the associated reasons of discontinuation from a registry database that included data from a plan in which patients with RA were provided with a 12-week supply of *Etanercept (ETN)* and the first 4 months were free of charge. They examined the population after those 4 months up to 5 years; the population was divided into 4 groups; (1) *ETN users*, (2) *ETN plus Methotrexate (MTX) users*, (3) *ETN plus MTX plus other medicine users* and (4) *ETN plus other medicine users*. Karaca-Mandic et al. [48] assessed the number of initiators and continuers of biologic users from 2000 to 2005. Initiators were assessed in the population of patients who were newly diagnosed with RA and continuers were assessed in the whole RA population. Hopson et al. [47] assessed the prescription abandonment rate and the likelihood of prescription refill among biologic users during a 6-month follow-up period.

Figure on adherence

Figures for adherence are reported in Table 3. The methods used to assess medication adherence were different across the 6 included studies. The adherence reported in the included studies ranged from 52% [44] to 81.8% [47].

Measuring out-of-pocket (OOP) costs

The figure for OOP costs was reported directly in 3 studies [44,48,49]. However, these studies were too heterogeneous to be compared; the population and setting of the studies varied, medication adherence was assessed with different RA medications and via different methods. Monthly medication OOP costs in these three studies varied from US$33.60 for new initiators of *etanercept* and *adalimumab* [44] to more than US$353 for *infliximab* users in non-generous plans (plans where the average OOP costs are in top quartile of the household OOP expenses) [48]. Of these 3 studies, the OOP costs were the lowest in the study that assessed newly initiated biologic users [44].

Of those studies that did not directly report the amount of OOP costs; Hopson et al. [47] divided the RA patients into 6 different categories according to their OOP costs; the highest number of patients paid less than US $25 (30.67%) and 26.04% paid between US $400 and US $550. More than half (64%) of the patients paid more than US $250 for their medications in a six-month period. Harrold et al. [46] did not report the OOP amount, the aim of this study was to assess the CRN, which refers to the prevalence of patients who decrease or skip doses or did not fill prescriptions due to the costs. Gibofsky et al. [45] considered continuation in 4 medication groups and investigated the reasons of discontinuation, they found that the most common reason for discontinuing *etanercept* was OOP costs.

Medication adherence and OOP costs

Data related to medication adherence and OOP costs is presented in Table 3. The relationship between OOP costs and medication adherence was assessed differently across the 6 included studies. Three studies directly considered this association as the main objective [44,46,47]. The other 3 studies considered it indirectly; that is, the main objective was not to assess this association however, this association was considered as one of their secondary objectives. These studies were assessing the factors that affect adherence, they found that OOP costs were a barrier to adherence [45,48,49].

Of those studies that considered this association as a main objective, Harrold et al. [46] referred to the issue of medication adherence and OOP cost, over a 5-year period, by employing the concept of CRN. CRN prevalence in patients with RA was higher than that of older adults with other chronic diseases. In adjusted analyses, Harrold et al. [46] found that the possibility of CRN in patients with RA was 3.5 times higher than other chronic conditions (OR 3.52; 95% CI: 2.63-4.71). Hopson et al. [47] also examined the relationship between OOP costs and initial prescription fill and subsequent refills of biologic DMARDs. Data were collected retrospectively from a national Medicare Advantage and Prescription Drug (MAPD) plan. They found that 18.2% of the studied population who attempted to initiate biologic therapy abandoned their prescription after a reversed (non-paid) claim for a biologic agent in the 180-day follow-up period. As for the population that were existing biologic users, the likelihood of refilling a prescription during the 180-day post-index period decreased with an increase in OOP costs (OR: $0-$250 (reference) = 1, $250–$400 = 0.27, $400–$550 = 0.27, > $550 = 0.27; $p < 0.0001$). The final study that assessed the association between OOP costs and medication adherence directly was conducted by Curkendall et al. [44], adherence to biologic DMARDs (*etanercept* and *adalimumab*) were assessed using MPR. Results from this study indicated that adherence was suboptimal (< 80%) despite patients paying only an average of 2.7% ± 4.9% of the total cost of the biologic DMARDs [44]. To support the hypothesis that even slight rises in costs may have an effect on adherence, Curkendall et al. [44] converted MPR to therapy days by multiplying MPR by 365 to determine how many days of adherence are lost when OOP costs increase. They found that a rise of US$5.50 in weekly OOP costs or a rise of 2.2% in a patient's share of biologic costs was equal to 1 week of therapy lost.

Of those studies that considered the association between OOP costs and medication adherence indirectly, Rkain et al. [49] found that monthly RA medication OOP cost was equivalent to more than one week's income on the minimum wage in Morocco and these expenses caused financial difficulties for 90% of patients, leading to 39% of patients with RA considered to be non-adherent. Karaca-Mandic et al. [48] examined the OOP costs across multiple health plans and assessed the initiation and continuation of biologic therapies. OOP costs were found to affect initiation and continuation of the biologic therapy and when other family members incurred high health care OOP costs, the initiation rate in RA patients decreased. Whilst Gibofsky et al. [45] did not specifically examine OOP costs, this study found that cost and ineffective treatment were the most common reasons for discontinuation, these OOP costs resulted in *ETN* discontinuation in about 5% of patients.

Discussion

Our study used a systematic search of the literature to identify and summarise data to determine whether OOP costs affect medication adherence in patients with RA. From our knowledge, this is the first systematic review focusing on the association of OOP costs and medication adherence in patients with RA.

Overall, 6 studies were found that fulfilled the inclusion criteria and 5 of these 6 studies were conducted in the USA. These studies measured adherence and OOP costs via different methods so the heterogeneity of the studies limited our ability to perform quantitative syntheses or any other comparisons between each study.

All 6 studies that were included in this review reported that in patients with RA, OOP costs affected medication adherence negatively and patients with RA are more likely to be non-adherent because of medication costs. The findings of this review are congruent to the findings of reviews conducted by Eaddy et al. [19] and Gibson et al. [29]. Eaddy et al.'s [19] systematic review reported that there was a decreasing linear relationship between

the magnitude of OOP costs and adherence in patients with different chronic conditions such as cardiovascular, diabetes, mental health, pulmonary, arthritis, infectious disease and gastrointestinal. The review by Eaddy et al. [19] examined changes in patient OOP costs and the effect on adherence in studies that were only conducted in the USA or Canada [19]. They found that when OOP costs increased by one American dollar, adherence dropped by 0.4%. In approximately 85% of the identified studies there was an inverse relationship between OOP costs and adherence, where an increase in OOP costs resulted in a decrease in adherence [19]. A review conducted by Gibson et al. [29] identified 4 studies that investigated the association between medication adherence and OOP costs. These 4 studies included patients taking statin, diabetic, congestive heart failure, antidepressant, epileptic and cardiac medications. One study found that there was no association between an increase in OOP costs and adherence among discharged myocardial infarction patients taking cardiac medications [50]. Among patients taking epileptic medications, adherence declined with an increase in OOP costs but the association was not significant, although this might be due to the small sample size studied [51]. This inverse relationship between OOP costs and medication adherence was also seen among other patients who were taking statin medication; antidiabetic medication; congestive heart failure medication; and antidepressant medication. Gibson et al. [29] revealed that in chronic rather than acute conditions, increasing OOP costs decreased medication adherence. Patients with a chronic condition are required to take medication long-term compared to patients with an acute condition so they are more sensitive to an increase in medication prices. The reviews conducted by Eaddy et al. [19] and Gibson et al. [29] reported an inverse relationship between OOP costs and medication adherence in patients with a chronic condition. RA is also a chronic condition that requires long-term adherence to the medication. The findings of this current systematic review are congruent with other previous reviews.

In 2 reviews by Elliot [52] and Pasma et al. [53] that investigated the reasons of non-adherence in patients with RA, medication cost was one of the most important factors that was found to influence non-adherence. In a study conducted by Harrold et al. [54], exploring changes to insurance coverage, results indicated that expanding insurance coverage without changing the OOP costs, resulted in increased biologic usage. These previous papers reinforce the findings of our systematic review.

Five of the 6 included studies in this systematic review were conducted in the USA, which may cause problems with *generalisability of our results with other populations*. This review highlights the lack of studies from different countries investigating OOP costs and medication adherence in the RA population and the need for further studies to be conducted in this area. Patients from low socio-economic levels with low income will be more susceptible to non-adherence as studies show that low income families encounter higher financial burden [55–58]. The relationship between OOP costs and medication adherence in patients with RA should be assessed in every country. Each country will have different policies in regards to medication funding, reimbursements and medication pricing. Investigating the relationship between OOP costs and medication adherence will assist policy makers establish policies on the appropriate amount of OOP costs in their own country. This has more significance among individuals with RA for several reasons. First, biologic agents are expensive, so more patients may conscientiously choose not to purchase the medication in a trade-off between paying for expensive medications and saving money for other purposes. Second, non-adherence has been shown to be common in patients with RA [15,16] and high OOP costs may intensify this problem. Third, biologic agents are the mainstay in RA treatment [34] and physicians are prescribing biologics to more patients, so biologic usage is expanding and it is important that health care systems facilitate their use.

Table A1
Key terms of searching according to the PICO[a] approach

P	I	C	O
Rheumatoid arthritis	Out-of-pocket payments	–	Medication adherence
	Out-of-pocket expenditure*[b]		Medication adherence
	Out of pocket expenditure*		Medication nonadherence
	Out-of-pocket payment*		Medication noncompliance
	Out of pocket payment*		Medication non-adherence
	Out-of-pocket cost*		Medication non adherence
	Out of pocket cost*		Medication persistence
	Out-of-pocket spending		Medication compliance
	Out of pocket spending		Medication non-compliance
	Out-of-pocket expense*		Medication non compliance
	Out of pocket expense*		Treatment adherence
	Medication payment*		Treatment nonadherence
	Medication cost*		Treatment noncompliance
	Medication expenditure*		Treatment non-adherence
	Medication spending		Treatment non adherence
	Medication expense*		Treatment persistence
	Drug cost*		Treatment compliance
	Drug expenditure*		Treatment non-compliance
	Drug spending		Treatment non compliance
	Drug expense*		Disease-modifying antirheumatoid drugs
			Disease modifying antirheumatoid drugs
			DMARD*
			Anti-rheumatic drugs
			Anti rheumatic drugs
			Anti-rheumatic agents
			Anti rheumatic agents
			Biologic agents
			Biologics

[a] P: population or patient, I: intervention or indicator, C: comparator or control, O: outcome.
[b] * = s.

In those studies that reported adherence levels in this current systematic review, adherence was low. These results are consistent with figures reported in a review of RA patients who were prescribed tumor necrosis factor-α (TNF-α) inhibitors, adherence ranged from 32% to 81% [15]. In another systematic review investigating adherence to DMARDs, steroids and non-steroidal anti-inflammatory medications in patients with RA the adherence was 66% (95% CI: 0.58–0.75) among the 19 studies identified [9]. According to Scheiman-Elazary et al. [9] there is no difference in adherence among different measurement methods. In the current systematic review, all tools employed in the included studies showed suboptimal adherence in patients with RA.

The type of medications assessed in regard to their price may have an effect on the relationship between OOP costs and medication adherence in patients with RA. Biologic medications are more expensive than traditional oral medications [31,59]. A study in the USA showed that among RA patients in Part D Medicare, the mean OOP cost of biologics was $2712 to $2774 before reaching the threshold phase, during which beneficiaries pay 5% of biologic costs [60]. Three studies assessed biologic medication, one study assessed traditional DMARDs and two assessed all types of RA medications. Therefore, it was predictable to find a robust relationship between OOP costs and medication adherence because higher the OOP costs, the more likely that patients will be unable afford the medication.

Only 2 studies of the 6 studies identified in this review reported the disease duration [45,49]. This information is important in OOP studies of chronic conditions like RA because it shows that how long patients may have been incurring OOP costs. Also this group of patients require long-term therapy [61] and it is common for adherence to decrease over time [62]. Furthermore, medication costs are ongoing expenses for patients with RA and depending on the economic status of the patient, result in cost-related non-adherence.

By employing PRISMA, authors tried to minimise potential biases. However, the current review has some limitations; the number of included studies was only six and they were highly heterogeneous in population and method. Therefore, a meta-analysis was not undertaken. According to the critical appraisal that was completed, all of the included studies were high quality. However, only 3 studies assessed the relationship between OOP costs and medication adherence as the main objective of their study. The lack of studies assessing OOP costs and medication adherence has weakened the level of evidence in this review.

Conclusion

Published data indicated that in patients with RA, higher OOP costs was associated with non-adherence to the prescribed RA medication. Studies conducted on the relationship of medication adherence and OOP costs are scarce and limited to the USA. Therefore, it would be beneficial for health policy makers in every country to find the right cost-sharing amount so OOP costs do not affect adherence whilst at the same time ensuring costs are not an intolerable burden for providers and insurers.

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Appendix A

Table A1.

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2.14. Assessment of medication adherence

As stated in section 1.4, one of the aims of the study was to assess medication adherence. There are various methods for medication adherence assessment including electronic monitoring, pill counts, clinical measures, prescription refills and self-report.

Each method of medication adherence assessment has advantages and disadvantages, and there is no best measurement method (Zullig et al., 2017). The appropriate method should be chosen based on several factors including the context (tightly controlled clinical trial setting vs. clinical setting), purpose of measuring adherence (research vs. clinical), available resources (data, personnel, materials, and funding), time (quick screening vs. comprehensive review), and phase of interest (initiation, implementation, or discontinuation) (Zullig et al., 2017). To choose a suitable method, based on the purpose of the project, the reliability and practicality, especially cost-effectiveness should be considered (Lam et al., 2015). In this section, an explanation of each method is presented to provide information on which method is the most appropriate measurement of adherence for this study.

2.13.1. Medication electronic monitoring

Medication electronic monitoring systems are devices and reporting mechanisms for keeping track of pill-taking behaviour that provides objective information for understanding pill-taking behaviour (Haberer, 2013). The first well-known device is the Medication Event Monitoring System (MEMS^{TM}) that is a bottle cap that contains a microelectronic switch, a clock and a memory chip. Every opening and closing of the MEMS cap records a time and date that is stored. The stored data can be downloaded to a computer via a USB cable and displayed graphically or in spreadsheet format for

analysis (Haberer, 2013). The advantage of this method is that it is considered as the closest tool to a gold standard for adherence measurement (de Klerk et al., 2003). The other advantage is that it provides extensive data. For example, adherence measured daily over a three-week period may result in 24 measures (Rohay, 2010). There are some disadvantages to these devices. First, each opening does not necessarily mean that the medication is taken. Second, one cap is suitable for one medication and for multiple medications, several caps are needed. Third, patients may take out multiple pills as a "pocket dose" at a time for later taking. Fourth, the data must be downloaded periodically into a computer for analysis, and if this period is long, it may be late for non-adherence diagnosis and an intervention to prevent the irreversible clinical consequences (Haberer, 2013). Other practical issues in using this method include obtaining unanimous agreement among the patient, pharmacy, and healthcare providers that the cap will be utilised and, patients and pharmacy staff are required to be trained (Williams et al., 2016). In RA, often patients take several medications including glucocorticoids and several sDMARDs (Smolen et al., 2017), while with electronic devices only adherence to one medication is assessed. Therefore, several bottles are needed for assessing adherence to all RA medications which makes the practicality of this tool unfavourable. Moreover, the majority of bDMARDs are administered subcutaneously or intravenously (van Vollenhoven, 2016). In addition, this method is more costly than other methods (Checchi et al., 2014). MEMS studies require large funds due to the high price of the device especially for studies with large populations (Lam et al., 2015). In a 2001 study that assessed medication adherence in patients with schizophrenia, an average of USD$274 per patient was spent to complete a 6-month study (Diaz et al., 2001). Also, it is possible that the patient loses the device. Seven

patients lost the devices and each lost device incurred a cost of $126 and data was lost (Diaz et al., 2001).

2.13.2. Pill counts

In the pill counting method, patients are given a specific number of pills, which is enough for a specific period of time, and they return the unused pills (Williams et al., 2013). Adherence is calculated as the ratio of the number of pills consumed to the number of days medication supplied (Liu et al., 2001; Williams et al., 2013). There are challenges in using this method. It is often the case that participants either fail to return empty medication bottles or dump their pills, leading to large amounts of missing data or biased reports (Pauler et al., 2002). In addition, adherence underestimation is probable, because this method uses the dispensed date as the start day of the consumption without considering the chance of taking surplus medication. It is common for patients with chronic diseases to refill the medication before running out (Vik et al., 2004). Moreover, the cut-off point to divide adherence and non-adherence, in this method, is generated arbitrarily (Farmer, 1999) that may result in discrepancy on identifying adherent and non-adherent patients and, comparing medication adherence across studies. Pill count was used in early studies of adherence in patients with RA (Marengo et al., 2015) but was replaced with electronic monitoring systems as the reference standard (Farmer, 1999). Similar to electronic monitoring systems, a reasonable pill count does not guarantee that the patient has taken the medication. In addition, similar to electronic monitoring systems, it is not a suitable method for measuring adherence to injectable medications.

2.13.3. Clinical measures

Clinical measures can be employed to measure how much medication is in the body at a specific point in time, and it provides an accurate indication of whether the person has taken their medication (Rohay, 2010). In RA, routine measurement of the blood levels of ESR, CRP, anti-cyclic citrullinated peptide antibody (Anti-CCP) and rheumatoid factor (RF) are part of the recommended routine diagnostic and monitoring for patients with RA (Pincus, 2006). These tests do not demonstrate the serum level of RA medications in the blood, they show the inflammatory activity of the body (Pincus, 2006). Nonetheless, the single laboratory tests are not enough to assess each individual patient with RA regarding the efficacy of medications (Goldsmith et al., 1993). ESR and CRP indicate the level of inflammation in the body. The level of ESR and CRP decrease with successful RA treatments. However, ESR and CRP are normal in about 40% of patients with RA, which makes these tests unsuitable for all patients with RA (Pincus, 2005; Wolfe et al., 1994). Another limitation with these tests is that while ESR and CRP decrease in most successful RA treatments, they tend to be stable in many patients, even with clinical improvement (Wolfe et al., 2001). Anti-CCP and RF are antibodies that have been used for RA diagnosis (Abdul Wahab et al., 2013). However, 30% to 40% of patients with RA do not have anti-CCP or RF. Therefore similar to ESR and CRP, these tests are not suitable as a single indication for RA treatment improvement or a measure of adherence (Riedemann et al., 2005).

Although the presence of a medication in a biologic fluid provides evidence that the patient has received a dose of the medication within some period before the test. These tests may not reflect the true nature of the person's medication adherence behaviour because they are specific to the time point of the test and clinical measures are

influenced by patient variations in absorption and metabolism. Several patients could have similar serum levels of the target medication, but each may have consumed medication in a different fashion (Farmer, 1999). The other practical issue is that frequent repeated sampling might be needed due to the short half-life of some medications and issues regarding white-coat adherence (adherence improves around the time of clinical appointment) (Cramer et al., 1990). Using a blood test, adherence to HCQ was examined in patients with systemic lupus erythematosus (an autoimmune disease). They reported blood HCQ assay is a reliable method to assess adherence to this medication due to the long-term half-life of HCQ (more than one month) and, finally they suggested using this method of adherence measurement where unscheduled and regular tests are feasible and the half-life of the medication is long-term (Costedoat-Chalumeau et al., 2007). However, this method is costly to implement if the tests are not routine tests that the patient is required to implement (Rohay, 2010). Considering that in RA the tests that measure the serum level of medications are not conducted routinely, this method could be costly and require additional staff.

2.13.4. Prescription refills

Medication adherence assessment using prescription refill data involves a secondary database, such as an electronic prescription service or insurance claim. Prescription refill data can be retrieved retrospectively and can be used to assess adherence to multiple medications over a long period of time (Calvert et al., 2012). This method is a convenient, non-invasive and inexpensive method. And it is mainly used for large populations (Carter et al., 2010; Lehmann et al., 2014). This method shows the amount of medication received but it does not necessarily mean that the medication is taken.

Therefore, this method might be accurate in identifying non-adherent patients but not those who are adherent (Andrade et al., 2006). Prescription refill data have been used frequently for adherence studies in patients with RA in developed countries (Borah et al., 2009; Curkendall et al., 2008; Hopson et al., 2016). However, this method of assessing adherence requires accurate data from pharmacy databases. Therefore, it is a suitable method in countries where prescriptions are linked with pharmacies or pharmacies have comprehensive databases (Been et al., 2017; Ho et al., 2009). In Iran, patients with RA, purchase their prescriptions only once, and no refill (repeat) prescriptions are given. Therefore they have to visit a rheumatologist again to obtain a prescription for RA medications (Zaboli et al., 2016). Therefore, this method is not a suitable method for adherence measurement in Iranian society.

2.13.5. Self-report

Self-report measurements involve healthcare providers' or patients' evaluation of their medication-taking behaviour (Lam et al., 2015). Patient self-report tools are among the most widely used and preferred methods because they are quick for implementation, inexpensive, and can be administered by lay people. Also, they reflect patient attitudes and experiences (Stirratt et al., 2015). A review article on self-report medication adherence measures showed moderate correspondence of these tools to other adherence tools and reported that they can significantly predict clinical outcomes (Stirratt et al., 2015). Also, they reported the quality of these tools have improved through efforts to use validated scales. However, an accurate outcome is highly dependent on patients' honesty and ability to recall the events (Choi et al., 2004), and it may be subject to social desirability (also known as faking good) resulting in adherence overestimation.

Participants may alter responses in the direction they perceive to be desired by the investigator and society (Huang et al., 1998). The opposite situation is also possible, where participants try to appear sick to qualify for support (also known as faking bad) (Aday et al., 2006). These biases can be minimised by wording the questions in a non-judgmental way inferring that socially undesirable behaviour is common and acceptable and, by providing adequate information to the participant (Morisky et al., 1986). Therefore, it is essential to choose an appropriate tool to ensure that the tool correctly assesses medication adherence.

As electronic monitoring systems are considered the gold standard in adherence assessment, several medication adherence self-report surveys were validated against electronic monitoring devices. A systematic review by Shi et al. (2010) was conducted to examine the association between medication adherence self-report questionnaires and electronic medication monitoring devices. They reported the majority of self-report questionnaires which are validated against electronic monitoring devices showed good reliability and validity and can be considered for assessing patient-reported adherence (Shi et al., 2010). One of these questionnaires was the Compliance Questionnaire Rheumatology (CQR) which is used in this project.

In RA, self-report questionnaires have been widely used to assess adherence (Marengo et al., 2015). Among the validated self-report tools, Morisky's Medication Adherence Scale (MMAS) and CQR are used frequently in RA studies (Gadallah et al., 2015; Pascual-Ramos et al., 2013; Spruill et al., 2014; Waimann et al., 2013). While MMAS is a general tool that has been used in many studies to assess medication adherence, it was originally developed and tested on patients with hypertension (Morisky et al., 2008). However, the CQR (de Klerk et al., 2003) specifically measures medication

adherence to oral antirheumatic medications which makes it an appropriate tool for adherence measurement in patients with RA. CQR was chosen for this thesis project and further information on this tool is presented in section 3.1.2.

2.15. Summary of Chapter 2

Chapter 2 has provided an overview of RA, introduced RA medications, the significance of adherence to RA medications and medication adherence determinants in patients with RA. Consequences of non-adherence to prescribed medications were also described that reported deviations from the prescribed regimen results in irreversible structural damage in joints and disability. Therefore, it is essential for patients with RA to remain adherent to their prescribed medication. The literature was systematically reviewed to examine the relationship between OOP costs and medication adherence that revealed this relationship was not well studied in patients with RA. Finally, different methods of adherence measurement were also described to indicate which method is suitable for this project. The following chapter presents the research methods that was used in this study.

Chapter 3

Methods

3. Chapter 3: Methods

This chapter outlines the design and methodology of the research. The mixed methods design is described, followed by the selected mixed methods design; that is, a concurrent multilevel mixed methods design. The conceptual model (Andersen's Behavioural Model of Health Services Use) that was used as a guide for study design and data analysis is also described. In addition, the instruments used, data collection processes, data analysis and ethical considerations are outlined in this chapter. Finally, the integration of the results of the quantitative and qualitative components are outlined.

3.1. Research design: Mixed methods approach

The mixed methods research is full of opportunities for the creative development of methodological advances to contribute to complex problems (Mertens et al., 2016). A mixed methods approach was used for this study. Mixed methods refers to a single project involving qualitative and quantitative data (Creswell et al., 2003; Halcomb et al., 2015). There are several instances that a mixed methods is an appropriate choice of research method (Halcomb et al., 2015). Where the researcher encounters a complex phenomenon, the mixed methods empowers the researcher to investigate the phenomenon from several aspects by integrating quantitative and qualitative research approaches (Creswell et al., 2003; Halcomb et al., 2015). Due to the complex nature of medication adherence, a mixed methods is a useful way to better understand the phenomenon and obtain data to improve adherence (Kumar et al., 2013). In addition, in studies where multiple perspectives are needed to understand the phenomenon, the mixed methods is recommended (Halcomb et al., 2015). Medication adherence is a multifaceted phenomenon that is associated with patient, healthcare provider and

healthcare system factors (Jimmy et al., 2011). The mixed methods is the most appropriate method for this thesis firstly because of the complexity of medication adherence phenomenon and secondly, two main aspects of the adherence phenomenon were included in this thesis: patients and their direct healthcare providers (rheumatologists).

3.1.1. Advantages and disadvantages of a mixed methods approach

In several ways a mixed methods approach is more valuable than a single qualitative or quantitative approach (Creswell et al., 2007; Zhang et al., 2013). The first reason is that it provides the strength that compensates the weakness of both qualitative and quantitative methods. While it is stated that quantitative is unable to understand people's talk, the qualitative method has potential bias due to personal interpretation and the limitation in generalisability (Creswell et al., 2007). Secondly, a mixed methods approach provides more extensive evidence than either qualitative or quantitative methods (Creswell et al., 2007; McKim, 2017). Thirdly, by employing a mixed methods approach, the researcher is not limited to one paradigm, and they can use multiple worldviews (Creswell et al., 2007). Finally, a mixed methods is practical because the researcher is not restricted in a particular method and also it provides a complete picture of a phenomenon including numbers and words (Creswell et al., 2007; McKim, 2017). From our knowledge, little is known on medication adherence in Iranian patients with RA and by using a mixed methods design, the phenomenon can be explored extensively. Also, evidence on rheumatologists' perspective is scarce worldwide. Interviews are the most appropriate tool where little is known about the study phenomenon (Gill et al., 2008). Therefore, by employing semi-structured

interviews with rheumatologists, deep information on rheumatologists' insight was provided.

A few disadvantages of using mixed methods approach have been identified. This approach may result in higher costs of study conduct, and may require a team of researchers to manage the data collection, analysis and reports. This approach also requires a researcher who is trained in both qualitative and quantitative methods for the quality of the combining the data to be assured. Moreover, publication of the results might be difficult if the reviewers are methodological purists (Johnson et al., 2004; Teddlie et al., 2009). The PhD researcher obtained a scholarship from Monash University to cover the tuition fee and living allowances. This thesis was funded by Monash University with a budget of $4000 AUD and the PhD researcher managed to conduct the study within this budget. The biggest expenditure was related to the professional translation and the transcription of interviews. The PhD researcher who was responsible for data collection and analysis had previous experience of conducting quantitative studies and was trained to conduct several qualitative methodologies during her PhD candidacy. Furthermore, all members of the supervision team were experienced researchers in both qualitative and quantitative methods.

3.1.2. Concurrent multilevel mixed methods design

Mixed methods designs are described by three basic design logics: concurrent, sequential quantitative or sequential qualitative (Creswell et al., 2018). These designs explain how quantitative and qualitative components can be implemented, concurrently or sequentially. The researcher should choose the right approach according to timing, integration and the priority of the quantitative and qualitative components. In sequential

designs, one component (qualitative or quantitative) has to be completed before the next begins (Plano Clark et al., 2016). This design is used when one component (qualitative or quantitative) explains or builds the other one (Creswell et al., 2018).

In concurrent design, also named the triangulation design by Creswell et al. (2003) the researcher aims to compare or merge the results of qualitative and quantitative components to reach a comprehensive and more validated conclusion (Figure 3.1). The implementation of the quantitative and qualitative components are independent of each other; each set of data is analysed separately and then the results are combined (Plano Clark et al., 2016). The advantage of this method is that the researcher can collect the data simultaneously that saves cost and time (Creswell et al., 2011). Due to the time limitation of the PhD project and the fact that the results of each component were not required for the explanation of the other one, the concurrent design was used in this thesis.

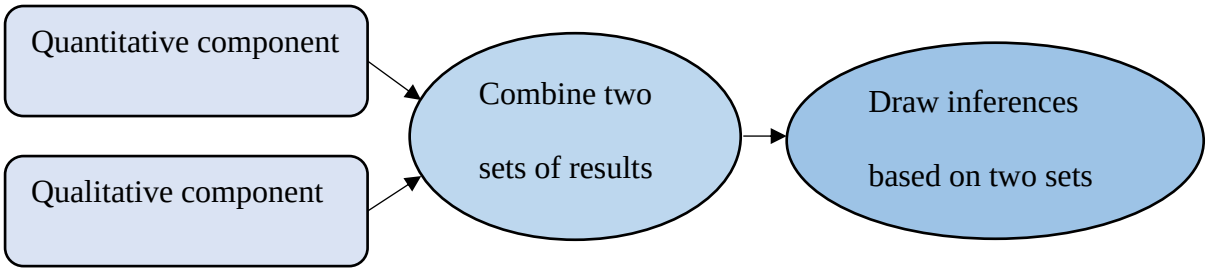

Figure 3.1. Concurrent mixed methods design. Extracted from Plano Clark and Ivankova (2016, p. 117)

One of the triangulation design variants is where the researcher investigates different levels within a system, which is named "multilevel research" (Tashakkori et al., 1998) or "indefinite triangulation" (Cicourel, 1974; Hammersley, 2008). The indefinite triangulation requires collecting accounts of the same event from several people with a

view to documenting how these accounts were assembled from different perspectives (Cicourel, 1974). This approach is exemplified as the examination of a physical object from two different viewpoints or angles; it provides different pictures of the object that might not be useful to validate each other but it provides a more complete picture of the phenomenon (Erzberger et al., 2003). Hammersley (2008, p. 26) interprets this as an approach close to the sociology of knowledge: "the interest is in why participants' accounts take the varying forms they do, or rather in how they have been put together". This approach enhances mutual understanding of a phenomenon, that helps the development of the future practice. In other words, this triangulation method, generates divergent interpretations, rather than only checking the validity of each source of data (Hammersley, 2008). Determinants of medication adherence are associated with patient, provider and healthcare system factors, with interactions among them (Jimmy et al., 2011). Therefore, in this study, both the patients and the rheumatologists were studied. Rheumatologists are direct healthcare providers of patients with RA and they are specialists for medication prescribing and counselling for RA. They play a key role in RA management (Bolge et al., 2013) and in affecting patients' adherence to medications by providing information, addressing perceptions about medication, and establishing trust in their management strategy (Pasma., 2015).

In concurrent multilevel design, there is no priority in either the qualitative or quantitative component because each component covers some aspect of the issue and provides different but complementary results (Plano Clark et al., 2016). In this study, at the patient level, medication adherence was assessed, and adherence determinants were explored by a quantitative design. At the rheumatologist level, by using a qualitative method, this study explored how rheumatologists assessed medication adherence and

based on rheumatologists' experience and expertise, adherence determinants were identified.

Figure 3.2 depicts the visual diagram of this study according to Ivankova et al.'s (2006) guideline. This figure is a graphical demonstration of the mixed methods design procedures and the products or outcomes of each research strand. It also depicts the place in the study where the integration of the results of both qualitative and quantitative components occurred.

Due to several reasons, a quantitative component was used for studying patients and a qualitative component was used for rheumatologists. The first aim of the study was to assess medication adherence. For an accurate assessment of medication adherence, a validated tool was required; this study employed a survey, which is explained further in section 3.4.3. Also, no valid tool has been introduced to assess adherence from healthcare providers' such as rheumatologists' perspective. Therefore, a quantitative study of the patients and a qualitative study of rheumatologists were conducted.

The second aim of the study was to determine adherence determinants and the effect of OOP costs on medication adherence. To achieve this aim, the findings from the survey, responses from an open-ended question at the end of the survey and a qualitative study of rheumatologists were explored. In an open-ended question at the end of the survey, we asked patients which factors, if any, affected them not taking their medication according to their rheumatologist's prescribed orders. A quantitative component was not appropriate for studying rheumatologists due to small population of rheumatologists (N=18) in our study setting. Quantitative analysis is more sensitive to larger sample sizes. The minimum sample size for a survey is 30 although based on the research aim and the number of variables studied a minimum of 100 subjects is recommended

(Delice, 2010). In addition, anonymous nature of surveys, allows for honest responses whereas, patients may be less inclined to discuss their adherence face to face.

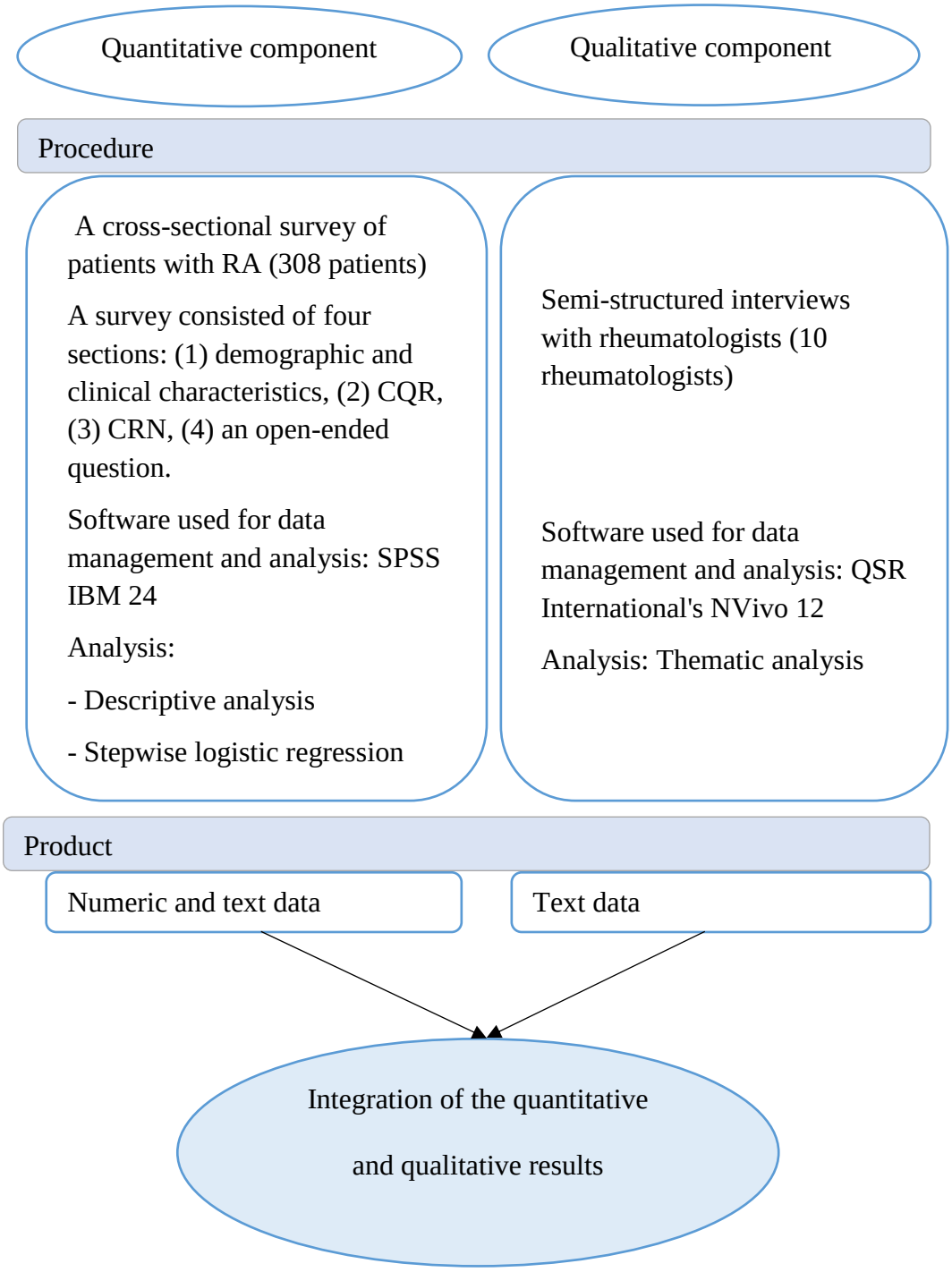

Figure 3.2. Visual diagram of this study design based on Ivankova et al. (2006) guideline.

3.2. Conceptual model

Using health behaviour theories is essential for medication adherence researchers as it facilitates the study design and interpretation of results (Ruppar, 2010). Conn et al. (2016) conducted a systematic review on studies that examined theory- or model-linked medication adherence interventions in healthy or physically ill adults excluding people with psychiatric disorders or, people taking sexual or reproductive function medications. They reported that the most common theories and models used for medication adherence interventions were motivational interviewing, social cognitive theory, health belief model, transtheoretical model, and self-regulation/common sense model (Conn et al., 2016). They reported these interventions have a significant but modest effect on medication adherence outcomes. They discussed that this modest effect might be due to inappropriate theory selection. Individuals were mostly the target of these models and, models that address adherence behaviour in families, communities and healthcare systems were not reported (Conn et al., 2016).

Health behaviour is not an independent phenomenon and it occurs in a context (Crosby et al., 2010). Future medication adherence intervention research should address the individual factors and, the social and environmental context of behaviour (Conn et al., 2016; Ruppar, 2010). Determinants of medication adherence are not only associated with the patient, but also the healthcare provider and healthcare system (Jimmy et al., 2011). Examples of such contextual factors are the patient's relationship with healthcare providers, family and community members. In addition, the health policies and healthcare system contribute to the availability of and accessibility to healthcare providers, health insurance and prescription medication coverage (Ruppar, 2010).

Therefore, it is essential to choose a model that integrates both the individual and environmental factors.

Andersen's (1995) behavioural model for health service utilisation is one of the well-accepted models that helps to better understand factors defining equitable access to healthcare services. Healthcare services are used when patients' needs meet the professional healthcare system (Ricketts et al., 2005). Andersen's model classifies the determinants of healthcare service use into three categories; predisposing factors, enabling factors, and need factors and each factor is influenced by the individual and context (Figure 3.3). Predisposing factors refer to the characteristics that shape attitudes toward healthcare services use. Enabling factors refer to resources that promote or impede healthcare services use. Need factors refer to the individual's disease that necessitates the use of healthcare services. This model evolved over five phases. The first and fundamental phase was developed in the 1960s in a study aimed at understanding why families use healthcare services. It reported people use healthcare services due to their predisposition to use healthcare services, factors which enable or impede them to use healthcare services and their need for care (Andersen, 1968). In phase two (1970s), the contextual factors including the healthcare system were included in the model to indicate the importance of national health policies. In the first two phases, the focus was on healthcare services use. In phase three (1980s), they identified other health behaviours including personal health activities such as diet, exercise or medication adherence that affect health services use. In phase four (1990s), they added feedback loops showing that outcomes, can affect subsequent predisposing, enabling, and need characteristics of the population and their use of health services. Finally, in phase five (2000s), they report that health behaviours are influenced by both individual

and contextual factors. Contextual factors refer to the health organisation and provider-related factors and community characteristics (Andersen, 2008; Andersen et al., 2007).

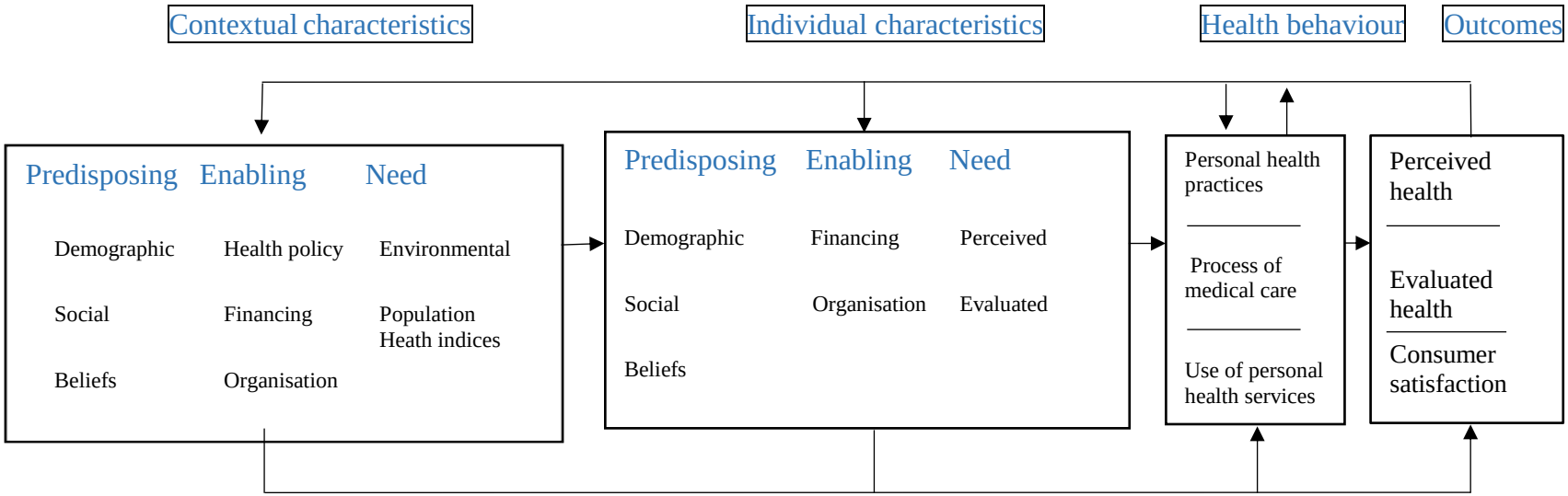

Figure 3.3. Andersen's Behavioural Model of Health Services Use. Extracted from Andersen (2008, p. 651). Copyright (2008) by Lippincott Williams & Wilkins.

Predisposing factors: Individual predisposing factors include demographic, social and health belief factors. Demographic factors include demographic characteristics such as age and gender. Social factors include the status of a person in the community such as education, occupation, and ethnicity. Health beliefs factors such as attitudes, values, and knowledge about health and healthcare services that can influence peoples' subsequent behaviour. Contextual predisposing characteristics are the same as the individual predisposing characteristics but on a larger scale representing the community. Demographic and social characteristics include the age, gender, marital status, education, ethnicity and employment level of the community. Beliefs refer to values and cultural norms of the community regarding how healthcare services should be organised and made accessible to the population that can influence peoples' subsequent behaviour (Andersen et al., 2007).

Enabling factors*:* Individual enabling characteristics include financing and organisation of healthcare services. Financing involves the income and wealth available to the individual to pay for healthcare services and the reasonable price of healthcare to the patient, determined by having health insurance and affordable OOP costs. High OOP costs limits patients access to medication and other healthcare services that may contribute to medication non-adherence. Healthcare services organisation refers to the source of care, the type of that source (private or public, emergency), transportation and travel time to and waiting time for healthcare service. Contextual enabling characteristics refer to health policies, financing and organisation that influence patients' access and availability of healthcare services and their subsequent health behaviour. Health policies include public and private at all levels from local to national. Financing characteristics refer to the resources potentially available to pay for healthcare services such as per capita community income, health insurance coverage, price of medical care

and other health-related goods and services, and method of compensating healthcare providers. Organisation characteristics refer to the amount, distribution and structure of healthcare services facilities and personnel such as the ratios of specialists and hospital beds to population, the structure of medical care regarding the delivery system where people receive care, facilities working hours and their location, and educational programs (Andersen et al., 2007).

Need factors*:* Individual need characteristics include perceived and evaluated need. Perceived need refers to how individuals view their own health. Perceptions about the importance and magnitude of a health problem or symptoms leading to a decision to be adherent or non-adherent to medications. Evaluated need refers to the health professional judgment that is usually determined by objective measurements such as physical examination, blood pressure measurement, temperature measurement, and laboratory tests results. Contextual need characteristics include environmental characteristics and population health indices. Environmental need characteristics include health-related measures of the physical environment, such as the quality of housing, water and air. Population health indices include mortality rates (such as age-adjusted mortality rate and mortality rates for different diseases); morbidity and disability (Andersen et al., 2007).

The Andersen's model has been widely used in studies to organise the determinants of healthcare services use (Babitsch et al., 2012). Also, it has been successfully used in previous studies to predict and explain the pattern and determinants of utilisation of medication prescriptions (Devine et al., 2005; Farley et al., 2004). In addition, the Andersen's model has been used in studies of medication adherence in diseases such as acquired immune deficiency syndrome (AIDS), asthma and heart disease (Holtzman et al., 2015; Unni et al., 2011; Ye et al., 2007). It was also used in patients with RA in

order to explore; the determinants of medical services use (Berkanovic et al., 1991), the association between adherence to physical activity and HR-QOL (Austin et al., 2012) and determinants of bDMARDs initiation (Desai et al., 2014). Desai et al. (2014) grouped variables according to the Andersen's model into predisposing variables including age, sex, and geographic location; enabling variables including insurance type and OOP costs, and need variables including severity of RA and presence of other comorbidities. Ye et al. (2007) used Andersen's model in a quantitative study to examine the effect of statin OOP costs on adherence to statin in patients with coronary heart disease (CHD) following discharge from hospital. They included the following variables as control variables in the model: predisposing (age and gender); enabling (health plan type, year of statin initiation, and under the care of a cardiologist) and need (comorbidities, number of other medications, and use of nonstatin lipid-lowering drugs).

The current study was not intended to test the Andersen's behavioural model related to medication adherence in patients with RA. However, this model was employed as a guide for designing the study and for data analysis as it best describes a behaviour by including both the individual and contextual factors.

3.3. Method for the quantitative component: Cross-sectional study of patients with RA

A cross-sectional survey was used to generate quantitative data to provide a broad understanding of medication adherence from the patients' perspective. The objectives were; to examine the demographic and clinical characteristics of patients with RA and, to assess medication adherence and finally to explore the effect of OOP costs on medication adherence. Moreover, other potential determinants of adherence were explored. In the following sections, the detailed method is presented.

3.3.1. Tool

A structured paper-based survey was used for data collection. The survey was developed drawing on the related literature reviewed in Chapter 2 and guided by the Andersen's behavioural model. The survey validity was examined by the supervision team and a statistician. Minor amendments were made according to their feedback. Then, the survey was translated into Persian by an accredited professional translator to ensure that the language used matched the English version and differentiated between formal and informal words. To obtain a conceptually equivalent survey, the translated version was back-translated to English. The back-translated version was found to be accurate by the researcher and the bilingual translator. The survey consisted of five sections (Appendix 1).

Section one contained nine questions that collected demographic information including gender, urban or rural residency, monthly income, employment status, education, marital status, living with whom, insurance coverage and type of insurance. These questions were developed based on the variables introduced in the Andersen's behavioural model and a systematic review of medication adherence in patients with RA, which reported conflicting

evidence on the association between medication adherence and age, socioeconomic status, marital status and place of residence (Pasma et al., 2013). Other studies reported factors associated with adherence these were; level of education, income (Xia et al., 2016), employment status (Ghosh et al., 2015) and living alone (De Cuyper et al., 2016). However, the findings have been inconsistent as the association between these factors and medication adherence were not significant in all studies (Marengo et al., 2015; Uckun et al., 2017). Therefore, it was deemed important to prove whether these determinants influenced medication adherence in Iranian patients with RA.

Section two contained 15 questions that explored the disease of the participant and included questions related to the duration since diagnosis and commencement of treatment, the RA medications prescribed (including oral RA medications and bDMARDs), the daily frequencies of oral medications and monthly frequencies of bDMARDs. Medication adherence has been found to be variable over time and among different DMARDs in patients with RA (Pasma et al., 2016). Patients with RA preferred lower duration and frequency of medication use (Poulos et al., 2014). However, conflicting evidence was reported for the relationship between adherence and frequency of medication use (Pasma et al., 2013). This section also included questions related to the diagnosis of other comorbidities (asthma, high blood pressure, diabetes, heart disease, depression, osteoarthritis, high cholesterol, chronic kidney disease and other comorbidities) if relevant and if participants had been hospitalised due to RA. A systematic review reported conflicting evidence for the relationship between adherence and, comorbidities and previous inpatient stay (Pasma et al., 2013). Other studies reported factors associated with adherence were; RA severity (Ghosh et al., 2015; Uckun et al., 2017), depression (Xia et al., 2016) and mental health status (De Cuyper et al., 2016).

According to the aim of the study, monthly medication OOP costs were also collected in this section of the survey by providing a blank space, so they could report the last amount they

remembered paying for their medication purchase. OOP costs were reported in the United States Dollar (USD) adjusted to the date of data collection (March 2017). It was discovered that patients with RA in Shiraz routinely visit the rheumatologist every three months. As recall bias was possible for OOP costs after three months, the questions in section four of the survey were included to substantiate the OOP costs incurred by each participant.

Section three assessed medication adherence. The Compliance Questionnaire Rheumatology (CQR) (de Klerk et al., 1999) was employed to measure medication adherence to oral RA medications. This questionnaire contained 19 questions with responses on a four-point Likert scale ranging from one (do not agree at all) to four (agree very much). CQR has been validated against electronic medication event monitoring, and it has been shown to have good reliability and validity (de Klerk et al., 2003). Conducting a multiple linear regression, weighted CQR score significantly predicts medication adherence ($p = 0.001$, $r^2 = 0.46$). In addition, discriminant analyses reported that sensitivity and specificity to detect medication adherence was 62% and 95%, respectively (de Klerk et al., 2003). This tool was deemed to be the most appropriate self-report tool for adherence measurement for the current study because it is specifically designed to assess medication adherence in rheumatology related diseases. It is not a general tool. Permission was obtained from the developers for its use in this study. CQR developers provided an automated Excel file in which by entering responses, participants were divided into two groups: either adherent or non-adherent. They provided different sheets within the Excel file for the cut-off adherence of 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% and 95%. They suggested 80% as the optimal cut-off for medication adherence in RA (de Klerk et al., 2003). As discussed in section 2.10, the cut-off point of 80% was chosen for this study. The forward and backward translation of CQR was conducted by professional translators, and the reliability was tested by standardised Cronbach's alpha (α=

0.71). The Cronbach's alpha more than 0.70 is the accepted standard that shows the reliability (Peterson, 1994).

Section four assessed cost as a barrier to adherence by using the cost-related medication non-adherence (CRN) questionnaire. CRN was first developed in the USA due to high OOP medication costs (Soumerai et al., 2006). The CRN questionnaire contains four questions to assess whether the participant had ever delayed, not refilled prescriptions, skipped doses or taken smaller doses of their medication due to cost during the last year. For each of the listed scenarios, the participants could choose from the options 'often', 'sometimes', or 'never'. Participants who answered 'sometimes' or 'often' were experiencing CRN. The results from the CRN questions were reported by percentage. The CRN questionnaire has been widely used and validated in the USA Medicare Current Beneficiary Survey (MCBS), which is conducted by the Centers for Medicare and Medicaid Services (CMS) ("Medicare Current Beneficiary Survey (MCBS),"). MCBS is a multipurpose continuous survey that has been collecting data on a nationally representative sample of the Medicare beneficiaries for over 25 years. Permission was obtained from the CMS for use of the tool. The central goals of this survey are to determine expenditure and sources of payment for all healthcare services including OOP costs, and to find outcomes over time such as changes in health status and patients' satisfaction with healthcare. The CRN questions were used in several other studies in the USA (Kang et al., 2018; Lee et al., 2018; Srinivasan et al., 2018) and other developed countries including Australia, Canada, France, Germany, the Netherlands, New Zealand, Norway, Sweden, Switzerland and the UK (Hennessy et al., 2016; Morgan et al., 2017).

Section five contained one open-ended question that asked participants which factors, if any, affected them taking their medication according to their rheumatologist's prescribed orders. Using an open-ended question enabled the researcher to discover the responses that individuals give spontaneously (Reja et al., 2003).

Disease activity measurement: To evaluate disease activity, the Disease Activity Score 28 (DAS-28) was assessed by the rheumatologist. Following patients' verbal agreement on participation in the study, rheumatologists assessed DAS-28 and recorded the score on top of a paper survey. The survey then was provided to the participant to complete in the waiting room. Completed surveys were placed in a sealed box in the RA clinic waiting room (section 3.3.3).

A systematic review was conducted to find the existing disease activity measures in RA by American College of Rheumatology (ACR) (Anderson et al., 2012). Fourteen measures were identified and nine of them were reported as the most useful and feasible measures by rheumatologists. From these nine measures, six measures had the strongest psychometric properties; the Clinical Disease Activity Index, DAS-28, Patient Activity Scale (PAS), PAS-II, Routine Assessment of Patient Index Data with three measures, and Simplified Disease Activity Index (Anderson et al., 2012). DAS-28 is a well-validated tool and the most widely used measure in assessing disease severity (Wells et al., 2009) in clinical trials and monitoring individual patients (Fransen et al., 2005). It is also the common measure for RA activity assessment in Iran (Alishiri et al., 2011; Mobini et al., 2017; Sandoughi et al., 2017). DAS stands for 'disease activity score' and the number 28 refers to the 28 joints that are examined in this assessment. As it requires a professional physical examination, in the current study, DAS-28 was assessed by the rheumatologist. DAS-28 was developed because in RA, the inflammatory activity cannot be measured using a single variable. This index combines information from swollen joints, tender joints, the blood markers of inflammation and general health (Fransen et al., 2005). To calculate the DAS-28 the rheumatologist counts the number of swollen joints (out of 28), counts the number of tender joints (out of 28), takes blood (or reads the results of the last blood test) to measure the erythrocyte sedimentation rate (ESR) or C reactive protein (CRP) and asks the patient to score their general health status

(indicated by marking a line between very good and very bad). These results are then inputted into a mathematical formula to produce the overall score which is a number on a scale from 0 to 10 indicating the RA activity according to the following categories: remission (<2.6), low (2.6-3.2), moderate (3.2–5.1), high (>5.1) disease activity.

3.3.2. Study setting

The study was conducted in Shiraz, Iran. Shiraz is the centre of Fars province and located in the south of Iran (Figure 3.4). With a population of 1.5 million, approximately 4,952 people living in Shiraz suffer from RA. Shiraz University of Medical Sciences (SUMS) is one of the major medical universities in Iran. Established in 1946, this university now has 41 hospitals (including 14 teaching hospitals), more than 10000 students and more than 18000 staff, that makes it the main healthcare provider in the south of Iran.

Figure 3.4. Shiraz location in Iran.

The data were collected at two private and two public rheumatology specialist outpatient clinics. These clinics are the main centres for RA treatment. The two public clinics were Motahari and Hafez. These two clinics are located in Nemazee and Hafez hospitals. With 912 and 167 hospital beds respectively, these hospitals are amongst the largest hospitals and they have the main rheumatology centres in Shiraz, affiliated with SUMS and are responsible for the care of rheumatology patients in the south of Iran. The outpatient clinics within the two public hospitals are government funded and these healthcare services are cheaper than private clinics. In order to achieve a broad sample of patients with RA, patients from two private rheumatology clinics were also recruited, which are not government funded.

3.3.3. Population and sampling

All patients who had been diagnosed with RA according to the ACR/EULAR criteria (Aletaha et al., 2010) for longer than three months and were 18 years of age or older were eligible to participate in the survey. Patients were excluded if they were deemed mentally unstable according to a diagnosis by a physician. Rheumatologists checked the patients' eligibility to participate in the survey. Consecutive, convenience sampling was used.

Data were collected between January 2017 and March 2017. Flyers were posted in the waiting rooms of the clinics for initial recruitment processes. The PhD researcher was at the waiting room in the outpatient clinics to provide interested participants with the explanatory statement and answer their potential questions. Thereafter patients visited the rheumatologists for their examination. The rheumatologist assessed the disease severity of all participants who agreed to participate using the DAS-28 tool and recorded the score at the top of the paper copy of the survey. Names of participants were not recorded to maintain anonymity. Participants were then given the survey to complete in the waiting room. They left the

completed survey in a provided box. The PhD researcher remained in the outpatient clinics during the recruitment period to answer any questions from participants. For illiterate patients, the researcher read the survey to each participant and completed the survey on their behalf. Illiteracy was determined through self‐report; participants asked the researcher to read the questions for them. There was no consent form. If the patient completed the survey, consent was implied. The explanatory statement explained that completion of the survey was completely voluntary and that researchers and rheumatologists are unable to determine who had completed the survey.

Sample size was determined using the formula for comparison of two proportions. Using a mean adherence rate of 66% (Scheiman-Elazary et al., 2016) and a difference of 10% in adherence between groups, the suggested sample size was 303 after considering a 10% non-response rate (CI=90%, power=80%).

3.3.4. Data analysis

Data were entered and coded into the Statistical Package for the Social Sciences (SPSS) version 24 (IBM, Armonk, NY, USA) for analysis and listwise deletion of missing records was employed to handle missing data. For reporting descriptive data, mean and standard deviation (SD) were used for continuous variables that were normally distributed, and median and inter-quartile range (IQR) were reported for skewed variables. Bivariate analysis of patients' characteristics between adherent and non-adherent patients were undertaken using Mann-Whitney U test for continuous skewed data and t-test for normally distributed continuous variables and chi-squared tests for dichotomous variables. The *p*-value of 0.05 or lower was considered significant.

Andersen's Behavioral Model of Health Services Use (Andersen, 2008) was employed as a guide to organise control variables in examining the relationship between medication adherence and OOP costs. Logistic regression was chosen for examining this relationship as adherence was reported as a binary outcome; adherent or non-adherent. Previous studies have reported factors associated with adherence in patients with RA and include: level of education, income, depression (Xia et al., 2016), age, RA treatment duration, hospitalization due to RA (Calip et al., 2017), presence of other diseases, the number of other diseases, living arrangements (Calip et al., 2017; De Cuyper et al., 2016), gender (Fidder et al., 2013), out-of-pocket costs (Heidari et al., 2018), oral medications frequency (Alten et al., 2016) and using biologics (Marengo et al., 2015). Due to a large number of variables, researchers chose the best-suited variables to include in the logistic regression model. Therefore, a stepwise logistic regression (backward) was conducted to find the association of OOP costs and medication adherence by controlling other potential determinants of adherence. Variables in the step ten of the logistic regression was chosen to be included in the model. These variables were treatment duration, depression, number of comorbidities and injectable medications. As the OOP cost was the main variable of interest in this study. OOP cost was also included in the model.

The text data from the open-ended question were entered into a Microsoft Excel sheet and analysed in four steps. First, responses were read several times for familiarisation. Second, responses were categorised by similar concepts to identify the barriers to medication adherence. Third, grouped responses were double checked to ensure that they were assigned to the appropriate category. Finally, the number of responses in each category were counted and reported as percentages (Cho, 2019).

3.4. Method for the qualitative component: Interview with rheumatologists

3.4.1. Sample

A semi-structured interview was chosen to collect data. In this method, the researcher focuses on the research questions and explores issues that arise spontaneously (Doody, 2013). Rheumatologists that work at SUMS were invited to participate in the semi-structured interviews. These rheumatologists provide care to patients with RA visiting the public clinics affiliated with the university and private centres. All rheumatologists working at SUMS were eligible to be included in the study and there was no exclusion criteria. The semi-structured interview guide was based on questions addressing the conceptual model underlying this study, Andersen's (2008) behavioural model of health services use and the literature review. The interview guide was designed to explore rheumatologists' insights regarding determinants of medication adherence in patients with RA and to explore how they assess medication adherence (Table 3.1).

Table 3.1. Semi-structured interview questions to explore medication adherence in patients with RA from the perspective of rheumatologists.

- **What medications do you usually prescribe to RA patients?**
- **What effect does the type of medication prescribed have on the patient's adherence to their medication?**
- **What are some of the problems associated with medication adherence RA patients?**
- **What do you think are the key barriers to medication adherence as seen by patients?**
- **What factors motivate patients with good adherence to adhere well?**
- **What percentage of your patients do you believe are non-adherent?**

- **Do you use any method to measure medication adherence? If yes, what methods do you use?**
- **Are there any organisational barriers that you think contribute to medication non-adherence?**
- **Do you think the costs of medications affect their adherence behaviour?**
- **What health professional factors affect adherence?**

3.4.2. Data collection

Eighteen rheumatologists were working at SUMS at the time of the study [January 2017]. All rheumatologists had weekly meetings on Mondays. The researcher asked permission from the head of the rheumatology department to attend one of these meetings to explain the study. The rheumatology department of SUMS covers all hospitals providing care to patients with RA. The researcher prepared a brief oral presentation to describe the study and provided each rheumatologist with a printed explanatory statement, which outlined the study further (Appendix 2). The rheumatologists had the opportunity to ask questions. Interested participants could contact the researcher directly from the contact details listed on the explanatory statement. Ten rheumatologists agreed to participate in the study. Eight rheumatologists declined to participate due to their busy schedules. Interviews were conducted at a time and place of the participants' choosing. All chose to be interviewed in their offices. Prior to the interview commencing, written, informed consent (Appendix 3) was obtained from each participant, along with their demographic details. Interviews were conducted between January 2017 and March 2017 in Persian language and translated to English by a professional translator. All interviews were conducted in a private setting and audio recorded with a digital voice recorder (Olympus) with a secure digital card to collect data electronically. The recorded files were translated into English and transcribed verbatim

by a paid professional transcription service. The service guaranteed to keep the information confidential as part of their terms and policy. The researcher listened to each of the recorded interviews and read the transcripts to assure the transcripts' accuracy. By reviewing the transcripts and listening to audio recordings, the researcher also was able to become familiarised with the data. The transcribed interviews were imported into NVivo software (Version 12, QSR, Australia). This software facilitates data management and analysis by eliminating many of the manual tasks associated with analysis, such as coding and classifying information (Bazeley et al., 2007).

3.4.3. Data analysis

Interview data were analysed using an inductive thematic analysis approach introduced by Braun and Clarke (2006) that involved searching across the data to find repeated patterns of meaning. The six key stages of this approach are familiarisation with your data, generating initial codes, searching for themes, reviewing themes, defining and naming themes and producing the report. Familiarisation involved listening to the audio recordings and reading the transcripts several times. During familiarisation, initial ideas were noted to identify and construct a thematic framework. The researcher and one of the supervisors coded four non-randomly selected transcripts. They elaborated the discrepancies and developed the coding framework. Additional codes were added where new codes were discovered for the remaining transcripts. Then, the initial codes were collated into potential themes and reviewed for accuracy. The discovered themes were employed to answer the study questions including what are the determinants of adherence and how do rheumatologists assess medication adherence. The identified themes were mapped into the Andersen's Behavioral Model of Health Services Use to report the adherence determinants.

3.5. Ethical considerations

Prior to data collection commencing, ethical approval was obtained from the Monash University Human Research Ethics Committee (0896) (Appendix 6) and the ethics committee at SUMS (2711-2016) (Appendix 7). This study was considered a low-risk study as no risks or harm to the participants were anticipated. All patients and rheumatologists were provided with a copy of the explanatory statement (Appendices 2 and 4) to ensure that participants were well informed of what the study involved prior to deciding to participate. It also ensured that both anonymity and confidentiality were described for potential participants. The PhD researcher explained the content of the explanatory statement to illiterate patients. All interview data were de-identified. According to Monash University regulations for data management, data were stored in LabArchives. LabArchives is a Monash supported cloud-based electronic notebook. Only researchers had access to data by using a personal username and password. Data will be stored for at least five years after the completion of this project, after which they will be disposed by deleting data files located in LabArchives.

3.5.1. Ethical considerations of the quantitative component

In the survey of patients, flyers were used for the initial recruitment process. The PhD researcher was at the waiting room in outpatient clinics to provide the interested participants with the explanatory statement (Appendix 4) and answer their potential questions. Then patients visited the rheumatologists for their examination. Whilst the rheumatologists completed the DAS-28 for participants and confirmed the eligibility of the interested participants, they ultimately did not know whether their patient completed the survey and returned it to the box. The researcher was present in the clinic during recruitment and was

available to address any questions from the interested participants. The voluntary nature of this research was explained in the explanatory statement and by the researcher, and participants were informed that participation did not affect their treatment process. Since the survey was anonymous, the written consent form was not obtained from the participants.

3.5.2. Ethical considerations of the qualitative component

As mentioned in section 3.5.2, the researcher attended the rheumatologists' weekly meeting to describe the study. There was no existing relationship between the researcher and the rheumatologists. The researcher provided an explanatory statement and consent form for them to review and ask questions regarding the study before accepting the invitation to participate. The interview files are only accessible to the researchers and the identity of the rheumatologists was de-identified by the PhD researcher.

3.6. Integration of quantitative and qualitative data

The quantitative and qualitative data were analysed separately, and the findings are reported separately in Chapters 4 and 5. The two sets of results are then compared side-by-side in a discussion to provide a complete picture of medication adherence in Iranian patients with RA (Creswell et al., 2018) in Chapter 6. In the side-by-side approach, the researcher compares the results within a discussion presenting first one set of results and then the other (Creswell et al., 2018). The interpretation in the triangulation approach is typically written into the discussion section of the study. The discussion section includes a comparison of results and notes whether there is convergence or divergence between the two sets of results (Creswell, 2015; Creswell et al., 2018). According to the overarching aim of the study, the integration

included the discussion of results regarding the assessment of medication adherence and the effect of OOP costs on medication adherence.

3.7. Summary of Chapter 3

This chapter has presented the methodology used to conduct this study. It included an explanation of the research design, the underlying conceptual model and a detailed procedure of conducting the two components of the study. Tools used for data collection, the characteristics of the sample, the recruiting process and data analyses were presented for each component. In addition, ethical considerations to protect the participants were described. The following two chapters will present the results of the quantitative and qualitative components.

Chapter 4

Quantitative Results

4. Chapter 4: Quantitative results

This chapter presents the results of the survey completed by patients with RA. These results are published in the International Journal of Rheumatic Diseases. The manuscript aimed to assess medication adherence to oral RA medications, to examine adherence determinants with a focus on the effect of medication OOP costs on medication adherence and to examine CRN in patients with RA. A total of 308 surveys were completed. The results, which were not included in the published manuscript are outlined following the article.

4.1. Published manuscript on the quantitative component of the study

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ORIGINAL ARTICLE

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Medication adherence and cost-related medication non-adherence in patients with rheumatoid arthritis: A cross-sectional study

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Abstract

Aim: First, to assess the clinical characteristics and medication adherence to oral rheumatoid arthritis (RA) medications in patients with RA. Second, to examine adherence determinants with a focus on the effect of medication out-of-pocket (OOP) costs on medication adherence to oral RA medications. Lastly, to examine cost-related medication non-adherence (CRN) in patients with RA.

Methods: A cross-sectional study of patients with RA was conducted at rheumatology outpatient clinics in Shiraz, Iran. The data collection survey consisted of 5 sections including demographic questions, disease-related questions, Compliance Questionnaire Rheumatology (CQR), CRN questions and an open-ended question. SPSS version 24 was used for analysis.

Results: A total of 308 completed surveys were collected. Adherence to oral RA medications was 40.3%. Just under 20% of participants were biologic disease-modifying antirheumatic drugs (bDMARDs) users and these bDMARDs users were 0.82 times less likely to be adherent to their oral RA medications compared to non-bDMARDs users ($P < 0.05$). There was no statistically significant association between OOP costs and adherence to oral RA medications ($P > 0.05$). However, 28.7% of participants reported not refilling, delaying to refill, skipping doses or taking smaller doses due to cost. In findings of the open-ended question, medication costs and affordability were the most commonly mentioned barriers to medication adherence.

Conclusion: Non-adherence to oral RA medications was prevalent among Iranian patients with RA and OOP costs were a barrier to medication adherence.

KEYWORDS

medication adherence, medication non-adherence, out-of-pocket costs, out-of-pocket payments, rheumatoid arthritis

1 | INTRODUCTION

As a chronic autoimmune disease, rheumatoid arthritis (RA) requires long-term treatment often with multiple medications[1]; symptom relief medications, synthetic disease-modifying antirheumatic drugs (sDMARDs) and biologic disease-modifying antirheumatic drugs (bDMARDs) are the most common pharmaceutical treatments for RA.[2] Medication adherence is essential for optimal health outcomes in patients with RA.[3] However, medication non-adherence is prevalent among patients with RA and is identified as a challenging problem.[3]

Two systematic reviews reported that the majority of studies investigating medication adherence in patients with RA were conducted in the USA and Europe.[4,5] Four single studies were found in Middle Eastern countries investigating medication adherence in patients with RA, including Saudi Arabia, Turkey, Egypt and Iran.[6-9] These four studies had small sample sizes, including 126, 82, 140 and 252 patients. These review findings highlight the lack of studies related to medication adherence in the Middle East region. These studies are important for Middle Eastern countries because, in terms of income and their development level, they differ from other regions in the World Health Organization and World Bank grouping.[10] The World Bank reported that 90% of the world's population receive 11% of the global health expenditure and from this, only 1.5% has been spent in the Middle East and North Africa.[11] Out-of-pocket (OOP) costs account for as much as 80% of the total health care expenditure in low-income countries.[12] From our knowledge, there was no study investigating medication adherence and OOP costs in patients with RA in Middle Eastern countries.

A systematic review[13] assessing the relationship between medication OOP costs and medication adherence in patients with RA, found six studies including five studies conducted in the USA and one in Morocco. The findings of this review suggest that OOP costs can contribute to non-adherence to RA medications in patients with RA.[13]

In Iran's healthcare system, the rate of OOP costs was estimated to be 50% (95% CI: 45%-57%)[14] which is higher in comparison to the world's average of 24%.[15] In 2014, Iran's government launched a Health Sector Evolution Plan for hospitals.[16] The main goals of this plan were to reduce healthcare costs for patients, improve quality of healthcare services and provide equal access to inpatient care.[16] Although OOP costs decreased instantly, the outcomes of this reform are still unknown.

Studies considering OOP costs and the treatment adherence relationship are beneficial for the decision-making process for policy-makers.[17] Therefore, this study aimed: to assess medication adherence to oral RA medications in patients with RA in Iran; second, to examine the effect of medication OOP costs on medication adherence to oral RA medications; and finally to examine the cost-related medication non-adherence (CRN) in all RA medications in patients with RA.

2 | METHODS

The recommendations of Strengthening the Reporting of Observational studies in Epidemiology (STROBE) initiative[18] was used to report this observational study (Table A1).

2.1 | Study design and setting

This cross-sectional study was conducted at two private rheumatology clinics and two public, tertiary hospitals that specialize in rheumatology care in Iran. The two hospitals are the main rheumatology centers in Shiraz, affiliated to Shiraz University of Medical Sciences and are responsible for the care of rheumatology patients in the south of Iran. The outpatient clinics within the two public hospitals are government-funded, whereas the private offices are not.

2.2 | Participants

Consecutive sampling was used. All patients who had been diagnosed with RA according to the American College of Rheumatology and European League Against Rheumatism (ACR/EULAR) criteria for longer than 3 months and were 18 years of age or older were eligible to participate in the survey which was provided in the Persian language.

2.3 | Ethics

The study was approved by the University Human Research Ethics Committee (0896) and the ethics committees at the participating hospitals in Shiraz.

2.4 | Data collection

All participants were given a paper copy of the survey which had been translated into Persian. The survey consisted of five sections. The 1st section collected demographic information including: gender, urban or rural residency, income, employment status, education, marital status, living with whom, insurance coverage and type of insurance. The 2nd section assessed the disease activity of the participant. This section included questions related to: the duration since diagnosis and commencement of treatment; the type of oral RA medications and bDMARDs prescribed; the daily frequencies of medications; the diagnosis of other comorbidities (asthma, high blood pressure, diabetes, heart disease, depression, osteoarthritis, high cholesterol, chronic kidney disease and other comorbidities) if relevant; if they had been hospitalized due to RA and monthly medication OOP costs. OOP costs were reported in US dollars (USD) adjusted to the date of data collection (March 2017). A recommended routine visit for patients with RA was every 3 months by rheumatologists. As recall bias was possible for OOP costs after 3 months, the questions in section 4 were included to substantiate the OOP costs incurred by each participant. The 3rd section assessed medication adherence, the 4th section assessed cost as a barrier to adherence and the final section contained one optional open-ended question that asked participants which factors, if any, affected them taking their medication according to their rheumatologist's prescribed orders.

2.5 | Adherence measurement

The Compliance Questionnaire Rheumatology (CQR)[19] was employed to measure medication adherence to oral antirheumatic medications in section 3 of the survey. It contained 19 questions with responses on a 4-point Likert scale ranging from 1 (do not agree at all) to 4 (agree very much).[19] CQR has been validated against electronic medication event monitoring and it has been shown to have good reliability and validity.[19] CQR developers have provided an

automated Excel file in which, by entering participants' responses, they were divided into two groups: either adherent or non-adherent. In this study, the cut-off point of 80% was chosen to define adherence. This was based on other studies that investigated medication adherence in RA where 80% was the cut-off used to identify patients as adherent or non-adherent.[20] To ensure that the Persian version of CQR was conceptually equivalent to the English version, it was translated forward and backward by professional translators and the reliability was tested by standardized Cronbach's alpha (α = 0.71).

2.6 | Cost-related medication non-adherence (CRN) measurement

The CRN questionnaire was utilized to assess cost as a barrier to adherence in section 4 of the survey. The CRN questionnaire contains four questions to assess whether the participant had ever delayed, not refilled prescriptions, skipped doses or taken smaller doses of their medication due to the cost. For each of the listed scenarios, the participants could choose from the options "often", "sometimes", or "never". Participants who answered "sometimes" or "often" were experiencing CRN. The CRN questionnaire has been widely used and validated in the US Medicare Current Beneficiary Survey (MCBS), which is a continuous survey conducted by the Centers for Medicare and Medicaid Services (CMS).[21] The results from the CRN questions were reported by percentage and mean of the 4 questions was reported as CRN prevalence.

2.7 | Disease activity measurement

For evaluation of disease activity, the Disease Activity Score of 28 joints (DAS-28) was used. DAS-28 provided a number on a scale from 0 to 10 indicating the RA activity according to the following categories: remission (<2.6), low (2.6-3.2), moderate (3.2-5.1), high (>5.1) disease activity. The rheumatologist agreed to assess the DAS-28.

2.8 | Recruitment

Between January 2017 and March 2017, patients attending the outpatient clinics at the participating centers were screened by the rheumatologist for their eligibility to participate in the study. Patients who met the inclusion criteria were notified of the study. The rheumatologist completed the DAS-28 for all participants who agreed to participate in the study and participants were given a paper copy of the survey to complete. One of the researchers remained in the outpatient clinics during the recruitment period to answer any questions from potential participants. For illiterate patients, the researcher read the survey to each participant and completed the survey on their behalf. Illiteracy was determined through self-reporting; participants asked the researcher to read the questions for them. To minimize the bias, the researcher tried to not engage in conversation with the participants and only read the questions and repeated them if needed. All the collected information was de-identified.

Sample size was determined by using the formula for comparison of two proportions. Using a mean adherence rate of 66%[22] and a difference of 10% in adherence between groups, the suggested sample size was 303 after considering a 10% non-response rate (CI = 90%, power = 80%).

2.9 | Analysis

Data were entered and coded into the Statistical Package for the Social Sciences (SPSS) version 24 (IBM, Armonk, NY, USA) for analysis and listwise deletion of missing records was employed to handle missing data. For reporting descriptive data, mean and standard deviations (SD) were used for continuous variables that were normally distributed, and median and inter-quartile ranges (IQR) were reported for skewed variables. Bivariate analysis of patients' characteristics between adherent and non-adherent patients were undertaken using Mann-Whitney *U* test for continuous skewed data and *t* test for normally distributed continuous variables and Chi-squared tests for dichotomous variables.

Andersen's Behavioral Model of Health Services Use[23] was employed as a guide for designing the survey and for data analysis. This model divides the determinants of health services use into: (a) Predisposing (b) Enabling and (c) Need factors. Andersen's Behavioral Model of Health Services Use has been used in several studies to predict and explain the medication adherence in diseases like HIV, heart disease and asthma.[24-26] The model suggests that demographic predisposing characteristics include age and gender, predisposing social factors include education and ethnicity, enabling factors include insurance and income and need factors include mortality, morbidity and disability rates.[23] Based on the aim of the study, this model was used as a guide to organize control variables in examining the relationship between medication adherence and OOP costs.

Previous studies have reported factors associated with adherence in patients with RA and they were: level of education, income, depression,[27] age, RA treatment duration, hospitalization due to RA,[28] presence of other diseases, the number of other diseases, living with whom,[28,29] gender,[30] OOP costs,[13] oral medications frequency[31] and using bDMARDs.[32] Due to the large number of variables, researchers had to choose the best suited variables to include in the logistic regression model. Therefore, a stepwise logistic regression was conducted to find the association of OOP costs and medication adherence by controlling for other potential determinants of adherence.

Data from the open-ended question were aggregated qualitatively in a Microsoft Excel sheet. Responses were grouped by similar concepts as determined by two researchers to reveal the barriers to medication adherence.

3 | RESULTS

3.1 | Demographic characteristics of the participants

A total of 308 completed surveys were collected. The demographic details of the survey respondents including gender, income,

TABLE 1 Demographic characteristics of patients with RA in Shiraz, Iran

Characteristics	n (%)
Gender, female, n = 308	265 (86.0)
Center type, public, n = 308	199 (64.6)
Residing in urban areas, n = 306	204 (66.7)
Monthly income, USD, n = 289	
None	197 (68.2)
Below 171	21(7.3)
Between 171.3-240	16 (5.5)
Between 240.3-330	21 (7.3)
Between 330.3-450	19 (6.6)
Between 450.3-630	8 (2.8)
More than 630	7 (2.4)
Employment status, n = 308	
Employed	28 (9.1)
Unemployed	13 (4.2)
Housewife	225 (73.1)
Retired	32 (10.4)
On disability allowance	10 (3.2)
Education, n = 307	
None	129 (42.0)
Primary school	89 (29.0)
Diploma	61 (19.9)
Bachelor	24 (7.8)
Post-graduate	4 (1.3)
Marital status, n = 306	
Single	16 (5.2)
Married	244 (79.7)
Divorced	4 (1.3)
Widowed	42 (13.7)
Living with whom, n = 307	
Spouse	241 (78.5)
Parents	17 (5.5)
Siblings	4 (1.3)
Children	29 (9.4)
Alone	16 (5.2)
Insurance coverage, n = 308	
None	1 (0.3)
Partial	295 (95.8)
Total coverage	12 (3.9)

employment status, education level, marital status, living status and insurance coverage are reported in Table 1. The majority of participants were female, married, living in urban areas, housewives, with no income and illiterate. The median age of the participants was 53 years of age (n = 300, IQR = 43-62), with a range from 19 to 87 years (Table 1). Only 19.9% had complementary insurance. Iran has two types of health insurance: private or government. Government insurance include Health, Social Security, Rural, Army, Khomeini Relief Foundation, Oil Company and Bank. There are many private insurance providers, which work as complementary insurance and cover the services that government insurance does not. Government insurance is the main source of insurance.

Participants who attended private centers were slightly more educated ($P < 0.05$) and slightly wealthier ($P < 0.05$), but there was no difference in adherence between public and private centers ($P > 0.05$). Therefore, the public and private patients were pooled for data analysis. However, the significances for the two groups (public and private) were checked separately. The P values were not greatly altered so we have only presented the analysis with the pooled data.

3.2 | Clinical characteristics of the participants

The median length of RA duration was 7 years (n = 305, IQR = 3-13) ranging from 3 months to 40 years. The median time that participants were being treated for RA was 6 years (n = 300, IQR = 3-12) ranging from 1 month to 40 years. The mean score on the DAS-28 was 3.85 (SD = 1.38) indicating moderate disease activity. The minimum and maximum scores on the DAS-28 were 0.91 and 8. DAS-28 was higher in women (mean = 3.94, SD = 1.41) than men (mean = 3.32, SD = 1.09) ($P < 0.05$). The most common prescribed oral RA medications were prednisolone, methotrexate, sulfasalazine, hydroxychloroquine and leflunamide. The majority of participants had never been hospitalized due to RA and 58.9% had other comorbidities, where high blood pressure was the most prevalent comorbidity. Table 2 represents the clinical characteristics of the participants.

3.3 | Medication adherence

According to the CQR, 59.7% were non-adherent to oral RA medications. The distribution of age ($P = 0.66$), RA duration ($P = 0.93$) and OOP costs ($P = 0.21$) were the same across adherent and non-adherent groups. Table 3 shows the distribution of participants' characteristics among adherent and non-adherent groups. A Chi-square test for independence revealed that significantly more non-adherent participants (78.0%) than adherent participants (22.0%) were using bDMARDs (Chi-square = 10.22, $P < 0.001$). There was no significant difference between adherent and non-adherent participants in regard to other variables (Table 3).

3.4 | Medication adherence and OOP costs

The median monthly medication OOP cost was 50 000 Toman,[a] which is equivalent to 15 USD (n = 274, IQR = 6-45 USD). In bDMARDs users, the median monthly medication OOP cost was 78 USD (n = 58, IQR = 33-180), while this number was 9.3 USD (n = 216, IQR = 4.5-30) for non-bDMARDs users. This question was not completed by 11% of participants. To find the association between OOP costs and medication adherence, a stepwise logistic regression was

[a]Iranian currency. Each 1000 Toman equals 0.30 US dollar (date: 29/3/2017).

TABLE 2 Clinical characteristics of patients with RA in Shiraz, Iran

Characteristics	n (%)
Oral RA medications, n = 302	
Hydroxychloroquine	104 (34.4)
Prednisolone	260 (86.1)
Sulfasalazine	204 (67.5)
Leflunamide	65 (21.5)
Methotrexate	213 (70.5)
Daily oral RA medications frequency, n = 293	
Once	93 (31.7)
Twice	131 (44.7)
3 times	54 (18.4)
More than 3	15 (5.1)
Using injectable bDMARDs, n = 307	61 (19.9)
BDMARDs type, n = 44	
Etanercept	27 (61.4)
Adalimumab	13 (29.5)
Infliximab	4 (9.1)
Monthly frequency of bDMARDs administration, n = 47	
Once	5 (10.6)
Twice	9 (19.1)
3 times	1 (2.1)
4 times	10 (21.3)
More than 4 times	22 (46.8)
Use of sDMARDs before bDMARDs, n = 58	56 (96.6)
Mode of administration, n = 58	
Subcutaneous	26 (44.8)
Intravenously	32 (55.2)
Comorbidities, n = 304	
Asthma	6 (3.3)
High blood pressure	70 (38.9)
Diabetes	40 (22.2)
Heart disease	23 (12.8)
Depression	25 (13.9)
Osteoarthritis	41 (22.8)
High cholesterol	35 (19.4)
Chronic kidney disease	25 (13.9)
Other comorbidities	78 (43.3)

bDMARDs, biologic disease-modifying antirheumatic drugs; RA, rheumatoid arthritis; sDMARDs, synthetic disease-modifying antirheumatic drugs.

conducted with dichotomous medication adherence evaluated by the CQR as the dependent variable (Table 4). There was no significant relationship between OOP costs and adherence. The only independent variable that was associated with adherence was the use of bDMARDs ($P < 0.001$).

The logistic regression model was statistically significant (Chi-square = 24.21, $P < 0.001$), indicating that the model was able to distinguish between adherent and non-adherent patients. The model as a whole only explained between 9.4% (Cox and Snell R^2) and 12.7% (Nagelkerke R^2) of the variance in adherence status, and correctly classified 62.2% of cases. As shown in Table 4, using bDMARDs made the only significant contribution to the model. The odds ratio of 0.18 for using bDMARDs was <1, indicating that bDMARDs users were 0.82 times less likely to be adherent to their oral RA medications, controlling for other factors in the model.

3.5 | Cost-related medication non-adherence

In terms of cost, 26.3% of patients had not refilled their prescription; 52.1% had delayed refilling their prescription; 18.2% had skipped doses; or 18.5% had taken less medication to make the medication last longer. Therefore, the mean CRN was 28.7%.

3.6 | Results of the open-ended question

The open-ended question in the survey was completed by 120 participants. There was no significant difference in adherence rates between the participants who responded and participants who did not respond ($P > 0.05$). Forty-three (35.8%) participants believed they were highly adherent to medication and they did not mention any adherence barriers. However, 77 (64.2%) participants listed the barriers to medication adherence, and some reported multiple barriers. Among the 98 barriers listed, medication costs and affordability (39.8%), preoccupied and forgetting (20.4%), side effects (12.2%) and disappointment in treatment (12.2%) were the most commonly mentioned barriers to medication adherence. OOP costs and medication affordability were the most commonly listed barriers: "I have financial difficulty for buying medication but because I have pain, I try to buy until I can afford" (P 217).

4 | DISCUSSION

In this study we investigated medication adherence and the association between medication adherence and OOP costs in people with RA in Iran. We found that 40.3% of the participants were adherent to their prescribed oral RA medications. This is congruent with a systematic review investigating medication adherence in patients with RA that reported adherence varied from 30% to 98%.[33]

The findings of other studies in Middle Eastern countries confirm that non-adherence is prevalent among patients with RA. The 8-item Morisky Medication Adherence Scale (MMAS-8) has been used in other studies to assess medication adherence in RA patients. A study in Saudi Arabia surveyed 126 patients and found 47.7% were adherent.[6] Another study in Turkey that surveyed 82 patients found 50% were highly adherent[9] and a study in Egypt that surveyed 140 patients found 9.4% were classified as moderately adherent and none classified as highly adherent.[7] MMAS-8 is a general tool that has been used in many studies to assess medication adherence; it was originally developed and tested on

TABLE 3 Differences between demographic and clinical characteristics of adherent and non-adherent patients with RA in Shiraz, Iran

Characteristics	Adherent, n (%)	Non-adherent, n (%)	*P* value
Gender, female	102 (39.4)	157 (60.6)	0.39
Center type, public	81 (41.5)	114 (58.5)	0.56
Education			
None	49 (38.6)	78 (61.4)	0.74
Primary school	38 (44.2)	48 (55.8)	
Diploma	24 (40.7)	35 (59.3)	
Bachelor and post-graduate	9 (33.3)	18 (66.7)	
Income			
None	81 (42.2)	111 (57.8)	0.15
Below 171	4 (20.0)	16 (80.0)	
Between 171.3-240	8 (53.3)	7 (46.7)	
More than 240.3	19 (35.8)	34 (64.2)	
Employment status			
Employed	12 (44.4)	15 (55.6)	0.69
Unemployed	3 (27.3)	8 (72.7)	
Housewife	87 (39.5)	133 (60.5)	
Retired and on disability allowance	19 (45.2)	23 (54.8)	
Site of residence, urban	82 (40.8)	119 (59.2)	0.78
Marital status			
Single	3 (18.8)	13 (81.3)	0.27
Married	100 (42.2)	137 (57.8)	
Divorced	1 (25.0)	3 (75.0)	
Widowed	16 (38.1)	26 (61.9)	
Living with whom			
Spouse	98 (41.9)	136 (58.1)	0.35
With parents, siblings or children	18 (36.7)	31 (63.3)	
Alone	4 (25.0)	12 (75.0)	
Insurance coverage			
None	1 (100.0)	0 (0.00)	0.42
Partial	116 (40.4)	171 (59.6)	
Total coverage	4 (33.3)	8 (66.7)	
Type of insurance			
Health	34 (44.2)	43 (55.8)	0.38
Social security	44 (36.1)	78 (63.9)	0.25
Rural	24 (43.6)	31 (56.4)	0.53
Army	10 (41.7)	14 (58.3)	0.85
Khomeini Committee	3 (37.5)	5 (62.5)	0.88
Oil Company	0 (00.0)	2 (100.0)	0.24
Bank	2 (28.6)	5 (71.4)	0.53
Complementary	25 (41.7)	35 (58.3)	0.75
Other	2 (66.7)	1 (33.3)	0.34
Hospitalized due to RA			
Never	85 (39.4)	131 (60.6)	0.29
More than 5 y ago	13 (54.2)	11 (45.8)	

(Continues)

TABLE 3 (Continued)

Characteristics	Adherent, n (%)	Non-adherent, n (%)	*P* value
During the last 5 y	20 (35.7)	36 (64.3)	
Daily oral RA medications frequency			
Once	35 (38.5)	56 (61.5)	0.29
Twice	56 (43.8)	72 (56.3)	
3 times and more	22 (32.4)	46 (67.6)	
Using injectable bDMARDs	13 (22.0)	46 (78.0)	0.001*
BDMARDs type			
Etanercept	9 (34.6)	17 (65.4)	0.56
Adalimumab	2 (15.4)	11 (84.6)	
Infliximab	1 (25.0)	3 (75.0)	
Monthly bDMARDs frequency			
Once	1 (20.0)	4 (80.0)	0.96
Twice	2 (25.0)	6 (75.0)	
3 times	0 (0.0)	1 (100.0)	
4 times	3 (30.0)	7 (70.0)	
More than 4 times	6 (27.3)	16 (72.7)	
Mode of administration			
Subcutaneous	6 (24.0)	19 (76.0)	0.90
Intravenously	7 (22.6)	24 (77.4)	
Other diseases, yes	68 (39.1)	106 (60.9)	0.45
Comorbidities			
Asthma	4 (66.7)	2 (33.3)	0.19
High blood pressure	28 (40.0)	42 (60.0)	0.89
Diabetes	18 (45.0)	22 (55.0)	0.54
Heart disease	8 (34.8)	15 (65.2)	0.54
Depression	12 (50.0)	12 (50.0)	0.33
Osteoarthritis	14 (35.9)	25 (64.1)	0.51
High cholesterol	14 (41.2)	20 (58.8)	0.95
Chronic kidney disease	8 (33.3)	16 (66.7)	0.44
Other comorbidities	29 (39.7)	44 (60.3)	0.84

bDMARDs, biologic disease-modifying antirheumatic drugs; RA, rheumatoid arthritis; sDMARDs, synthetic disease-modifying antirheumatic drugs.
*$P < 0.01$.

patients with hypertension.[34] Although small sample sizes of these three studies limits the generalizability of the findings, all three studies showed low adherence (<80%) that indicates non-adherence as an issue among the Middle Eastern population with RA. A study in Tehran using the CQR in 252 patients found 65% were adherent.[8] The findings of this study are different from our current study which is associated with the method of the calculation of adherence. While the current study calculated the adherence using the Excel file which the developers of CQR suggested, the other study calculated the total score by summing the value of 19 individual items unweighted, while developers believed that weighting scores assigned to individual items was an important factor in the calculation of adherence.[19]

Similar to this current study, several other studies have also used the CQR for assessing adherence in people with RA. A study in Spain with the sample size of 234 patients found 79.1% of patients as adherent[35]; a study in Belgium found 85.7% were adherent (n = 129)[29] and a study in Netherlands found adherence of 70%, 60.9%, 55.2% and 59.2% after 3, 6, 9 and 12 months from diagnosis (n = 170, 156, 143, 142).[36] The findings from this study and previous studies suggest that medication adherence in people with RA is higher in European countries than Middle Eastern countries. Education and income are among the determinants of adherence, the difference of education and income level among these two regions might contribute to the difference in the adherence. The majority of the participants in this current study were unemployed.

While bDMARDs were a revolution in RA treatment, decreasing joint erosions and improving patient quality of life[37]; in this study their use was limited to only 19.9% of the participants compared to 41.1% in a study in the USA.[38] According to ACR recommendations,

TABLE 4 Logistic regression analysis: medication adherence determinants in patients with RA in Shiraz, Iran

	B	SE	Wald	*P* value	OR	95% CI
Medicine treatment duration	0.02	0.01	1.91	0.16	1.02	0.98-1.06
Depression	0.84	0.55	2.33	0.12	2.31	0.78-6.81
Using bDMARDs	−1.69	0.51	10.97	0.001*	0.18	0.06-0.50
Frequency of oral RA medications: once a day			3.08	0.21		
Frequency of oral RA medications: twice a day	0.17	0.31	0.28	0.59	1.18	0.63-2.21
Frequency of oral RA medications: 3 times and more in a day	−0.43	0.37	1.39	0.23	0.64	0.31-1.33
OOP costs	0.00	0.00	0.13	0.71	1.00	1.00-1.00
Constant	−0.382	0.29	1.67	0.19	0.68	

80% cut-off was used to divide patients into adherent and non-adherent patients.
bDMARDs, biologic disease-modifying antirheumatic drugs; OOP, out-of-pocket; RA, rheumatoid arthritis.
*$P < 0.01$.

RA treatment starts with sDMARDs, then bDMARDs are added or substituted.[2] One reason for low prescription of bDMARDs is their higher prices.[39] In Iran, with the introduction of the Health Sector Evolution Plan, government insurance improved the coverage of the bDMARDs costs up to 70% for the total cost of adalimumab and 90% of the total cost for etanercept and infliximab (personal correspondence with pharmacists at the participating hospitals). Although this improvement in the cover of medication costs resulted in more prescribing of bDMARDs, this current study found the OOP costs remained intolerable where 28.7% of the participants experienced not refilling, delaying prescriptions, skipping or taking smaller doses due to cost. The CRN prevalence in the current study (28.7%) was higher than the CRN in the large population studied in the MCBS in the USA (18.4%).[40] Given that the majority of the population studied had no income, even low OOP costs of the oral RA medications can be a burden. The responses recorded on the open-ended question confirm these results. Therefore, affordability of bDMARDs in countries where people's incomes are low is an essential issue for consideration. A study across 46 European countries found that in lower-income countries, people with RA were less able to afford bDMARDs.[41] In the USA, although approximately all health insurance plans cover at least one bDMARD, medication OOP cost is still a financial burden to patients.[42]

The findings of this study suggest that non-adherence to oral RA medications were prevalent among bDMARDs users. This finding is in line with the finding of a study in the USA, where the majority of bDMARDs users had <60% adherence with oral RA medications.[43] Due to the higher effectiveness of bDMARDs than sDMARDs, researchers believe that patients may underestimate the effect of sDMARDs and neglect taking them. While adherence to oral RA medications in bDMARDs users may be improved by educating patients in terms of RA mechanisms and medication functions, addressing bDMARDs' OOP costs is the job of policy-makers. Pharmaceutical policy-makers have an important role in improving access, quality, cost of pharmaceutical products in the healthcare delivery system.[44]

Results from the open-ended question found OOP costs, forgetting, side effects and disappointment in treatment as barriers to medication adherence. A previous qualitative study conducted in Germany which interviewed 18 patients with RA also found side effects and disappointment in treatment as adherence determinants in the domain of "outcome expectations".[45] The researchers of this German study reported that participants' decisions on being adherent or non-adherent were guided by expectations about the effects of their medication. In addition, they found patients' experiences and trust in physicians as factors influencing adherence.[45]

4.1 | Limitations

There are several limitations to this study. This self-report survey means that participants' answers could not be validated. The study relied on patients recalling their medications, OOP costs and CRN. Researchers believe that recall bias may limit the accuracy of the medication OOP costs reported because patients were only visiting the rheumatologists every 3 months and 11% of patients failed to answer the question on OOP costs. However, as we anticipated recall bias, we used CRN questions to substantiate the results. Lastly, due to small sample size of bDMARDs users (n = 61), conducting statistical tests may not find the true (actual) associations between variables.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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APPENDIX

TABLE A1 STROBE Statement—Checklist of items that should be included in reports of cross-sectional studies

	Item no.	Recommendation	
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	*
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	*
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	*
Objectives	3	State specific objectives, including any prespecified hypotheses	*
Methods			
Study design	4	Present key elements of study design early in the paper	*
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	*
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	*
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	*
Data sources/ measurement	8[a]	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*
Bias	9	Describe any efforts to address potential sources of bias	*
Study size	10	Explain how the study size was arrived at	*
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	*
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	*
		(b) Describe any methods used to examine subgroups and interactions	*
		(c) Explain how missing data were addressed	*
		(d) If applicable, describe analytical methods taking account of sampling strategy	*
		(e) Describe any sensitivity analyses	NA
Results			
Participants	13[a]	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14[a]	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	*
		(b) Indicate number of participants with missing data for each variable of interest	*
Outcome data	15[a]	Report numbers of outcome events or summary measures	*
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	*
		(b) Report category boundaries when continuous variables were categorized	*
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	*
Discussion			
Key results	18	Summarize key results with reference to study objectives	*

(Continues)

TABLE A1 (Continued)

	Item no.	Recommendation	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	*
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	*
Generalizability	21	Discuss the generalizability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA

Note. An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of *PLoS Medicine* at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

*Give information separately for exposed and unexposed groups. NA: Not applicable.

4.2. Compliance Questionnaire Rheumatology responses

This section presents the findings of each of the 19 items of the Compliance Questionnaire Rheumatology (CQR) which were not included in the published manuscript (Table 4.1).

Table 4. 1. Participants' responses to the Compliance Questionnaire Rheumatology (CQR).

Questions	N	Don't agree at all, N (%)	Don't agree, N (%)	Agree, N (%)	Agree very much, N (%)
1. If the rheumatologist tells me to take the medicines, I do so.	305	0 (0.0)	2 (0.7)	146 (47.9)	157 (51.5)
2. I take my anti-rheumatic medicines because I then have fewer problems.	304	6 (2.0)	18 (5.9)	153 (50.3)	127 (41.8)
3. I definitely don't dare to miss my anti-rheumatic medications.	301	24 (8.0)	27 (9.0)	111 (36.9)	139 (46.2)
4. If I can help myself with alternative therapies, I prefer that to what my rheumatologist prescribes.	302	85 (28.1)	113 (37.4)	55 (18.2)	49 (16.2)
5. My medicines are always stored in the same place, and that's why I don't forget them.	308	4 (1.3)	8 (2.6)	133 (43.2)	163 (52.9)
6. I take my medicines because I have complete confidence in my rheumatologist.	308	2 (0.6)	2 (0.6)	120 (39.0)	184 (59.7)
7. The most important reason to take my anti-rheumatic medicines is that I can still do what I want to do.	300	0 (0.0)	5 (1.7)	152 (50.7)	143 (47.7)
8. I don't like to take medicines. If I can do without them, I will.	303	42 (13.9)	73 (24.1)	118 (38.9)	70 (23.1)
9. When I am on vacation, it sometimes happens that I don't take my medicines.	307	130 (42.3)	82 (26.7)	55 (17.9)	40 (13.0)
10. I take my anti-rheumatic drugs, for otherwise what's the point of consulting a rheumatologist?	307	32 (10.4)	15 (4.9)	171 (55.7)	89 (29.0)
11. I don't expect miracles from my anti-rheumatic medicines.	301	61 (20.3)	71 (23.6)	94 (31.2)	75 (24.9)
12. If you can't stand the medicines you might say: "throw it away, no matter what".	304	141 (46.4)	103 (33.9)	37 (12.2)	23 (7.6)
13. If I don't take my anti-rheumatic medicines regularly, the inflammation returns.	300	5 (1.7)	8 (2.7)	85 (28.3)	202 (67.3)
14. If I don't take my anti-rheumatic medicines, my body warns me.	302	2 (0.7)	5 (1.7)	99 (32.8)	196 (64.9)

15. My health goes above everything else and if I have to take medicines to keep well, I will.	302	0 (0.00	2 (0.7)	117 (38.7)	183 (60.6)
16. I use a dose organiser for my medications.	300	122 (40.7)	105 (35.0)	40 (13.3)	33 (11.0)
17. What the doctor tells me, I hang on to.	301	0 (0.0)	6 (2.0)	126 (41.7)	169 (56.3)
18. If I don't take my anti-rheumatic medicines, I have more complaints.	301	1 (0.3)	4 (1.3)	108 (35.9)	188 (62.5)
19. It happens every now and then, I go out for the weekend and then I don't take my medicines.	307	131 (42.7)	83 (27.0)	70 (22.8)	23 (7.5)

More than 98% of participants agreed that they follow the rheumatologist's instruction on medications (items number 1 and 17). Participants (30%) acknowledged that they do not take medications on weekends or on vacation (items number 9 and 19). More than 96% of participants agreed that their medications are always stored in the same place and they do not forget taking them. Nearly all participants (92%) agreed that by taking their medications, they have less problem (items number 2, 7, 13, 14 and 18). Over three quarters (75%) of participants did not use a dose organiser for their medications (item number 16).

4.3. Cost-related medication non-adherence (CRN) questionnaire

The following Table (Table 4.2) presents the participants' responses to the cost-related medication non-adherence (CRN) questionnaire. CRN contains four questions to assess cost as a barrier to medication adherence. Responses of "sometimes" or "often" indicate non-adherence due to cost.

Table 4. 2. Participants' responses to the cost-related medication non-adherence (CRN) questionnaire.

Questions: During the current year how often did you:	N	Often, N (%)	Sometimes, N (%)	Never, N (%)
Decide not to fill or refill a prescription because the medicine cost too much?	304	17 (5.6)	63 (20.7)	224 (73.7)
Delay getting a prescription filled or refilled because the medicine cost too much?	305	45 (14.8)	114 (37.4)	146 (47.9)
Skip doses to make the medicine last longer?	303	15 (5.0)	40 (13.2)	248 (81.8)
Take smaller doses to make the medicine last longer?	303	12 (4.0)	44 (14.5)	247 (81.5)

According to CRN questionnaire (Table 4.2), 80 participants (26.3% of participants) decided not to fill or refill a prescription because the medication cost too much. One hundred and fifty-two participants (52.1% of participants) delayed purchasing a prescription because the medication cost too much. Fifty-five participants (18.2% of participants) skipped doses to make the medication last longer. Fifty-six participants (18.5% of participants) took smaller doses to make the medication last longer.

4.4. The relationship between the responses of the CQR and the open-ended question

One hundred and twenty participants responded to the open-ended question. Among the respondents, 36% (43 participants) wrote that they were adherent to their medications with responses such as "I take my medications according to the doctor's prescription" or "Because I trust my doctor, I completely adhere to medications" or "I totally adhere to medications and it was working for me. I am better now". Among these 43 participants that perceived themselves as adherent, only 13 participants (30%) were identified as adherent by the CQR. A chi-square test revealed that there was no statistical relationship between adherence

perceived by participants in the open-ended question and the adherence measured by the CQR (Chi-square = 1.58, p = 0.20).

4.5. Summary of Chapter 4

This chapter has presented the results of the quantitative component of the study, which was a survey of patients with RA. A total of 308 surveys were collected. The majority of patients with RA were female, married, living in urban areas, housewives, with no independent income and illiterate. All participants were using oral RA medications and 20% were bDMARDs users. Analysis revealed that adherence to oral RA medications was sub-optimal in Iranian patients with RA and approximately 29% of patients reported not refilling, delaying to refill, skipping doses or taking smaller doses due to cost. Medication out-of-pocket (OOP) costs were reported as barriers to adherence in the responses to the open-ended question. The following chapter will present the results of the qualitative component.

Chapter 5

Qualitative Results

5. Chapter 5: Qualitative results

This chapter presents the results of the interviews with rheumatologists. In-depth semi-structured interviews provided detailed information on rheumatologists' perspective on medication adherence in patients with RA. The objectives of conducting these interviews were; to explore how rheumatologists assess medication adherence in patients with RA and, to explore medication adherence determinants in patients with RA from the perspective of rheumatologists with a focus on the effect of OOP costs on medication adherence. The findings of this component of the study are published in the International Journal of Rheumatic Diseases.

5.1. Published manuscript on the qualitative component of the study

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ORIGINAL ARTICLE

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Rheumatologists' insight into medication adherence in patients with rheumatoid arthritis: A qualitative study

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Abstract

Background: Medication non-adherence is prevalent among patients with rheumatoid arthritis (RA). Rheumatologists are specialists in medication prescribing and counselling for RA, but their insights regarding medication adherence have not been studied.

Objective: To explore rheumatologists' insights into medication adherence in patients with RA.

Methods: A qualitative study using semi-structured interviews with 10 rheumatologists in Iran was undertaken. Thematic analysis was conducted to identify how rheumatologists assess medication adherence and their perceived determinants of adherence. The identified determinants of adherence were mapped according to the Andersen's Behavioral Model of Health Service Use.

Results: Six participants were male, and the mean age was 47 years. The mean years of experience as a rheumatologist was 8.6 (SD = 7.1) years. Rheumatologists did not use a validated tool for medication adherence assessment. They assessed medication adherence either by asking their patients simple questions or using laboratory test results. The identified determinants of adherence were divided into 3 groups: patient-, rheumatologist- and healthcare organization-related determinants. The proposed suggestions to improve adherence were: (a) to understand a patient's financial situation before prescribing more expensive medications; (b) to employ a dose-reducing strategy; (c) to give hope to patients regarding remission; and (d) to arrange a session with the nurse educator.

Conclusion: The findings of this study provide insight into rheumatologists' perspectives on medication adherence of patients with RA. The identified determinants of adherence could be considered when developing initiatives to improve medication adherence in this group of patients.

KEYWORDS
medication adherence, medication non-adherence, physician, rheumatoid arthritis, rheumatologist

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory condition which results in severe articular and extra-articular morbidity and increased mortality from accelerated cardiovascular disease. People with RA often require long-term treatment with several medications.[1] Medications for symptom relief, synthetic disease-modifying antirheumatic drugs (sDMARDs) and biologic disease-modifying antirheumatic drugs (bDMARDs) are the most common medication treatments.[2] Early treatment with sDMARDs and bDMARDs is essential[3] to prevent structural damage in joints and improve patients' quality of life, including functional outcomes.[3,4] Although patients' adherence to medications is essential in RA management,[5] findings from previous quantitative studies have reported low medication adherence in these patients.[6-8]

A systematic review of quantitative studies examining determinants of adherence in patients with RA found that adherence rates are highly variable and there is no consistency in determinants of non-adherence.[9] Due to the complex nature of medication adherence, qualitative studies have the potential to provide a more robust understanding of this phenomenon.[10] Qualitative studies published to date addressing determinants of adherence in people with RA have mainly targeted patients' perspectives.[11-14] Patients reported that their beliefs, expectations, information about and experiences with medications affected their adherence. Other determinants include doctor-patient communication focused on trust building and patient education (treatment plan explanation), disease severity, financial problems and medication characteristics.[11-14]

A systematic review and meta-analysis of interventions improving medication adherence reported that interventions that targeted healthcare professionals, significantly improved medication adherence in adults.[15] Rheumatologists play a key role in RA management.[16] They are well-positioned to provide information related to RA management, to influence patients' perceptions about medication, and to discuss the importance of medication adherence.[13] Their insight, expertise and experience should be researched to obtain a better understanding of medication adherence.[17,18] As rheumatologists are specialists in medication prescribing and counselling for RA, the aim of this study was to investigate rheumatologists' insights regarding medication adherence in patients with RA.

2 | METHODS

2.1 | Study design and setting

A qualitative study was conducted using semi-structured interviews. The interview guide was designed to explore rheumatologists' insights regarding determinants of medication adherence in patients with RA (Table 1). The study was conducted in Iran and, all rheumatologists who work at one of the major medical universities in Iran were invited to participate in the study. Established in 1946, this University has 41 hospitals (including 14 teaching hospitals), more than 10 000 students and more than 18 000 staff, which makes it the main healthcare provider in the south of Iran. These rheumatologists provide care to patients with RA visiting the public clinics affiliated with the University and private centers. Each rheumatologist regularly has an average of 50 face-to-face consultations with patients per day. Iran has two types of health insurance: private or public-governmental. The public-governmental insurance organizations are the main health insurers that cover 70% of the costs of medications on the insureds' coverage lists, and 90% of public hospital costs.

2.2 | Data collection

A PhD candidate who designed the study conducted the interviews. There was no existing relationship between the interviewer and the potential participants. The researcher asked permission to attend one of the weekly meetings of the rheumatologists to explain the study. All rheumatologists were provided with information about the study and had the opportunity to ask questions. Participants were informed that their participation was completely voluntary and de-identified data would be analyzed. Interested participants could contact the researcher using the contact details included in the study information sheet. The time and venue for the interviews were arranged according to the participants' choices, which were mostly in the rheumatologists' offices in their non-consulting time. Prior to the interview, written informed consent was obtained from each participant and their demographic details collected. Eighteen rheumatologists were working at the recruitment site at the time of data collection. Of those, 10 agreed to participate in the study. Eight rheumatologists refused to participate. "Being very busy" was the main reason for refusal. Interviews were conducted between January 2017 and March 2017 in Persian language and translated into English by a professional translator. The mean duration of the interview was 22 minutes ranging from 11 minutes to 35 minutes.

The study was conducted according to the Helsinki Declaration. The Human Research Ethics Committee of the University that the PhD project is affiliated with (0896) and the Ethics Committee of the Medical University (2711-2016) approved the study.

TABLE 1 Semi-structured interview questions to explore medication adherence in patients with rheumatoid arthritis (RA) from the perspective of rheumatologists

What medications do you usually prescribe to RA patients?
What effect does the type of medication prescribed have on the patient's adherence to their medication?
What are some of the problems associated with medication adherence for RA patients?
What do you think are the key barriers to medication adherence as seen by patients?
What factors motivate those with good adherence to adhere well?
What percentage of your patients do you believe are non-adherent?
Do you use any method to measure medication adherence? If yes, what methods do you use?
Are there any organizational barriers that you think contribute to medication non-adherence?
Do you think the costs of medications affect their adherence behavior?
What health professional factors affect adherence?

2.3 | Conceptual model

Andersen's Behavioral Model of Health Service Use[19] was used to develop the interview questions and guide the analysis. Interview questions were based on a literature review investigating determinants of adherence in patients with RA and Andersen's Model, which divided the determinants into individual and environmental. This Model has been successfully used in previous studies to predict and explain the utilization of medication prescriptions[20,21] and medication adherence reported by participants suffering from acquired immune deficiency syndrome (AIDS), heart disease and asthma.[22-24] This theoretical Model is a validated framework that explains how individual and environmental characteristics impact on people's health behaviors, including medication adherence. The Model divides the determinants of health behavior into: (a) predisposing; (b) enabling; and (c) need factors (Figure 1). Therefore, an individual's medication adherence is related to their predisposition to adhere to medications, factors which enable or impede their medication adherence and their need to be adherent to medications. Predisposing factors are defined as those factors that shape attitudes toward medication adherence including demographics (age, gender), social factors (education), patients' health beliefs and community demographics. Enabling factors are defined as those resources that impede or promote medication adherence, including insurance, income and social support. The need factors represent the individual's illness that necessitates the medication adherence, including the patient's perception of their illness and severity of the disease as assessed by the physician.

2.4 | Data analyses

All interviews were audio recorded and transcribed by a professional. The first author checked all transcripts against the voice files to ensure data quality and imported the transcripts into NVivo software (Version 12, QSR). Interview data were analyzed using an inductive thematic analysis approach that involved searching across the data to find repeated patterns of meaning.[25] Two researchers coded four non-randomly selected transcripts. To ensure consistency of codes, they discussed the discrepancies in codes and developed the coding framework. Additional codes were added when new topics were discovered in the remaining transcripts. Data saturation was achieved at the 7th interview. Analysis of the 8th, 9th and 10th interview did not add any new information to the existing theory. Therefore, no effort was conducted for recruiting more participants after the 10th interview transcript was analyzed. Data were analyzed using two levels of coding. All repeated determinants were coded. Further, the discovered determinants were mapped into the Andersen's Behavioral Model of Health Service Use.

3 | RESULTS

3.1 | Participant characteristics

Ten rheumatologists (P1-P10) agreed to participate and were interviewed. Six participants were male and four participants were female; the mean age was 47.1 (range 35-59) years. The mean years of experience as a rheumatologist was 8.6 (SD = 7.1) years.

3.1.1 | How rheumatologists assess medication adherence

When rheumatologists were asked whether they use any method to assess medication adherence in patients with RA, responses revealed that they do not employ a validated tool for medication adherence assessment. However, they do employ several other strategies. They either directly ask whether their patients regularly take the prescribed medications or use medical examination and laboratory test results in which RA severity is revealed to conclude whether patients were adherent to their medications. Rheumatologists assume that if a patient visits them regularly, then that patient is likely to be highly adherent. They stated that irregular attendance indicates non-adherence because medications are prescribed for a specific period of time and a prescription should be renewed thereafter. Therefore, if patients do not visit their rheumatologists to renew their prescriptions, they have stopped taking their medications. RA medications including sDMARDs and bDMARDs can be purchased only with rheumatologists' prescriptions.

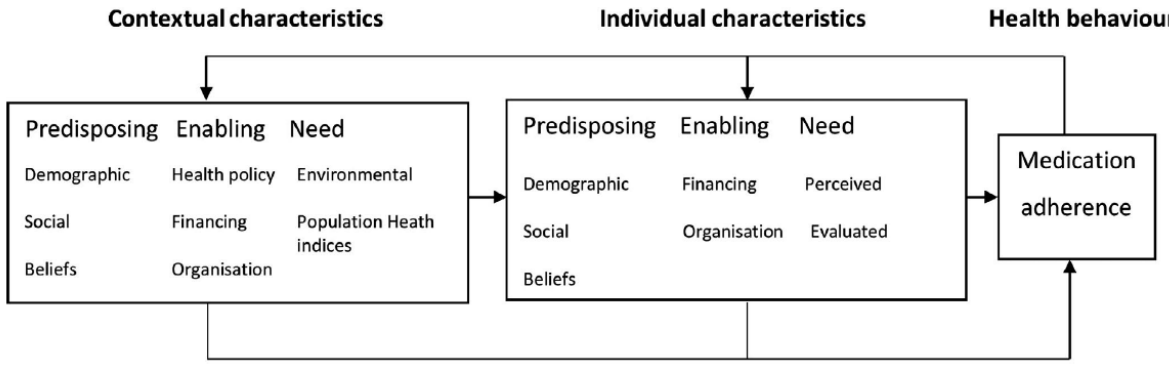

FIGURE 1
Adapted from Andersen's Behavioral Model of Health Service Use, 2008

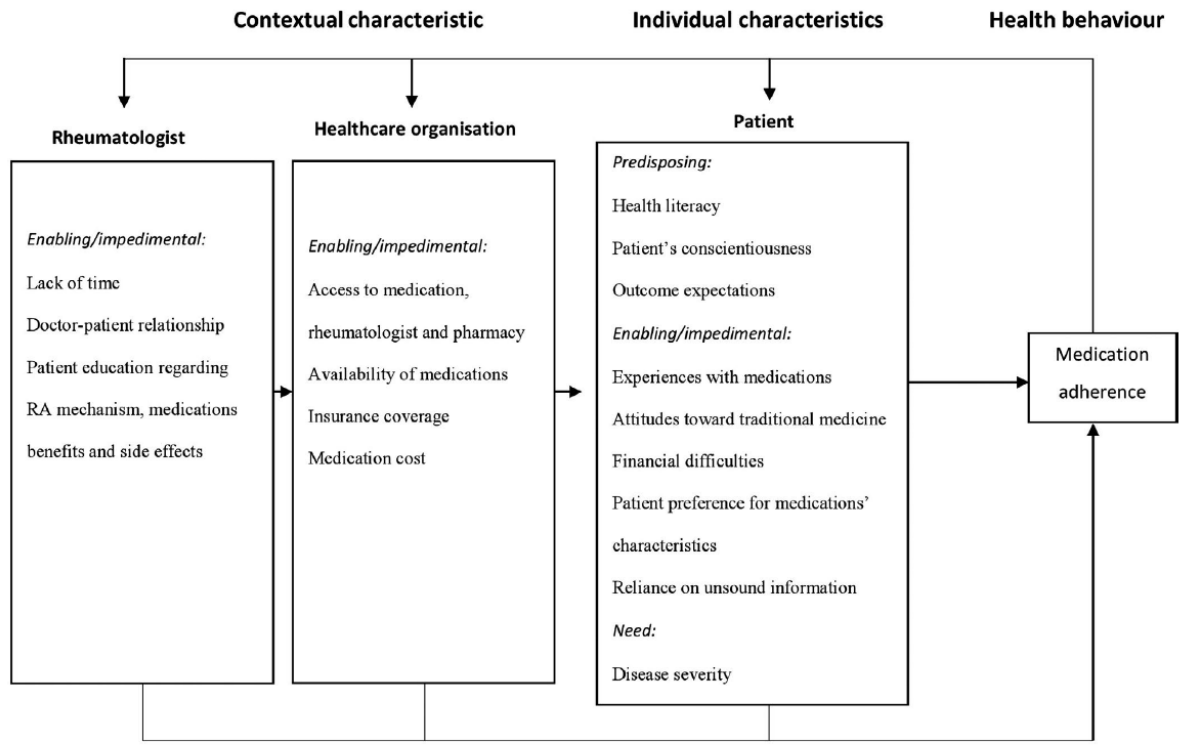

FIGURE 2 Determinants of medication adherence in patients with rheumatoid arthritis from the perspective of rheumatologists in Andersen's Behavioral Model of Health Services Use

> Nothing special. Just the routine. I take their history, I examine them, and then I see test results. If my patient's health has not improved, the first thing that comes to my mind is poor medication adherence … I always ask 'Do you take your medication as I told you?' P3

Rheumatologists considered their patients as highly adherent to the prescribed RA medications, with some rheumatologists suggesting that there are "not many" that are non-adherent. Nevertheless, responding to the question regarding the percentage of patients they believed are non-adherent, they gave percentages between 1% and 30%.

> Cannot give you an exact percentage. But the vast majority of my patients adhere to treatment unless they are faced with one of those barriers that I mentioned. P2

Rheumatologists believed that those patients who are non-adherent will recommence taking their medication when their disease relapses again.

> When patients suffer from a relapse, which is caused by poor medication adherence, the next time they follow the prescription well. P6

3.2 | Rheumatologist-identified determinants of medication adherence

Determinants of medication adherence were mapped into the Andersen's Behavioral Model of Health Service Use (Figure 2) and divided into three groups: patient-, healthcare organization- and rheumatologist-related. Tables 2, 3 and 4 represent the patient-related determinants, healthcare organization-related determinants and rheumatologist-related determinants, respectively.

3.2.1 | Patient-related determinants

Rheumatologists stated several determinants of adherence that were associated with the patient's characteristics and beliefs.

Health literacy

Rheumatologists stated that patients with low levels of education and health knowledge were more susceptible to medication non-adherence. Moreover, they reported that patients had poor knowledge of RA as a chronic disease. They reported that patients were not familiar with the concept of chronic disease. Therefore, they ceased medication after a few months because they thought the treatment course was completed. They may also cease medication after several treatment courses when they did not observe the desired treatment efficacy and became disappointed.

TABLE 2 Patient-related determinants of medication adherence in patients with rheumatoid arthritis (RA) from the perspective of rheumatologists

Determinant	Description	Selected quotes
Health literacy	General health literacy	"Those people who are less health-literate do not believe in the effectiveness of medications." P1
	Knowledge of RA and treatment	"There is another reason why patients stop the medication, and that's lack of information or misinformation about the disease." P2
Experiences with medications	Experiencing treatment efficacy	"When a patient observes the considerable effects of treatment, they adhere to their medication to have a good quality of life." P5
	Experiencing side effects	"Due to side effects, sometimes a patient stops taking medication before seeing a doctor again." P2
Outcome expectations	Unrealistic expectations of medications	"Some patients think that a medication works a miracle" P9 "A patient may have progressed a lot, but when I ask them about it, they say they have not changed. It is because their expectation is too high. They want to be totally healthy." P5
	When patients' expectations regarding remission are not met after a period of medication use, patients become disappointed	"Getting tired of taking medications. Since they have to take medications for a very long time, they feel frustrated and hopeless and stop the medication for some time." P5
	Expecting side effects	"I had a patient for whom I prescribed hydroxychloroquine. An important side effect of this medication is damage to the retina. That's why we prescribe patients to see an ophthalmologist every 6 months or every year. Next time my patient came back saying 'Did you want to blind me? I did not take the medication at all, and I am not going to come back to see you again. Goodbye!" P10
Patient's conscientiousness		"Most people don't even follow their prescription when they catch a cold. It differs with each individual. Some are more disciplined, some are not, and this is reflected in their medication adherence." P9
Attitudes toward traditional medicine		"Sometimes traditional medicine gets in the way. A practitioner of traditional medicine, or an attar (someone who sells traditional medications), may convince a patient not to take 'chemical medications' and to replace them with medicinal plants." P2
Financial difficulties		"Although medications are not expensive compared to other countries, they are expensive compared to the financial situation of our people." P5 "Some of them have financial difficulties. Some ask me not to prescribe medications for a whole period of 3 months but only for 1 month." P10
Patients' preference for medication characteristics		"Some patients prefer oral medications. Some prefer shots. Some patients cannot take oral medications or shots due to some conditions. For example, digestive problems in case of oral medications or financial difficulties in the case of shots. Therefore, types of medications affect medication adherence." P5
Disease severity		"Those who suffer from a severe disease have to take medication, if not they cannot do their routines well. So, the severity of illness has an important role in medication adherence." P7 "They observe that whenever they take their medications they feel no pain and when they don't take them, they feel pain. So they wait to have pain, and then they take their medications. If there is no pain, they don't take medications." "Sometimes they say they have stopped because they thought they are cured." P5
Reliance on invalid information		"They hear from someone that this medication is for chemotherapy. Merely hearing the word 'chemotherapy' frightens them and causes them to stop their medication, or friends and family talk them out of taking medication. They might tell a patient 'This is not a good medication, why your doctor has prescribed it? You shouldn't take it.'" P2 "A new problem related to information is the internet. Some patients search something and receive partial information about a medication and decide based on that biased data. Perhaps this is the key factor which causes a patient to stop the medication." P3

Experiences with medications

Rheumatologists stated that a patient's previous experience of negative medication side effects, including digestion problems and abdominal pain, hindered adherence to medications, whereas, when patients perceived that the treatment was effective and they had progressed in their treatment, they continued taking medications.

Outcome expectations

Rheumatologists stated that patient adherence was highly related to the patient expectations of the medication's effect. Expecting side effects or having high expectations from medications for an ultimate cure, may lead to disappointment and medication cessation.

TABLE 3 Healthcare organization-related determinants of medication adherence in patients with rheumatoid arthritis (RA) from the perspective of rheumatologists

Determinant	Description	Selected quotes
Access to medication, rheumatologist and pharmacy	Long distance to access to a rheumatologist and a pharmacy	"There are patients who live in remote areas and it is difficult for them to travel back and forth." P2 "Traveling for them is very difficult, especially in winters during bad cold weather." P1
	Whether rheumatologist tell/do not tell the patient about bDMARDs affect patients' access to medications	"There are some people who are so poor that I don't let them know such medications exist. Because if they know such expensive medications exist, they think they must either do whatever it takes to buy a shot or never be cured." P1 "I think it is our duty to tell a patient that such an expensive medication also exists. If they can afford it, they buy it. But if I don't mention it, there is a chance of permanent deformity. I don't ask them if they can afford a medication before I prescribe it. I prescribe what I should prescribe. Some can afford, and some come back saying that they couldn't afford the prescription. Then, I prescribe a cheaper medication, and I won't be responsible for the consequences of not prescribing a better medication." P8
	MDs cannot prescribe some RA medications	"There are also some patients who cannot see me regularly, and I tell them to go to a nearby MD to get the same prescription and show their tests to those doctors… here a MD cannot write a prescription, and if they do it, the insurance will not cover the medications. Methotrexate is an example." P8
	Issues with scheduling appointments in public clinics	"A patient must first come and pay the fees and the next day they can see a doctor. If a patient loses the appointment to pay the fees, the next appointment is in 6 months." P10
Availability of medications	Some RA medications are scarce, and pharmacies sell half a dosage	"Another issue is that because some medications are rare, a pharmacist might sell half of a prescribed amount to my patient. After 3 months, my patient comes back telling me 'I only have medications for a month, I did not take medications in the past 2 months." P10
	Issues with the availability of medications in the market (pharmacies)	"Sometimes I see some of my patients did not buy medication because they could not find it on the market. Then I realize that the medication is not available for some time." P3
	Issues with importation of medications	"There are also some issues concerning medication importation. Is a medication going to be available at the right time? Does it have clever marketing? Sometimes trade issues and sanctions affect medication importation, and as a result, a medication may become unobtainable. Then a patient has to stop the medication and the doctor has to prescribe something else." P2
	Some RA medications are not available in every pharmacy	"Some medications are not available in every pharmacy. A patient has to spend hours to find medications." P10
Insurance coverage	Insurance coverage	"Recently, in past 2 or 3 years, patient coverage has improved. Medication coverage has also improved but it still needs to progress. If it happens, it would be easier for patients to afford medications and their adherence would improve." P5 "The most important issue in this regard is insurance coverage. Most people have either Iran Health Insurance or Social Security Insurance; only a few people have other insurances. Unfortunately, those 2 do not cover many of new medications. It takes time for them to accept and cover a few new medications. So, in this regard, the most important issue is affordability. However, some patients have a sort of complementary insurance which covers a part of expenses." P8
	Insurance bureaucracy	"Some forms must be filled in…Approved forms are usually valid for 1 year, but insurances don't approve forms easily." P10
	Insurance does not recognize "negative RF" as RA indication	"Many patients who suffer from arthritis have a negative RF or anti-CCP. Insurance companies say these patients do not suffer from rheumatism. Therefore the companies do not cover the prescribed medications." P10
Medication cost	bDMARDs costs	"A brother and a sister are my patients. The brother works and can afford his medications. The sister does not work, she lives off her parents, and cannot afford her medications. She takes half a dosage, which is futile. The medication won't be effective. So, as for expensive medications, the main problems is affordability." P3 "Biologics are expensive. Meanwhile, we are prescribing them more and more. This situation exacerbates the negative role of medication cost." P3
	Medications costs	"Well, medication cost is quite effective. Some patients have difficulty to pay for even common medications." P1

Abbreviations: bDMARDs, biologic disease-modifying antirheumatic drugs; MD, medical doctor; RF, rheumatoid factor.

Patient's conscientiousness

Rheumatologists referred to conscientiousness characteristic as an adherence determinant. They defined a conscientious patient as a person with a high level of self-discipline who took medications and regularly visited the rheumatologists.

Attitudes toward traditional medicine

Rheumatologists reported a few cases of patients with high disease severity taking traditional medicine. Patients admitted they were influenced by the seller of traditional medicine to replace the prescribed medications with traditional medicines, including medicinal plants.

Financial difficulties

Rheumatologists considered patients' financial difficulties as one of the significant barriers to medication adherence. They stated that patients who had difficulty paying for the prescribed medication, laboratory tests and travel to the clinical site were more susceptible to non-adherence. With regard to medication costs, rheumatologists stated that financial difficulties mostly affected medication adherence to the more expensive product, bDMARDs, rather than conventional sDMARDs. Patients with low socioeconomic status were unable to pay even for the least expensive conventional medications.

Patient preference for medication characteristics

Rheumatologists said that patients had variable adherence to oral and injectable medications. While some believed the oral form was preferable to patients, others believed the injectable form was. Rheumatologists believed that patients who suffered from the side effects of oral medications preferred injections. However, due to the high cost of injectable bDMARDs, some of their patients preferred oral medications.

Disease severity

Rheumatologists believed that RA severity is also one of the most important determinants of medication adherence. They stated that patients who had high pain intensity were more adherent to their medications.

Reliance on unsound information

Rheumatologists stated that some patients were very sensitive about the information that their families, friends and community shared with them and the information they found on the internet. Rheumatologists believed that patients might discontinue their medications upon other people's suggestions that medication has side effects. Inaccurate information about side effects available on the internet or provided by lay people may influence medication adherence.

3.2.2 | Healthcare organization-related determinants

The determinants of adherence that were related to healthcare organizations include access to medication, rheumatologists and a pharmacy; availability of medications, insurance and medication cost. These determinants were considered unintentional factors that influence patient adherence to RA medications and were outside the patients' control.

Access to medication, rheumatologists and a pharmacy

Rheumatologists stated that patients living in rural areas or small towns, where specialist facilities were not available, had difficulty traveling due to ageing, travel expenses or having no-one to accompany them. As bDMARDs are expensive, rheumatologists had different perspectives about prescribing bDMARDs to their patients. Although the majority of them did not tell their underprivileged patients about these medications, the remainder believed that it was a patient's right to know about all available medications. In addition, medical doctors (MDs) were not permitted to prescribe some medications, such as methotrexate, which limits patients' access to these medications in local healthcare settings where there were no rheumatologists. Public clinics charged low fees, so most patients opted to attend these clinics, resulting in overcrowding and difficulties accessing a rheumatologist. If a patient did not attend the scheduled visit, they were placed on a long waiting list, possibly for several months, and were unable to renew the prescribed medication.

TABLE 4 Rheumatologist-related determinants of medication adherence in patients with rheumatoid arthritis (RA) from the perspective of rheumatologists

Determinant	Selected quotes
Lack of time	"Unfortunately, a doctor usually has to see lots of patients, and therefore there is not enough time to establish a good doctor-patient relationship." P5 "In my office, I see 15 to 20 patients per day, and I have enough time to devote to them. But in a public clinic, when I have to see 50 to 60 patients in a few hours, it is not possible to give all the information." P6
Doctor-patient relationship	"When a patient comes to see me, it means they already have an initial trust. Then if I establish a good relationship, they will definitely stick to the prescription." P3 "Some doctors communicate better, and therefore their patients adhere to their medications. This group of doctors are not necessarily more knowledgeable, but they can convince their patients to take their medications… Such a skill is related to a doctor's character." P9
Patient education regarding RA mechanism, medications benefits and side effects	"If patients are not informed, they stop the medication when they don't feel pain for a few days thinking that they are cured. To solve this issue, doctors should explain that it is their duty to decide about decreasing medications so that patients won't suffer a relapse." P6 "Our patient education is not powerful." P10

Availability of medications

Sometimes, RA medications were either not available or scarce in the market due to distribution and importation issues. Further, due to pharmaceutical industry regulations, not all pharmacies in Iran were permitted to sell some RA medications, including methotrexate.

Insurance coverage

Rheumatologists believed that government insurance coverage of the cost of conventional sDMARDs at the time of interviews was good; bDMARDs were also covered by the government insurance since 2014. However, rheumatologists thought that many people from lower socioeconomic backgrounds were still unable to afford bDMARDs, although the coverage had increased up to 70% for the total cost of adalimumab and 90% for the total cost of etanercept and infliximab. Rheumatologists explained that patient access to bDMARDs was subject to insurance approval of their prescription. In addition, they stated that insurance companies had some requirements for the reimbursement approval of bDMARDs, including a copy of the blood test result to confirm the presence of rheumatoid factor (RF). Patients were unable to purchase bDMARDs, unless these requirements were met.

Cost

Rheumatologists believed that medication costs were a significant influence on medication adherence for both conventional sDMARDs and bDMARDs. Although conventional sDMARDs were much cheaper than bDMARDs, rheumatologists mentioned that there were patients who still had difficulty affording them. bDMARDs were becoming more popular for RA management and at present rheumatologists prescribed them more frequently. However, their costs were still the main barrier to their access.

3.2.3 | Rheumatologist-related determinants

Specific determinants related to rheumatologists include lack of time, the doctor-patient relationship and patient education. Determinants in this category could affect adherence individually or in combination with the other determinants. For example, time limitation affected the quality of the doctor-patient relationship and consequently the quality of patient education.

Lack of time

Due to the low consultation fees in public clinics, many patients tended to utilize these clinics and, therefore, the consultation time per patient was decreased. Shorter consultation time limited rheumatologists' abilities to thoroughly discuss the importance of medications and treatment.

Doctor-patient relationship

In public clinics, patients had the choice to visit the same rheumatologist each clinic visit. Therefore, rheumatologists stated that a well-established relationship between the rheumatologist and the patient motivates patients to come back for follow-up visits and adhere to their prescribed treatment. They stated that it was important to establish a friendly and respectful relationship with patients to build trust and allocate time in the consultation to discuss the disease and medications.

Patient education

Rheumatologists stated that patient education about disease mechanisms, medication benefits and side effects was crucial for their medication adherence. In particular, rheumatologists believed that such education should include information regarding the chronicity of RA and the need for long-term use of medications. Patients must also be informed that the medications take time to get the desired effect; and even if they feel better, the treatment must be continued.

3.3 | Rheumatologists' suggestions

3.3.1 | Understanding patients' financial situation

Rheumatologists believed they should discuss medication costs with their patients before prescribing the more expensive medications. In particular, because bDMARDs were more expensive than sDMARDs, the majority of rheumatologists believed they should discuss affordability before prescribing these medications.

> For me, a patient's financial situation is of critical importance. I always ask such a question before writing a prescription, and because of financial limitation, I usually prescribe non-biologic DMARDs to treat RA. I always try to write my prescription based on the financial situation of my patients, so that few difficulties arise. P2

3.3.2 | Employing a dose-reducing strategy

Rheumatologists believed that reducing medication dosage and frequency encouraged patients to be adherent to their medication regimens. They suggested to their fellow rheumatologists to employ this strategy after observing an improvement in disease activity.

> When a patient sees that dosages are decreasing, they are encouraged to continue the treatment. For example, I tell a patient that next time I will stop prescribing corticosteroids. As a result, next time my patient definitely comes to see me. It is an incentive. P10

3.3.3 | Giving hope to patients regarding remission

Rheumatologists believed that giving hope to patients regarding treatment encouraged them to adhere to their prescribed medications.

> We should give them hope – and it's not a forlorn hope – by letting them know that if medications are taken, and the disease is under control after a while dosages gradually reduce; and the patient can finally stop the medication. So, they become hopeful about being cured and continue to take medications.
>
> P1

3.3.4 | Employing a nurse educator

Rheumatologists stated that there were no educators in public clinics. They believed that the presence of a nurse educator could be a facilitator to medication adherence, providing information including disease mechanisms, medication benefits and side effects.

> There is not enough time to explain everything to all patients ...This problem could be solved by well-educated nurses. P8

4 | DISCUSSION

Rheumatologists showed they have rich experience regarding their patients' medication adherence. However, they do not use any validated tool for the assessment of medication adherence. They do not have regular conversations about it with their patients, and medication adherence in general was not part of their routine patient consultation. Our study is in line with other studies.[18,26] Ammoury et al[18] conducted a survey in Lebanon to explore physicians' beliefs regarding medication adherence in immune-mediated inflammatory diseases. Eighty-two physicians including 22 rheumatologists, 30 gastroenterologists and 30 dermatologists were surveyed. They found that 74% of the participants did not assess patients' medication adherence. Tarn et al[26] conducted audio recordings of 632 visits in the offices of 28 primary care physicians in the USA. They recorded visits of patients 65 years and older, who were taking at least 1 medication for a chronic disease. They found that physicians simply asked about current medication use in 31.5% of visits and in-depth questions regarding adherence only in 4.3% of visits. In our study, rheumatologists stated that 1 of their strategies to assess medication adherence was simply asking patients whether they take medications. Tarn et al[26] revealed that among non-adherent patients, only half of them disclosed their non-adherence. Curtis et al[27] also found that the majority of patients with RA did not disclose their non-adherence to methotrexate in a response to a simple question of whether they are still taking methotrexate. Therefore, non-adherent patients are less likely to be identified if asked simple questions.

A cross-sectional study in Iran reported that less than half (40%) of Iranian patients with RA were adherent to their RA medications.[28] However, rheumatologists in our study perceived that their patients were highly adherent. The findings are consistent with the findings of a survey of 430 patients with RA participating in a US registry. Although the rheumatologists believed their patients were adherent to methotrexate, the results of the survey found that 13% (of the 228) reported either not taking methotrexate at all or had missed some doses.[27] This overestimation of adherence is also found in Miller et al's[29] study with HIV-infected patients. They aimed to investigate how accurate nurses, residents, fellows and physicians estimate their patients' adherence to the combination antiretroviral therapy. They found that clinicians overestimated adherence by 8.9% on average. Meddings et al[30] conducted a cross-sectional study of 1016 people with diabetes who were prescribed medications for blood pressure control. They investigated how healthcare providers, including nurses and physicians, estimate adherence to blood pressure medications. They found that non-adherence was recognized only in less than half of non-adherent patients.

This study extends the research on Andersen's Behavioral Model of Health Service Use, indicating that medication adherence in patients with RA is a multifaceted phenomenon that includes the patient-, rheumatologist- and healthcare organization-related determinants. This Model was well-suited to the explanation of findings of our study because unlike other models, such as the Health Belief Model[31] and Theory of Planned Behavior,[32] it considers both individual and environmental determinants of medication adherence as a health behavior.[33]

The identified determinants of adherence in our study were similar to other studies that explored clinicians' insights. For example, in a survey conducted in Lebanon, clinicians were asked to select the most important determinants of adherence from a list of 12 items. Similar to our study, they reported expecting side effects (38%), doctor-patient relationship (38%), outcome expectations (33%), disease knowledge (28%) and disease severity (27%) as determinants of adherence. Other reported determinants that were not identified in our study were depression (34%), disease duration (32%), relationship with nurse (23%), ease of medication administration (28%), age (19%), gender (18%) and smoking (7%).[18]

The determinants of medication adherence expressed by the rheumatologists in our study were consistent with the majority of the determinants expressed by patients in the qualitative study conducted by Voshaar et al[14] in the Netherlands. They explored determinants of adherence in patients with inflammatory rheumatic diseases (71% of participants had RA). Similar to our study, patients' health literacy, medication characteristics, expectations and experiences with medications, disease severity, access to and availability of rheumatologist and medications, insurance, medication costs and doctor-patient relationship were found as determinants of adherence. However, they found other determinants that were not identified in our study. For example, when patients received a sense of understanding of their disease from family members and friends, they were more likely to be adherent.[14] In our study, although rheumatologists believed that a good doctor-patient relationship is an adherence facilitator, they did not state the support from other networks as an adherence determinant.

Brandstetter et al[11] conducted a qualitative study of determinants of medication adherence from the perspective of patients with RA in Germany. Determinants related to adherence included experiences with medication, outcome expectations, knowledge of disease and

medications, patient's conscientiousness, belief in medical progress, medication characteristics, trust-based relationship with a rheumatologist, and autonomy. Except for autonomy, rheumatologists' insights in our study were similar to patients regarding the determinants of adherence. Brandstetter et al found that patients enjoy a degree of freedom in their disease control. For example, they felt pride when the rheumatologist assigned responsibility for managing some of the medications (particularly analgesics) to them; so they take them as needed.[11] Although in our study, rheumatologists stated that the promise of dose reduction strategy is an adherence facilitator, they did not mention whether they engage patients in the decision-making process. This might be because shared decision-making is not part of health practice in Iran.[34] Garcia Popa-Lisseanu et al[12] conducted a qualitative study of ethnically diverse and economically disadvantaged patients with RA and systemic lupus erythematosus (SLE) in the USA. Similar to our study, fear of side effects, financial difficulties, experiences with medications and several determinants regarding access and availability of healthcare services were identified. A determinant that was not identified in the current study was difficulty in navigating the public health system which is among the determinants that can be specific to a country's healthcare system.

Several identified determinants relating specifically to Iran include traditional medicine, access to medication, rheumatologists and pharmacies, availability of medications, insurance and medication cost. Despite this study being conducted solely in Iran, these determinants may exist in other countries. Healthcare organization-related determinants are identified in other studies.[35] However, as healthcare systems vary across different countries, determinants identified in this study may be specific to Iran. For example, issues on medication importation were due to sanctions against Iran by the USA.[36] Although the sanctions had been lifted at the time of data collection (February 2017), their consequences still existed. Regarding insurance determinants, while RF was present in 75%–80% of patients with RA,[37] in Iran, insurance does not recognize people with negative RF as diagnosed with RA. Therefore, this group of patients cannot be reimbursed for the costs of their medications.

Our findings can be useful in the design of future interventions to improve medication adherence. By mapping the determinants of adherence to Andersen's Behavioral Model, we identified patient-, rheumatologist- and healthcare organization-related targets for potential interventions. Taking into account the complex nature of the adherence concept and multiple determinants of adherence, we suggest that complex, multifaceted programs are more likely to be successful. Patient-focused initiatives could be aimed at improving patient knowledge regarding RA as a chronic illness, conventional medications and their side effects, and harmful effects of traditional medicines. Rheumatologist-focused initiatives could be designed to empower rheumatologists to establish a trust-based relationship and dedicate more time for patient education. Healthcare organization-focused initiatives may target health policies regarding the facilitation of equitable access to and availability of medication, rheumatologists and pharmacies particularly for rural areas, the improvement in insurance coverage and reimbursement process, further subsidizing bDMARDs costs, and to off-load rheumatologists and allow more time per patient consultation. In addition, initiatives that target developing education programs within clinics in combination with other initiatives and the availability of nurse-educators may influence adherence.

There is a limitation in this study. The study participants were recruited from 1 city only and the experiences of rheumatologists from other cities as well as other countries might be different. However, there are aspects of this study that are important to rheumatologists worldwide.

5 | CONCLUSION

Rheumatologists are a key element in RA management. The findings of this study provide insight into their perspectives on medication adherence of patients with RA. The identified determinants should be considered in developing initiatives to improve medication adherence of this group of patients.

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CONFLICT OF INTEREST

Authors declare no conflicts of interest.

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5.2. Summary of Chapter 5

This chapter has presented the results of the qualitative component of the study which included interviews with 10 rheumatologists. Findings revealed that rheumatologists in this sample do not use any validated tool for the assessment of medication adherence and they do not have regular conversations about adherence with their patients. However, they had rich experiences regarding the determinants of adherence. The identified determinants of adherence were mapped according to the Andersen's Behavioural Model of Health Service Use and divided into three groups: patient-, rheumatologist- and healthcare organisation-related determinants which reported medication adherence is a multifaceted phenomenon.

The following chapter will discuss the key findings of this study.

Chapter 6

Discussion and Integration of results

6. Chapter 6: Discussion and integration of results

This chapter explains and interprets the principal findings of this study. The first section discusses the findings of the quantitative component. The second section discusses the findings of the qualitative component. Following that, the main research questions are discussed by comparing the findings of each component of this thesis with the literature by using the side-by-side approach introduced by Creswell et al. (2018).

The main aim of this mixed methods study was to assess medication adherence to oral RA medications and its determinants with a focus on the effect of out-of-pocket (OOP) costs on medication adherence. The quantitative component used a survey of patients with RA to firstly assess medication adherence and secondly to examine determinants of adherence; in particular, the effect of OOP costs. The qualitative component used interviews to explore rheumatologists' experience regarding medication adherence in patients with RA, how they assess adherence and their perspective on the effect of OOP costs on medication adherence.

6.1. Quantitative results

Medication adherence was measured by Compliance Questionnaire Rheumatology (CQR) (de Klerk et al., 1999). Although some questions were missed in the questionnaire, such as the question asking about using a dose organiser, the total score well-recognised the adherent and non-adherent patients (the reliability was 0.71). The majority of participants who perceived themselves as being adherent were not identified adherent by the CQR. Finding no statistical association between the CQR measure and the open-ended question also confirms the use of CQR compared to a simple question.

CQR reported 40% of Iranian patients with RA were adherent to their oral RA medications. This finding shows that medication adherence is sub-optimal in this group of patients. From

my knowledge, there was only one study conducted in Iran that assessed medication adherence in patients with RA (Salehi et al., 2017). Like this study, CQR was used to assess medication adherence and adherence was also reported to be sub-optimal (65%) (Salehi et al., 2017). However, the results of that study are questionable due to the limitations in adherence calculation. While the current study calculated the adherence using the Excel file which the developers of CQR suggested (de Klerk et al., 1999), the other study by Salehi et al. (2017) calculated the total score by summing the value of the 19 individual items unweighted. The developers of this validated tool advised that weighting scores assigned to individual items was an important factor in the calculation of adherence. The detailed comparison with the results of other studies that used self-report tools for adherence measurement was provided in the published manuscript (section 4). Medication adherence was found to be lower among people with RA in Middle Eastern countries than in European countries (see section 4.1). The difference in education and income level between these two regions might contribute to the difference in the adherence. Education level and income are higher in European countries than Middle Eastern countries. While the GDP per capita in European countries was US$ 39,996 in 2018, this figure was US$ 8,057 in Middle East and North Africa and US$ 5,627 in Iran in 2017 (World Bank, 2018). In 2016, the literacy rate was 99% in European countries. This figure was 80% in Middle East and North Africa and 86% in Iran (World Bank, 2018). The majority of the participants in this study were unemployed and illiterate.

6.1.1. Medication adherence and demographic characteristics

The demographic characteristics of the participants reflect the epidemiology of RA in Iran. The demographic information reported in this study were similar to other Iranian studies which reported the majority of patients with RA were female, married, housewives, with low

level of education and residing in urban areas (Hosseini Moghadam et al., 2018; Sandoughi et al., 2017; Yousefi et al., 2015). In this study, no statistical relationship was found between medication adherence and demographic characteristics including age, gender, site of residency, income, employment, education, marital status, living with whom and insurance. One reason might be that the majority of the Iranian patients with RA were female, married, living in urban areas, housewives, with no independent income and illiterate, so the statistical tests may not have found the actual relationship between medication adherence and demographic characteristics. A systematic review was conducted to investigate medication adherence measured by refill data in the USA in patients with RA. The review reported male gender and older age associated with higher medication adherence (Murage et al., 2018). Pasma et al. (2013) conducted a systematic review to identify the determinants of medication adherence in patients with RA. They identified 18 studies. They reported conflicting evidence regarding the relationship between adherence and age; while four of the included studies reported that older patients had higher adherence due to their not busy schedules, six of the included studies agreed with this study and found no significant relationship.

Previous studies found inconsistent results regarding the association between demographic characteristics and medication adherence in patients with RA (Marengo et al., 2015; Uckun et al., 2017). The following demographic factors have been found to be associated with adherence in patients with RA; level of education, income (Xia et al., 2016), employment status (Ghosh et al., 2015) and living alone (De Cuyper et al., 2016). In the systematic review conducted by Pasma et al. (2013) similar to this study, no relationship was identified between medication adherence and, gender, education, employment and marital status. As adherence is a complex phenomenon, demographic information may not necessarily determine medication adherence. The other reason might be due to the small sample size in different demographic groups which have not provided sufficient statistical power to determine the

association between these characteristics and medication adherence. These results suggest that medication adherence is multi-faceted so demographic characteristics alone cannot influence medication adherence.

6.1.2. Medication adherence and disease-related characteristics

In this study, no statistically significant association was found between disease severity, which was measured by DAS-28 and medication adherence. The median score of DAS-28 reported moderate disease activity among patients with RA. Similar to this study, no association was reported between adherence and DAS-28 score in Japanese patients who have had RA for more than 4.6 years. They reported that a high DAS-28 score was highly associated with medication adherence in the early stages of RA (Nakagawa et al., 2018). Given that disease severity is associated with medication adherence in the early-stage of the disease, finding no statistical association in our study might be explained; the median RA duration was seven years in the current study. On the contrary, Waimann et al. (2013) reported lower disease activity in adherent patients in a sample of 107 patients in a prospective cohort study. Differences in study designs can contribute to different results. Also, the association between disease activity and medication adherence is unpredictable and dynamic which results in different findings.

Like this study, no significant association was found between the adherence measured by a self-report tool [Medication Adherence Report Scale (MARS)] and disease duration in a cross-sectional study of 108 patients with RA in the USA (Salt et al., 2011). In the mentioned systematic review conducted by Pasma et al. (2013), also no association was found between medication adherence and disease duration. In contrary to our finding, Berner et al. (2019) reported patients who had shorter disease duration were more likely to adhere to medications. Berner et al. (2019) conducted a cross-sectional study of 120 patients who had a disease

duration of more than one year. They reported a statistically significant relationship between disease duration and medication adherence. They reported patients with disease duration more than 10 years are in higher risk of being non-adherent than patients with less than 10 years disease duration. The difference between the population studied might explain the difference between the findings of Berner et al.'s study and the current study. Therefore, the disease duration variable requires more investigation in other populations and larger sample sizes, while ensuring that there is adequate variability in disease duration.

BDMARDs users were more likely to be non-adherent to oral RA medications. BDMARDs are more effective and faster in action than oral RA medications including sDMARDs. Patients may feel better after bDMARDs use. Therefore, they may underestimate the importance of oral RA medications and neglect taking them. A study in the USA that used refill data for adherence assessment reported similar result that the majority of bDMARDs users had adherence rate of less than 60% to oral RA medications (Engel-Nitz et al., 2012).

The logistic regression model only explained a small portion of variance. Potentially, other determinants of medication adherence have been missed in the survey. These determinants might include personality characteristics, quality of communication with the rheumatologist, and, confidence and information regarding RA and treatment.

6.1.3. Open-ended question

Seventy-seven patients listed several barriers to medication adherence in response to the open-ended question. Medication costs and affordability, preoccupied and forgetting, side effects and disappointment in treatment were the most commonly mentioned barriers to medication adherence. These findings confirm that patients have financial difficulty in purchasing medications. Although a statistically insignificant association was found between

employment and income with medication adherence, most participants were unemployed and had no independent income, which can explain their difficulty in purchasing medications. More discussions regarding the effect of OOP costs are made in section 6.3.2. Participants mentioned being preoccupied and forgetful as barriers to medication adherence. Congruent with this current study, Uckun et al. (2017) and Barbosa et al. (2015) also reported forgetfulness as adherence barriers. The findings of the CQR reported approximately 30% of participants (Table 4.1) do not take their medications during a vacation or weekends. Change in routine may result in medication non-adherence.

Despite the benefits of RA medications, they cause numerous side effects that influence patients' decision on adherence behaviour. In the trade-offs between side effects and possible benefits of RA medications, patients might choose not to have side effects, so they may cease medications or take smaller doses to minimise the side effects (Eisenberg, 2012). A qualitative study conducted in Germany which interviewed 18 patients with RA also found side effects as barriers to medication adherence (Brandstetter et al., 2016). Ma et al. (2019) studied 200 patients with RA and reported the most common medication-related problem was medications side effects. Patients mentioned disappointment of treatment as adherence barriers. They expect to be cured through the medications. When their expectations are not met after a period of medication adherence, it may lead to disappointment in treatment and ceasing of the medication. Similar to our study, Brandstetter et al. (2016) reported disappointment in treatment as barriers to medication adherence. Providing sufficient information regarding RA mechanism and medications' benefits and side effects might influence patients' perceptions and expectations.

6.2. Qualitative results

6.2.1. Patient-related determinants of medication adherence

Rheumatologists stated several determinants of adherence that were associated with the patient's characteristics and beliefs.

Rheumatologists stated that patients with low levels of education and health knowledge were more susceptible to medication non-adherence. In particular, they stated patients' poor health literacy and poor knowledge regarding the chronicity of RA were barriers to adherence. This finding is consistent with the finding of other studies. Joplin et al. (2015) conducted a systematic review of experimental and longitudinal studies that examined medication adherence in patients with RA. They reported that low level of education and low health literacy were barriers to medication adherence. Voshaar et al. (2016) conducted a mixed methods study including a survey of 120 patients with inflammatory rheumatic diseases and focus groups of 21 patients to identify the determinants of adherence to DMARDs. Similar to this study, they reported that the patient's knowledge regarding disease and treatment is one of the determinants of adherence (Voshaar et al., 2016). The majority of participants in this study were illiterate; they could not read a text and did not have the opportunity to be educated regarding the health-related topics. Therefore, they could not access written forms of educational information regarding RA and medications and, also their knowledge regarding health-related topics was limited. Although studies have not proven that high level of education improves adherence (Pasma et al., 2013), rheumatologists perceived low literacy as a barrier to medication adherence, which might be addressed by providing non-written educational programs utilising verbal and visual educational material.

Rheumatologists stated that patients' adherence was highly related to the expectations of the medication's effect, experiences with medication, characteristics of medications and the

patients' conscientiousness trait. Brandstetter et al. (2016) interviewed 18 patients with RA to investigate the determinants of medication adherence, similar determinants were reported in their study. These findings might show that rheumatologists did not provide sufficient information for their patients to shape realistic expectations. As a chronic disease, RA requires long-term pharmaceutical treatment. Patient's knowledge regarding the necessity of the medications is essential for long-term adherence, which can be influenced by the information the rheumatologist provides to the patient. Negative experiences with medications, expecting side effects or having high expectations from medications for an ultimate cure, may lead to disappointment and medication cessation. Negative experiences with medications and disappointment of treatment were also found in the open-ended question of the survey as adherence barriers (section 6.1.3). Pasma et al. (2015) conducted a qualitative study of 33 patients with inflammatory arthritis. Similar to this study, they discovered that experiences with medication were determinants of adherence in the initiation of DMARDs.

Rheumatologists reported a few cases of patients who admitted that they were influenced by the salesperson of traditional medicine to replace the prescribed medications with traditional medicines, including medicinal plants. A patient's lack of knowledge regarding their disease and low level of health literacy may contribute to their use of traditional medicines instead of the prescribed medications. However, rheumatologists stated that this issue also happened in educated patients. As RA is a long term disease, during the years of treatment with pharmaceutical treatment, even educated patients might want to test the effect of traditional medicines to see the actual outcome. Rheumatologists stated that these patients become adherent to the prescribed medications after a relapse in their disease. Although rheumatologists recognised this issue as a barrier to medication adherence, they did not mention any action to address the issue. Kobue et al. (2017) conducted a qualitative study of

18 women with RA in South Africa. Patients reported that they added traditional medicines to their prescribed medications, which may interfere with the function of the prescribed medications. Low level of health literacy and patients' perception regarding the effect of the traditional medicines might be the reason for replacing the prescribed medication with traditional medicines.

Rheumatologists stated that some patients were influenced by the unsound information that they found on the Internet or their families and community shared with them. Townsend et al. (2013) reported the same finding in their qualitative study of 38 patients who were diagnosed with RA for less than 12 months. They reported that patients' decision on taking their medications were influenced by the information gathered from family members and the Internet. They also explained that this issue, in particular, happened in patients who did not have the opportunity to discuss medications with their rheumatologist.

In this study, as rheumatologists stated, lack of time hindered them from spending sufficient time with patients. Consequently, patients seek information on the Internet or they absorb the information that the community and family members have provided to them. Consulting less patients provides more time for each patient, so the rheumatologists can explain the disease and treatment thoroughly. However, this might not be feasible. Therefore, a different approach may involve rheumatologists providing more detailed information to newly diagnosed patients so patients establish good medication taking behaviours early, which might be maintained long-term. In addition, results demonstrated that disease duration was not associated with adherence, so patients could also be provided with an annual education refresher program. This education could be conducted by a clinic nurse covering information regarding RA mechanism, the importance of the medications and medication side effects.

6.2.2. Rheumatologist-related determinants of medication adherence

Rheumatologists stated that lack of time, the quality of doctor-patient relationship and patient education were determinants of adherence that were related to them. Consulting 50 patients a day limits the rheumatologists' time to educate patients regarding the significance of medication adherence and build a good relationship [based on trust-building and active participation of patients] with patients. A good rheumatologist-patient relationship is essential for adherence improvement and establishing a good relationship requires spending sufficient time. If rheumatologists provide repeat prescriptions or prescribe medications for a period longer than three months, patients would not need to return to the rheumatologist as frequently for a prescription, which would result in a reduction in the number of patients in the clinics. Therefore, rheumatologists would have more time for each patient consultation. If feasible, recruiting more rheumatologists for public clinics can be another suggestion to divide the number of patients into more groups that provides each rheumatologist more time for each individual consultation. Haugli et al. (2004) conducted three focus group interviews with in hospital patients with RA. Patients stated that they need to spend time with the rheumatologist to establish a dialogue with them that provides them with the opportunity to know the rheumatologist sufficiently to establish a good relationship. Street et al. (2005) conducted a study that confirms the finding that doctors might not be able to establish a good relationship with their patients if they do not spend sufficient time with them. They conducted a cross-sectional study of 279 physician-patient interactions. They reported that supportive conversations such as encouragement, praise, reassurance, and empathy occurred in only 38% of the interactions between the patient and the physician. Voshaar et al. (2016) reported that a physician can influence patients' decision on medication adherence. Similar to this study, they reported that a good relationship between the physician and patient enhances trust and communication about disease management resulting in adherence improvement.

They also reported that patients' knowledge regarding treatment efficacy, side effects and costs was one of the determinants of adherence (Voshaar et al., 2016). Georgopoulou et al. (2018) conducted a systematic review on studies investigating the physician-patient communication in patients with rheumatic diseases. They reported that a good physician-patient relationship [a relationship based on trust-building and active participation of patients] was associated with improved health outcomes, which was improved with medication adherence (Georgopoulou et al., 2018). Salt et al. (2010) conducted a qualitative study with the grounded theory approach to describe how female patients with RA decide on being adherent or non-adherent to the prescribed medications. Similar to this study, they identified that a trust-based relationship with the healthcare provider was an important component of the decision-making process. The findings of these studies show the significance of the quality of rheumatologist-patient relationship. To assist with the development of this rheumatologist-patient relationship, the RA clinics were already providing patients with the option to consult with the same rheumatologist, assisting with the delivery of continuity in care.

6.2.3. Healthcare organisation-related determinants

Rheumatologists stated that there were numerous determinants of adherence that were related to healthcare organisations including access to medication, rheumatologists and a pharmacy; availability of medications; insurance and medication cost. Healthcare organisation-related determinants are out of the patients' control and cause unintentional non-adherence. These determinants define patients' capability to access healthcare services and medications. Public funding policies have a strong effect on access to healthcare services and medications and, consequently medication adherence. Devine et al. (2018) conducted a systematic review to identify systematic reviews that addressed the barriers to medication adherence in all chronic

diseases. They identified 31 systematic reviews. The barriers that were cited more than six times were reported. Similar to this study, medication cost, insurance coverage, and access to healthcare facilities were reported as determinants of adherence.

Rheumatologists stated that patients living in rural areas or small towns who had difficulty traveling to access a rheumatologist or pharmacy were often non-adherent. Transportation barriers are barriers to access to the healthcare system (Syed et al., 2013). These barriers have consequences such as rescheduled or missed clinic appointments and, missed or delayed medication use (Syed et al., 2013). Rheumatologists also stated that Medical Doctors [equivalent to GPs] were not permitted to prescribe some RA medications such as MTX. Therefore, patients had to travel to visit a rheumatologist to access RA medications. Travel costs and travel difficulties for aged patients, in particular patients living in rural areas and small towns, were barriers to medication adherence. Also, some RA medications such as MTX are not available in all pharmacies and patients were required to travel to find a pharmacy that has authorisation to dispense these medications. Providing repeat prescriptions or prescribing medications that last for a longer period of time can improve patients' access to RA medications that would result in an improvement to medication adherence.

Other determinants in this category including availability of medications, insurance and medication cost are discussed in section 6.3.2.

6.3. Integration

6.3.1. Medication adherence

While the results of the quantitative component reported only 40% of patients were adherent to their prescribed medications, the results of the qualitative component reported that rheumatologists have not thought about the non-adherence phenomenon and they perceived

their patients were highly adherent. They stated a range of one percent to 30% of their patients were likely non-adherent to their medications. This finding shows the significance of using a valid tool for medication adherence assessment and also shows that rheumatologists overestimate patients' adherence to medications. The findings are consistent with the findings of a survey of 430 patients with RA participating in a US registry. Methotrexate (MTX) had been prescribed for 228 patients, and rheumatologists recorded in the registry that all 228 patients were adherent to MTX. A self-report survey was designed to ask patients how many doses of MTX they have taken in the last four weeks (the usual dose of MTX is once weekly). The results of the survey found that 13% (n= 228) reported either not taking MTX at all or had missed some doses (Curtis et al., 2016). This overestimation of adherence by health professionals is also found in studies on other diseases. Miller et al. (2002) conducted a study on HIV infected patients. They aimed to describe how accurate health professionals including nurses, residents, fellows and physicians estimate patients' adherence to combination antiretroviral therapy. They used a self-report survey that asked health professionals what percentage of times they thought patients took their prescribed medications during the last four weeks. Patients' adherence was measured using a composite scale including data from MEMS, pill count and a self-report survey. By calculating the difference between these two measures, they reported health professionals overestimated adherence by 8.9%. Meddings et al. (2012) conducted a cross-sectional study of 1016 people with diabetes prescribed medications for blood pressure control. They investigated how healthcare providers including nurses and physicians estimated adherence to blood pressure medications. Adherence was measured by refill data and a self-report survey was used for healthcare providers. They reported healthcare providers recognised non-adherence for less than half of the non-adherent patients.

The overestimation of adherence can be explained by the findings of the qualitative component of the study where it was found that rheumatologists do not investigate medication adherence during patient visits. Generally, they do not ask about medication adherence because they think they have provided sufficient information for patients to follow their prescribed instructions and they have not considered non-adherence as an issue. On occasions where they do investigate adherence, they do not use a validated tool for medication adherence assessment. They stated that following a physical examination if they have not observed an improvement in health outcomes, they might ask simple questions such as "did you take your medications as I told you?", which are not valid assessment methods. These questions were proven not to identify non-adherence. Patients will often provide the health professionals with the socially desirable response (Huang et al., 1998) that they do take their medications and will avoid an uncomfortable situation of confessing non-adherence. Our study is in line with other studies (Ammoury et al., 2017; Tarn et al., 2012). Ammoury et al. (2017) conducted a survey to explore physicians' beliefs regarding medication adherence in immune-mediated inflammatory diseases. Eighty-two physicians including 25 rheumatologists, 37 gastroenterologists and 38 dermatologists were surveyed. They reported 74% of the participants did not assess adherence in their practice due to lack of time and nursing support. Tarn et al. (2012) conducted a qualitative study by audio recording 632 visits in the offices of 28 primary care physicians. Visits were with patients older than 65 years of age who were taking at least one medication for a chronic disease. They reported a total of 410 medications were prescribed for patients. Of these, 254 (62%) were discussed in the visits in a way that might address adherence. They discussed medication adherence by asking questions about; taking a medication, medication administration, whether the patient had ever missed or skipped a medication, medication efficacy, affordability and side effects. Physicians simply asked about current medication use for 31.5% of medications, and they

asked in-depth questions regarding adherence for only 4.3% of medications. Although healthcare providers felt responsible for assessing adherence and for addressing factors associated with non-adherence, they considered their patients as ultimately responsible and they voiced reluctance about confronting patients about non-adherence (Tarn et al., 2012). The doctor-patient relationship is different in Iran from developed countries. Shared decision making is not part of the health practice in Iran (Abbasgholizadeh-Rahimi, 2017), which affects the quality of the doctor-patient relationship; and this issue mainly relates to the cultural barriers that include both patients and physicians. Some Iranian physicians think that including the patient in the decision making is interpreted as an indication of the physician's lack of experience and knowledge (Abbasgholizadeh-Rahimi, 2017). Also, patients are not informed of the shared decision making concept, not familiar with their rights or not well-educated to contribute to the decision making (Abbasgholizadeh-Rahimi, 2017). Due to the paternalistic approach in Iran, in the relationship between the rheumatologist and the patient, the rheumatologist is the party who provides information and there is limited opportunity for patient to disclose non-adherence and its reasons. Lack of time in each consultation also facilitates this approach.

In this study, rheumatologists stated that one of their strategies to assess medication adherence was simply asking patients whether they take medications. This finding shows that a simple question cannot identify non-adherence. It also shows the significance of using a validated tool such as CQR for adherence measurement. Tarn et al. (2012) revealed that among non-adherent patients, only half of them disclosed their non-adherence. Curtis et al. (2016) also reported rheumatologists should be aware that most patients with RA did not disclose their non-adherence to MTX in response to a simple question of whether they are still taking MTX. Therefore, the strategy of asking simple questions is less likely to identify non-adherent patients. The CQR, which is a validated tool was used in this study and the

Cronbach's alpha was 0.71 for the Persian version of the CQR, which shows the tool is a reliable tool for identifying non-adherent patients in Iran.

6.3.2. OOP costs and medication adherence

Although the results of the logistic regression did not show a statistically significant relationship between medication adherence and OOP costs, findings of the CRN, the open-ended question in the survey and interviews confirm that OOP costs are barriers to adherence. BDMARDs are more expensive than csDMARDs and the low number of bDMARDs users may explain why a statistically significant relationship was not found; the majority of the participants were csDMARDs users. The findings are consistent with the findings of the included studies in the systematic review, provided in section 2.12. Twelve databases were systematically reviewed to identify studies that investigated the relationship between OOP costs and medication adherence in patients with RA. Six studies were included in the systematic review. Although the methods and the population of the included studies varied widely, they found an inverse relationship between OOP costs and RA medication adherence. Findings of studies on other diseases are also consistent with this finding. In a qualitative study of asthma patients, pulmonologist physicians and allied health professionals providing care to asthma patients, all participants agreed that medication costs were high and limits their access to the healthcare system and results in lower medication adherence (Peláez et al., 2014). Another study of 223,730 patients with diabetes prescribed new cardiometabolic medications found an inverse relationship between OOP costs, and first fill and the second refill of medications. Seven percent of patients had never purchased the new medication when OOP cost was more than 11 USD ($p< 0.0001$). For the second refill, more than 20% of the time, patients did not have enough medication due to OOP costs (Karter et al., 2017). Bestvina et al., (2014) found in a survey of 300 adults receiving anticancer treatment, 27% of

participants were non-adherent. 16% reported that they had financial distress. Fourteen percent of participants skipped doses, and 11% took less medication than prescribed to make the prescription last longer. Twenty-two percent did not fill their prescription due to cost. They also reported financial distress ($p< 0.001$) and high financial burden ($p< 0.01$) were associated with increased odds of non-adherence (Bestvina et al., 2014). Results of these studies show that, in patients with RA as well as other chronic diseases, OOP costs are barriers to adherence. As chronic diseases are life-long, the medications' costs incurred are a long-term financial burden that affects patients' decision to be adherent. Rheumatologists stated that as bDMARDs were expensive, Iran's government increased the coverage of the price of bDMARDs up to 70% for the total cost of adalimumab and 90% of the total cost for etanercept and infliximab. However, in this study the OOP costs were still a huge financial burden to patients as the majority of the patients with RA were unemployed, illiterate and had no independent income. Several rheumatologists stated that they do not inform their patients with low socioeconomic status about bDMARDs. They believed that patients who cannot afford bDMARDs will be disappointed if they realise that there is a better medication for treatment but they cannot afford due to the high cost. Therefore, rheumatologists do not prescribe bDMARDs to the majority of their patients. This paternalistic approach as well as patients' difficulty in purchasing medications limit patients' access to bDMARDs. In a qualitative study conducted by Kalkan et al. (2014) in Sweden, 26 interviews were conducted with rheumatologists to explore the factors that have affected their decision to prescribe bDMARDs. One of the identified factors was bDMARDs costs. Rheumatologists stated that due to the high costs of bDMARDs, they think twice before prescribing these medications. They believed that prescription of bDMARDs had a substantial budgetary impact that should be considered before prescribing. Dewitt et al. (2009) examined factors associated with the initiation of bDMARDs in a study of 1545 patients with RA in the US over eight years. They

reported 41.4% of 679 patients remaining in the study had used bDMARDs. They reported lower income of patients was associated with lower bDMARDs use. In the current study, no statistical association was found between income and bDMARDs use due to the low number of participants in the upper income categories; the majority of participants had no independent income. In conclusion, the economic aspect of bDMARDs influence the rate of bDMARDs use that consequently affects adherence.

There are discussions on the efficacy of the Health Sector Evolution Plan in Iran. The households' Catastrophic Health Expenditure (CHE) index improved from 2.9% to 2.3% and the total healthcare OOP costs decreased (Piroozi et al., 2016). However, the decrease in the OOP costs assisted inpatients mostly and outpatients were not advantaged by this Plan (Heshmati et al., 2016). The OOP costs for outpatient services was almost constant or had slightly increased (Assari Arani et al., 2018). The main criticism regarding this Plan were the disregard of outpatients (Zahirian Moghadam et al., 2019).

On the other hand, sanctions imposed on Iran by the USA due to Iran's nuclear program had negative effects on medications availability. In addition, these sanctions impacted the Iranian government's financial power to support the Health Sector Evolution plan, particularly subsidising medication. Firstly, sanctions imposed on Iran by the USA led to medications scarcity and consequently affected the costs of medications (Namazi, 2013). By the time the data was collected for this study, the sanctions were lifted. However, the consequences still existed due to the time-consuming process of re-joining the global pharmaceutical market. A new round of sanctions have been imposed on Iran from November 2018 (Aloosh et al., 2019). Findings of a narrative review found that the sanctions increased living costs and unemployment and limited access to medications (Aloosh et al., 2019). In addition, sanctions negatively affected the production of generic medications by forcing the country to import medications and raw materials with lower or questionable quality (Setayesh et al., 2016).

Therefore, sanctions mostly impacted the vulnerable people such as patients, because the government was unable to provide sufficient social and medical support (Aloosh et al., 2019). Low quality domestic medications, scarcity of international medications and high medication OOP costs are barriers to medication adherence.

Chapter 7

Conclusion and Recommendations

7. Chapter 7: Conclusion and recommendations

7.1. Conclusion

In this study, we examined medication adherence and its determinants in Iranian patients with RA, with a focus on the effect of OOP costs on medication adherence. By including patients and rheumatologists, this study provides a comprehensive description of medication adherence status in Iranian patients with RA. Key findings were:

1. Only 40% of the participants were adherent to their prescribed oral RA medications.
2. Only 20% of patients with RA were bDMARDs users.
3. BDMARDs users were more likely to be non-adherent to oral RA medications.
4. Approximately 29% of Iranian patients with RA experienced non-adherence due to OOP costs. Both patients and rheumatologists stated that OOP costs are significant barriers to medication adherence. Also, there was no significant relationship between OOP costs and adherence in the survey results.
5. Rheumatologists did not use any validated tool to assess medication adherence.
6. Rheumatologists overestimated medication adherence of patients with RA.
7. Determinants of medication adherence are related to patient, rheumatologist and healthcare organisation.

7.2. Recommendations

The findings of this project have practical implications for practice, policy and further research.

7.2.1. Recommendations for practice and policy

As medication adherence was found to be sub-optimal in Iranian patients with RA, developing interventions to improve medication adherence is recommended. By mapping the determinants of adherence to Andersen's Behavioural Model, we identified patient-, rheumatologist- and healthcare organisation-related targets for potential interventions. Considering the complex nature of the adherence concept and multiple determinants of adherence, it is suggested that complex, multifaceted programs are more likely to be successful. It is recommended that interventions are developed to target patients, rheumatologists, healthcare providers and health policy makers.

Patient-focused initiatives could be aimed at improving patient's knowledge regarding RA as a chronic illness, the importance of the medication and possible side effects, and harmful effects of replacing prescribed medications with traditional medicines. These considerations should be considered while developing interventions targeting patients: Particular emphasis can be given to bDMARDs users who were more likely to be non-adherent to oral RA medications and, newly diagnosed patients who will be educated on the importance of the medication and their chronic condition. This will be followed by an annual education refresher program. The educational must be delivered through a non-judgement approach and material must be inclusive of illiterate patients using pamphlets with pictures, symbols and language without medical jargons.

Medication adherence was not well perceived/understood by rheumatologists and they did not give enough attention to this phenomenon. Therefore, it is important that rheumatologists are informed of the results of this study, highlighting the rate of non-adherence in their RA patients. Results were communicated through in leading discipline journals such as International Journal of Rheumatic Diseases or Seminars in Arthritis and Rheumatism. Rheumatologists working at SUMS will be provided with a summary of the key findings of

the study and disseminated to RA clinics. In addition, rheumatologists should utilise different adherence measurement tools in their practice to identify non-adherent patients. The Compliance Questionnaire Rheumatology (CQR) is recommended because, in this study, it was translated to Persian and reliability was acceptable by standardised Cronbach's alpha (α= 0.71). In addition, it is easy to administer, quick to score and patients can complete it while waiting in the clinic. Rheumatologist-focused initiatives could also be designed to educate rheumatologists regarding the significance of their role in medication adherence and empower rheumatologists to establish a trust-based relationship by providing more information to patients and involving patients in decisions.

The majority of the patient participants in this study were unemployed and had no income; therefore, they had difficulty purchasing medications. Although government insurance covers the majority of medication costs, the OOP costs are still intolerable for patients with RA. It is recommended that policy makers consider the feasibility of decreasing medication OOP costs. Policy makers should be aware that despite the high financial burden of bDMARDs, the long-term outcome such as lower hospitalisation rates, better functional status and a lower incidence of work disability offsets the costs. In addition, access to medication, rheumatologists and a pharmacy; availability of medications and insurance coverage were found to be determinants of adherence. Healthcare organisation-focused initiatives may target health policies regarding the facilitation of equitable access to and availability of medication, rheumatologist and pharmacy particularly for rural areas; the improvement in insurance coverage and reimbursement process; further subsidise bDMARDs costs; and to off-load rheumatologists and allow more time per patient consultation. It is also recommended that healthcare providers and policy makers develop education programs within clinics in combination with other initiatives and provide nurse-educators to facilitate this initiative.

7.2.2. Recommendations for further research

As adherence to RA medications are vital for disease treatment, developing interventions to improve medication adherence is recommended due to the sub-optimal adherence in Iranian patients with RA. Regarding the development of future interventions, previous effective interventions for patients with RA should be identified. It is recommended that a literature review on interventions targeting medication adherence for patients with RA should be conducted to explore which interventions were effective at improving medication adherence.

The focus of this study was to explore the effect of OOP costs on medication adherence. Although several determinants were identified in this thesis, we recommend other determinants of adherence are also studied in-depth, such as investigating the relationship between medication adherence and the following variables;

- The use of traditional medicine
- Influence of community, family and friends' beliefs
- Time spent in each consultation with the rheumatologist
- Patient's personality traits
- Each medication's side effects

Although 80% was used as a cut-off for medication adherence categorisation in studies of medication adherence in patients with RA, there was no clinical study to support that adherence more than 80% is optimal or less than 80% is harmful. A future clinical study with participants who are patients with RA could provide valuable evidence.

7.3. Limitations

There are a number of study limitations in this thesis. Several determinants of medication adherence were identified in the qualitative component of the study that were not examined in

the quantitative component. Because the main aim of this project was to investigate the effect of OOP costs on medication adherence, other determinants of medication adherence were not studied in-depth.

Medication adherence was assessed at one point in time and no follow up was conducted. Follow-up assessments could provide a better description of medication adherence status. As medication adherence is an ever-changing phenomenon, patients should receive long-term follow up to describe this phenomenon thoroughly. Due to the anonymity of the survey and time constraints, identifying the same participants for follow-up was not feasible.

Based on previous studies of medication adherence in patients with RA, 80% was used as the cut-off to divide patients into adherent and non-adherent. Different cut-off points may have different results for the relationship between medication adherence and OOP costs.

Another limitation is related to the generalisability of the findings. First, CQR investigated adherence to oral RA medications and findings may not be generalisable to other medications of other comorbidities in patients with RA. However, CRN assessed medication non-adherence due to cost in all medications that patients with RA used. Secondly, the study was conducted in Iran only, and the results may have limited generalisability to other countries due to different economic and social characteristics. Finally, the sample of patients in this study was recruited from private and public centres. However, the majority of the patients were illiterate, unemployed and had no income. This limits the generalisability of the findings to other populations.

7.4. Strengths

In spite of these limitations, this study has several strengths compared to the existing evidence. While WHO stated that the determinants of medication adherence are associated with not only the patient but the contextual factors such as the healthcare system and

healthcare provider, most studies to date limited their scope to patients' perspective. In this thesis, both patients and rheumatologists were studied. In addition, from our knowledge, the qualitative component of this study was the first qualitative study that explored rheumatologists' insight into medication adherence.

Previous studies reported that medication adherence was sub-optimal in patients with RA. However, there was no quality evidence on the status of medication adherence in the Iranian setting. Only one Iranian study was found that had been published in the Persian language and it did not report adherence according to the guideline that the CQR developers provided. This erroneous reporting may have resulted in an inaccurate adherence measurement. In this study, medication adherence was measured according to the guideline that the CQR developers provided and findings were published in an English high rank journal.

By launching the Health Sector Evolution Plan in Iran, the government claimed that equality in healthcare services would be improved. Our study was the first study that explored the influence of this Plan on medication adherence in patients with RA. No study was found before the Plan was implemented, therefore a comparison was not feasible.

Finally, this study used multiple measures to explore the effect of OOP costs on medication adherence; a logistic regression of the relationship between OOP costs and medication adherence, CRN, the open-ended question in the survey and interviews with rheumatologists. Comparing these multiple methods enabled us to draw a detailed conclusion on the status of adherence in Iranian patients with RA.

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Appendices

Appendix 1: Structured survey for the cross-sectional study

Section 1

The following are a few questions about you

1. Gender: female/ male
2. Age: …… years
3. Education: none/primary school/ diploma/ academic degree
4. Monthly income (Toman): in Persian category below 570,000/ 571,000 to 800,000/ 801,000 to 1,100,000/ 1,101,000 to 1,500,000/1,501,000 to 2,100,000/ 2,101,000 to 3,000,000/ 3,001,000 to 4,200,000/ 4,201,000 to 5,800,000/ 5,801,000 to 8,100,000/ more than 8,100,000
5. Site of residence: rural/ urban
6. Marital status: Single /Married / Divorced / Widowed
7. Type of insurance: in Persian category: Salamat/ Tamin e ejtemaii/ Artesh/ komite emdad/ sherkate naft/ bank/ other
8. What is your current employment status? Employed/ unemployed/ home maker/ retired/ on disability allowance/ student
9. Which of the following best describes your current living situation? Living with a partner/Living with parents/ Living with siblings/ Living with children/ Living with friends/Living alone/ Other

Section 2

The following are a few questions about your Rheumatoid Arthritis (RA)

10. How long have you had RA? …… years…….months
11. Does your insurance cover your RA medicine expenses: none/partial/total
12. Have you been hospitalised for your RA? during the last year ☐during the last 5 years ☐ More than 5 years ☐ never ☐
13. How long have you had medicine treatment for RA: …… years……..months
14. How many medicines do you take for RA in a day? 1 ☐ 2 ☐ 3 ☐ more than 3☐
15. Choose medications that you take from the pictures.
16. How many times in a day do you take RA medicines? 1 ☐ 2 ☐3 ☐ more than 3 ☐
17. Do you use injectable medicines for RA? Yes/no
18. If yes, how many times did you inject during the last month? 1 ☐ 2 ☐ 3 ☐ 4 ☐more than 3 ☐
19. Choose the injectable medication that you used from the pictures.
20. Have you taken oral DMARDs before start using the injectable medicines? Yes/ no
21. How do you inject it? Self-injected/ In clinic
22. Do you suffer from any other disorders? Yes/no

    If yes, what are these disorders? Asthma/high blood pressure/diabetes/ heart disease/depression/osteoarthritis/ high cholesterol /chronic kidney disease/ others: …….

23. How much did you pay for your RA medicines (both oral and injectables) during last month that insurance will not reimburse? $ …….

Section 3

Please Place an X in the box which best describes your RA medication taking.

	don't agree at all	don't agree	agree	agree very much
1. If the rheumatologist tells me to take the medicines, I do so.				
2. I take my anti-rheumatic medicines because I then have fewer problems.				
3. I definitely don't dare to miss my anti-rheumatic medications.				
4. If I can help myself with alternative therapies, I prefer that to what my rheumatologist prescribes.				
5. My medicines are always stored in the same place, and that's why I don't forget them.				
6. I take my medicines because I have complete confidence in my rheumatologist.				
7. The most important reason to take my anti-rheumatic medicines is that I can still do what I				

want to do.

8. I don’t like to take medicines. If I can do without them, I will.

9. When I am on vacation, it sometimes happens that I don’t take my medicines.

10. I take my anti-rheumatic drugs, for otherwise what’s the point of consulting a rheumatologist?

11. I don’t expect miracles from my anti-rheumatic medicines.

12. If you can’t stand the medicines you might say: “throw it away, no matter what”.

13. If I don’t take my anti-rheumatic medicines regularly, the inflammation returns.

14. If I don’t take my anti-rheumatic medicines, my body warns me.

15. My health goes above everything else and if I have to take medicines to keep well, I will.

16. I use a dose organizer for my medications.

17. What the doctor tells me, I hang on to.

18. If I don't take my anti-rheumatic medicines, I have more complaints.

19. It happens every now and then, I go out for the weekend and then I don't take my medicines.

Section 4

Please think about the medicines you have obtained during the current year; how often did you do any of the following things for these medicines.

Did you:	often	sometimes	never
Decide not to fill or refill a prescription because the medicine cost too much?			
Delay getting a prescription filled or refilled because the medicine cost too much?			
Skip doses to make the medicine last longer?			
Take smaller doses to make the medicine last longer?			

Section 5

Overall, what factors do you think influence you to not use your medicines according to the prescription?

We thank you for your time spent taking this survey.

Appendix 2: The explanatory statement for rheumatologists.

MONASH University

EXPLANATORY STATEMENT

(Health professional participants)

Project: Medication adherence in rheumatoid arthritis patients.

Chief Investigator's name

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Research Fellow

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You are invited to take part in this study. Please read this Explanatory Statement in full before deciding whether or not to participate in this research. If you would like further information regarding any aspect of this project, you are encouraged to contact the researchers via the phone numbers or email addresses listed above.

What does the research involve?

The aim of this study is to assess the medication adherence in rheumatoid arthritis patients and adherence barriers with the focus on finding the relationship between medication

adherence and medication out-of-pocket costs. So, in the case of nonadherence, future interventions will be done to improve medication adherence.

Researchers would like to interview you to gather your recent experiences on medication adherence and its barriers in rheumatoid arthritis patients visiting you in rheumatology clinics. The interview will be conducted in a place of your choice, it will last for approximately 45-60 minutes and it will be tape recorded. The interview questions will explore what are the barriers to medication adherence in rheumatoid arthritis patients and medication out-of-pocket costs in rheumatoid arthritis patients.

Firstly, demographic data will be asked. Then these questions will be proposed:

What medications do you usually prescribe for RA patients?

Did RA patients adhere to their medications?

How do you check adherence in RA patients?

What are the barriers of adherence?

What is the most common reason of nonadherence?

Do you think high costs of medications affect their adherence behaviour?

What is your suggestion for improving the adherence?

Why were you chosen for this research?

We explore the relationship between medication adherence and out-of-pocket costs in rheumatoid arthritis patients and for deep considerations researchers will interview rheumatologists. All rheumatologists working in the rheumatology clinics at hospitals of Shiraz University of Medical Sciences were invited to participate in this study. You were chosen as a potential participant because you are a rheumatologist that works closely with patients with rheumatoid arthritis and have an expertise in RA medications.

Consenting to participate in the project and withdrawing from the research

Participation in any research project is entirely voluntary. If you do not wish to take part, you do not have to. If you do decide to take part, the researcher will give you a consent form to sign and you will be given a copy to keep. An appointment will be made according to your time schedule.

If you do consent to participate, you may withdraw. If you decide to withdraw from the project, please notify a member of the research team before you withdraw. If you do withdraw, you will be asked to complete and sign a 'Withdrawal of Consent' form; this will be provided to you by the research team. However, once the interview audio is transcribed and de-identified, researchers are unable to identify which data belongs to which participant and your data will be included in the study analysis.

Possible benefits and risks to participants

Benefits: Based on the data, Iran's healthcare system will be aware of the medication adherence rate and prevalence of cost-related medication adherence (CRN) in rheumatoid arthritis patients in the National Health Plan. In addition, the studies in this area is scarce. So, the relationship between medication adherence and out-of-pocket costs will be found in rheumatoid arthritis patients.

Risks: involvement in the research carries no risk for participants.

Payment

A gift from Monash University will be given to you.

Confidentiality

All the information are confidential and only researchers have access to them. All information collected from each participant will be de-identified, and any further use of these

findings in publications or conference presentations will be of a general nature, not attributable to an individual.

Storage of data

Data will be stored according to the Monash University regulations. Data will be stored at least for 5 years after ending the project. Audio files, data from questionnaires and scan of consent forms will be stored in LabArchive (a secure environment that only accessible by researchers).

Use of data for other purposes

Only aggregate de-identified data will be used for this project and potential future projects where ethics approval has been granted. Data will be published in the PhD thesis, articles or conference abstracts.

Results

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that participants cannot be identified. If you would like a summary of the results, please contact the researcher.

Complaints

Should you have any concerns or complaints about the conduct of the project, you can contact the Vice-Chancellor for Research, Shiraz University of Medical Sciences, Zand Blvd., Shiraz, Iran Postal Code; 71345-1978

Tel: +98 71 32357282, **Fax:** +98 71 32307594

E-mail: vcrdep@sums.ac.ir

Thank you,

Appendix 3: Informed consent form for rheumatologists.

MONASH University

CONSENT FORM

(Health professional participants)

Project: 'Medication adherence in rheumatoid arthritis patients'

Chief Investigator: Dr Kimberley Crawford

I have been asked to take part in the Monash University research project specified above. I have read and understood the Explanatory Statement and I hereby consent to participate in this project.

I consent to the following:	Yes	No
Audio recording during the interview.		
I have read Explanatory Statement or someone has read it to me in a language that I understand.		
I understand the purposes, procedures and risks of the research described in the project.		
I have had an opportunity to ask questions and I am satisfied with the answers I have received.		
I freely agree to participate in this research project as described.		

Name of Participant _____

Participant Signature _____ Date _____

Appendix 4: The explanatory statement for patients

MONASH University

EXPLANATORY STATEMENT

(Rheumatoid arthritis patients)

Project: Medication adherence in rheumatoid arthritis patients.

Chief Investigator's name
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Email: Parvaneh.heidari@monash.edu

You are invited to take part in this study. Please read this Explanatory Statement in full before deciding whether or not to participate in this research. If you would like further information regarding any aspect of this project, you are encouraged to contact the researchers via the phone numbers or email addresses listed above.

What does the research involve?

The aim of this study is to explore the medication adherence in rheumatoid arthritis (RA) patients and adherence barriers with the focus on finding the relationship between medication adherence and medication out-of-pocket costs. You will be asked to fill out the questionnaire.

The questionnaire contains a demographic survey, medication adherence survey, disease activity survey and medication out-of-pocket costs. It will take about 15 to 20 minutes.

Why were you chosen for this research?

The literature has reported medication adherence is suboptimal in RA patients. The Studies have investigated the relationship between medication adherence and out-of-pocket costs in RA patients are scarce. Therefore, we explore the relationship between medication adherence and out-of-pocket costs in RA patients. All RA patients visiting rheumatologists in the rheumatology clinics at hospitals of Shiraz University of Medical Sciences were invited to participate in this study. You were chosen as a potential participant because the aim of this study is assessing medication adherence in RA patients.

Consenting to participate in the project and withdrawing from the research

Participation in any research project is entirely voluntary. If you do not wish to take part, you do not have to. If you do decide to take part, the researcher will give you the questionnaire to fill out. It is possible to withdraw from the project prior to completing the survey without any prejudice and implication. Withdrawal after submitting the survey is not possible because the questionnaires are anonymous.

Possible benefits and risks to participants

Benefits: Based on the data, Iran's healthcare system will be aware of the medication adherence rate and prevalence of cost-related medication adherence (CRN) in RA patients in the National Health Plan. In addition, the studies in this area is scarce. So, the relationship between medication adherence and out-of-pocket costs will be found in RA patients.

Risks: if the participant has difficulty for paying the medicines costs, they may recall their financial hardship situations that they had previously experienced and make them upset. There is no other risk for the participants.

Payment

No payment or reward will be given to the participants.

Confidentiality

The questionnaires are anonymous. All the information are confidential and only researchers have access to them. All information collected from each participant is de-identified, and any further use of these findings in publications or conference presentations will be of a general nature, not attributable to an individual.

Storage of data

Data will be stored according to the Monash University regulations. Data will be stored at least for 5 years after ending the project. Audio files, data from questionnaires and scan of consent forms will be stored in LabArchive (a secure environment that only accessible by researchers). After analysing data and publishing articles, by researchers' agreement, the de-identified data will be published in Figshare (https://monash.figshare.com/). Publishing data is recommended by Monash University as other researchers can have access to the de-identified data of other researchers.

Use of data for other purposes

Only aggregate de-identified data will be used for this project and potential future projects where ethics approval has been granted. Data will be published in thesis, articles or seminar abstracts.

Results

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that participants cannot be identified.

Complaints

Should you have any concerns or complaints about the conduct of the project, you can contact the Vice-Chancellor for Research, Shiraz University of Medical Sciences, Zand Blvd., Shiraz, Iran Postal Code; 71345-1978

Tel: +98 71 32357282

Fax: +98 71 32307594

E-mail: vcrdep@sums.ac.ir

Thank you,

Appendix 5: Length of interview with ten rheumatologists.

ID	1	2	3	4	5	6	7	8	9	10
Duration of interview (minutes)	15	22	29	14	19	24	11	35	17	30

Appendix 6: Ethics approval from Monash University Human Research Ethics Committee

Monash University Human Research Ethics Committee

Approval Certificate

This is to certify that the project below was considered by the Monash University Human Research Ethics Committee. The Committee was satisfied that the proposal meets the requirements of the *National Statement on Ethical Conduct in Human Research* and has granted approval.

Project Number: 0896
Project Title: Medication adherence in rheumatoid arthritis patients.
Chief Investigator: Dr Kimberley Crawford
Expiry Date: 04/11/2021

Terms of approval - failure to comply with the terms below is in breach of your approval and the *Australian Code for the Responsible Conduct of Research*.

1. The Chief Investigator is responsible for ensuring that permission letters are obtained, if relevant, before any data can occur at the specified organisation.
2. Approval is only valid whilst your hold a position at Monash University.
3. It is responsibility of the Chief Investigator to ensure that all investigators are aware of the terms of approval and to ensure the project is conducted as approved by MUHREC.
4. You should notify MUHREC immediately of any serious or unexpected adverse effects on participants or unforeseen events affecting the ethical acceptability of the project.
5. The Explanatory Statement must be on Monash letterhead and the Monash University complaints clause must include your project number.
6. Amendments to approved projects including changes to personnel must not commence without written approval from MHUREC.
7. Annual Report - continued approval of this project is dependent on the submission of an Annual Report.
8. Final Report - should be provided at the conclusion of the project. MUHREC should be notified if the project is discontinued before the expected completion date.
9. Monitoring - project may be subject to an audit or any other form of monitoring by MUHREC at any time.
10. Retention and storage of data - The Chief Investigator is responsible fo the storage and retention of the original data pertaining to the project for a minimum period of five years.

Thank you for your assistance.

Professor Nip Thomson

Chair, MUHREC

Page 1 of 1

Appendix 7: Ethics approval from ethics committee at SUMS.

MONASH University

Parvaneh Heidariorojloo <parvaneh.heidariorojloo@monash.edu>

Collaboration on Miss Parvaneh Heidari`s project

2 messages

researchethic <researchethic@sums.ac.ir> 4 December 2016 at 23:41
To: kimberley.crawford@monash.edu
Cc: parvaneh.heidariorojloo@monash.edu, ali_po58@yahoo.com, hashemib@sums.ac.ir

Dear Dr Kimbrerley Crawford

With regard to your letter dated 26 September 2016 concerning Monash University collaboration on Miss Parvaneh Heidari`s project under supervision of Dr Mohammad Ali Nazarinia, We are pleased to inform you that it has been proposed and approved in Research Ethics Committee of Shiraz University of Medical Sciences (Session held on 27 November 2016).

please do not hesitate to contact us for further assistance.

Respectfully,

Seyed Basir Hashemi, MD.

Vice-Chancellor for Research

Shiraz University of Medical Sciences

Shiraz, Iran

Kimberley Crawford <kimberley.crawford@monash.edu> 5 December 2016 at 08:27
To: researchethic <researchethic@sums.ac.ir>
Cc: Parvaneh Heidariorojloo <parvaneh.heidariorojloo@monash.edu>

Dear Seyed Basir Hashemi,

Thank you for your email and for considering our project for ethics approval.

We are really looking forward to conducting our study with Shiraz University of Medical Sciences.

Kind regards

Kim Crawford
[Quoted text hidden]
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