Studies on Expenditure, Prices, and Value of Disease-Modifying Antirheumatic Drugs

by

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Abstract

Objectives: To determine the expenditure of rheumatoid arthritis (RA) and price changes, and to elicit the preference-based value of disease-modifying antirheumatic drugs (DMARDs).

Methods: First, Medical Expenditure Panel Survey (MEPS) data from 2008-2020 were used to estimate the expenditure for RA patients. Secondly, IBM Micromedex®-REDBOOK® data from 1998 to 2021 were used to assess the impact of new brand-name DMARD entries on the price trends of existing drugs. Thirdly, a web-based discrete choice experiment (DCE) was conducted to elicit the preference-based value of DMARDs.

Results: The covariate-adjusted results showed a 75% ($17,791 to $31,105) increase in direct costs for the RA cohort from 2008-2020, primarily driven by rising prescription drug costs, 192% ($5,381 to $15,639) in 2020 dollars. Despite the competition, prices for brand-name DMARDs continued to rise, with variable effects of new entries on existing DMARD prices. The study also found that reducing pain was the most important attribute of DMARDs for RA patients, followed by out-of-pocket cost, improving physical function, reducing fatigue, experiencing severe adverse events, and the way the medication is taken. Preference heterogeneity was observed, and the preference-based value ranged from $91 to $231 per month.

Conclusion: This study highlighted the increasing trend in the economic burden of RA, and the prices of DMARDs. Patient preferences and affordability should be considered when making treatment decisions.

Implications and future research: The increasing trend of RA expenditure, largely driven by the rising costs of DMARDs and the variable impact of competition, highlights the need for a multifaceted approach beyond market competition to tackle the increasing trend of RA

expenditure. Given the rising price of DMARDs, clinicians should consider affordability and patient preference when selecting DMARDs. Future research should explore additional data sources to generate a more comprehensive economic burden, investigate the impact of biosimilars on the existing price trends and explore practical methods for incorporating patient preference into policy decisions.

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List of Abbreviations

ACR	American College of Rheumatology
AWP	Average Wholesale Price
bDMARDs	Biological Original Disease-Modifying Antirheumatic Drugs
CA	Conjoint Analysis
cDMARDs	Conventional Synthetic Disease-Modifying Antirheumatic Drugs
CEA	Cost-Effectiveness Analysis
CPI	Consumer Price Index
CUA	Cost Utility Analysis
DCE	Discrete Choice Experiment
DMARDs	Disease-Modifying Antirheumatic Drugs
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
ITS	Interrupted Time Series
JAK	Janus Kinase
LCA	Latent class analysis
MEPS	Medical Expenditure Panel Survey
ML	Mixed logit

MNL	Multinomial Logit
QALY	Quality Adjusted Life Year
RA	Rheumatoid Arthritis
RUT	Random Utility Theory
tDMARDs	Targeted Synthetic Disease-Modifying Antirheumatic Drugs
WAC	Wholesale Acquisition Cost
WTP	Willingness To Pay

Chapter 1 Introduction

1.1 Background

Rheumatoid Arthritis (RA) is a chronic, autoimmune inflammatory condition characterized by immune system malfunction, leading to attack of the lining of the joints (synovium).[1-3] RA patients manifest symptoms such as swelling of synovium, joint inflammation, pain, and bone destruction.[2,4] Although RA commonly affects small joints of the hands, feet, and wrists, it can affect almost any joint areas, e.g., hands, knees, ankles, or multiple joints.[5,6] If RA is left untreated, RA can have impact on heart, lung, and skeleton.[2,4,6,7] To date, the exact cause of RA remains largely unknown, but patient-related characteristics (e.g., age, gender, smoking, obesity), genetic factors, environmental factors, and immune response are identified as the major risk factors.[2,3,6,7]

RA affected approximately 20 million people worldwide.[8,9] In the U.S., 0.53 to 0.55% (1.28 to 1.66 million) adult population were diagnosed with RA.[10,11] RA is more prevalent among older individuals (2% for age 60 and older, and 0.5-0.55% for general population), female (3.6% for women and 1.7% for men), and native American populations (5% for native American and 0.5-0.55% for the general population).[3,12-14] RA patients might experience prolonged disease-related disability, psychological impairment, comorbidities, and depression, requiring twice the personal care of disease-free individuals.[15,16] Mortality hazards among RA patients were approximately 60-70% higher than the general population, primarily due to cardiovascular diseases.[15,17] Additionally, caregivers for RA patients suffered from health loss, stress, depression or psychological disturbance, and disruption in their normal schedules.[18]

RA has no cure.[19] The treatment goal of RA is to minimize the inflammation to its lowest level to achieve remission, alleviate symptoms, prevent joint and organ damage, and improve functioning.[19,20] Disease-modifying antirheumatic drugs (DMARDs) are used to delay the

progression of RA.[1] A list of U.S. Food and Drug Administration (FDA)-approved brand-name DMARDs for RA is provided in Appendix 1. As of Feb 2021, more than two dozen brand-name DMARDs were approved by the U.S. FDA for RA. While the first DMARD, etanercept (Enbrel®), was approved in 1998, fifteen DMARDs, including three conventional synthetic DMARDs (cDMARDs), seven biological original DMARDs (bDMARDs), and five targeted synthetic DMARDs (tDMARDs), have been approved since 2009.[21]

Methotrexate, a cDMARD, is commonly preferred as the first-line therapy for RA. A significant portion of RA patients with methotrexate (25%-40%) attained low disease activity or remission in the early stage of the disease.[1,22] However, because of the progressive nature of the disease, some patients who did not achieve remission or the goal of a treat-to-target approach with methotrexate required bDMARDs as monotherapy or combination therapy with cDMARDs.[1,22] Patients who were unresponsive or have an inadequate response to monotherapy or combination therapy of bDMARDs and cDMARDs would be treated with tDMARDs.[23] The first tDMARDs, Janus kinase (JAK) inhibitors, tofactinib (Xeljanz®), was approved by the U.S. FDA in 2012.[24] Although other drugs, e.g., non-steroid anti-inflammatory drugs (NSAIDs) or glucocorticoids, may be used to alleviate RA symptoms, they do not prevent disability progression. Therefore, they are recommended to be used at the lowest possible dose and for the shortest possible time due to serious side effects.[1,3,22]

Several studies demonstrated that RA caused a substantial economic burden on the U.S. healthcare system.[25-32] A recent study estimated RA-related healthcare costs at $33.8 ($28.9 to $37.7) billion in 2016 dollars.[28] Indirect costs due to absenteeism or productivity loss, or disease-related disabilities also contributed to a significant economic burden for patients with RA.[33] In a previous study, RA's indirect costs were estimated to be approximately $10.9 billion in 2005

dollars.[25] Additionally, a study indicated that RA patients missed a significantly higher number of workdays (14 days per year) compared to those without RA (10 days per year), and the incremental per capita cost for annual lost workdays for RA patients was $596.[34] This amounted to the indirect cost of $257 million annually in 2008 dollars.

High costs of bDMARDs and tDMARDs made a significant portion of the total RA costs.[23,35] A study suggested that $28.4 billion in 2016 dollars, or 84% of the healthcare cost of RA patients in the U.S., was attributed to DMARDs.[28] Based on a systematic review, the estimated total annual direct medical costs per patient were $3,723 for all RA patients and $20,262 for those using DMARDs in 2015 dollars.[31] Additionally, spending on total healthcare per specialty medication (e.g., bDMARDs) user was $14,570 higher than traditional medication (i.e., non-bDMARDs) user.[36]

Over time, the increase in spending related to DMARDs has impacted RA's annual direct health costs. A study estimated that, between 2012 and 2017, Medicare drug spending on cDMARD increased from $98 million to $579 million, whereas the expenditure on bDMARDs increased from $4.3 to $10 billion.[37] On the other hand, recent advancements in DMARDs might help patients to lower the indirect costs of RA by achieving treatment goals, including remissions and improving labor force participation.[38] Some direct cost components also decreased. For instance, a study reported a significant reduction in the excess hospital days and emergency department visits for RA patients from 1997 to 2006 was potentially attributed to the introduction of new DMARDs.[39] Additionally, a recent systematic review suggested that costs for hospitalization among RA patients systematically decreased over time.[33] In other words, recent advancements made in RA management with DMARDs might shift the contribution of each cost component for the economic burden of RA.

However, previous cross-sectional studies to estimate RA's economic burden failed to capture the changing dynamics of RA costs with the introduction of high efficacy and high-cost DMARDs.[25,34,40-42] Also, most did not include indirect costs, which could be a major source of economic burden.[28,31,33,35,43] It was suggested that if studies did not incorporate or appropriately measure the indirect costs, they would underestimate RA's full economic impact.[33,38] To our best knowledge, two previous studies published in 2012 estimated the economic consequences or trends of RA over time.[39,44] First study used Medical Expenditure Panel Survey (MEPS) data (2004-2006) to estimate RA's economic consequences.[44] This study included the indirect costs (i.e., work absenteeism, workforce participation, and income effect).[44] Another study used administrative claims data from the privately insured population (1997-2006).[39] Medically related absences and disability were used as the indirect workplace costs.[39] However, these studies were outdated and did not capture the economic impact of DMARDs launched in the past decade. Thus, there was a need to examine the trend in the expenditure for RA, for patients with RA in the U.S. A comprehensive study on the change in the expenditure for RA and the contribution of individual cost components, including drug costs, would allow policymakers to predict the future RA-related costs and make informed decisions to allocate healthcare resources appropriately.

Furthermore, despite the availability of multiple DMARDs, the prices for brand-name DMARDs had historically increased.[43,45,46] For instance, the median total costs of Enbrel® (etanercept), Humira® (adalimumab), Orencia® (abatacept), Simponi® (golimumab), and Xeljanz® (tofacitinib) increased by 133% ($1862 to $4334), 124% ($1940 to $4338), 55% ($2482 to $3777), 107% ($1978 to $4094) and 79% ($2,108 to $3757) from 2012 to 2017, respectively.[46] Market exclusivity, either in the form of regulatory exclusivity or patient-related exclusivity, allowed manufacturers to set high drug prices and practice monopoly for brand-name drugs.[47,48]

Additionally, a study showed the list prices of tumor necrosis factor (TNF) alpha inhibitors increased by 166% from 2007 to 2018. In contrast, the discounts only increased by 56% and could not offset the price increases.[49] Despite having health insurance, a study showed that high drug costs increased patients' out-of-pocket costs, e.g., deductible, leading to lower patient access and adherence to prescription drugs, including RA drugs, and suboptimal outcomes.[28] Also, a study suggested that about 95% of health plans required prior authorization for bDMARDs.[50] Those RA patients, who were uninsured or could not pay for cost sharing, e.g., deductible, copayment, and coinsurance, were forced to pay for DMARDs at pre-rebate pharmacy list prices.[51,52]

Introducing competition through new product entry was often discussed as one of the possible solutions to curve rising prices.[52,53] However, the evidence to support this argument remained poor. While a previous study suggested that the prices of brand-name drugs in the U.S. market increased with the entry of new products, only one study explicitly assessed the influences of new product entry on DMARDs' rising prices. It used a TNF inhibitor as a case study.[45] The impact of new DMARD entry on the price trend of existing brand-name DMARDs was not examined.

Also, while the increasing prices could be a key driver for higher DMARD costs and were targeted by policymakers[54], value assessment has been used to increase patient access to DMARDs. Primarily, cost-effectiveness analysis (CEA) with quality-adjusted life-year (QALY) was used to assess the values of DMARDs.[55-58] However, the QALY metric is controversial. It is a single-dimensional generic health measure and fails to incorporate patient preference and heterogeneity of preference during the assessment and reimbursement decisions.[59,60] As a previous study suggested, patients had unobserved heterogeneity in taste or preference for DMARDs' attributes.[61] Other issues, including failure to consider equity or unmet need, non-monetary

benefits, and oversimplification of the complex issue as such health during the value assessment, also limited the CEA with the QALY application.[59,62] The 2015 American College of Rheumatology (ACR) guideline for RA treatments suggested that treatment decisions should be made through a shared decision-making process between patients and their clinicians, considering patients' preferences.[22]

Discrete choice experiment (DCE) is a stated preference method used to capture health preferences that are not captured by the widely used value assessment tool, such as CEA with QALY. If cost is included as one of the attributes, DCE can estimate the willingness to pay (WTP), a monetary welfare measure to estimate the preference-based value for DMARDs.[63,64] A systematic review[65] showed that two previous studies used a DCE to examine patients' preferences for DMARDs,[66,67] but these studies did not explicitly examine the heterogeneity of preference. The other five studies used conjoint analysis (CA).[68-72] However, literature indicated that the CA is generally inconsistent with economic theory and unsuitable for applied economics.[73] Another study used DCE to examine the value of DMARDs based on patients' preferences or WTP and preference heterogeneity.[61] However, this study was conducted in 2009 before several new DMARDs, e.g., sarilumab (Kevzara), oral baricitinib (Olumiant®) and oral upadacitinib (Rinvoq®) with different risk and benefit profiles, were launched to the U.S. market. More importantly, several studies indicated that fatigue is a crucial outcome domain for RA patients.[74-76] Qualitative interviews conducted by Innovation and Value Initiative (IVI) and Arthritis Foundation recently reported that fatigue was one of the important domains patients with RA factored in their choices of DMARDs. However, none of the previous patient preference studies included fatigue and therefore provided an incomplete picture of patient preferences for DMARDs. Thus, there was a need to examine preference-based values for DMARDs.

1.2 Objective and Specific Aims

The long-term goal of this study is to increase patient access to affordable and preferred DMARDs and facilitate informed choices consistent with patients' goals and values. The objective of this study is to determine the changes in expenditure and prices and assess the preference-based value of DMARDs. This study proposed the following specific aims.

Specific Aim 1: To determine the expenditure for RA in the nationally representative U.S. population between 2008 and 2020 from the societal perspective. A serial cross-sectional design was used to estimate the expenditure for RA from the average annual cost per person, including both direct and indirect costs, for the RA cohort, compared to the no-RA (control) cohort, using two-part models.[81,82] The study hypothesized that the expenditure of the RA cohort was higher than no RA cohort, primarily due to the prescription drug cost.

Specific Aim 2: To determine the impact of new brand-name DMARD entry on the price trend within the three classes of DMARDs. Segmental regression analyses of the interrupted time series data were used to determine the effects of new product entries on the brand-name DMARDs' price trends. We hypothesized that the prices of existing DMARDs increased when new brand-name DMARDs entered the market.[53]

Specific Aim 3: To assess the preference-based value of DMARDs for RA. A cross-sectional DCE was used to determine the relative importance of the attributes of DMARDs, including the heterogeneity of preference and patients' WTPs for DMARDs. This study hypothesized that the chance of pain reduced by 50% or more, the chance of physical function improved by 50% or more, the chance of fatigue reduced by 10 points or more, the chance of serious side effects, the way you take the medication, and out-of-pocket cost per month were associated with patients' preferences for DMARDs.

1.3 Innovation of this study

This study included several novel contributions. After more than a dozen DMARDs were launched in the past decade, this study evaluates the contribution of the drug costs to the overall RA costs, which comprised the direct and indirect costs of RA, and to assess the preference-based value of DMARDs. Also, it was the first preference-based value assessment of DMARDs to assess the value of fatigue reduction. The study comprehensively examined how introducing new brand-name DMARDs affected the pricing trends of existing brand-name DMARDs. The study demonstrated an economic survey of the expenditure, price, and value of the drug, which should be simultaneously considered when treatment decisions or policies are made. This study used multiple data sources and various analyses, i.e., a serial cross-sectional analysis, an interrupted time series, a mixed logit model, and a latent class model, to examine the expenditure, prices, and preference-based value of DMARDs for RA patients in the U.S.

1.4 Significance of the study

The study results were significant in different ways for patients, clinicians, payers or policymakers, and the pharmaceutical industry. First, the knowledge regarding the trend in RA-related costs and each component's contribution could be used to estimate future RA-related costs. The results would help payers or policymakers (e.g., Centers for Medicare & Medicaid Services) allocate healthcare resources to ensure the sustainability of the U.S. healthcare system. Second, the information from the impact of new DMARD entry on the price trend of existing DMARDs would help payers or policymakers prepare resources or introduce policies, e.g., value-based reimbursement, when any new DMARDs are launched to the market and highlight the potential accessibility challenges to ensure patient access to DMARDs. Third, the preference-based value of DMARDs would inform clinicians and patients when they make treatment decisions and support

payers or policymakers for reimbursement decisions. Specifically, the patients' preferences for DMARDs could be used to develop treatment guidelines.[77] The value of DMARDs, based on patients' preferences and heterogeneity of preference, could be used to design value-based reimbursement to improve patient access to affordable and preferred DMARDs. The pharmaceutical industry could also use the patient preference results to design future DMARDs that meet patients' needs.

Chapter 2 Literature review

2.1 Rheumatoid arthritis (RA)

RA is the most common chronic, inflammatory, autoimmune disease of joints.[1-3] In RA, the synovial membrane is infiltrated by the T-cells, B-cells, and monocytes, leading to the expansion of the synovial lining.[1] This expanded lining invades the bone at a bone-cartilage junction, leading to bone erosion and cartilage destruction.[1] The clinical manifestation of RA includes inflammation and swelling of synovium, joint pain, antibody production (rheumatoid factor, RF, and anti-citrullinated protein antibody, ACPA), and cartilage bone destruction (deformity).[1,2,4] RA predominantly affects small joints, such as joints in the hands, knees, or ankles, or those in multiple joint areas on both sides of the body.[5,6] Pain and swelling are often accompanied by joint stiffness that usually lasts 30 minutes or more and lasts six weeks or longer.[1,5] However, RA is a heterogeneous disease. Thus it can manifest different clinical presentations and pathological mechanisms across individuals.[3] If RA is left untreated, it can also have systemic effects, e.g., effects on the heart, lungs, and skeleton, leading to serious physical impairment, comorbidities, and premature mortality primarily due to cardiovascular complications.[1,2,4,6,7]

No gold standard diagnostic criteria for RA exist.[3,78] However, the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Collaborative Initiative provides classification criteria to identify RA patients based on the number of joints involved, serological test, acute phase reaction, and duration of symptoms (Table 1).[78] Patients with a score of six or higher are considered to have RA.

Table 1. The 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for rheumatoid arthritis

		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 the score of categories A–D; A score of >=6/10 is needed for the 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

Abbreviations: ACPA, anti-citrullinated protein antibody; CRP, C-reactive protein; ESR,

Erythrocyte sedimentation rate; RF, rheumatoid factor

The exact cause of RA remains largely unknown. However, patient-related characteristics (e.g., gender, smoking, and obesity), genetic factors, environmental factors, periodontal disease, and immune response were identified as the major risk factors.[2,3,6,79] RA was more common in people with older age (prevalence 2% for age 60 and older and 0.5-0.55% for the general population).[13] Women were two to three times more likely to be affected by RA than men (prevalence 3.6% for women and 1.7% for men), and native Americans were at higher risk (prevalence 5% for native Americans and 0.5-0.55% for the general population).[3,12,14] Smoking tobacco raised the risk of acquiring RA by two folds.[80] Obese individuals were 1.3 times more likely to develop RA.[81] For twins, studies showed that the heritability of RA was approximately 60%.[82,83] Silica or textile dust exposure was also associated with the increased risk of RA.[84,85]

Globally, 20 million people were affected by RA, with an age-standardized prevalence rate of 246.6 per 100,000.[8,9] In other words, RA occurred in five per 1000 adults worldwide.[1] Globally, the age-adjusted point prevalence rate for RA increased by 7.4% from 1990 to 2017.[9] In developed countries, approximately 0.5-1% of the adult population was diagnosed with RA.[3] In the U.S., the prevalence of RA among the adult population was estimated to be 0.53 to 0.55% (1.28-1.66 million patients).[10,11,32,86]

There are various consequences of RA. RA causes progressive disability, systematic complications, and early death, associated with higher socioeconomic costs.[2,3] RA patients could be forced to live with a disease-related disability, psychological impairment, comorbidities, and depression.[15] They were twice in need of personal care compared to that disease-free individuals.[16] Mortality hazards, most commonly due to cardiovascular disease, were approximately 60-70% higher among RA patients than in the general population.[15,17] The patients and the caregivers of

RA patients also suffer from health loss, exhibit stress, depression or psychological disturbance, and disruption in their normal schedule.[18] Also, healthcare resources required for RA management were significant to society.[28]

2.2 Overview of RA treatments

Currently, there is no cure for RA.[3,19] The treatment goal is to improve functioning, prevent joint and organ damage, and reduce inflammation to its lowest level until there is no visible sign and symptom (remission).[19,20] The ACR/EULAR task force defined the remission as a tender joint count, swollen joint count, C-reactive protein level (mg/dl), and patient global assessment of ≤1 each or a simplified Disease Activity Score (DAS) of ≤3.3, 1 of 6 ACR-endorsed disease activity measures.[22]

Pharmacological treatments for RA include NSAIDs, glucocorticoids, and DMARDs.[7,22] NSAIDs, such as ibuprofen, diclofenac sodium, or celecoxib, are used for the symptomatic relief of pain, stiffness and the improvement of physical function in RA. However, these drugs do not prevent disease progression.[1,3] Glucocorticoids, such as prednisolone, are administrated along with DMARDs to offer rapid symptomatic relief and disease-modifying effects.[1] However, given the serious nature of side effects associated with glucocorticoids, they are only recommended for the shortest period (three to four months).[1,3]

DMARDs can reduce structural damage and prevent disease progression.[1] DMARDs are classified into two types: synthetic DMARDs, which are small chemical molecules given orally, and bDMARDs are proteins administered parenterally.[1] Synthetic DMARDs are further categorized into cDMARDs that are not based on a specific mechanism of action and tDMARDs that have target-specific molecular structures.[87] Each DMARD has a unique mechanism of action that ultimately interferes with inflammation pathways.[88] The ACR classification of DMARDs,

along with the route of administration and recommended dosage, are listed in Table 2.[89]

ACR and the EULAR have put forth the guidelines for RA management with DMARDs.[22] Although the recommendation in the guidelines may vary for patients with early RA (disease/symptom of < 6 months), established RA (disease/symptom of ≥ 6 months), or with high-risk comorbid conditions, the overall objective of RA treatment is to obtain low disease activity or remission using the treat-to-target approach.[22,90] The treat-to-target approach recommends setting up a disease activity target (remission or low disease activity) in all patients upon the start of therapy. It is to be reviewed at the end of three to six months.[91]

Table 2. ACR classification, route of administration, and recommended dosage for FDA-approved DMARDs

DMARDs	Route	Recommended dose	Ref
Abatacept	SC, IV	Use as monotherapy or with DMARDs other than TNFα inhibitors; iv infusion dosed by weight [<60 kg 500 mg, 60100 kg 750 mg, >100 kg 1000 mg], at weeks 0, 2, and 4, then every 4 weeks or 125 mg SC injection once weekly	56
Adalimumab	SC	40 mg every other week; some patients not receiving MTX may benefit from taking 40 mg every week	56,58
Baricitinib	O	2 mg once daily	58
Certolizumab	SC	With or without concomitant MTX, 400 mg at Weeks 0, 2, and 4, followed by 200 mg every other week: for maintenance dosing, 400 mg every 4 weeks	56
Etanercept	SC	50 mg once weekly with or without MTX	56
Golimumab	SC, IV	In combination with MTX, 50 mg SC injection once a month or 2 mg/kg iv infusion at weeks 0 and 4, then every 8 weeks	56
Hydroxychloroquine	O	400 mg to 600 mg daily. Maintenance dose: 200 mg to 400 mg daily.	92
Infliximab	IV	In combination with MTX, 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks; may increase dose up to 10 mg/kg or treat as often as every 4 weeks	56
Leflunomide	O	20 mg once daily	92
Methotrexate	O	2.5 mg	56,58

Rituximab	IV	In combination with MTX, two-1000 mg iv infusions separated by 2 weeks every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks	[56]
Sarilumab	SC	150 mg-200 mg every 2 weeks	[93]
Sulfasalazine	O	2 g daily in evenly divided doses.	[92]
Tocilizumab	SC, IV	In combination with DMARDs or as monotherapy, start with 4 mg/kg every 4 weeks followed by an increase to 8 mg/kg every 4 weeks based on clinical response; 16 2mg subcutaneous injection every other week, increased to every week based on clinical response (or if patient weighs ≥100 kg)	[56]
Tofacitinib	O	5 mg twice daily or 11 mg once daily (extended-release form)	[58]
Upadacitinib	O	15 mg once daily	[58]

Abbreviations: IV, Intravenous; O, Oral; SC, Subcutaneous

Both guidelines suggest methotrexate as the first-line therapy for treatment naïve patients. Many patients showed significant improvement with methotrexate monotherapy (approximately 25-40%) or in combination with glucocorticoids (over 50%).[1] In case of treatment failure to methotrexate or in patients with moderate or high disease activity, bDMARDs or tDMARDs are recommended as an add-on therapy to methotrexate or as the first-line therapy to achieve targeted responses.[1,22] Treatment is to be continued even after achieving remission.[22]

2.3 Economic burden of RA

Numerous studies indicated that RA is associated with a significant economic burden to the patients, caregivers, and society in the U.S.[25-28,30,31,94-98] Direct, indirect, and intangible costs contributed to the total economic burden of RA.[99-102] The direct costs include medical visits and prescriptions, e.g., hospitalization, clinic visits, laboratory monitoring and imaging, medical assistive device, treatment, detection, and prevention.[97,99,102,103] Loss of work capacity due to a disability, cost of family members, formal or informal caregiving and absenteeism, etc., are categorized as indirect costs.[25,97,99,102-104] Finally, the intangible costs include costs arising from pain, frustration, lack of self-esteem, depression, anxiety, and quality of life deterioration.[25,99,102,103]

Previous studies indicated that RA-related total economic burden ranged from $39.2 to 52 billion dollars.[25,95,97] For instance, a study published in 2010 reported the total societal cost of RA to be $39.2 billion (in 2005 dollars).[25] Similarly, a review published in 2008 reported that the total cost for RA in the U.S. was $51 billion in 2006 dollars with an average annual cost per person of $25,700.[97] Additionally, a recent systematic review estimated the all-cause total healthcare cost for RA in the U.S. to be $52 billion per year, in 2019 dollars.[95]

In general, the direct costs contributed the highest to RA's economic burden and ranged from $8.4 billion to $40.5 billion.[25,28,95,97] For instance, a recent systematic review suggested the RA-related direct costs be $40.5 billion in 2019 dollars with annual costs per person ranging from $13,800 to $24,255.[95] Similarly, a study estimated that the direct health care spending for RA to be 33.8 (28.9-37.7) billion in 2016 dollars.[28] Two other studies reported $8.4 billion in 2005 dollars and $22.3 billion in 2008 dollars for the RA-related direct costs with an annual cost per person of $13,012.[94] Another study reported that the direct costs accounted for 28 billion in 2006 dollars with the mean annual direct cost per-person of $14,219.[97] Furthermore, various studies for RA estimated the total annual direct cost per patient ranged from $1,967 to $13,549.[26,27,30,96,98,105]

The indirect costs also comprised a substantial portion of the economic burden for RA. Previous studies suggested that the indirect costs ranged from $252 million to $14.8 billion.[25,34,95,97] For instance, a systematic review reported that the indirect costs resulting from absenteeism and earning loss accounted for $298 million ($704 per person per year) and $14.8 billion ($9,896 per person per year), respectively.[95] A study reported the indirect costs at $11 billion in 2006 dollars ($5,351 per person per year).[97] One study estimated the indirect costs at $10.9 billion in 2005 dollars.[25] A study estimated the indirect costs of RA-related absenteeism at $252 million annually in 2008 dollars ($596 per person per year).[34] Similarly, another study estimated

that the indirect costs due to the annual loss of earnings of patients with RA were between $2,319 and $3,407, with an overall reduction of household income by $6,287 in 2002 dollars.[106] Moreover, other systematic reviews for RA estimated that the total indirect cost per patient ranged from $1,367 to $41,248.[27,98]

Additionally, the intangible costs of depression and multimorbidity, such as cardiovascular disease, increased RA's economic burden. A study estimated the intangible costs for RA at 19.9 billion in 2005 dollars.[25]

Thus, the direct, indirect, and intangible costs would contribute to the economic burden for RA. Economic studies that included only the direct costs would underestimate the full economic impact of RA.[33,38]

Shifting trend in the economic burden of RA

Despite the availability of previous studies on the economic burden of RA, additional information is needed to support policy decisions. Various studies conducted cross-sectional analyses to examine the economic burden of RA. However, they failed to capture the RA costs across time, which could change due to the rapid advancement and relatively high spending of DMARDs.[25,34,40-42] Previous systematic reviews indicated the shift in the cost components over time.[33] For instance, a systematic review suggested a decreasing trend in the inpatient costs while signaling a cost shift towards the other components of the direct costs.[33] Another review study reported that the advancement of treatments could shift the direct medical costs of RA, primarily due to the increase in expensive DMARDs.[97] However, given the variation in methods and sample sizes across these studies and slight differences in the change in RA management during the study periods, they failed to reveal any changes across time. Additionally, Institute for Clinical and

Economic Review (ICER) reported that a point-in-time measure would fail to capture the lability of RA as the disease burden varied over time.[56]

Several studies assessed the shifting trend in the economic burden of RA patients in the U.S.[39,44,97,107] In 2012, a study examined the change in the costs for patients with RA between 1997 to 2006 and suggested that the excess per-patient direct costs were unchanged. The drug costs increased by $633 per patient, but the medical costs decreased by $618 per patient in 2006 dollars.[39] The study also suggested an increase in the number of emergency department visits by 1.1 visits per patient. The number of days hospitalized decreased by 0.9 days per patient, while the rheumatologist visit increased by 0.9 visits per patient.[39] Similarly, a study reported the total medical cost for older Medicare beneficiaries with RA did not increase significantly over time ($16,563 in 2000 vs. $19,510 in 2006).[101,107] However, the total prescription drug costs increased from $2,645 in 2000 to $4,685 in 2006 dollars.[107] Another study estimated the healthcare costs of RA at $4422, $2903, and $1882 in 2004, 2005, and 2006, respectively.[46] However, individuals with RA were less likely employed by 36.8%, 39.5%, and 44%, compared to 70.5%, 69.8%, and 71% for those without RA in 2004, 2005, and 2006, respectively. Also, RA significantly reduced incomes by $2,404, $2,207, and $1,212.[46] The individuals with RA also missed more workdays 4.86, 1.70, and 2.99.[46] However, these studies mostly examined only the direct costs or assessed the trend until 2006.[39,44,97,107] They likely either underestimated the full impact of RA since the indirect costs could be a major source of economic burden for patients with RA or failed to capture the recent RA costs with the advancement of DMARDs in the last decade.[31,33,36,43]

Thus, there was a need to conduct a study to assess the change in expenditure for RA, including the direct and indirect costs of RA patients over time in the U.S. Knowledge regarding the change in RA-related costs and the contribution of each component could be used to estimate

future RA related costs. This would also help decision makers prioritize healthcare resources to ensure the sustainability of the U.S. healthcare system.

2.4 Economic burden of DMARDs.

DMARDs made a significant portion of RA-related healthcare costs.[28,31,97,108,109] A recent study reported that prescription drugs, primarily DMARDs, accounted for 84% of the RA healthcare cost or $28.4 billion (in 2016 dollars) in the U.S.[28] A systematic review also suggested that drug costs, including DMARDs, were the main component (up to 87%) of the direct costs for RA that had an increasing trajectory over time.[33] Other studies supported these findings by highlighting that the contribution of prescription drugs could range from 66%-74.6%.[75,108] Particularly, the use of costly bDMARDs was associated with higher healthcare costs. A systematic review and meta-analysis reported that the all-cause total direct medical costs for the RA patients using any treatment regimen were $12,509 ($7,451–$21,001), and for those using bDMARD was $36,053 (32,138–40,445) in 2015 dollars.[31] The RA-specific costs were estimated at $3,723 (2,408–5,762) for those patients using any treatment and $20,262 (17,480–23,487) for those using bDMARD.[31] In 2019, a study reported that the average total healthcare costs for a traditional medication user and a specialty medication user were $10,809 and $16,716 in 2015 dollars, respectively.[36]

Table 3. Annual acquisition cost for DMARDs

DMARDs	Route	Dose	Annual WAC	Ref
Abatacept	SC, IV	125 mg (SC), 250 mg (IV)	$27,637 (IV), $42,306 (SC)	[56]
Adalimumab	SC	40 mg	$40,415-$67,263	[56,58]
Baricitinib	O	2 mg Tab	$26,017	[58]
Certolizumab	SC	200 mg	$34,775	[56]
Etanercept	SC	50 mg	$40,422	[56]
Golimumab	SC, IV	50 mg	$34,863 (SC), $29,719 (IV)	[56]
Hydroxychloroquine	O	200 mg	$240-$9154*	[92]
Infliximab	IV	100 mg	$28,906 (iv)	[56]

Leflunomide	O	20 mg	$1825-$16546*	[92]
Methotrexate	O	2.5 mg	$796-$1,155	[56,58]
Rituximab	IV	100 mg	$30,764 (IV)	[56]
Sarilumab	SC	200 mg	$39,000	[93]
Sulfasalazine	O	2 g	$269-$2215*	[92]
Tocilizumab	SC, IV	162 mg (SC), 20 mg (IV)	$27,627 (IV), $21,861 (SC)	[56]
Tofacitinib	O	5 mg Tab	$54,552	[58]
Upadacitinib	O	15 mg Tab	$59,860	[58]

Abbreviations: IV, Intravenous; O, Oral; SC, Subcutaneous; WAC, Wholesale Acquisition Cost. **Note:** Annual acquisition cost was calculated based on Micromedex Red Book price for the year 2021.

Table 3 shows the annual wholesale acquisition cost (WAC) for DMARDs.[56,58,92] From the table, biological agents ($21,861-$67,263) were substantially more expensive than conventional DMARDs ($240-$16546). A systematic review supported this evidence and suggested that the annual cost for the conventional agent was $1,500-2,000, while the cost of the drug for biological agents was $30,000 per year.[31] The WAC of newer target-specific molecules or tDMARDs ($26,017-$59,860) were as high as bDMARDs.

The costs of DMARDs also increased over time, primarily due to the price increase.[29,37,43,110] A study suggested that the annual spending on ten bDMARDs doubled from 2012 to 2016 ($3.8 billion to $8.6 billion in 2016 dollars) for Medicare part D and Medicaid.[110] The increase in unit price alone accounted for 57% of the increased cost, whereas only 37% was due to increased uptake.[110] Similarly, a recent study estimated that the total Medicare spending on cDMARDs increased by five folds from $98 million to $579 million. In contrast, the expenditure on bDMARDs increased from $4.3 billion to 10 billion between 2012 to 2017.[37] The increase in this spending was largely driven by the unit costs of drugs rather than the number of beneficiaries.[37] A study also reported that bDMARDs costs among the privately insured population increased from $166 million in 2004 to $243 million in 2013; however, such an increase was due to increased utilization of bDMARDs.[43] Additionally, another study suggested that five of the 49 top-selling

brand-name prescription drugs in the U.S. were drugs used for RA, including Enbrel®(etanercept), Humira®(adalimumab), Orencia®(abatacept), Simponi® (golimumab), and Xeljanz®(tofacitinib). Their median total costs (sum of the out-of-pocket cost paid by a plan member and cost paid by the insurer) increased by 133% ($1862 to $4334), 124% ($1940 to $4338), 55% ($2482 to $3777), 107% ($1978 to $4049), and 79% ($2108 to $3757) from 2012 to 2017, respectively.[48]

Despite having insurance, prior authorization, step therapy, and cost-sharing as cost-control measures could still reduce patient access to DMARDs.[29,46,52,111,112] A study suggested that about 95% of health plans required prior authorization for bDMARDs.[50] Additionally, higher prices increased patients' out-of-pocket cost[29,51,52,111] and deductible[28], ultimately leading to lower patient access and adherence[113-115] and suboptimal treatment-related outcomes. A study indicated the average annual out-of-pocket cost per person for bDMARDs of an average plan for 2000-2005 was $1,518 under the medical benefit and $426 under the pharmacy benefit.[116] Another study suggested that Medicare part D beneficiaries out-of-pocket costs increased from $4,026 in 2011 to $4,801 in 2019, primarily due to an increase in the list price as Medicare part D beneficiaries paid 25% of the brand-name list price in the coverage gap.[29] The same study reported that the mean annual out-of-pocket costs for Medicare Part D patients taking specialty biologics for RA were $4,801 in 2019 dollars.[29] Furthermore, the RA patients, who were not able to pay for cost sharing or were uninsured, were forced to pay the DMARD costs based on the pre-rebate pharmacy list price, reducing their access to DMARDs.[51,52]

New product entry and price trend for DMARDs

Mostly, price increase for existing brand-name drug was the reason for the rising cost of drugs.[117] Patent protection provided brand-name drugs with greater negotiating power and market monopoly to increase prices.[47,118,119] An increase in the number of competitors was proposed as

one solution to curve the increase in drug prices.[52,53] However, a recent systematic review suggested that brand-brand competition in the same class did not lower drug prices.[53] Previous studies showed that the prices of injectable anticancer drugs and disease-modifying therapies (DMTs) for multiple sclerosis increased regardless of competition.[120]

Despite the availability of multiple competing products, the prices increased over the years for DMARDs.[45,46,49] A study on the price trend for popular brand-name prescription drugs, including that of DMARDs, suggested that prices of Enbrel® (etanercept), Humira® (adalimumab), Orencia® (abatacept), Simponi® (golimumab), and Xeljanz® (tofacitinib) increased by 133% ($1,862 to $4,334), 124% ($1,940 to $4,338), 55% ($2,482 to $3,777), 107% ($1,978 to $4,094) and 79% ($2,108 to $3,757) from 2012 to 2017, respectively.[46] Another study reported that the list and net prices of TNF alpha inhibitors increased by 166% and 73%, respectively. In contrast, the discount only increased by 56% from 2007 to 2018.[49] However, these studies did not capture the effect of the new DMARD entry on the price trend of existing DMARDs. One study assessed the influence of new DMARDs on the existing price trend, but it only used TNF inhibitors as a case study.[45] Thus, there was a need to assess the impact of the new DMARD entry on the existing price trend across all DMARDs, including cDMARDs, bDMARDs, and tDMARDs. This information would help decision makers introduce value-based pricing and reimbursement policies when new DMARDs are launched to the market to ensure patient access to DMARDs.

2.5 Value of DMARDs.

Cost-effectiveness analysis studies of DMARDs

Increasing prices can be a key driver for higher costs and a barrier to patient access to DMARDs.[54,112] Value assessment can improve patient access by assisting in decision making for efficient resource allocation and informing price negotiation and coverage or reimbursement

decisions.[112,121,122] Different value assessment frameworks from various institutions, such as the American College of Cardiology (ACC)/American Heart Association (AHA), the American Society of Clinical Oncology (ASCO), the Institute for Clinical and Economic Review (ICER), the Memorial Sloan Kettering Cancer Center (MSKCC), and the National Comprehensive Cancer Network (NCCN), are available in the U.S.[123] Among these frameworks, CEA with QALY is widely used to assess the value of DMARDs.[55-58]

Briefly, CEA is a tool to quantify the relative benefits and costs among two or more alternatives used to aid decisions.[62,124] CEA helps payers determine if the value/benefit of an intervention or a treatment justifies its costs.[125] Generally, an incremental cost-effectiveness ratio (ICER) is calculated in CEA. The denominator of ICER is a gain in health (benefits of intervention A-benefits of intervention B), and the numerator is the costs associated with the health gain (cost of intervention A-cost of intervention B).[62] The most frequently used benefit measure is a quality-adjusted life year (QALY).[123]

Previously, various systematic reviews[55,57] and reports[56,58] summarized the findings for the cost-effectiveness analyses of DMARDs. For instance, a report for the effectiveness and value of JAK inhibitors and biosimilars suggested that the ICER of the upadacitinib and adalimumab was approximately $92,000 per QALY, and it lied below the cost-effectiveness threshold of $150,000 per QALY.[58] When comparing the outcomes of adalimumab and tofacitinib to their respective cDMARD comparators, QALY gains were similar to cDMARD. Still, adalimumab and tofacitinib were found to be of higher costs.[58] Another study suggested that, compared to conventional DMARDs, the lowest ICER was observed for tocilizumab ($168,660 per QALY), which was higher than the cost-effectiveness threshold of $150,000 per QALY.[56] When compared to the most commonly used DMARD (adalimumab), tocilizumab monotherapy was less costly and more

effective, while etanercept was more costly with the ICER of approximately $103,000 per QALY gained.[56]

However, the CEA with QALY as an outcome measure to assess value is controversial since QALY is a single-dimensional generic health measure and fails to capture patient preference and heterogeneity of preference.[59,60] CEA was performed using the population average, and it had limited flexibility to account for patients' heterogeneity.[59] QALY also failed to consider various elements of value, such as equity or unmet need.[59] Also, the variation in the cost-effectiveness threshold values, ranging from $100,000 to $150,000 per additional QALY in the U.S., could lead to different inferences for cost-effective treatments, thus adding complexity in the decision making process.[62]

Patients' preferences and preference studies for DMARDs

Patient's preference is defined as the "qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions".[126] Patient's preference involves measuring the patient's value for a specific component, or attribute, either in absolute terms or to another attribute.[127] Patient's preference was increasingly used in healthcare policy decisions and treatment recommendations.[22,89,128,129] Specifically, preferences could be applied in benefit-risk assessment (BRA), pricing, and clinical care decisions.[130,131]

The 2015 American College of Rheumatology (ACR) Guideline for the treatment recommendation using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria for RA also suggested that treatment decisions should be made through a shared decision-making process between clinicians and patients, considering the patients' values and preferences.[22,89] Taking this into consideration, the updated ACR recommendation guidelines

include patient's preference and value as one of the criteria in making treatment recommendations for RA.[89] Similarly, the U.S. FDA guidance for the voluntary submission of patient preference information for the pre-market approval highlighted the need for incorporating patient preference information in the value assessment and pre-market approval.[129] There was evidence that the FDA could use patient preference information to conduct pre-market clinical studies, benefit-risk assessments, and post-market evaluations of medical devices.[126] Additionally, Medical Device Innovation Consortium (MDIC) Patient-Centered Benefit-Risk (PCBR) framework was developed to recognize the need to incorporate the patient perspective into the regulatory approval process and in the reimbursement, marketing, and shared medical decision.[132] PCBR framework suggested that, of many other applications, patient preference information could be used to frame the benefit-risk issues, to identify patients who would prefer the use of a particular technology, and to provide the information to build a quantitative benefit-risk model.[132]

Furthermore, given the vast array of DMARDs with varying mechanisms of action, no superior treatment, the need for multiple successive therapies throughout the life of RA patients, and DMARD costs, patient's preference might vary across individuals (i.e., preference heterogeneity). Such heterogeneity could come from not only observable sociodemographic characteristics (i.e., age, gender, or income) but also unobserved variables or attributes that were difficult to measure.[61] The U.S. FDA recognized the importance of capturing heterogeneity while considering patient preference information.[129] Similarly, the EULAR guideline recommended considering preference heterogeneity in making a treatment decision for RA.[90] Hong Kong Society of Rheumatology also recommended that the treatment decision for RA should be tailored to individual patients, considering various factors, such as disease activity, comorbidities, prognostic factors, safety, cost, and patient's preference.[133] Thus, eliciting and incorporating patient's

preference and heterogeneity of preference into the value assessment of RA treatments are important.

Two different methods, including revealed preference and stated preference, are used to elicit patients' preferences.[134] The revealed preference provides information on the choice made by a patient in the real-world setting and is measured using observational data.[132,135] On the other hand, stated preference elicits preferences from hypothetical options and is elicited in an experimental framework.[132,135] Although the revealed preference method offers the advantage of predicting actual behavior and incorporates the clinical and emotional aspects of the decision, it has some limitations.[127] It is not applicable when the drug profile of interest is not yet available or under review.[129] On the other hand, the stated preference method can provide the flexibility of experimental control and can be used to evaluate hypothetical interventions or treatments.[127,136] CA, DCE, best-worst scaling, direct elicitation, and tradeoff technique are most commonly used to elicit stated preferences.[137]

Previously, several literature reviews summarized the patient preference studies for RA treatments in U.S.[65,138] First, a scoping review indicated that eleven studies examined the patients' subjective experiences or revealed preferences for escalating, tapering, stopping, or switching of DMARDs.[138] Among these studies, four of them conducted semi-structured or face-to-face interviews[70,139-141], six studies conducted online survey[142-147], and another study conducted a single-blinded randomized control trial[148] to explore RA patients' preferences. However, studies that evaluated patients' preferences for medication attributes or attributes for DMARDs were not included. Moreover, it was difficult to have the subjective measures, such as attitude, feelings, awareness, knowledge, beliefs, or satisfaction from these studies, to estimate the preference-based value for DMARDs or make decisions.

Table 4 summarizes the patient preference studies for DMARDs in U.S.[65] Among eight studies that elicited patients' preferences for DMARDs, five studies used CA.[68-72] However, literature indicated that the CA is generally inconsistent with economic theory and unsuitable for applied economics.[73] CA was derived from the theory of conjoint management (CM), which is purely mathematical and thus cannot be used to elicit human preference.[73] Two other studies used a DCE to examine patients' preferences for DMARDs among RA patients in the U.S.[66,67] However, these studies did not explicitly examine the heterogeneity of preference. Another study used DCE to examine the value of DMARDs based on patients' preferences (patients' WTP) and preference heterogeneity, but this study was conducted in 2009 and required an update.[61]

More importantly, a systematic review and a study with nominal group technique indicated that fatigue was a crucial outcome domain for RA patients,[74-76] Also, IVI and Arthritis Foundation conducted qualitative interviews and reported that fatigue was one of the important domains patients with RA factored in their choices of DMARDs. However, previous patient preference studies never examined fatigue and therefore provided an incomplete picture of patient preferences for DMARDs.[74]

Table 4. Summary of the methods used in previous studies that elicited RA patients' preferences for DMARDs in the U.S.

Author	Year	Sample size	Objective	Survey	Analysis	Heterogeneity	Treatment characteristics
Fraenkel et.al.[71]	2018	1273	To develop preference phenotypes to facilitate shared decision-making at the point of care for patients failing methotrexate monotherapy.	CA	Latent class analysis	Identified preference phenotype	Route of administration, Onset of action, Bothersome side effects, Serious Infection, very rare side effects, Amount of Information available, Cost
Husni et.al.[66]	2017	510	To quantify the thresholds of benefit-risk trade-offs that patients are willing to accept in the treatment of RA in the U.S.	DCE	Multivariable logistic regression	Conducted subgroup analysis	Reduction in the number of swollen joints, Reduction in pain, Improvement in physical function, Abnormal laboratory results, Cancer, Serious infection, Route of administration, Dose frequency, Out-of-pocket cost per month
Louder et al.,[72]	2016	380	To investigate patient preferences for attributes associated with RA treatments.	CA	Hierarchical Bayes model	Not examined	Route of administration, Frequency of administration, Chance of serious side effects, Monthly cost to you (commercial), Medication burden (taken with another medication), Ability to reduce daily joint pain and joint swelling, Improvement in ability to perform daily tasks and activities

Fraenkel et al.,[70]	2015	156	To examine the influence of subjective numeracy on RA-patient preference for the status quo and to determine whether age modifies this relationship.	ACA	Logistic regression	Examined based on Subjective Numeracy Scale	Decreased joint pain and swelling, Ability to get around and participate in social or leisure activities outside of the house, Slowing or stopping joint damage seen on X-rays, Ability to work, Risk of injection or infusion reaction, Risk of infection, Risk of tuberculosis, Risk of neurologic disease.
Poulos et al.,[67]	2014	901	To quantify the rate at which RA patients are willing to tradeoff between the time required to administer treatment (duration) and treatment frequency.	DCE	Mixed logit	Examined based on Mixed logit model	Change of medicine working, Mode of administration, Time needed for infusion, how often injection/infusions are taken, chance of immediate serious treatment reaction, chance of immediate mild treatment reaction
Constantinescu et.al,[68]	2009	136	To determine whether African American and white RA patients differ in how they evaluate the specific risks and benefits related to medications.	CA	Multivariate logistic regression	Examined based on difference by Race	Remission, Improvement, Radiographic progression, Route, Injection site reaction, Reversible adverse events, Risk of lung injury, Risk of tuberculosis, extremely rare adverse events, Risk of cancer

Özdemir et al.,[61]	2009	463	To analyze the effect of a split-sample, cheap-talk experiment on patients' preferences for rheumatoid arthritis treatments in an SC survey.	WTP	Mixed logit	Examined based on Mixed logit model	Change of efficacy, Onset of effect, Mode/frequency, Irritation, Serious infection, and Cost
Fraenkel et al.,[69]	2004	120	To elicit treatment preferences of patients with rheumatoid arthritis for disease-modifying antirheumatic drugs with varying risk profiles.	ACA	Not clear	Not examined	Route, Physician experience, Onset, Chance of benefit, Bone erosions, Injection site reaction, Rash, Oral ulcers, Alopecia, Nausea/vomiting, Diarrhea, Cancer, Nephrotoxicity, Pneumonitis, Cost

Abbreviation: ACA, Adaptive Conjoint Analysis; CA, Conjoint Analysis; DCE, Discrete Choice Experiment; WTP, Willingness to pay

Discrete choice experiment (DCE) studies of DMARDs

DCE is an attribute-based survey method based on a random utility theory (RUT).[149] RUT assumes that a person has a "perceived utility" or attractiveness for each choice alternative and selects the alternative that maximizes this utility.[73,150] DCE is used to estimate individual preference, assuming that individuals make a rational decision.[150] The relative preference for object A over object B is determined based on the relative frequency in which object A is preferred over object B with some degrees of error. DCE elicits people's preferences for goods and services based on their choices over different hypothetical situations with different levels of characteristics ("attributes") of that goods or services.[151] Instead of ranking or rating different features, DCE compares hypothetical alternatives and asks respondents to choose among them.[152] Thus, the respondents are forced to make tradeoffs between attributes and their levels, allowing them to determine the relative importance of attributes.[153]

DCE-based preference studies have become a commonly used technique to address wide health-related policy concerns.[64,130,131,150,154] DCE has grown in popularity to examine patients' value for important treatment characteristics by understanding the trade-off between the benefits and harms of the treatment.[130,131] The value of treatment characteristics is expressed in terms of preference weights or how much a patient's utility change for one unit change in a characteristic of the treatment. Additionally, if cost is included as one of the attributes, DCE can elicit monetary valuation through the WTP, which may also be used as input in the cost-benefit economic evaluation CEA/CUA to inform the decision.[130,149,155] DCE offers the advantage of eliciting preferences and values for different therapies and treatments that are not yet available in the market.[149] DCE-based studies can also examine the preference heterogeneity using appropriate statistical techniques, such as mixed logit (ML) or latent class analysis (LCA), to support policy

decisions.[156] In reimbursement and health technology assessment, DCE can elicit patients' preferences as additional information for the authorities to consider the value, pricing, and reimbursement of treatments.[130,131]

As shown in Table 4 previously, two studies explicitly mentioned using DCE to examine patients' preferences for DMARDs among RA patients in the U.S.[66,67] A study assessed the patients' willingness to tradeoff between the duration and frequency of RA treatments.[67] The study results suggested that the relative preference for a one-hour change in duration (from two hours) of a quarterly infusion was more than six times greater than the relative preference for an increase in annual treatment frequency by one (from 12 times per year). Another study examined the benefit-risk trade-offs of treatment decisions for moderate-to-severe RA patients.[66] The results suggested that patients with moderate-to-severe RA would accept increased treatment risks for improved physical function and disease control. One study implicitly used DCE to analyze the effect of a cheap talk script, information to the participants of an experiment, ensuring their awareness regarding the presence of the hypothetical bias to discourage them from making insincere or unrealistic responses, on a patent's preference for RA treatment in WTP space instead of conventional utility space.[61] The findings of this study suggested that the cheap talk had an impact on the coefficients of the treatment attributes and subsequently on the WTPs for RA treatments. However, these studies did not explicitly examine the preference-based value of DMARDs and the heterogeneity of preference. Additionally, preference-based value for the reduction in fatigue has never been examined. Thus, there is a need to examine the preference-based value for DMARDs.

Chapter 3 Manuscript 1

3.1 Abstract

Objectives: To determine the expenditure for RA in the nationally representative U.S. population between 2008 and 2020 from the societal perspective

Methods: This study used Medical Expenditure Panel Survey (MEPS) data for the years 2008 to 2015 and 2017 to 2020 to identify the cohorts of RA patients (RA) and individuals with no RA (control). Expenditure, including direct cost components and indirect cost, was estimated. The absenteeism-related cost was used to estimate the indirect cost. Covariates (age, sex, race, insurance coverage, marital status, education, any limitation, total annual income, and modified Carlson comorbidity index) adjusted two-part regression model, the first part being logistic regression and the second part used generalized estimating equation (GEE) with log link, and gamma distribution was estimated. Costs for the RA cohort were compared to the control cohort to generate incremental costs.

Results: The covariate-adjusted average annual total direct costs per person of the RA cohort for the years 2008-2009, 2010-2011, 2012-2013, 2014-2015, 2017-2018, and 2019-2020 were $17,791, $18,374, $22,049, $19,408, $25,128 and $31,105, respectively, in 2020 U.S. dollars. For the control cohort, the costs were $6,163, $6,245, $5,840, $6,221, $7,040, and $7,610 in 2020 U.S. dollars. The average annual incremental total costs per person of the RA cohort compared to the control cohort were $11,628, $12,129, $16,209, $13,187, $18,088, and $23,495. The average annual incremental prescription drug costs per person of the RA cohort, compared to control cohorts, were $4,013, $5,455, $64,03, $7,041, $9,864, and $13,961. These estimates were statistically significant. The average annual absenteeism costs per person RA vs. control cohort

for the years 2008-2009, 2010-2011, 2012-2013,2014-2015, 2017-2018, and 2019-2020 was $2511 vs. $1640, $2652 vs. $1651, $3001 vs. $1696, $2464 vs. $1335, $1832 vs. $1403, and $2546 vs. $1873, respectively.

Conclusion: The expenditure of individuals with RA in the U.S. has significantly risen from 2008 to 2020, with the primary contributor being the costs associated with prescription drugs. Absenteeism-related costs were higher among the RA cohort. Future research should comprehensively explore the expenditure of RA by considering multiple sources of indirect costs.

3.2 Introduction

Rheumatoid Arthritis (RA) is a chronic autoimmune inflammatory disease where the patient's immune system attacks the lining of the joints (synovium) and subsequently can lead to bone destruction and thus is a major public health concern.[1-3] In the U.S., approximately 0.53 to 0.55% (1.3 to 1.7 million) of adults suffered from RA.[10,11] RA posed a significant economic burden to the U.S. healthcare system.[25-32] It was estimated that RA-related direct healthcare costs amounted to $33.8 (28.9 to 37.7) billion in 2016 dollars.[28] Furthermore, productivity loss due to absenteeism and reduced workforce participation, disease-related disabilities, and psychological impairment due to RA could amount to a significant indirect economic burden.[33,34] RA's related indirect costs were estimated to be around $10.9 billion in 2005 dollars.[25]

DMARDs are used to manage RA, i.e., to reduce inflammation to its lowest level, delay disease progression, and achieve remission (no disease activity).[1,19,20] Recent advancements in DMARDs, the introduction of newer biologic and target-specific DMARDs, helped patients to achieve their treatment goals, including remissions and improving workforce participation, potentially reducing indirect costs.[38] Newer DMARDs could reduce excess hospitalization and emergency department visits.[33,39] However, these treatments could shift the direct costs of RA, primarily due to the increase in DMARD-related costs over time.[97] For instance, Dalal and colleagues estimated that, between 2012 and 2017, Medicare drug spending on biologic DMARDs (bDMARDs) increased from $4.3 to $10 billion.[37] A systematic review suggested a decreasing trend in the inpatient costs while signaling a cost shift towards the other components of the direct costs.[33] In other words, recent advancements made in RA management with DMARDs might change the contribution of each cost component to the economic burden of RA.

Previous cross-sectional studies to estimate RA's economic burden neither captured the

changing dynamics of RA costs with the introduction of high efficacy and high-cost DMARDs.[25,34,40-42] nor included indirect costs, which could be a major source of economic burden.[28,31,33,36,43] It was suggested that studies that did not incorporate or appropriately measure the indirect costs would underestimate RA's full economic impact.[33,38] In 2017, Institute for Clinical and Economic Review (ICER) also reported that a point-in-time measure would fail to capture the lability of RA as the disease burden varied over time.[56] To our knowledge, two studies published in 2012 estimated the economic consequences or trend of RA over time and included indirect costs.[39,44] First study used MEPS data (2004-2006) to estimate RA's economic consequences.[44] This study included the indirect costs (i.e., work absenteeism, workforce participation, and income effect).[44] Another study used administrative claims data from the privately insured population (1997-2006).[39] Medically related absences and disability were used as the indirect workplace costs.[39] However, these studies were obsolete and did not capture the economic impact of DMARDs launched in the past decade. Thus, the objective of this study was to determine the expenditure of RA in the U.S. between 2008 and 2020 from a societal perspective.

3.3 Methods

Study design

A serial cross-sectional study design[158-160], a special type of cross-sectional study where the data were collected on the same target population at different points in time[158,160], was used to estimate and compare the average annual costs per person of the RA cohort and cohort with no RA (controls).[25,161] Institutional Review Board approval was not required since this study used publicly available deidentified data.

Data source

We used the retrospective MEPS data. Briefly, MEPS is a nationally representative large-scale survey of families and individuals, their medical providers (e.g., clinicians, hospitals, pharmacies, etc.), and employers, administered annually by the Agency for Healthcare Research and Quality (AHRQ) for the civilian non-institutionalized U.S. population.[162] In exception for the year 2020, which features nine rounds, the panel design of the survey features five rounds of interviewing at the personal and household levels that cover two full calendar years for each individual panel.[163] A new panel is selected each year. MEPS data were previously used to estimate the expenditure for arthritic conditions in the U.S.[40,41,94]

In this study, we used the household component of MEPS data for 2008 to 2015 and 2017 to 2020.[164] Year 2016 was dropped because RA patients were masked or RA patients could not be identified as there was no associated medical condition diagnostic code. The household component contained information on demographic characteristics, health conditions, health status, use of medical care services, charges and payments, access to care, satisfaction with care, health insurance coverage, income, and employment.[165] We then merged the MEPS Household Components' full-year consolidated and the medical conditions files for each year from 2008 to 2020 to create annual files with sociodemographic characteristics, medical conditions, and medical costs to examine the trend in the expenditure for RA. Furthermore, to obtain precise estimates,[159,166] we pooled data from six 2-year cycles, i.e., 2008-2009, 2010-2011, 2012-2013, 2014-2015, 2017-2018, and 2019-2020, by combining the individual year data and reconciling the discrepancies in variable names.[167] Pooled variance structure, i.e., STRA9620 and PSU9620 variables, was attached to each cycle.[167] The person-level weight variable (PERWT08F—PERWT20F) was divided by two (number of pooled years) to generate estimates of the average annual direct and indirect cost per person.[167] Overall, the data for each year were divided into two

cohorts: RA patients (RA), and patients with no RA (control). All costs were converted to the 2020 U.S. dollars using the medical consumer price Index (CPI).[168]

Study samples

Self-reported RA patients were identified from the medical condition file using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9- CM) for another inflammatory polyarthritis (714) or Clinical classification Software Refined (CCSR) code for RA and related disease (202) for each of the year 2008-2015 and the *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) for other rheumatoid arthritis (M06) or CCSR code for RA and related disease (MUS003) for each of the year 2017-2020.[94,161,169] All other individuals, who did not have RA, were treated as controls. Only individuals of age greater than 18 years old were included. Those individuals with a person-weight (PERWT08F—PERWT20F) ≤ 0 and individuals with any missing observation for the covariates age, sex, race, insurance coverage, marital status, education, any limitation, person's total income, and modified Charlson Comorbidity Index (CCI) were excluded.[170,171]

Costs and covariates

This study determined and compared the average annual direct and indirect costs per person of RA and no RA (control) cohorts. The study also determined the direct cost components, i.e., office-based visits, outpatient visits, emergency room visits, inpatient hospital stays, prescription medicine, and other costs (the sum of the dental visit, home health care, vision aid, and other medical supply and equipment costs).

We defined total direct cost (TOTEXP08—TOTEXP20) as the sum of direct payments for the office-based visit (OBVEXP08—OBVEXP20), outpatient visit (OPTEXP08—OPTEXP20), emergency room visit (ERTEXP08—ERTEXP20), inpatient hospital stay (IPTEXP08—

IPTEXP20), prescription medicine (RXEXP08—RXEXP20), and other costs (the sum of dental visit (DVTEXP08—DVTEXP20), home health care ((HHAEXP08+HHNEXP08) — (HHAEXP20+HHNEXP20)), vision aid (VISEXP08—VISEXP20), and other medical supply and equipment (OTHEXP08—OTHEXP20) costs). The payment sources included out-of-pocket costs, Medicare, Medicaid, private insurance, veteran's administration/CHAMPVA, TRICARE, and other resources.

The indirect cost was defined as the productivity loss and was estimated using absenteeism-related cost as the productivity loss measure.[44] Absenteeism (DDNWRK08—DDNWRK20) represented the number of times the person lost a half-day or more from work because of illness, injury, or mental or emotional problems during the calendar year.[172] We used the human capital method, multiplying the number of absent days for the working age (>=18 years old and =<64 years old) population with their hourly wages (HRWG31X or NHRWG31, HRWG42X or NHRWG42, HRWG53X or NHRWG53) assuming eight hours of work per day, to estimate the absenteeism related indirect costs. The indirect cost was calculated using the workforce participation variable (EMPST31/EMPSTH31+ EMPST42/EMPSTH42+ EMPST53/EMPSTH53) for individuals currently employed or with a job to return.

The direct and indirect costs were adjusted for the following covariates; age (18 - 64 years and 65 - 85 years), sex (male and female), race (white only and others), insurance coverage (any private, public only, and uninsured), marital status (married and others), education (grade 12 or less and college education 1 year or more), any Instrumental Activities of Daily living (IADL), Activities of Daily Living (ADL), functional, or activity limitation (Yes and No), person's annual total income (< $30,000, and >=$30,000) and modified Charlson Comorbidity Index (CCI) score (0,1, and 2 or greater) for myocardial infarction, heart failure, peripheral vascular disease,

cerebrovascular disease, dementia, chronic pulmonary disease, peptic ulcer disease, liver diseases, diabetes mellitus, renal disease, cancer, and acquired immunodeficiency syndrome (AIDS)/human immunodeficiency virus (HIV).

Statistical analysis

SAS 9.4 (© SAS Institute Inc., Cary, NC) was used to perform all statistical analyses. Descriptive statistics, including mean and frequency for all three cohorts, were generated using SURVEYMEANS or SURVEYFREQ procedures. The SURVEY procedure accounted for sampling weights, variance estimation stratum, and primary sampling unit (clustering) to generate national estimates.[173] The annual means of total direct cost per person and its components, e.g., office-based visit, prescription drug, inpatient visit, outpatient visit, emergency department visit, and home health care, for the two cohorts were estimated using two-part regression models.[41,174] The two-part regression model accounted for the excess zero and non-normality distribution of healthcare costs.[174] In the first part, a logistic regression model was used to determine the covariates adjusted probability of non-zero healthcare costs using the SURVEYLOGISTIC procedure (i.e., Prob ($y_i > 0|x_i$)). In the second part, a generalized estimating equation (GEE), an extension of the generalized linear model (GLM), conditioned on the positive cost and adjusted for covariates, was used to estimate the mean direct costs using the GENMOD procedure (i.e., E ($y_i|x_i, y_i > 0$)).[94,159] Sampling weights, variance estimation stratum, and primary sampling unit (clustering) were accounted for in the estimates. The Modified Park test was used to verify the use of a gamma distribution with a log link.[175] The GEE was preferred over ordinary least squares regression (OLS) since the OLS would not consider the correlation, heteroscedasticity, severe skewness, and non-normality of the medical cost data.[94,176] Finally, the predicted probability of non-zero costs obtained from the logistic regression model was multiplied by the predicted costs

from the GEE to generate the final covariate-adjusted direct costs (i.e., $E(y_i|x_i) = Prob\ (y_i > 0|x_i)\ E\ (y_i|x_i, y_i > 0)$).[41,177] For the number of absent days and absenteeism-related indirect cost, we used only the generalized estimating equation (GEE) with Poisson and Gamma distributions, respectively, with log links. Covariates for this model remained the same as in the previous estimates.

The incremental expenditure for the RA cohorts and control cohort was estimated simply as the difference between the predicted values for the RA cohorts to that of the control cohort using the DIFFMEANS procedure.

3.4 Results

A total of 1,273 out of 69,921 (1.82%); 1,268 out of 68,159 (1.86%); 1,421 out of 75,914 (1.87%); 1,428 out of 70,302 (2.03%); 1,184 out of 62,341(1.90%); and 856 out of 56,317 (1.52%) unique patients were initially identified as RA patients from the data for the years 2008-2009, 2010-2011, 2012-2013, 2014-2015, 2017-2018, and 2019-2020, respectively. However, based on our inclusion criteria, 1,189 out of 44258 (2.69%); 1,209 out of 44,115 (2.74%); 972 out of 36,658 (2.65%); 379 out of 12,513 (3.03%); 844 out of 29,942 (2.82%); and 820 out of 40,682 (2.02%) RA patients from the data for the years 2008-2009, 2010-2011, 2012-2013, 2014-2015, 2017-2018, and 2019-2020, respectively were included in our analyses.

Table 5 shows the demographic characteristics of the two cohorts for the six study periods. For the RA cohort, the majority of them were 18-64 years of age (54%- 60%), female (62%-69%), and white (50%-82%). Most of them reported some forms of limitations (63%-75%), and had an annual income of $30,000 or less (64%-73%). Some patients were married (48%-54%) and had private insurance (48%-55%). However, the proportion of RA patients, who had one or more years

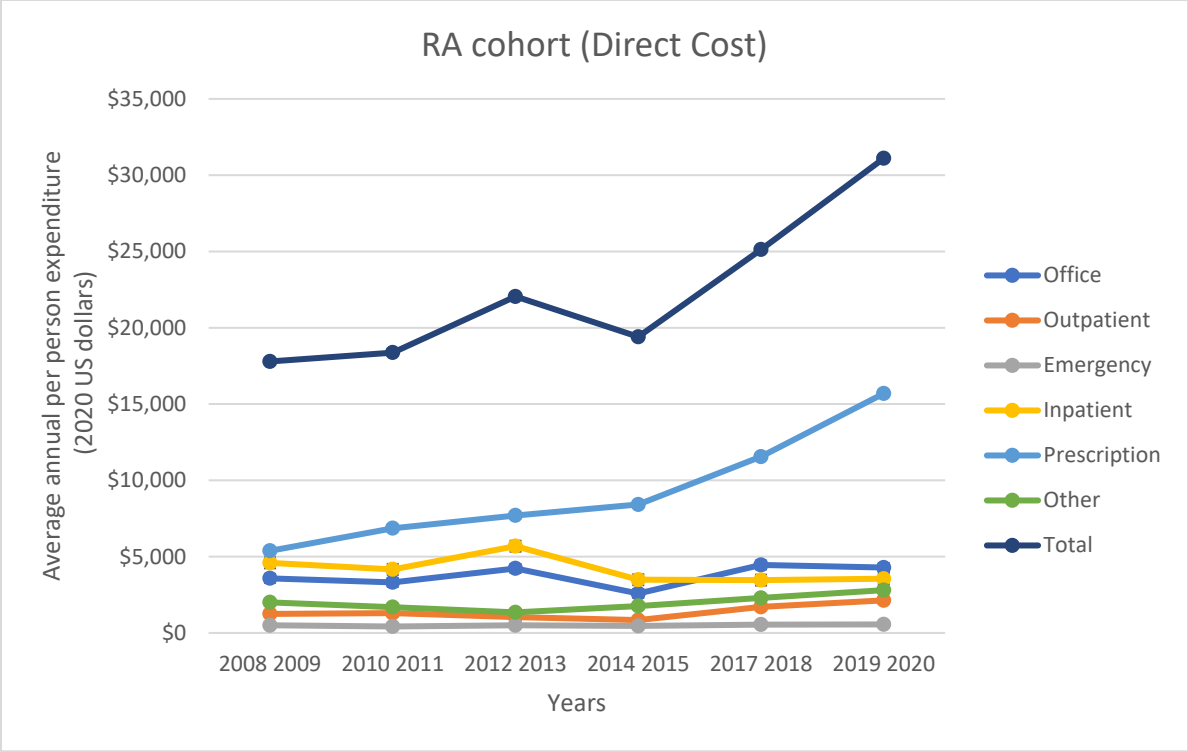
of college education (22%-47%) or had two or more comorbid conditions (26%-72%), varied over time. Similarly, in the control cohort majority of the individuals were 18-64 years of age (58%-84%), female (51%-52%), and white (53%-81%). Most of them reported no limitations (74%-81%), and had private insurance (67%-71%). A number of them were married (46%-54%) and had an annual income of $30,000 or less (45%-56%). The number of individuals with two or more comorbid conditions (12%-44%) and with one or more years of college education (28%-60%) varied over time.

Table 6 shows the results of the unadjusted and adjusted average annual direct cost per person. For the RA cohort, the unadjusted analysis results showed that the average annual total direct costs increased by 38% ($1,6980 to $ 2,3354 per person) from the first (2008-2009) to the last (2019-2020) periods of this study. The average annual prescription drug costs increased by 111% ($4,734 to $9,981 per person), office-based costs increased by 35% ($3,338 to $4,520 per person), outpatient costs increased by 85% ($1,208 to $2,230 per person), emergency room visit costs increased by 14% ($512 to $585 per person), inpatient costs decreased by 29% ($4,704 to $3,349 per person) and other costs increased by 8% ($2,484 to $2,690 per person). After these costs were adjusted by the covariates, such as age, sex, race, insurance coverage, marital status, education, any limitation, a person's annual total income, and comorbid condition, the average annual total direct medical costs increased by 75% ($17,791 to $31,105 per person). The average annual prescription drug costs increased by 192% ($5,381 to $15,693 per person), office-based costs increased by 20% ($3,579 to $4,284 per person), outpatient costs increased by 71% ($1,250 to $2,133 per person), emergency room visit costs increased by 12% ($498 to $558 per person), inpatient costs decreased by 23% ($4,594 to $3,548 per person) and other costs increased by 40% ($2,005 to $2,804 per person).

For the control cohort, the unadjusted analyses showed that the average annual total direct costs increased by 21% ($6,128 to $ 7,404 per person). The average annual prescription drug costs increased by 26% ($1,368 to $1,720 per person), office-based costs increased by 26% ($1,533 to $1,936 per person), outpatient costs increased by 47% ($589 to $864 per person), emergency room visit costs remain unchanged ($248 per person), inpatient costs decreased by 4% ($1,663 to $1,600 per person) and other costs increased by 42% ($728 to $1,036 per person). On the other hand, the adjusted analyses showed that the average annual total direct costs increased by 23% ($6,163 to $ 7,610 per person). The average annual prescription drug costs increased by 27% ($1,369 to $1,732 per person), office-based costs increased by 27% ($1,543 to $1,961 per person), outpatient costs increased by 48% ($583 to $862 per person), emergency room visit costs remains unchanged ($248 per person), inpatient costs decreased by 4% ($1,658 to 1,590 per person), and other costs increased by 41% ($720 to $1,015 per person).

Figure 1A shows the trends of the direct costs of RA cohorts, and Figure 1B shows the trends of the direct costs of no RA (control) cohort for the six study periods. For the RA cohort, the covariate-adjusted average annual total direct cost per person for the RA cohort increased by $11,697 ($1,9408 to $31,105) from the 2014-2015 to 2019-2020 periods. Similarly, the average annual prescription drug cost per person for the RA cohort increased by $7,276 ($8417 to $15,693) between the same periods. Although for the 2012-2013 to 2014-15 period, the average annual total direct costs per person for the RA cohort had a downward trend ($22,049 to $19,408), the average annual prescription drug costs per person continued its upward trend ($7,699 to $8,417).

A. RA cohort [n=1189 (2008-2009), 1209 (2010-2011), 972 (2012-2013), 379 (2014-2015), 844(2017-2018), 820(2019-2020)]



B. Control cohort [n=44258 (2008-2009), 44115 (2010-2011), 36658 (2012-2013), 12513 (2014-2015), 29942 (2017-2018), 40682 (2019-2020)]

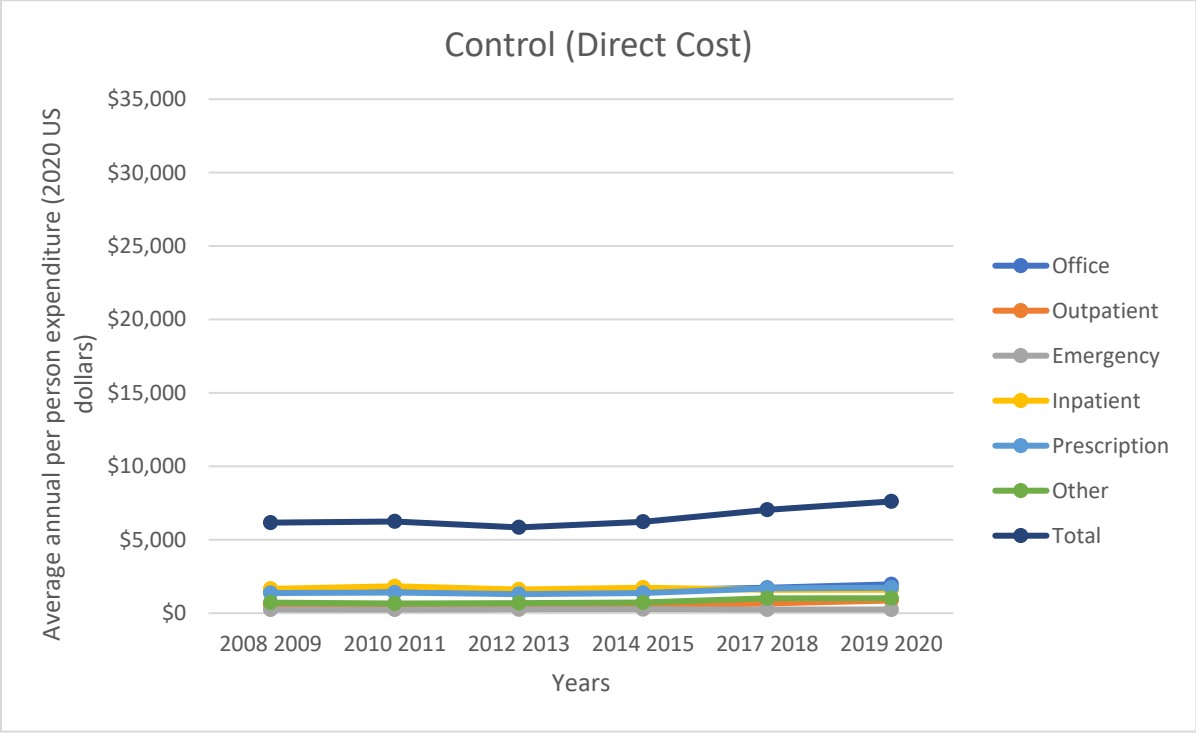


Figure 1. Average annual direct costs per person for Rheumatoid Arthritis patients and control cohorts in six study periods.

Data Source: Medical Expenditure Panel Survey (MEPS), 2008-2020: 2008-2009, 2010-2011, 2012-2013, 2014-2015, and 2017-2018, 2019-2020. **Notes** Average annual direct cost per person was not available for the year 2016.

Table 6 also shows the results of the unadjusted and adjusted average annual indirect cost per person. Our unadjusted analyses showed that the average number of working days missed due to illness or injury per person from the first (2008-2009) to last (2019-2020) periods of the RA and control cohorts increased by 11% (9.4 days to 10.5 days), and 10% (3.9 days to 4.3 days), respectively. They corresponded to the average annual increase in absenteeism-related costs by 6% ($1,591 to $1,689 per person), and 4% ($892 to $929 per person), respectively. On the other hand, the adjusted analyses showed the average number of working days missed due to illness or injury per person remains unchanged (9.1 days) for the RA cohort and increased by 9% (3.9 to 4.3 days) for the control cohort. The corresponding increase in an adjusted average annual absenteeism-related cost increased by 1% ($2,511 to $2,546) and 14% ($1,640 to $1,873) for the RA cohort and control cohort, respectively.

Table 7 shows the comparisons of the unadjusted average annual total direct costs per person among the RA cohort and control cohorts in six study periods. The incremental cost in the average annual total direct costs per person for RA cohort was $10,852 (95% CI: $8,683-$13,020), $9,962 (95% CI: $8,223-$11,700), $12,965 (95% CI: $9,884-$16,046), $8,919 (95% CI: $6,390-$11,447), $12,495 (95% CI: $10,331-$14,659), and $15,950 ($11,646-$20,254) for the 2008-2009, 2010-2011, 2012-2013, 2014-2015, 2017-2018, and 2019-2020 periods, respectively. Similarly, the adjusted incremental cost in the average annual total direct costs per person were $11,628 (95% CI: $10,867-$12,388), $12,129 (95% CI: $11,256-$13,002), $16,209 (95% CI: $15,176-$17,241),

$13,187 (95% CI: $11,731-$14,643), $18,088 (95% CI: $16,577-$19,600), and $23,495 ($21,541-$25,448) for the six study periods.

Since the prescription drug costs contributed most to the total direct costs, Table 7 shows the comparison of the unadjusted average annual prescription drug costs per person among the RA, and control cohorts for the 2008-2009, 2010-2011, 2012-2013, 2014-2015, 2017-2018, and 2019-2020 periods. The incremental cost in the average annual prescription drug costs per person for the RA and control cohorts were $3,365 (95% CI: $2,733-$3,997), $4120 (95% CI: $3,328-$4,912), $4,645 (95% CI: $3,116-$6,173), $4,355 (95% CI: $3,089-$5,621), $5,545 (95% CI:$4,307-$6,783), and $8,261 (95% CI:$5,630-$10,893) for the six study periods. Similarly, the adjusted incremental cost in the average annual prescription drug costs per person for the RA and control cohorts were $4,013 (95% CI: $3,792-$4,233), $5,455 (95% CI: $5,195-$5,715), $6,403 (95% CI: $6,077-$6,728), $7,041 (95% CI: $6,453-$7,629), $9,864 (95% CI:$9,164-$10,564), and $13,961 (95% CI:$12,981-$14,941) for the six study periods.

Table 7 also shows the comparisons of the unadjusted average annual absenteeism costs per person among the RA and control cohorts for the 2008-2009, 2010-2011, 2012-2013, 2014-2015, 2017-2018, and 2019-2020 periods. The incremental cost in the unadjusted average annual absenteeism costs per person of the RA and control cohorts were $700 (95% CI: $151-$1,248), $718 (95% CI: $203-$1,234), $1,099 (95% CI: $331-$1,867), $797 (95% CI: -$116-$1,710), $612 (95% CI:$119-$1,104), and $760 (95% CI:$83-$1,438) per patient for the six study periods. Similarly, the incremental cost in the adjusted average annual absenteeism costs per person of the RA and control cohorts were $871 (95% CI: $628-$1,114), $1,001 (95% CI: $758-$1,243), $1,305 (95% CI: $938-$1,671), $1,129 (95% CI: -$785-$1,473), $430 (95% CI:$164-$696), and $672 (95% CI:$458-$887) per patient for the six study periods.

3.5 Discussions

In this study, we estimated the expenditure, including direct and indirect costs, of the RA cohorts and compared them to the expenditure for the No-RA (control) cohort. Due to the similarities and differences in the characteristics of these cohorts, we primarily discussed the results from the adjusted analyses.

Direct costs

Our study suggested that the average annual total direct cost per person for the RA cohort increased by 75% ($17,791 to $31,105) between 2008-2009 and 2019-2020. This observation was similar to previous studies, which suggested that all-cause healthcare costs for RA patients were $18,545 ($1,3012 in 2008 dollars) in 2008 and $19,054 ($17,800 in 2018 dollars) in 2018 (2020 dollars).[94,197] Primarily, an increase in the prescription drug cost by 192% ($5,381 to $15,693) was one of the key drivers for the increase in the direct cost for the RA cohort. Increases in the prices of existing DMARDs might be one reason for the higher prescription drug costs.[33,45,198] According to a prior investigation, the annual costs for treating RA using TNF inhibitors rose 144% between 2009 and 2016 ($15809 in 2009 to $38574 in 2016 dollars).[45] Similarly, changes in the competitive DMARD landscape, i.e., the introduction of various costly bDMARDs and their uptakes, might result in the increases in prescription drug costs. A recent comprehensive review also indicates that the expense of drugs constitutes the primary factor (up to 87%) in the overall direct costs.[33]

While the prescription drug costs increased over these periods, they were somewhat offset by the declining trends of inpatient costs. Inpatient costs decreased by 23% ($4594 to $3548) from 2008-2009 to 2019-2020. On the other hand, during the same period, the cost for office-based visit and outpatient facility increased by 20% ($3,579 to $4284) and 71% ($1250 to $2,133), respectively. One possible reason could be the improved control of RA symptoms with newer

DMARDs, which might lead to decreased utilization of inpatient facilities but an increase in office visits or outpatient facilities for administering newer DMARDs. It was also possible that new DMARDs could help these patients to avoid inpatient costs and eventually cause the downward trend of direct medical costs.[33]

The comparisons of the adjusted direct medical costs among the two cohorts (RA vs. control) shed light on the incremental expenditure of RA. The average annual direct medical costs per person for the RA cohort were between $11,628 (2008-2009) to $23,494 (2019-2020) higher than the control cohort. The key driver of this burden was the prescription drug costs since the average annual prescription drug costs per person for the RA cohort were between $4,013 (2008-2009) to $13,961 (2019-2020) higher than the control cohort. This indicated that prescription drug contributes substantially to the incremental direct cost of RA patients.

Indirect costs

The absenteeism-related costs made 7-13% contribution to the overall economic burden of RA patients in our study. A previous study suggests that indirect cost, primarily absenteeism and work disability accounted for 39% and 86% of the overall cost.[33] Inclusion of only absenteeism related cost might be the reason for lower estimates of indirect cost in our study. Overall absenteeism-related costs of the RA cohort increased from 2008-2009 ($2511) to 2012-2013 ($3000) but then steadily declined up until 2019-2020 ($2546). One of the reasons for the decrease in the absenteeism related cost might be attributed to the introduction, greater utilization, and aggressive treatment with newer boDMARDs.[34,199] These results might reflect the benefits of DMARDs. Compared to the control cohort, the average annual absenteeism costs per person for the RA cohort were $429 to $1304 higher, and the average number of absent days was 4-8 days higher. These estimates were similar to a previous study which suggested that from 1996-2006,

the incremental per capita cost in annual lost workdays for the RA cohort compared to the control cohort was $849 in 2020 dollars ($596 in 2008 dollars).[34] Time off from work due to sick leaves might be the reason for the higher absent days and cost among the RA cohort.

The findings of this study had various implications. For instance, policymakers could use the expenditure of RA to prepare healthcare resources needed for this patient population in the US. They could also use the study findings to design cost containment strategies for each cost component. Healthcare payers could use the findings to evaluate the costs and benefits of DMARDs and design their coverages for better patient access to DMARDs since DMARDs tended to be costly and were a key driver of the increase in healthcare cost, but they provided direct and indirect benefits to the patients.

Our study should be interpreted considering these limitations. First, this study did not control the severity and duration of RA since they were not available. They likely influenced the direct medical costs and absenteeism-related costs. Second, MEPS surveys were subject to self-report bias, which could potentially influence the disease prevalence and costs. Third, MEPS only includes non-institutional US individuals, so our findings could not be generalizable to those in institutional settings. Last, this study based the indirect cost on only the absenteeism-related cost. Costs due to other types of productivity loss, such as reduced productivity while at work (presenteeism), loss of employment, caregiver burden, or decrease in the quality of life, were not included. Therefore, this study might not reflect the true indirect cost estimates.

3.6 Conclusion

The expenditure considerably increased from 2008-2009 to 2019-2020 for patients with RA. Notably, a substantial increase was observed between 2014-2015 and 2019-2020. This upward trend in expenditure was primarily driven by prescription drug costs, which continued to rise over

time. Absenteeism-related costs were higher for the RA cohort than the control cohort but were relatively stable during the study period. Future research should comprehensively explore the economic burden of RA by considering multiple sources of indirect costs.

Table 5. Demographic characteristics of Rheumatoid Arthritis (RA) patients and control in each study period.

Years		Cycle 1 Year (2008-2009)		Cycle 2 Year (2010-2011)		Cycle 3 Year (2012-2013)		Cycle4 Year (2014-2015)		Cycle5 Year (2017-2018)		Cycle6 Year (2019-2020)	
Variables		RA (N=1189)	Control (N=44258)	RA (N=1209)	Control (N=44115)	RA (N=972)	Control (36658)	RA (N=379)	Control (N=12513)	RA (N=844)	Control (N=29942)	RA (N=820)	Control (N=40682)
Age	18-64 years	732 (57.96%)	37799 (83.73%)	738 (57.67%)	37222 (57.67%)	626 (59.56%)	31303 (81.82%)	241 (57.24%)	10372 (80.98%)	464 (56.03%)	22584 (76.99%)	406 (53.93%)	30255 (78.75%)
	65-85 years	457 (42.04%)	6459 (16.27%)	471 (42.33%)	6893 (42.33%)	346 (40.44%)	5355 (18.18%)	138 (42.76%)	2141 (19.02%)	380 (43.97%)	7358 (23.01%)	414 (46.07%)	10427 (21.25%)
Sex	Male	378 (37.15%)	20523 (48.63%)	348 (33.05%)	20610 (48.70%)	287 (34.15%)	17170 (48.52%)	128 (38.39%)	5874 (48.49%)	238 (32.69%)	13951 (48.53%)	237 (30.60%)	19048 (48.56%)
	Female	811 (62.85%)	23735 (51.37%)	861 (66.95%)	23505 (51.30%)	685 (65.85%)	19488 (51.48%)	251 (61.61%)	6639 (51.51%)	606 (67.31%)	15991 (51.47%)	583 (69.40%)	21634 (51.54%)
Race	White (No other race reported)	827 (81.62%)	31377 (81.37%)	790 (79.00%)	31044 (81.09%)	376 (49.96%)	16571 (52.97%)	242 (76.47%)	8772 (78.63%)	574 (75.28%)	21916 (77.85%)	589 (76.85%)	31036 (77.75%)
	Others	362 (18.38%)	12881 (18.63%)	419 (21.00%)	13071 (18.91%)	596 (50.04%)	20087 (47.03%)	137 (23.53%)	3741 (21.37%)	270 (24.72%)	8026 (22.15%)	231 (23.15%)	9646 (22.25%)
Marital Status	Married	617 (54.23%)	23202 (53.83%)	562 (51.67%)	22087 (52.97%)	434 (50.64%)	17641 (52.75%)	166 (49.92%)	6050 (53.27%)	356 (48.21%)	13293 (45.90%)	375 (52.37%)	20073 (51.44%)
	Others	572 (45.77%)	21056 (46.17%)	647 (48.33%)	22028 (47.03%)	538 (49.35%)	19017 (47.25%)	213(50.08%)	6463 (46.73%)	488 (51.79%)	16649 (54.10%)	445 (47.63%)	20609 (48.56%)
Education	Grade 12 or less	784 (60.96%)	24428 (48.37%)	808 (57.79%)	23473 (43.59%)	784 (77.67%)	27277(72.40%)	248 (59.34%)	6554 (44.17%)	509 (52.51%)	14623 (40.56%)	508 (55.84%)	18505 (39.72%)
	College education 1 years or more	405 (39.04%)	19830 (51.63%)	401 (42.21%)	20642 (56.51%)	188 (22.33%)	9381 (27.60%)	131 (40.66%)	5959 (55.83%)	335 (47.49%)	15319 (59.44%)	312 (44.16%)	22177 (60.28%)
Any limitation	Yes	837 (69.24%)	10713 (25.75%)	853 (70.63%)	10299 (24.90%)	698 (74.98%)	8217 (24.95%)	284 (73.78%)	2983 (24.32%)	563 (64.91%)	6903 (20.86%)	554 (62.84%)	9131 (19.38%)
	No	352 (30.76%)	33545 (74.25%)	356 (29.37%)	33816 (75.10%)	274 (25.02%)	28441 (75.05%)	95 (26.22%)	9530 (75.68%)	281 (35.09%)	23039 (79.14%)	266 (37.16%)	31551 (80.62%)

Insurance type	Any private	531 (53.88%)	26765 (68.69%)	537 (53.74%)	25703 (68.39%)	371 (47.66%)	20256 (66.89%)	149 (47.95%)	7516 (70.89%)	383 (55.16%)	18518 (69.95%)	360 (51.46%)	25381 (69.09%)
	Public only	529 (37.15%)	8550 (15.76%)	559 (39.44%)	9223 (16.65%)	506 (43.95%)	8172 (17.75%)	207 (47.20%)	3258 (19.78%)	436(42.29 %)	8546(22.44 %)	452 (47.24%)	11815 (23.39%)
	Uninsured	129 (8.97%)	8943 (15.55%)	113 (6.82%)	9189 (14.96%)	95 (8.39%)	8230 (15.36%)	23 (4.85%)	1739 (9.33%)	25(2.55%)	2878(7.61 %)	8 (1.30%)	3486 (7.52%)
Income	< $30,000	946 (73.24%)	28321 (55.88%)	935 (68.93%)	28435 (56.23%)	773 (69.97%)	23419 (54.83%)	289 (66.58%)	7617 (50.96%)	614 (63.86%)	16488 (47.84%)	578 (65.11%)	20558 (45.23%)
	>= $30,000	243 (26.75%)	15937 (44.12%)	274 (31.07%)	15680 (43.77%)	199 (30.03%)	13239 (45.17%)	90 (33.42%)	4896 (49.04%)	230(36.14 %)	13454(52.1 6%)	242 (34.89%)	20124 (54.77%)
Charlson Comorbidity Index (CCI)	0	297 (25.16%)	24334 (52.52%)	288 (22.39%)	24432 (51.51%)	223 (20.09%)	20168 (49.95%)	81 (21.98%)	6604 (50.26%)	406 (48.74%)	21696 (74.05%)	417 (54.80%)	31134 (79.24%)
	1	110 (8.62%)	2948 (6.56%)	133 (9.41%)	2909 (6.25%)	99 (8.16%)	2210 (5.58%)	38 (8.17%)	789 (5.51%)	189 (21.14%)	3698 (10.98%)	184 (19.60%)	4372 (9.25%)
	2 or greater	782 (66.22%)	16976 (40.92%)	788 (68.20%)	16774 (42.24%)	650 (71.75%)	14280 (44.47%)	260 (69.85%)	5120 (44.23%)	249 (30.12%)	4548 (14.97%)	219 (25.60%)	5176 (11.51%)

Abbreviations: RA, RA cohort; Control, control group or group with no rheumatoid arthritis**. Data Source:** Medical Expenditure Panel Survey (MEPS). **Notes** Average annual cost per person was not available for the year 2016.

Table 6. Direct and indirect cost for patients with Rheumatoid Arthritis (RA) and control from 2008-2020.

	Group 1: Rheumatoid Arthritis											
	Unadjusted						Adjusted					
Direct Expenditure	2008 2009	2010 2011	2012 2013	2014 2015	2017 2018	2019 2020	2008 2009	2010 2011	2012 2013	2014 2015	2017 2018	2019 2020
Office based expenditure	3338	2934	4170	2345	4084	4520	3579	3316	4226	2585	4454	4284
Outpatient expenditure	1208	1269	1077	858	1672	2230	1250	1294	1034	841	1707	2133
Emergency room expenditure	512	416	504	506	514	585	497	420	498	458	544	558
Inpatient expenditure	4704	4224	5697	3621	3548	3349	4594	4164	5685	3486	3462	3548
Prescription drug expenditure	4734	5522	5942	5732	7234	9981	5381	6856	7699	8417	11550	15693
Other expenditure (Dental care+ home health agency, home health non-agency, glass contact lenses expenditure, other equipment, and supplies)	2484	1840	1410	2036	2388	2690	2005	1690	1346	1763	2293	2804
Total expenditure	16980	16205	18801	15099	19440	23354	17791	18374	22049	19408	25128	31105
Indirect Expenditure (Age >=18 to =64<, Weight>0, employed or has a job to return to, has >=0 missed days, has >0 hourly wage value, 2020 nominal dollars)												
Wage Income	51581	57429	45118	50427	50441	53572	43656	46668	36711	43295	43141	47797
Number of days missed due to illness or injury	9	8	11	6	8	10	9	8	11	7	8	9
Mean hourly wage	26	30	24	25	27	27	26	29	24	24	26	28
Absenteeism related cost (# Absent days*hourly wage*8)	1591	1589	2020	1534	1339	1689	2511	2652	3000	2464	1832	2546

Data Source: Medical Expenditure Panel Survey (MEPS). **Notes** Person weight>0 indicates only those individuals whose person-weight was >0 was included in this analysis. The average annual cost per person was not available for the year 2016.

	Group 2: No Rheumatoid Arthritis (control)											
	Unadjusted						Adjusted					
Direct Expenditure	2008 2009	2010 2011	2012 2013	2014 2015	2017 2018	2019 2020	2008 2009	2010 2011	2012 2013	2014 2015	2017 2018	2019 2020
Office based expenditure	1533	1510	1470	1570	1722	1936	1543	1519	1473	1573	1730	1961
Outpatient expenditure	589	587	495	501	660	864	583	587	496	503	660	862
Emergency room expenditure	248	240	256	268	246	248	248	240	256	270	245	248
Inpatient expenditure	1663	1835	1620	1719	1593	1600	1658	1828	1615	1732	1593	1590
Prescription drug expenditure	1368	1402	1297	1377	1688	1720	1369	1401	1297	1375	1686	1732
Other expenditure (Dental care+ home health agency, home health non-agency, glass contact lenses expenditure, other equipment, and supplies)	728	670	699	744	1036	1036	720	660	689	723	1008	1015
Total expenditure	6128	6243	5836	6180	6945	7404	6163	6245	5840	6221	7040	7610
Indirect Expenditure (Age >=18 to =64<, Weight>0, employed or has a job to return to, has >=0 missed days, has >0 hourly wage value, 2020 nominal dollars)												
Wage Income	58178	56897	55380	56274	55536	58224	52842	51422	50241	51618	51324	53762
Number of days missed due to illness or injury	4	4	4	3	3	4	4	4	4	3	3	4
Mean hourly wage	30	29	28	28	28	30	30	29	28	28	28	29
Absenteeism related cost (# Absent days*hourly wage*8)	892	870	921	737	728	929	1640	1651	1696	1335	1403	1873

Data Source: Medical Expenditure Panel Survey (MEPS). **Notes** Person weight>0 indicates only those individuals whose person-weight was >0 was included in this analysis. The average annual cost per person was not available for the year 2016.

Table 7. Incremental direct and indirect cost for patients with Rheumatoid Arthritis (RA) to control cohort from 2008-2020.

	Incremental direct and indirect cost for patient with RA (Unadjusted for covariates)																	
	2008-2009			2010-2011			2012-2013			2014-2015			2017-2018			2019-2020		
Direct Expenditure	Diff	95% CL		Diff	95% CL		Diff	95% CL		Diff	95% CL		Diff	95% CL		Diff	95% CL	
Office based expenditure	1805	1367	2244	1424	1099	1749	2700	1641	3760	776	260	1291	2363	1525	3200	2584	431	4736
Outpatient expenditure	619	69	1169	682	139	1225	581	248	915	356	24	689	1012	562	1463	1365	319	2412
Emergency room expenditure	264	102	427	176	46	306	249	110	388	238	-53	528	267	118	416	337	131	543
Inpatient expenditure	3042	1948	4136	2390	1431	3348	4078	2655	5500	1902	374	3429	1956	992	2919	1748	570	2927
Prescription drug expenditure	3365	2733	3997	4120	3328	4912	4645	3116	6173	4355	3089	5621	5545	4307	6783	8261	5630	10893
Other expenditure (Dental care+ home health agency, home health non-agency, glass contact lenses expenditure, other equipment and supplies)	1756	407	3105	1170	666	1674	712	306	1117	1292	396	2188	1352	691	2013	1655	1070	2240
Total expenditure	10852	8683	13020	9962	8223	11700	12965	9884	16046	8919	6390	11447	12495	10331	14659	15950	11646	20254
Indirect Expenditure (Age >=18 to =64<, Weight>0, employed or has a job to return to, has >=0 missed days, has >0 hourly wage value, 2020 nominal dollars)																		
Wage Income	-6597	-13115	-80	532	-9331	10394	-10262	-16923	-3600	-5847	-16642	4947	-5095	-14336	4146	-4652	-12826	3522
Number of days missed due to illness or injury	5	2	9	4	2	6	6	2	10	3	1	5	4	1	7	6	2	11
Mean hourly wage	-4	-7	-1	1	-4	5	-4	-7	-1	-3	-8	2	-1	-6	3	-3	-7	1
Absenteeism related cost (# Absent days*hourly wage*8)	700	151	1248	718	203	1234	1099	331	1867	797	-116	1710	612	119	1104	760	83	1438

	Incremental direct and indirect cost for patient with RA (Adjusted for covariates)																	
	2008-2009			2010-2011			2012-2013			2014-2015			2017-2018			2019-2020		
Direct Expenditure	Diff	95% CL		Diff	95% CL		Diff	95% CL		Diff	95% CL		Diff	95% CL		Diff	95% CL	
Office based expenditure	2035	1903	2168	1797	1628	1966	2753	2548	2958	1012	845	1180	2723	2508	2939	2323	2087	2560
Outpatient expenditure	667	606	728	707	631	783	538	485	591	338	279	398	1047	949	1145	1271	1127	1416
Emergency room expenditure	249	229	270	181	163	198	242	219	266	188	153	224	300	279	321	310	280	339
Inpatient expenditure	2936	2701	3172	2336	2095	2578	4070	3756	4383	1753	1431	2075	1868	1618	2118	1958	1720	2196
Prescription drug expenditure	4013	3792	4233	5455	5195	5715	6403	6077	6728	7041	6453	7629	9864	9164	10564	13961	12981	14941
Other expenditure (Dental care+ home health agency, home health non-agency, glass contact lenses expenditure, other equipment, and supplies)	1285	1197	1374	1030	942	1117	657	589	724	1040	895	1186	1285	1148	1421	1790	1638	1942
Total expenditure	11628	10867	12388	12129	11256	13002	16209	15176	17241	13187	11731	14643	18088	16577	19600	23495	21541	25448
Indirect Expenditure (Age >=18 to =64<, Weight>0, employed or has a job to return to, has >=0 missed days, has >0 hourly wage value, 2020 nominal dollars)																		
Wage Income	-9186	-14534	-3839	-4754	-9790	282	-13530	-19162	-7898	-8323	16072	-575	-8183	-14152	-2214	-5965	-11154	-777
Number of days missed due to illness or injury	5	4	7	4	3	5	7	6	9	4	2	5	5	4	6	5	4	6
Mean hourly wage	-4	-6	-2	0	-2	2	-4	-6	-2	-4	-6	-1	-2	-4	0	-1	-3	0
Absenteeism related cost (# Absent days*hourly wage*8)	871	628	1114	1001	758	1243	1305	938	1671	1129	785	1473	430	164	696	672	458	887

Chapter 4 Manuscript 2

4.1 Abstract

Objective: To determine the impact of new brand-name DMARD entry on the price trend within the three classes of DMARDs.

Methods: We estimated the price trends for brand-name conventional synthetic DMARDs (cDMARDs), biologic DMARDs (bDMARDs), and targeted synthetic DMARDs (tDMARDs) for rheumatoid arthritis (RA) using price data from IBM Micromedex®-REDBOOK® from September 1998 to June 2021. To develop the price trend, monthly estimates of the average annual acquisition costs were determined from the maintenance dose of each DMARD, and wholesale acquisition cost (WAC) estimated from the average wholesale price (AWP). A segmental regression analysis with interrupted time series (ITS) was constructed to determine the impact of new brand-name DMARD entries on the price trends of existing brand-name DMARDs.

Results: A total of thirteen DMARDs were included. From the launch to the year 2021, the prices of Arava® and Azulfidine EN®, which are cDMARDs, increased by 211% (annual 5.4%) and 265% (annual 6.2%), respectively, while the price of Otrexup® decreased by 3% (annual 0.4%). For the bDMARDs, the price increases for Enbrel®, Humira®, Kevzara®, Remicade®, Rituxan®, Simponi®, and Simponi Aria® were 205% (annual 5.2%), 205% (annual 6.2%), 10% (annual 2.7%), 14% (annual 0.6%), 26% (annual 1.5%), 139% (annual 7.3%), and 41% (annual 4.5%), respectively. The prices of Olumiant®, Rinvoq®, and Xeljanz®, which are tDMARDs, increased by 7% (annual 2.6%), 3% (annual 2.4%), and 92% (annual 7.7%), respectively. The ITS results showed that the price of Arava® and Azulfidine EN® did not change with the market entry of a new cDMARD. The price trends of bDMARDs, including Enbrel®, Humira®, and Remicade®, increased at a higher

rate, following the market entries of Simponi® and Simponi Aria®. On the other hand, the price trends of Enbrel®, Humira® Remicade®, Rituxan®, Simponi®, and Simponi Aria® decreased following the market entry of Kevzara®. The impact of within-class new product entries on the price trends for other bDMARDs varied. For tDMARD, the price of Olumiant® immediately decreased with the market entry of Upadacitinib (Rinvoq®).

Conclusion: Overall prices of brand-name cDMARDs, bDMARDs, and tDMARDs used for the RA treatments increased over time. New within-class brand-name DMARD entries had variable effects on the price trends of the existing DMARDs. The impact of new DMARD entries on the price trends of existing DMARDs should be further investigated and monitored.

4.2 Introduction

Rheumatoid Arthritis (RA) related healthcare cost in the U.S. has significantly increased over the years.[28,43,45,46] From a standardized annualized increase of 10.4% from 1996, the estimated healthcare spending for RA in 2016 was $33.8 billion.[28] Most of this spending, $28.4 billion (84%), was attributed to prescription drugs, especially disease modifying antirheumatic drugs (DMARDs).[1,3] For instance, the median total costs per month for etanercept (Enbrel®), adalimumab (Humira®), abatacept (Orencia®), golimumab (Simponi®) and tofacitinib (Xeljanz®) from January 2012 to December 2017 increased by 133% ($1862 to $4334), 124% ($1940 to $4338), 55% ($2482 to $3777), 107% ($1978 to $4094) and 79% ($2,108 to $3757), respectively.[46] One of the major reasons for the high-cost DMARDs was the increase in the prices of existing DMARDs.[47,117] Despite the availability of multiple competing drugs, the prices of brand-name DMARDs dramatically increased.[45,46,49] Discounts and rebates were not able to offset the increasing prices.[49] For instance, the list prices and net prices for tumor necrosis factor (TNF) alpha inhibitors increased by 166% and 73%, respectively, from 2007 to 2018. However, only 56% of the list price increases were offset by discounts and rebates.[49] Consequently, the increase in price was likely to increase RA patients' out-of-pocket costs and reduced patient access to DMARDs.[29,46,54,111,112]

Introducing competition through new product entry has often been discussed as one of the possible solutions to curve rising prices for drugs, including DMARDs.[200] However, the evidence for this argument remained unclear as a recent systematic review suggested that brand–brand competition in the same class was less likely to lower the list prices.[53] A previous study examined the impact of market entries of the competitors on the price trends for existing DMARDs as a case study.[45] Only six brand-name TNF alpha inhibitors, i.e., etanercept, infliximab, adalimumab,

subcutaneous (SC) golimumab, certolizumab pegol, and intravenous (IV) golimumab, were included. The study suggested that the annual treatment costs of existing TNF alpha inhibitors increased by 144% (from $15,809 to $38,574) from April 2009 to December 2016 after new drugs' entries, compared with a 34% (from $15,809 to $21,184) increase expected in the absence of new drugs' entries. However, the impact of new brand-name product entries on other DMARDs remained unknown. Thus, the objective of this study was to determine the impact of new brand-name DMARD entries on the price trends within the three classes of DMARDs, i.e., conventional synthetic DMARDs (cDMARDs), biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tDMARDs).

4.3 Methods

A quasi-experimental interrupted time series (ITS) design was used to study the effects of within-class new brand-name DMARD entries on the price trends of existing brand-name DMARDs. Specifically, a segmental regression analysis with ITS, the strongest quasi-experimental design[45,178,179], was used to assess how much the new DMARD entries changed the prices of existing brand-name DMARDs immediately and over time. Institutional review board approval for this study was not required as the study was based on publicly available information and did not involve patient records. The study followed the STROBE reporting guideline.[180]

Data collection

This study included Food and Drug Administration (FDA)-approved brand-name DMARDs. Four steps were performed to identify the brand-name DMARDs and obtain their price data. First, the American College of Rheumatology (ACR) updated the guideline: Project Plan was used to identify and classify DMARDs.[89] According to the ACR guideline, DMARDs were classified into three different types: cDMARDs (i.e., hydroxychloroquine, leflunomide, methotrexate, and sulfasalazine), bDMARDs (i.e., abatacept, adalimumab, certolizumab,

etanercept, golimumab, infliximab, rituximab, sarilumab, and tocilizumab) and tDMARDs (i.e., baricitinib and tofacitinib). Upadacitinib, recently approved by the FDA, was identified as one of the tDMARDs. Second, Drugs@FDA: FDA-Approved Drugs, an online repository for the names, approval dates, and labels for FDA-approved DMARDs, was searched using the drug names to identify the brand-name DMARDs (DMARDs with New Drug Application (NDA) status).[92] Third, IBM Micromedex®-REDBOOK® was searched to identify the historical records of prices on the brand-name DMARDs.[181] Fourth, only those DMARDs with price data available for at least 24 months, 12 months prior, and 12 months after the entry of new DMARDs in the IBM Micromedex®-REDBOOK® before June 2021 were included.[178] DMARDs that were initially approved but later withdrawn from the market or were not indicated as RA treatments based on FDA-approved product labels were excluded.

This study used estimated wholesale acquisition cost (WAC), generally considered the manufacturer's list price for a drug to a wholesaler or direct purchaser before prompt pay or other discounts, rebates, or reduction in price[182,183], to determine DMARD prices. To estimate WAC, first, retrospective data of unit average wholesale price (AWP) were obtained from the IBM Micromedex®-REDBOOK®.[181] Similar to previous studies[183,184] that indicated AWP=1.2* WAC, this study adjusted the AWPs downward by a factor of 1.2 to generate WAC estimates.[120,185,186]

The number of units required per year for each DMARD was based on FDA-recommended doses for RA treatments available at Drugs@FDA.[92] For DMARDs that should be administered in a loading dose along with a maintenance dose, their numbers of units required per year were based on their maintenance doses only.

Data analysis

We used monthly estimates of annual acquisition costs to standardize the differences in

dosing frequencies across DMARDs. The annual acquisition cost for each DMARD was calculated as the estimated WAC price multiplied by the estimated number of units required per year. For instance, the FDA-recommended dose of Rasuvo® autoinjector for RA is 7.5 mg once a week (one unit). Based on this information, the annual dose of the Rasuvo® autoinjector required for RA treatment was estimated to be 52 units (1 unit per week). If each unit dose of autoinjector costs $123.25 in 2021 U.S. dollars, then the annual acquisition cost for 2021 would be $6422 (52*$123.25). Subsequently, the monthly estimates of the annual acquisition cost were calculated by dividing the annual acquisition cost by 12. Therefore, the monthly estimate of the annual acquisition cost for the Rasuvo® autoinjector would be $535.17 ($6422/12). DMARDs with the same molecule but different routes of administration, e.g., subcutaneous (SC) or intravenous (IV), were treated as separate drugs. Similarly, DMARDs with varying dosage forms but with the same route of administration, e.g., Xeljanz® and Xeljanz XR®, were treated as single DMARDs. The acquisition costs were adjusted for inflation using the medical consumer price index to 2021 U.S. dollars.[168]

Our main analysis was to determine the impact of new DMARD entries on the price trends of existing DMARDs using ITS.[45,178,179] In this study, the dependent variables for the ITS were the monthly estimates of the average annual costs of an individual DMARD. The independent variables included the time (in month), an indicator variable to represent the entry of a new brand-name DMARD (0=before entry of a DMARD, 1=after the entry of a DMARD), and time (in month) after the introduction of a brand-name DMARD (0=before entry of a DMARD, 1 to n=after the entry of a DMARD).[45,120] Specifically, the ITS model was shown here,

$$Y_t=\beta_0+\beta_1 month_t+\beta_2 DMARD_n+\beta_3\, time\ after\ introduction\ of\ DMARD_n+e_t.$$

where "Y_t" was the monthly estimate of the annual acquisition cost for month t and "$month_t$"

was a continuous variable that indicated the time in month. "*$DMARD_n$"* was an indicator for an intervention or a new brand-name DMARD entry (before the entry of new $DMARD_n$=0, after the entry of new $DMARD_n$=1). "*time after the introduction of $DMARD_n$"* was the number of months after the intervention, and coded 0 before the entry of a new brand-name DMARD and a continuous value in months after the entry of a new brand-name DMARD. β_0 and β_1 estimated the baseline intercept (level) and slope (trend) before the intervention, respectively. β_2 and β_3 indicated the absolute intercept (level) and slope (trend) changes after the intervention, respectively. e_t is an error term. All estimates were based on the autoregressive error model with maximum likelihood estimates to account for the correlation between error terms for the time series data. All significant levels were set at 0.05. All statistical analyses were performed using PROC AUTOREG in SAS 9.4 (@Carry, NC).

4.4 Results

Twenty-two FDA-approved brand-name DMARDs (six cDMARDs, twelve bDMARDs, and four tDMARDs) for the RA treatments were initially identified. The cDMARDs included oral hydroxychloroquine (Plaquenil®), approved on April 18, 1995, oral leflunomide (Arava®), approved on September 10, 1998, and oral sulfasalazine (Azulfidine EN®), approved on August 18, 2000. Methotrexate was approved in 1988.[201] The brand-name products of SC methotrexate included Otrexup® approved on October 11, 2013, Rasuvo® approved on July 10, 2014, and Reditrex® approved on November 27, 2019. The bDMARDs included SC etanercept (Enbrel®), approved on November 2, 1988; IV infliximab (Remicade®), approved on April 1, 1999; SC adalimumab (Humira®), approved on December 31, 2002, abatacept IV (Orencia®) approved on December 23, 2005, IV rituximab (Rituxan®) approved on February 28, 2006, SC certolizumab pegol (Cimzia®) approved on June 13, 2009, SC golimumab (Simponi®) approved on April 24,

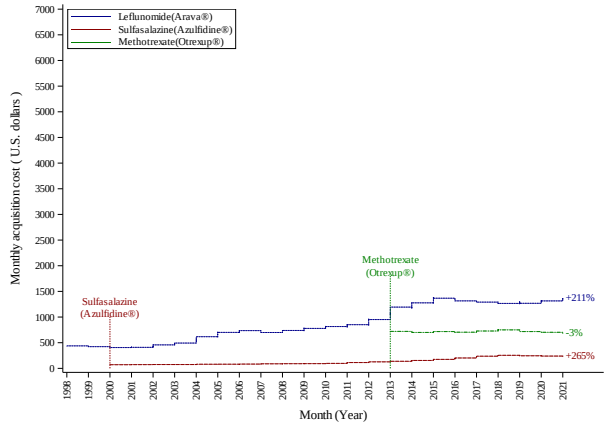
2009, IV tocilizumab (Actemra®) approved on January 8, 2010, SC abatacept (Orencia®) approved on July 29, 2011, IV golimumab (Simponi Aria®) approved on July 18, 2013, SC tocilizumab (Actemra®) approved on October 21, 2013, and SC sarilumab (Kevzara®) approved on May 22, 2017. The tDMARDs included oral tofacitinib citrate (Xeljanz®), approved on November 6, 2012, oral tofacitinib citrate extended release (Xeljanz XR®) approved on February 23, 2016, oral baricitinib (Oluminat®) approved on June 31, 2018, and oral upadacitinib (Rinvoq®) approved on August 16, 2019. However, Plaquenil®, Reditrex®, and Orencia® (SC and IV) were excluded from the study analyses because their data in Micromedex® RED BOOK were incomplete. Additionally, Rasuvo®, Cimzia®, and Actemra® (SC and IV) were excluded since they had less than twelve data points for the ITS to estimate the seasonal variation[178] Xeljanz® and Xeljanz XR® was considered as one drug approved on November 6, 2012, as they have the similar route of administration. Finally, this study included thirteen DMARDs, including three cDMARDs (i.e., Arava®, Azulfidine EN®, Otrexup®), seven bDMARDs (i.e., Enbrel®, Humira®, Kevzara®, Remicade®, Rituxan®, Simponi®, Simponi Aria®,), and three tDMARDs (i.e., Olumiant®, Rinvoq®, and Xeljanz®).

Price trends of cDMARDs, bDMARDs, and tDMARDs

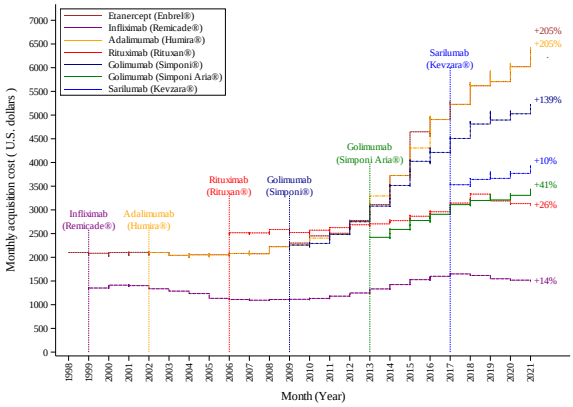
cDMARDs

The monthly price trends of cDMARD are shown in Figure 2A. The price of Arava® increased from $440 in the year 1998 to $1369 in the year 2021, which was equal to 211%, and the annualized change was $40 (5%). Similarly, the price of Azulfidine EN® increased from $66 in the year 2000 to $239 in the year 2021, which equaled 265%, and the annualized change was $8 (6%). However, the Otrexup® price decreased from $719.58 in 2013 to $698.4 in 2021 or by 3%. The annualized change was -$2.86 (-0.37%).

A



B



C

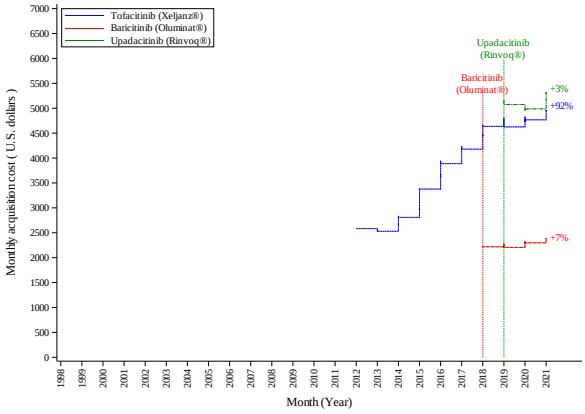


Figure 2. Trend in the monthly price for brand-name disease-modifying antirheumatic drugs (DMARDs) in the U.S. from September 1998 to June 2021.

Data sources IBM Micromedex®-REDBOOK® and Drugs@FDA. **Notes** Percentage shown in the graph represents the relative increase in the list price from the time of its introduction or FDA approval for the treatment of RA. Vertical lines indicate the year in which the drug was approved by the FDA to treat RA.

bDMARDs

The monthly price trends of bDMARD are shown in Figure 2B. The price of Enberel® increased from $2106 in 1998 to $6415 in 2021, which equaled 205%, and the annualized change

was $188 (5%). The price of Humira® increased from $2101 in year 2002 to $6414 in year 2021, which equaled 205%, and the annualized change was $227 (6%). Similarly, the price of Simponi® increased from $2184 in 2009 to $5225 in 2021, which equaled 139%, and the annualized change was $247 (7%). The price of Remicade®, Rituxan®, Simponi Aria®, and Kevzara® increased from $1320 in year 1999 to $1506 in year 2021 (14%), $2465 in year 2006 to $3107 in year 2021 (26%), $2434 in year 2013 to $3438 in year 2021 (41%) and $3561 in year 2017 to $3930 in year 2021 (10%), the annualized increase of $7 (1%), $39 (1%), $127 (5%), and $100 (3%), respectively.

tDMARDs

The monthly price trend for tDMARD is shown in Figure 2C. The price of Xeljanz XR® increased from $2582 in 2012 to $2959 in 2021, which equaled 92%, and the annualized change was $264.13 (8%). Similarly, the prices of Oluminat® and Upadacitinib Rinvoq® increased from $2229 in year 2018 to $2392 (7%) in year 2021 and $5163 in year 2019 to $5311 (3%) in year 2021, with an annualized increase of $58 (3%) and $230 (2%), respectively.

Impact of new DMARDs entries on the price trends of existing DMARDs

cDMARDs

Table 8 shows the results from the ITS for cDMARDs. Before the market entries of the competitors, the average price of Arava® was $424.73 ($p<.0001$) in the year 1998. The price trend insignificantly decreased at $2.71 ($p=.445$) per month. With the market entry of Azulfidine EN® in the year 2000, the estimated mean price level for Arava® immediately dropped by $7.36 ($p=0.714$), whereas the average price trend increased at the rate of $7.25 ($p=0.056$) per month. However, these changes were not statistically significant. With the market entry of Otrexup® in the year 2013, the estimated mean price level of Arava® immediately increased by $21.08 ($p=0.296$), whereas the average price trend decreased at the rate of $1.18 ($p=0.361$) per month. These changes

were also not statistically significant. For Azulfidine EN®, before the market entries of the competitors, the average price was $56.26 (p=<.0004) in the year 2000 and significantly increased at the rate of $0.53 (p=.0006) per month. Right after the market entry of Otrexup® in the year 2013, the estimated mean price level dropped slightly by $0.14 (p=0.960), and the price trend increased at the rate of $0.66 (p=0.065) per month. However, these changes were not statistically significant.

Table 8. Interrupted time series regression coefficients for the impact of new brand-name conventional disease-modifying antirheumatic drugs (cDMARD) entry on the price trend of existing brand-name cDMARDs.

cDMARDs	Absolute change	P-value	CI (95%)
Leflunomide (Arava®)			
Intercept (β0)	424.73*	<.0001	(285.4363, 564.0237)
Months (β1)	-2.7084	0.4445	(-9.6405, 4.2237)
Sulfasalazine (Azulfidine EN®) (β2)	-7.3567	0.714	(-46.6574, 31.9440)
Months after Intervention 1 (β3)	7.2464	0.0561	(-0.1571, 14.6499)
Methotrexate (Otrexup®) (β4)	21.0758	0.2957	(-18.3472, 60.4988)
Months after Intervention 2 (β5)	-1.1765	0.3617	(-3.7, 1.347)
Sulfasalazine (Azulfidine EN®)			
Intercept (β0)	56.2615*	0.0004	(25.3045, 87.21)
Months (β1)	0.5329*	0.0006	(0.2344, 0.8314)
Methotrexate (Otrexup®) (β2)	0.1402	0.9596	(-5.2776, 5.558)
Months after Intervention 2 (β3)	0.6584	0.0651	(-0.0382, 1.3549)

* Statistically significant at a p-value of 0.05

Notes The table shows the interrupted time series regression coefficients (absolute change), relative change, and 95% CI for absolute and relative change for the impact of brand-name conventional disease modifying antirheumatic drugs (cDMARDs) for Rheumatoid arthritis (RA). The relative change was estimated as the ratio of the intervention coefficient (intercept or slope) to the baseline coefficient (intercept or slope). For example, the relative change for the baseline intercept of Leflunomide (Arava®) with the introduction of Methotrexate (Otrexup®) was estimated by dividing β4 (21.0758) to β0 (424.73) corresponding to 5% relative change. 95% confidence interval (CI) for absolute change was estimated as the beta coefficient ± 1.96*se.

bDMARDs

Table 9 shows the results from the ITS for bDMARDs. Before the market entries of the competing DMARDs, the average price of Enbrel® was $2059 (p<.0001) in the year 1988 and insignificantly increased at the rate of $0.24 (p=.864) per month. Following the market entry of Humira® in the year 2002, the average price level dropped immediately by $10.30 (p=0.837), and the price trend decreased at the rate of $0.77 (p=0.763) per month. However, these changes were not statistically significant. With the market entry of Rituxan® in 2006, the price level of Enbrel® decreased by $4.42 (p=0.932), and the price trend increased at $4.52 (p=0.1219) per month. These changes were also not statistically significant. Following the market entry of Simponi® in the year 2009, the averages price level of Enbrel® dropped immediately but insignificantly by $28.60 (p=0.563), and the price trend increased significantly at the rate of $10.50 (p<0.001) per month. With the market entry of Simponi Aria® in the year 2013, the averages price level of Enbrel® dropped immediately but insignificantly by $72.77 (p=0.134), and the price trend increased significantly at the rate of $37.59 (p=<0.001) per month. Similarly, Following the market entry of Kevzara® in the year 2017, the averages price level of Enbrel® increased immediately but insignificantly by $52.09 (p=0.283), and the price trend decreased significantly at the rate of $31.09 (p=<0.001) per month.

Before the market entries of the competing DMARDs, the average price level of Remicade® was $1360 (p<.0001) in the year 1999 and insignificantly increased at the rate of $0.36 (p=.541) per month. Following the market entry of Humira® the year 2002, the average price of Remicade® dropped immediately but insignificantly by $5.31 (p=0.650), whereas the price trend decreased significantly at the rate of $6.25 (p<0.001). With the market entry of Rituxan® in the year 2006, the average price of Remicade® dropped immediately but insignificantly by $15.43 (p=0.189), whereas the price trend increased significantly at the rate of $4.46 (p=<0.001).

Following the market entry of Simponi® in the year 2009, the average price increased immediately by $25.97 (p=0.025), and the price trend increased at the rate of $4.60 (p=<0.001). Both changes were statistically significant. With the market entry of Simponi Aria® in the year 2013, the average price of Remicade® increased immediately but insignificantly by $6.19 (p=0.591), whereas the price trend increased significantly at the rate of $5.30 (p=<0.001). Following the market entry of Kevzara® in the year 2017, the average price increased immediately but insignificantly by $9.74 (p=0.3938), whereas the price trend decreased significantly at the rate of $11.96 (p=<0.001).

Before the market entries of the competing DMARDs, the average price level of Humira® was $2072 (p<.0001) in the year 2002 and insignificantly decreased at the rate of $1.15 (p=.613) per month. Following the market entry of Rituxan® the year 2006, the average price of Humira® increased immediately by $3.74 (p=0.946), and the price trend increased at the rate of $4.643 (p=0.189). However, these changes were not statistically significant. Subsequently, with the market entry of Simponi® in the year 2009, the average price of Humira® decreased immediately but insignificantly by $65.64 (p=0.218), whereas the price trend significantly increased at the rate of $11.58 (p<0.001). Following the market entry of Simponi Aria® in the year 2013, the average price of Humira® decreased immediately but insignificantly by $29.44 (p=0.576), whereas the price trend significantly decreased at the rate of $37.68 (p<0.0001). With the market entry of Kevzara® in the year 2017, the average price of Humira® decreased immediately but insignificantly by $26.86 (p=0.610), whereas the price trend significantly decreased at the rate of $30.68 (p<0.001).

Before the market entries of the competing DMARDs, the average price level of Rituxan® was $2472 (p<.0001) in the year 2006 and insignificantly increased at the rate of $2.79 (p=.625) per month. Subsequently, with the market entry of Simponi® in the year 2009, the average price of Rituxan® decreased immediately and significantly by $105.64 (p<0.0001), whereas the price trend

insignificantly increased at the rate of $0.40 (p=0.914). Following the market entry of Simponi Aria® in the year 2013, the average price of Rituxan® increased immediately by $43.10 (p=0.004), and the price trend increased at the rate of $6.40 (p<0.046). These changes were statistically significant. With the market entry of Kevzara® in the year 2017, the average price of Rituxan® increased immediately but insignificantly by $7.31 (p=0.617), whereas the price trend significantly decreased at the rate of $8.77 (p<0.008).

Before the market entries of the competing DMARDs, the average price level of Simponi® was $2070 (p<.0001) in the year 2009 and significantly increased at the rate of $16.030 (p<.0001) per month. Following the market entry of Simponi Aria® in the year 2013, the average price of Simponi® increased immediately but insignificantly by $9.98 (p=0.854), and the price trend significantly increased at the rate of $19.68 (p<0.001). With the market entry of Kevzara® in the year 2017, the average price of Simponi® increased immediately but insignificantly by $33.45 (p=0.536), whereas the price trend significantly decreased at the rate of $22.522 (p<0.001).

Before the market entries of the competing DMARDs, the average price level of Simponi Aria® was $2361 (p<0.0001) in the year 2013 and significantly increased at the rate of $13.89 (p<0.001) per month. The average price of Simponi Aria® increased immediately but insignificantly, by $46.83 (p=0.108) after the market entry of Kevzara® in the year 2017, whereas the price trend significantly decreased at the rate of $6.28 (p<0.0002).

Table 9. Interrupted time series regression coefficients for the impact of new brand-name biological disease-modifying antirheumatic drugs (bDMARD) entry on the price trend of existing brand-name bDMARDs.

bDMARDs	Absolute change	P-value	CI (95%)
Etanercept (Enbrel®)			
Intercept (β0)	2059*	<.0001	(1974.80, 2143.198)
Months (β1)	0.2422	0.8638	(-2.519, 3.004)
Adalimumab (Humira®) (β2)	-10.2972	0.8372	(-108.3973, 87.80)

Months after Intervention 1 (β3)	-0.774	0.7625	(-5.789, 4.241)
Rituximab (Rituxan®) (β4)	-4.4154	0.9315	(-104.975, 96.144)
Months after Intervention 2 (β5)	4.5226	0.1219	(-1.189, 10.234)
Golimumab SC (Simponi®) (β6)	-28.597	0.5629	(-125.357, 68.163)
Months after Intervention 3 (β7)	10.5001*	<.0001	(5.62, 15.379)
Golimumab IV (Simponi Aria®) (β8)	-72.7674	0.1335	(-167.515, 21.98)
Months after Intervention 4 (β9)	37.5894*	<.0001	(33.37, 41.804)
Sarilumab (Kevzara®) (β10)	52.0896	0.2832	(-42.85, 147.033)
Months after Intervention 5 (β11)	-31.0903*	<.0001	(-35.39, -26.78)
Infliximab (Remicade®)			
Intercept (β0)	1360*	<.0001	(1326.72, 1392.713)
Months (β1)	0.3546	0.5414	(-0.7816, 1.4908)
Adalimumab (Humira®) (β2)	-5.3054	0.6503	(-28.2121, 17.6013)
Months after Intervention 1 (β3)	-6.2479*	<.0001	(-8.2863, -4.2095)
Rituximab (Rituxan®) (β4)	-15.4327	0.1889	(-38.3933, 7.5279)
Months after Intervention 2 (β5)	4.4564*	<.0001	(2.3074, 6.6053)
Golimumab SC (Simponi®) (β6)	25.9647*	0.0254	(3.32, 48.6036)
Months after Intervention 3 (β7)	4.5956*	<.0001	(2.7602, 6.4309)
Golimumab IV (Simponi Aria®) (β8)	6.1933	0.591	(-16.3645, 28.7511)
Months after Intervention 4 (β9)	5.3012*	<.0001	(3.6993, 6.9031)
Sarilumab (Kevzara®) (β10)	9.7389	0.3983	(-12.8223, 32.3001)
Months after Intervention 5 (β11)	-11.9605*	<.0001	(-13.6143, -10.3067)
Adalimumab (Humira®)			
Intercept (β0)	2072*	<.0001	(1957.32, 2186.68)
Months (β1)	-1.1457	0.6133	(-5.59, 3.30)
Rituximab (Rituxan®) (β2)	3.7383	0.9455	(-103.19, 110.6665)
Months after Intervention 1 (β3)	4.6436	0.1889	(-2.2614, 11.5486)
Golimumab SC (Simponi®) (β4)	-65.6379	0.2181	(-169.793, 38.5170)
Months after Intervention 2 (β5)	11.5801*	0.0002	(5.5795, 17.5806)
Golimumab IV (Simponi Aria®) (β6)	-29.4392	0.5757	(-132.37, 73.4915)
Months after Intervention 3 (β7)	37.6808*	<.0001	(32.348, 43.013)
Sarilumab (Kevzara®) (β8)	-26.8563	0.6097	(-129.802, 76.0895)
Months after Intervention 4 (β9)	-30.6756*	<.0001	(-36.0848, -25.2664)
Rituximab (Rituxan®)			
Intercept (β0)	2472*	<.0001	(2346.66, 2597.031)

Months (β1)	2.7921	0.2521	(-1.9703, 7.5545)
Golimumab SC (Simponi®) (β2)	-105.604*	<.0001	(-134.158, -77.049)
Months after Intervention 1 (β3)	0.3999	0.9137	(-6.8209, 7.6207)
Golimumab IV (Simponi Aria®) (β4)	43.096*	0.0036	(14.4974, 71.6945)
Months after Intervention 2 (β5)	6.3952*	0.0455	(0.1737, 12.6166)
Sarilumab (Kevzara®) (β6)	7.3141	0.6166	(-21.2637, 35.891)
Months after Intervention 3 (β7)	-8.771*	0.008	(-15.1777, -2.3643)
Golimumab SC (Simponi®)			
Intercept (β0)	2070*	<.0001	(1946.102, 2193.898)
Months (β1)	16.0299*	<.0001	(12.4031, 19.6566)
Golimumab IV (Simponi Aria®) (β2)	9.9762	0.8536	(-95.7687, 115.7211)
Months after Intervention 1 (β3)	19.6786*	<.0001	(13.5524, 25.804)
Sarilumab (Kevzara®) (β4)	33.4528	0.5361	(-72.24, 139.1456)
Months after Intervention 2 (β5)	-22.5219*	<.0001	(-28.708, -16.335)
Golimumab IV (Simponi Aria®)			
Intercept (β0)	2361*	<.0001	(2298.311, 2423.689)
Months (β1)	13.8895*	<.0001	(11.8371, 15.941)
Sarilumab (Kevzara®) (β2)	46.8309	0.1084	(-9.758, 103.42)
Months after Intervention 1 (β3)	-6.2803*	0.0002	(-9.4202, -3.1403)

* Statistically significant at a p-value of 0.05

Notes The table shows the interrupted time series regression coefficients (absolute change), relative change, and 95% CI for absolute and relative change for the impact of brand-name conventional disease modifying antirheumatic drugs (cDMARDs) for Rheumatoid arthritis (RA). The relative change was estimated as the ratio of the intervention coefficient (intercept or slope) to the baseline coefficient (intercept or slope). For example, the relative change for the baseline intercept of Golimumab IV (Simponi Aria®) with the introduction of Sarilumab (Kevzara®) was estimated by dividing β2 (46.8309) to β0 (2361) corresponding to 2% relative change. 95% confidence interval (CI) for absolute change was estimated as the beta coefficient ± 1.96*se.

tDMARDs

Table 10 presents the results from the ITS for tDMARDs. Before the market entry of the competing DMARDs, the average price level of Xeljanz® was $2257 (p<0.001) in the year 2012 and significantly increased at the rate of $33.14 (p<0.001) per month. Following the market entry of Oliumiant® in 2018, the average price of Xeljanz® decreased immediately but insignificantly by $8.19 (p=0.926), and the price trend decreased at the rate of $11.46 (p=0.397). However, these

changes were statistically not significant. Similarly, with the market entry of Rinvoq® in 2019, the average price of Xeljanz® decreased immediately by $58.25 (p=0.506), and the price trend decreased at the rate of $11.46 (p=0.516). However, these changes were not statistically significant.

Before the market entry of the competing DMARDs, the average price of Olumiant® level was $2214 (p<.0001) in the year 2018 and significantly increased at the rate of $3.456 (p=.019) per month. The average price of Olumiant® dropped immediately and significantly by $34.00 (p=0.021) after the market entry of Rinvoq® in 2019, whereas the price trend insignificantly increased by $2.76 (p=0.096).

Table 10. Interrupted time series regression coefficients for the impact of new brand-name targeted synthetic disease-modifying antirheumatic drugs (tDMARD) entry on the price trend of existing brand-name tDMARDs.

tDMARDs	Absolute change	P-value	CI (95%)
Tofacitinib Citrate (Xeljanz®)			
Intercept (β0)	2257*	<.0001	(2059.13, 2454.87)
Months (β1)	33.1394*	<.0001	(28.2419, 38.0368)
Baricitinib (Olumiant®) (β3)	-8.1887	0.9264	(-181.465, 165.0875)
Months after Intervention 1 (β4)	-11.4592	0.3971	(-37.8639, 14.9455)
Upadacitinib (Rinvoq®) (β5)	-58.2529	0.5064	(-229.44, 112.9343)
Months after Intervention 1 (β6)	-11.8439	0.5158	(-47.432, 23.7442)
Baricitinib (Olumiant®)			
Intercept (β0)	2214*	<.0001	(2174.388, 2253.612)
Months (β1)	3.4566*	0.0188	(0.7104, 6.192)
Upadacitinib (Rinvoq®) (β2)	-33.9983*	0.021	(-61.4422, -6.5543)
Months after Intervention 1 (β3)	2.7646	0.0959	(-0.3935, 5.9227)

* Statistically significant at a p-value of 0.05

Notes The table shows the interrupted time series regression coefficients (absolute change), relative change, and 95% CI for absolute and relative change for the impact of brand-name conventional disease modifying antirheumatic drugs (cDMARDs) for Rheumatoid arthritis (RA). The relative change was estimated as the ratio of the intervention coefficient (intercept or slope) to the baseline coefficient (intercept or slope). For example, the relative change for the baseline intercept of Baricitinib (Olumiant®) with the introduction of Upadacitinib (Rinvoq®) was estimated by dividing β2 (-33.9983) to β0 (2214) corresponding to -2% relative change. 95% confidence interval (CI) for absolute change was estimated as the beta coefficient ± 1.96*se. 95%

CI for relative change was estimated from the bootstrapping method suggested by Zhang et al., 2009.

4.5 Discussions

Our findings suggested that, despite the market entries of new products, the prices of DMARDs (cDMARDs, bDMARDs, and tDMARDs) increased from their launch dates to the year 2021, except for Otrexup®. The impact of new DMARD entries on the price trends of existing DMARDs varied.

The prices of Arava® and Azulfidine EN® continued to increase over time. However, the new DMARD entries did not significantly impact their price trends. One of the reasons might be the small number of competitors, and the manufacturers could continuously increase the prices of these DMARDs.[37] Another reason might be that bDMARDs were expensive. This provided an opportunity for the manufacturers of Azulfidine® and Arava® to raise their prices.[37] On the contrary, we observed that the price of Otrexup® decreased by 3% (annualized rate of 0.37%) from its launch date to 2021. One of the reasons might be the presence of multiple competing molecular products, i.e., branded and generic methotrexate, for Otrexup®. These findings were consistent with a previous study, which suggested that the unit costs of branded leflunomide and hydroxychloroquine increased by 50% and 76%, respectively, whereas the unit cost of branded injectable methotrexate decreased by 2% for Medicare beneficiaries between 2012 to 2017.[37]

The impact of new DMARD entries on the price trends of cDMARDs was relatively small compared to those of bDMARDs and tDMARDs. Generally, the prices of bDMARDs continued to rise from their launch dates to year 2021, despite the market entries of new bDMARDs. One of the reasons might be the market exclusivity for bDMARDs protected by monopoly rights and patents.[47] Lack of competition from low-price biosimilar products during the market exclusivity period might allow the manufacturers of existing bDMARDs to set the prices based on what the

market would bear, leading to continuous price increases.[51] Another reason might be that bDMARDs competed in the rebate space for preferred branded drug status in formularies.[49,202] Thus, the manufacturers might increase the prices of bDMARDs to offer a larger rebate to pharmacy benefit managers (PBMs) or payers as well as to compete and gain favorable formulary placement.[53,200] Furthermore, clinical practice, such as prescriber preferences for the bDMARDs with documented safety and effectiveness profiles, clinical guidelines recommending treat-to-target strategy prompting physicians to select the most effective treatment irrespective of price, and lack of incentive for prescribers to select the most cost-effective treatment, might seal bDMARDs from the effects of price competition leading to the continuous price increases.[43,53,203,204] The parallel price increases of Enbrel® and Humira® in this study also suggested the possibility of collusion among manufacturers to keep off the competition, which could be a reason for the continuous price increases.[46] Thus, consistent with previous studies, the within-class competition did not necessarily reduce the prices of bDMARDs.[45,53] Also, the prices of tDMARDs increased from its launch date to the year 2021, probably for similar reasons. However, the price changes of these tDMARDs and the reasons for these changes needed to be investigated further since two out of three tDMARDs in this study were launched to the market in less than five years.

In this study, only the prices of Remicade®, Rituxan®, and Olumiant® significantly changed in response to the entries of four new DMARDs. Only two of the study DMARDs, i.e., Rituxan® and Olumiant®, experienced significant price decreases after the entries of the first DMARDs within their respective classes. On the other hand, the prices of Remicade® and Rituxan® increased significantly after the entries of the third and second DMARDs, respectively. It was possible that

the manufacturers of some branded DMARDs might reduce their prices to ensure their competitiveness only when facing the first new competitors in the market.

Interestingly, the impact of the entries of Simponi®, Simponi Aria®, and Kevzara® on the price trends of Enbrel®, Remicade®, and Humira® shared some similarities. The significant increasing price trends of Enbrel®, Remicade®, and Humira® following the market entries of Simponi® in the year 2009 and Simponi Aria® in the year 2013, and the significant decreasing price trends following the market entry of Kevzara® in the year 2017 were found. For the increasing price trends after the entries of Simponi® and Simponi Aria®, it was possible that the manufacturers of Enbrel®, Remicade®, and Humira® might not need to reduce their prices to compete with Simponi® and Simponi Aria® since they all are TNF inhibitors. On the other hand, they might drop their prices to compete with Kevzara®, an interleukin-6 inhibitor that is a newer drug and could possibly provide better efficacy and safety.[205] Similarly, the decreasing price trends of Simponi® and Simponi Aria® after the entry of Kevzara®. These results were like a previous study showing the increasing price trends of existing branded TNF inhibitors after the entries of new TNF inhibitors.[45] A recent systematic review also indicated that the competition among branded drugs in the same class would likely not result in lower drug prices.[53]

The case of Rituxan®, a B-cell inhibitor, was slightly different. The price trend of Rituxan® did not significantly change after the entry of Simponi®. Later, when Simponi Aria® entered the market, the price trend of Rituxan® significantly increased until after the entry of Kevzara®. One of the reasons was that the manufacturer of Rituxan® might decide to immediately drop the price to compete with Simponi®. Since it was a big decrease, the manufacturer might find it unnecessary to reduce the price of Rituxan® later. Also, the manufacturer might learn from the competition with Simponi® and decide to increase the price of Rituxan® after the entry of Simponi Aria®, which is

another TNF inhibitor. On the other hand, when Kevzara® entered the market, the decreasing price trend of Rituxan® was found for a similar reason as the decreasing price trends of Enbrel®, Remicade®, and Humira® after the entry of Kevzara®. For the tDMARDs, the new entries did not seem to affect the price trends of existing tDMARDs. One reason could be that all these tDMARDs are in the same class, which is Janus kinase inhibitors.

Our findings have several implications for patients, clinicians, payers or policymakers, and the pharmaceutical industry. For instance, patients might continue to face high out-of-pocket costs for DMARDs, which could affect their ability to adhere to treatment and achieve optimal health outcomes due to the increasing price trends of DMARDs. They needed to work with clinicians to consider alternative treatment options, e.g., lower-cost DMARDs. Also, they needed to seek health insurance coverage that allowed them to access costly DMARDs. Payers or policymakers might need to explore other strategies to address high drug prices, e.g., increasing transparency, promoting the use of biosimilars, or implementing regulations on drug pricing. Finally, the pharmaceutical industry could use the study findings to set up the competitive prices of DMARDs since they knew that the new DMARD entries historically had low or no impact on the price trends of existing DMARDs.

Our study had several limitations. One potential concern might be the likelihood of the inflated estimation of monthly acquisition cost using AWP. AWP was phased out in 2011[206] in favor of WAC[183] and it did not reflect the ultimate cost to the payer due to discounts and rebates. However, this study tried to minimize such overestimation by adjusting the AWP by a factor of 1.2, as the literature suggested.[185] Also, AWP had been the prevailing prices for reimbursement for decades, and recent studies indicated that AWP could provide a consistent measure of price comparisons over time.[120] Second, given the proprietary nature of discounts and rebates, it was not

feasible to estimate real acquisition costs. Brand-brand competition might occur in the rebate and discount space with different price trends, compared to our study, which partially explained a seemingly growing difference between net and list prices.[53] Third, in addition to the brand-name DMARDs, the entries of biosimilars might impact the price trends of DMARDs because of within-molecule competitions and their lower prices. However, this impact was likely small, given the first biosimilar Inflectra® (infliximab) approved in 2016, the protection of market exclusivity for the originator through patient extension, and the lengthy process to demonstrate the safety and efficacy of biosimilars. Additionally, biosimilars were not considered a generic substitute for brand-named biologics unless approved as interchangeable biosimilar by US FDA.[46] Last, since this study used publicly available data, which were sometimes incomplete, our analyses were limited to a small number of brand name DMARDs.

4.6 Conclusion

Despite the presence of competition in the pharmaceutical industry, the prices of brand-name cDMARDs, bDMARDs, and tDMARDs used to treat RA continued to rise over time. New within-class brand-name DMARD entries had variable effects on the price trends of the existing DMARDs. These findings highlighted the complex nature of the U.S. pharmaceutical market, suggesting that the issue of rising DMARDs prices required a multifaceted approach and should be further investigated.

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5.1 Abstract

Objective: To assess the preference-based value of disease-modifying antirheumatic drugs (DMARDs) for rheumatoid arthritis (RA).

Methods: A cross-sectional, web-based discrete choice experiment (DCE) survey was conducted among U.S. patients with RA. Based on a literature review, think aloud method, and a pilot survey, six DMARD attributes, including the chance of pain reduced by 50% or more, the chance of physical function improved by 50% or more, the chance of fatigue reduced by 10 points or more, the chance of serious side effects, the way you take the medication, and out-of-pocket cost per month, were chosen. A Bayesian efficient design was used to generate nine DCE choice tasks per questionnaire. Each choice task contained two hypothetical DMARD alternatives and a follow-up opt-out alternative. Using a mixed logit (ML) model and latent class (LC) model, the conditional relative importance of each attribute was determined. Willingness-to-pay (WTP) values were calculated for all DMARD attributes.

Results: Responses from 228 patients were analyzed. ML model showed that the chance of reducing pain by 50% or more had the highest conditional relative importance, followed by out-of-pocket cost, the chance of improving physical function by 50% or more, the chance of reducing fatigue by 10 points or more, the chance of experiencing severe adverse events, and the way the medication is taken. The LC model identified two patient classes. For class 1, the chance of reducing pain by 50% or more was most important, whereas, for class 2, the out-of-pocket cost was the most important. Patients in class 1 preferred subcutaneous (SC) injection or intravenous (IV) infusion DMARDs with various frequencies of administration than oral DMARDs with daily

administration, while patients in class 2 preferred oral with daily administration. The chance of serious side effects was statistically significant for patients in class 1 but class 2. The ML model based WTPs were $2.07, $1.25, $1.04, and -$3.87 for each level change of the pain, physical function, fatigue, and serious side effects attributes, respectively. Similarly, WTPs were $16.42 for SC injection, -$6.63 for IV infusion four or eight weeks, and -$12.01 for IV infusion six or 12 months, compared to oral with daily administration DMARDs. RA patients' WTPs for DMARDs varied from $91 to $231 per month.

Conclusion

RA patients had different preference weights and values across DMARDs attributes. Preference heterogeneity was observed among RA patients, who considered fatigue reduction as a significant attribute of DMARDs while making a treatment decision.

5.2 Introduction

Rheumatoid arthritis (RA) is a long-term autoimmune condition where the immune system mistakenly attacks the synovium or the lining of the joints.[1-3] This can result in synovial swelling, joint inflammation, pain, and in severe cases, bone damage and disability.[2,4,207] It is estimated that approximately 0.53% to 0.55% (1.28 to 1.66 million) of US adults were diagnosed with RA.[10,11] RA was associated with a significant economic burden to the U.S. healthcare system.[25-32] A recent study estimated that RA-related healthcare cost was $33.8 (28.9 to 37.7) billion in 2016 dollars.[28]

Patients with RA must be treated with disease-modifying antirheumatic drugs (DMARDs) to reduce symptoms (e.g., pain, stiffness, and swelling), improve fatigue, prevent damage to joints and organs, improve physical functioning, and achieve remission.[1,19,20,207] A conventional synthetic DMARD (cDMARD), methotrexate, is often used as the first line of treatment and can lead to low disease activity or remission in 25-50% of patients.[22,207] Other cDMARDs include sulfasalazine, leflunomide, and hydroxychloroquine. However, given the progressive nature of the disease, biological DMARDs (bDMARDs), such as tumor necrosis factor [TNF] inhibitors (i.e., etanercept, adalimumab, certolizumab, golimumab, infliximab), abatacept, rituximab, interleukin (IL)-6 receptor inhibitors (e.g., tocilizumab and sarilumab), and targeted synthetic (tDMARDs), such as Janus kinase (JAK) inhibitors (e.g., tofacitinib, baricitinib, and upadacitinib), may be required as monotherapy or combination therapy for patients who do not respond to methotrexate.[1,21] However, these DMARDs are costly. The estimated annual direct medical costs per RA patient using DMARDs was $20,262, compared to $3,723 for all RA patients using other treatment regimens (2015 dollars).[31] These higher costs were a significant barrier to patient access to DMARDs. Therefore, the values of DMARDs for money needed to be assessed.

Cost-effectiveness analysis (CEA) with quality-adjusted life-years (QALYs) is a widely

used method for assessing the value of DMARDs.[56,58] Institute for Clinical and Economic Review (ICER) suggested that, as compared to cDMARDs, targeted immune modulators (rituximab, abatacept, tocilizumab, tofacitinib, adalimumab, certolizumab pegol, etanercept, golimumab and, infliximab) exceeded the commonly cited willingness-to-pay threshold of $150,000/QALY and were not cost effective.[56] On the other hand, compared to adalimumab, most were less costly and more effective.[56,58] However, using QALYs as an outcome measure in CEA has been controversial since it is a single-dimensional measure that does not reflect patient preferences and preference heterogeneity.[59,60] Due to a wide variety of DMARDs with varying efficacy and side effects and the need for multiple treatments throughout a patient's life, patient preferences for DMARDs might differ. Such preference heterogeneity could stem from not only observed variables or factors like age, gender, or income but also unobserved variables or attributes of DMARDs.[61] The 2015 American College of Rheumatology (ACR) guideline recommends that treatment decisions should be made through a shared process between clinicians and patients, taking into account the patient's values and preferences.[30,89,208] The European Alliance of Associations for Rheumatology (EULAR) guideline also advises considering preference heterogeneity when making treatment decisions for RA.[90] Additionally, the US Food and Drug Administration (FDA) recognized the significance of capturing this heterogeneity in patient preference information.[129] Hence, it is important to include patient preferences and preference heterogeneity in the value assessment of DMARDs.

A systematic review summarized the findings from eight studies[61,66-72] on patient preferences for DMARDs in the U.S.[65] Five studies[61,68-72] used conjoint analysis (CA), which might not be suitable for economic applications and cannot measure human preference.[73] Two studies used a DCE to examine patient preferences for DMARDs but did not consider preference

heterogeneity.[66,67] Another study used DCE to evaluate the value of DMARDs based on patient preferences and heterogeneity, but it was conducted in 2009 or before various DMARDs, e.g., subcutaneous and intravenous tocilizumab (Actemra®), subcutaneous abatacept (Orencia®), intravenous golimumab (Simponi Aria®), subcutaneous sarilumab (Kevzara®), tofacitinib citrate (Xeljanz®/Xeljanz XR®), oral baricitinib (Oluminat®), and oral upadacitinib (Rinvoq®), were launched.[61] More importantly, a systematic review and a study with nominal group technique indicated that fatigue was a crucial outcome domain for RA patients,[74-76] Also, Innovation and Value Initiative (IVI) and Arthritis Foundation conducted qualitative interviews and reported that fatigue was one of the important domains patients with RA factored in their choices of DMARDs. However, previous patient preference studies never examined fatigue and provided an incomplete picture of patient preferences for DMARDs.[74] Thus, the objective of this study was to assess the preference-based value of DMARDs. This study also intended to examine the value of the reduction in fatigue and preference heterogeneity.

5.3 Methods

A cross-sectional, web-based DCE questionnaire survey was used to evaluate the preference-based value for DMARDs for patients with RA. DCE is a stated preference-based survey method that relies on the Random Utility Theory (RUT) and involves multiple attributes.[70] According to RUT, an individual's "utility" for each choice option is inherent but cannot be directly observed by researchers.[70,150] In a DCE survey, several choice tasks, including hypothetical options or alternatives described by various attributes and levels, are presented to participants.[149] Participants are then asked to choose an alternative based on their preferences in each task. This study followed User's DCE guide and the Good Research Practices Task Force report from The Professional Society for Health Economics and Outcomes Research (ISPOR).[149,187,188] Willingness

to pay (WTP), a monetary welfare metric, was calculated to determine the preference-based values of DMARDs.[75,76] The study protocol was approved by Auburn University Institutional Review Board (IRB).

Study sample

The study was conducted among RA patients in the U.S. who were 18 years and older, proficient in English and used DMARDs. The patients were recruited through a national online Qualtrics^{XM} panel, a market research company, between January 29 to February 10, 2023. Only those patients who indicated if a doctor or other health professionals ever told them that they have RA and have previously taken DMARD were included. The sample size was determined using various methods, including Good Research Practices, a published practical guide, and sample-size efficiency.[189] Based on the approach from the published practical guide[187], prior parameters from a pilot study were used to ensure sufficient power to detect a reasonable effect size.

Study attributes and levels

A list of the important DMARD-related attributes was generated from the systematic literature search. Appendix II provides the details of the search strategy and literature reviewed. Based on the systematic reviews[74,190-192] and the discussion with five RA patients and a rheumatologist, the six most important attributes were selected in this study. These attributes included the chance of pain reduced by 50% or more, the chance of physical function improved by 50% or more, the chance of fatigue reduced by 10 points or more (on the visual analogue scale of 0= no fatigue and 100=worst fatigue), the chance of serious side effects (e.g. heart failure, serious viral infection, or serious bacterial infection that may require intravenous (IV) treatments), the route and frequency of administration (the way to take medicine), and out-of-pocket cost per month (See Table 11). The levels of the benefit and risk attributes and the route and frequency of administration were obtained from the clinical trials of all DMARDs. [92] Appendix III provides the

details of the literature used to determine the levels of the benefits, risks, and route and frequency of administration attributes. The levels of the cost attribute were based on the maximum willingness to pay estimate obtained from a pilot study.

Table 11. Attributes and Levels for the Discrete Choice Experiments (DCE) Survey Instrument

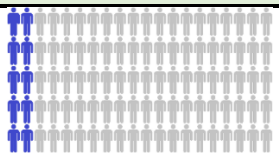
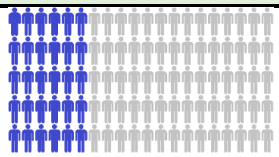
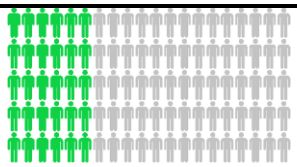
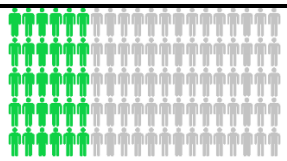
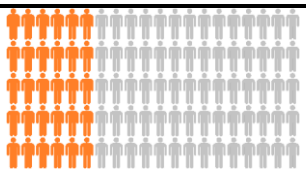
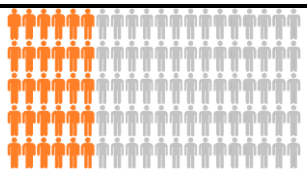
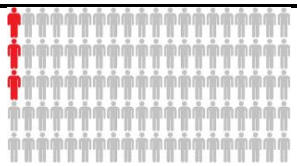
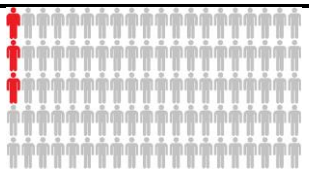
	Attributes	**Levels**
1	Chance of pain reduced by 50% or more	70 out of 100 (70%) patients
		30 out of 100 (30%) patients
		10 out of 100 (10%) patients
2	Chance of physical function improved by 50% or more	70 out of 100 (70%) patients
		30 out of 100 (30%) patients
		10 out of 100 (10%) patients
3	Chance of fatigue reduced by 10 points or more	70 out of 100 (70%) patients
		30 out of 100 (30%) patients
		10 out of 100 (10%) patients
4	Chance of serious side effects	10 out of 100 (10%) patients
		3 out of 100 (3%) patients
		0 out of 100 (0%) patients
5	The way you take the medication	Oral, daily
		Subcutaneous (SC) injection, every 1 week or every 2 weeks

		Intravenous (IV) infusion, every 4 weeks, or every 8 weeks
		Intravenous (IV) infusion, every 6 months, or every 12 months
6	Out-of-pocket cost per month	$ (No Cost) per month
		$ 25 per month
		$ 75 per month
		$ 150 per month

Survey development

A Bayesian efficient design was used to draw 36 choice tasks from all possible combinations of the selected attributes and levels.[188,193] The algorithm of the Bayesian efficient design entailed an iterative procedure that compared statistical efficiency among various designs. The statistical efficiency was computed from the Halton draws of prior parameters obtained from a pilot study with 30 RA patients. These 36 choice tasks were divided into four blocks. Each choice task consisted of two unlabeled alternatives describing hypothetical DMARDs: Medication A or Medication B. Patients with RA were asked to choose one of these hypothetical medications and then were allowed to choose neither medication A nor medication B to resemble real-world choices. An example of the DCE choice set is presented in Figure 3. Two validity check choice tasks were added. The first validity check choice task contained the within task dominant alternative, i.e., a medication with the highest benefits, lowest risks, and lowest cost. Patients who understood the survey were expected to choose the dominant alternative. Also, a choice task was repeated to examine the stability of patient response. Questions on patient characteristics and RA experiences were also added to the survey instrument.

Q. Please choose your preferred DMARD medication option

Characteristics	Medication A	Medication B
Chance of pain reduced by 50% or more	 10 out of 100 (10%) patients	 30 out of 100 (30%) patients
Chance of physical function improved by 50% or more	 30 out of 100 (30%) patients	 30 out of 100 (30%) patients
Chance of fatigue reduced by 10 points or more	 30 out of 100 (30%) patients	 30 out of 100 (30%) patients
Chance of serious side effects	 3 out of 100 (3%) patients	 3 out of 100 (3%) patients
The way you take the medication	 Subcutaneous (SC) injection, every 1 week or every 2 weeks	 Oral, daily
Out-of-pocket cost per month	$ 75 per month	$ 25 per month

I prefer to choose:

☐ Medication A

☐ Medication B

If you have the option not to choose any of these two medications, will your choice remain the same?

☐ Yes, my choice will remain the same.

☐ No, my choice will change; now I prefer not to choose any of these two medications.

Figure 3. An example DCE choice set

To ensure the patient's understanding of the study attributes, lay language was used to name each attribute. Also, clear explanations were provided using the tutorial on the attributes and their values. After patients read the description of each attribute, they were asked to respond to practice questions to assess their understanding. The correct answers with brief explanations were then displayed to ensure their understanding. The cheap talk was included to improve the validity of the survey responses. A clinical expert and two social scientists reviewed the survey before the survey was validated with five patients with RA using a think aloud method. The survey was then piloted with 30 patients through the Qualtrics^{XM} panel. Various changes were made based on the pilot study results to improve the survey. For instance, the maximum level of the cost attribute was determined as $150 per month. Similarly, the number of practice questions for each attribute to evaluate patients' understanding were reduced from three questions for each attribute to two questions for each attribute due to the cognitive burden.

Data analysis

Demographic characteristics of the patients were descriptively analyzed using mean for continuous variables and frequency for count variables. Based on RUT, individuals' responses for each choice set were observed and analyzed. For the pilot study, a multinomial logit (MNL) model was developed to determine the perceived utility or attractiveness of an alternative with the utility function (U^n_{sj}) for patient n with a choice set s, alternative j, and attribute k;

$$U^n_{sj} = V^n_{sj} + \varepsilon^n_{sj}, \text{ (Where, } V^n_{sj} = \sum_{k=1}^{K} \beta_k X^n_{sjk} \text{)}$$

Here, V^n_{sj} was the systematic utility or mean expected utility perceived by all patients having the same choice alternatives and attributes, ε^n_{sj} was a random component that followed an independent and identically distributed (iid) assumption, X^n_{sjk} was the full vector of observed attributes relating to individual n and alternative j on the choice set s, and β_k was the coefficient or the mean attribute weight of attribute k. The value of each coefficient indicated the relative

importance of each attribute, while the sign of the coefficient reflected whether the attribute had a positive or a negative effect on utility or preference compared with the base level of the attribute.

Mixed logit (ML) and latent class (LC) models were developed to examine patient preferences and preference heterogeneity from the data of the main survey. Effect codes were used. The general form of the utility function (U_{nsj}) of the ML model was:

$$U^{n}_{sj} = \sum_{k=1}^{K}(\beta_k + \acute{\eta}^{i}_{k})X^{n}_{sjk} + \tau^{n}_{j}$$

Here, U^{n}_{sj} was the utility function relating to individual n and alternative j on the choice set s. X^{n}_{sjk} was the full vector of observed attributes relating to individual n and alternative j on the choice set s, and β_k was the vector of individual-specific coefficients of attribute k. $\acute{\eta}^{n}_{k}$ was the random error term whose distribution depends on alternative j and individual n. τ^{n}_{j} was the error distribution that did not depend on underlying parameters or data. The interpretations of the value and sign of each coefficient were similar to the interpretations described for the MNL model. The conditional relative importance for each attribute was determined by comparing the changes in preference weights between its most and least favorable levels. Preference heterogeneity from the ML model was determined by examining the variation in coefficients across individuals in the sample. In the ML model, each individual was assumed to have its own set of preferences, which were modeled as random coefficients. The variation in the estimated mean of these coefficients across individuals reflected preference heterogeneity.[194]

The LC model assumes that individual behavior depends on observable attributes and on latent heterogeneity that differs from factors that are unobserved by researchers.[195] Thus, the LC model distinguishes the groups of individual patients with similar preferences. To determine the preference estimates for different groups or characteristics of patients, this study fitted the LC models to c classes (unknown to the researchers) by using various model fit parameters, e.g.,

Akaike Information Criteria (AIC). Given the membership of class c, the following utility function for alternative j ($U^{n}_{sj|c}$) was estimated.

$$U^{n}_{sj|c} = \sum_{k=1}^{K} \beta_{k} X^{n}_{sjk|c} + \varepsilon^{n}_{sj|c},$$

where U^{n}_{sj} was the utility function relating to individual n and alternative j on the choice set s belonging to class c. $X^{n}_{sjk|c}$ was the full vector of observed attributes relating to individual n and alternative j on the choice set s and belonging to class c, and β_{k} was the vector of class-specific coefficients of attribute k. $\varepsilon^{n}_{sj|c}$ was the class specific error term whose distribution depended on alternative j and individual n.

To estimate the WTPs of the DMARD attributes, another ML model, assuming linear continuous specifications of all attributes, except the route and frequency of administration, was developed. Also, only the marginal WTP of each attribute was calculated by taking the ratio between the mean coefficients of each attribute and the cost attribute. Each represented the patient's WTP for a one-unit change of each attribute or reflected the value of DMARD attributes. A Krinsky and Robb method was used to estimate 95% confidence intervals of WTPs of the attributes.[196] Using this information, the WTP for each of the existing DMARDs, such as Humira®, could be estimated by multiplying the marginal WTP with the attribute values specific to each DMARD obtained from the literature.

5.4 Results

This study included a total of 228 patients with RA in the analyses. The patients were evenly distributed across the four blocks of the survey, with 57 patients in each block. These patients accurately responded to the validity choice tasks. Table 12 shows their demographic characteristics. The average age of these patients was 50.3 (SD 13.7) years, and the average disease duration was 33.2 (SD 9.2) years. Most patients were female (82.5%) and white (87.7%). Most

household incomes were less than $50,000 per year (57.9%). Most had less than a 4-year college degree (81.4%) and insurance (96.5%). Almost half of the patients were married or in a domestic partnership (49.6%) and were employed full-time, part-time, or self-employed (42.5%). The most common comorbid conditions were high blood pressure (43.0%), back pain (65.3%), and depression (58.3%). Most of these patients described their overall health status as good or fair (77.2%) and reported that the survey was easy or very easy to understand (67%). Most patients correctly answered the practice questions related to attributes and levels of pain (85.1%), physical function (74.6%), fatigue (93.4%), serious side effects (87.3%), and method of administration (95.2%).

Preference weights of the DMARD attributes from the ML model

Figure 4 illustrates the preference weights for the study attributes from the ML model. The preference weights for all attributes, except the chance of fatigue reduced by 10 points or more, were in the expected directions. The higher chances of reducing pain and improving physical function by 50% or more, lower chance of serious side effects, and lower out-of-pocket cost had higher preference weights. While all adjacent levels of the chances of reducing pain and improving physical function by 50% or more were significantly different from one another, only the difference between the preference weights of the medications with the chances of serious side effects at 3% and 10% was significant. On the other hand, only the difference between the preference weights of the out-of-pocket cost at $0 (no cost) and $25 per month was not statistically significant. No adjacent level of the route and frequency of administration attribute was significantly different. A kink in preferences for increasing the chance of reducing fatigue was observed. Compared with a 10% chance of reducing fatigue, patients significantly preferred a 30% chance of reducing fatigue. However, there was a significant reduction in the preference weight

between medications offering a 70% chance and a 30% chance of reducing fatigue.

The highest conditional relative importance estimate was attributed to the chance of pain reduced by 50% or more (2.4), followed by the out-of-pocket cost (2.1), the chance of physical function improved by 50% or more (1.6), the chance fatigue reduced by 10 points or more (1.1), the chance of experiencing severe adverse events (0.6), and the way you take the medication (0.03). The standard deviations of the preference weights of all attributes were statistically significant, indicating the presence of preference heterogeneity for these study attributes.

Preference weights of the DMARDs attributes from the LC model

Based on the AIC values, the best LC model suggested two distinct classes. Figure 5 displays the preference weights of DMARDs attributes for RA patients in both classes. The LC model assigned 163 patients to class 1 and 65 to class 2.

Similar to the results of the ML model, the preference weights for all attributes, except the chance of fatigue reduced by 10 points or more, in both classes tended to have expected directions. In class 1, only all adjacent levels of the chance of reducing pain were significantly different from one another. Only the difference between the preference weights of medications offering a 10% chance and a 30% chance of improving physical function by 50% or more were significantly different. All adjacent levels of the out-of-pocket cost, except the difference between the preference weights of $0 and $25 per month, were significantly different. No adjacent level of the chance of serious side effects was significantly different. For the route and frequency of administration, the preference weight of the IV infusion every six- or 12-months medications was significantly higher than the IV infusion every four or eight weeks medications. In class 2, all adjacent levels of the chance of reducing pain, improving physical function, and serious side effects were significantly different from one another. All adjacent levels of the out-of-pocket cost,

except the difference between the preference weights of $0 and $25 per month, were significantly different. For the route and frequency of administration, the preference weight of the oral, daily medications was significantly higher than the subcutaneous injection every one- or two-weeks medications. A kink in preferences for increasing the chance of reducing fatigue for this class was similar to the ML results. Compared with a 10% chance of reducing fatigue, patients significantly preferred a 30% chance of reducing fatigue. Also, there was a significant reduction in the preference weight between medications offering a 70% chance and a 30% chance of reducing fatigue. A kink in preferences for increasing the chance of reducing fatigue was found in both classes. Compared with a 10% chance of reducing fatigue, patients in these two classes significantly preferred a 30% chance of reducing fatigue. Also, there was a significant reduction in the preference weight between medications offering a 70% chance and a 30% chance of reducing fatigue.

In class 1, the conditional relative importance estimate of the chance of pain reduced by 50% or more was the highest (1.8), followed by the out-of-pocket cost (1.4), the chance of physical function improved by 50% or more (1.2), the chance of fatigue reduced by 10 points or more (0.8), the way you take the medication (0.5), and the chance of serious side effects (0.5). In class 2, the highest conditional relative importance estimate was the out-of-pocket cost attribute (2.4), the chance of pain reduced by 50% or more (1.4), the chance of physical function improved by 50% or more (1.3), the way you take the medication (1.2), the chance of fatigue reduced by 10 points or more (0.9), and the chance of serious side effects (0.8).

Preference-based value for DMARDs

The WTPs for the attributes of DMARD based on the ML model were estimated in the preference space. For any DMARD with a 1% increase in the chance of pain reduced by 50% or

more, the estimated WTP was $2.07 (95% CI: $1.73, $2.5). For any DMARD with a 1% increase in the chance of physical function improved by 50% or more, the estimated WTP was $1.25 (95% CI: $0.97, $1.59). For any DMARD with a 1% increase in the chance of fatigue reduced by 10 points or more, the estimated WTP was $1.04 (95% CI: $0.79, $1.33) for the chance of fatigue reduced by 10 points or more. For any DMARD with a 1% increase in the chance of serious side effects, the estimated WTP was -$3.87 (95% CI: -$5.37, -$2.57). Compared to any oral, daily DMARD, the estimated WTP for an SC injection, every one week or every two weeks DMARD was $16.42 (95% CI: $6.58, $26.56). Compared to any oral, daily DMARD, the estimated WTP for an IV infusion, every four weeks or every eight weeks DMARD was -$6.63 (95% CI: -$17.06, $3.56). Compared to any oral, daily DMARD, the estimated WTP for an IV infusion, every six months or every 12 months DMARD was -$12.01 (95% CI: -$22.99, -$1.23).

Table 13 shows the WTPs for the DMARDs currently available in the US markets. Based on our estimates, the RA patients in this study were willing to pay the highest amount ($231 per month) for upadicidnib, whereas they were willing to pay the lowest amount ($91 per month) for hydroxychloroquine, leflunomide, or sulfasalazine.

5.5 Discussions

This study utilized DCE to determine the preference-based value of DMARDs. To our knowledge, this was the first patient preference study that included the reduction in fatigue as a DMARD benefit.

The findings from the ML model revealed that patients with RA generally preferred DMARDs that provided greater chances of pain reduction and improvement in physical function, a lower chance of severe side effects, and a lower out-of-pocket cost. These findings were intuitive and consistent with the findings of previous studies.[65,66,69,72,190,209-211] However, the results

suggested that patients with RA had a higher preference weight only for a 30% chance of the reduction in fatigue, compared with a 10% chance of the reduction in fatigue. The change of the preference weight from a 30% chance of the reduction in fatigue to a 70% chance of the reduction in fatigue was counterintuitive. Further analyses, including combinations of the chance of improvement in physical function and the chance of reduction in fatigue in the ML model, were performed to explore these results (see supplement). The results showed that, for each of the three levels of chance of improvement in physical function, a 30% chance of reduction in fatigue had higher preference weight compared to a 10% chance of improvement. For a 30% chance of improving physical function, the preference weight was marginally significant. These results suggested that patients with RA had similar preferences for a 30% chance and a 70% chance of reduction in fatigue when DMARDs provided either a low or higher chance of improvement in physical function. It was possible that when DMARDs performed well for the chance of improvement in physical function, patients might perceive the chance of reduction in fatigue as only an additional benefit, and this benefit might no longer matter for their preferences after achieving a certain level. On the other hand, the high chance of reduction in fatigue might not matter for patients with RA if DMARDs performed poorly for the chance of improvement in physical function since the patients could not be active due to their limited physical function. When DMARDs moderately performed for the chance of improvement in physical function, patients might not carefully consider the chance of reduction in fatigue, leading to the counterintuitive results of the change of the preference weight from a 30% chance of the reduction in fatigue to a 70% chance of the reduction in fatigue.

The ML results also showed no difference in the preference weights among various levels of the route and frequency of administration attribute. These findings could not be compared

directly to the findings of previous U.S.-based DCE studies since the levels of the route and frequency of administration attribute were defined differently in this study. While the previous studies suggested that RA patients in the U.S. preferred oral treatment to SC injection or IV infusion and SC injection to IV infusion and preferred lower frequency to higher frequency of administration,[66,67,69,72] patients with RA might tradeoff among different routes and frequencies in this study and found that the convenience resulted from a lower frequency of administration could offset the inconvenience from the injection.

Several choice-based studies have investigated the conditional relative importance of DMARDs attributes in the U.S.[61,66-72] The conditional relative importance of chance of pain reduction, followed by out-of-pocket cost, physical function improvement, and serious side effects, was in line with the previous findings. However, the findings of this study added the importance of the reduction in fatigue to the literature.[74] The chance of reduction fatigue had a significant impact on the patient's choice of DMARDs. Its importance was slightly lower than the improvement in physical function and 1.7 times as important as the chance of serious side effects. These findings were consistent with the findings of various studies indicating that fatigue could affect as many as 80%-98% of patients with RA, causing significant disruption and distress that had a detrimental effect on their quality of life.[212-215] Also, previous qualitative studies suggested that fatigue could be as important as the improvement in pain and physical function.[65,190,216-218]

According to the LC model, two distinct patient classes were identified based on their preferences for DMARDs. Both classes demonstrated significant alternative-specific constants, with values of 2.81 and -0.97 for classes 1 and 2, respectively. This finding suggests that only patients in class 1 preferred using the treatment alternatives described by the DMARDs attributes. Class 1 prioritized the probability of pain reduction the most, while class 2 placed greater emphasis

on out-of-pocket costs. However, both classes considered pain reduction and out-of-pocket costs to be the top two important attributes. Greater importance on the treatment benefit, such as the chance of improvement in the pain, was expected.[65,211] Despite having insurance, a larger number of older age people (average age 50 years), who were not employed (58%), and had less than $50,000 in annual income (58%) might be the reasons for the greater importance given to the cost attribute by RA patients in this study. This suggested the need for shared decision making among the patients and providers regarding the affordability of the DMARD medication.

Interestingly, patients in class 1 were indifferent for the different levels of serious side effects effect. These findings were consistent with a previous study, which suggested that a certain group of patients with RA might be less concerned about the risk of serious side effects.[71] They also favored IV infusion over SC injection or oral, daily medication. The greater preference weight given to IV therapy might be attributed to a reluctance to self-inject, less frequent dosing requirements, and a preference for administration by a healthcare professional.[219] For patients in class 2, the preference weights significantly decreased with the increase in the chance of serious side effects. These findings suggested that patients in class 2 were more sensitive to the serious side effects and were reluctant to use injectable DMARDs.[68,71,220] It was possible that these patients might have different levels of experience with DMARDs. They could be the patients with longer duration of RA might give high importance to avoiding rare but serious side effects and injection.[65] On the other hand, they could be the patients with less experience with RA and DMARDs. They, therefore, preferred to avoid serious effects and were not familiar with the injection.

This study estimated the WTP both on preference space and WTP space based on the linear continuous specification for all attributes except for the route and frequency of administration. Given the similarity of the results, we reported the WTP for the preference space as the coefficients

were easy to interpret. WTP estimates from our study was generally in line with the WTP estimates from Husni et.al[66] but were lower than that of Özdemir et al.[61] One of the reason for lower WTP estimates from that of Ozdemir et al. might be because of the difference in attribute and levels between these studies. According to our research findings, upadacitinib emerged as the most valuable treatment option, with a monthly cost of $231. This was attributed to its superior efficacy in reducing pain and fatigue and enhancing physical function. Interestingly, patients did not prioritize the risk of serious side effects or the mode of administration in determining the value of the treatment. On the other hand, hydroxychloroquine, leflunomide, and sulfasalazine were ranked the least valuable, with a monthly cost of $91. This was largely due to their lower effectiveness in reducing pain and fatigue and improving physical function.

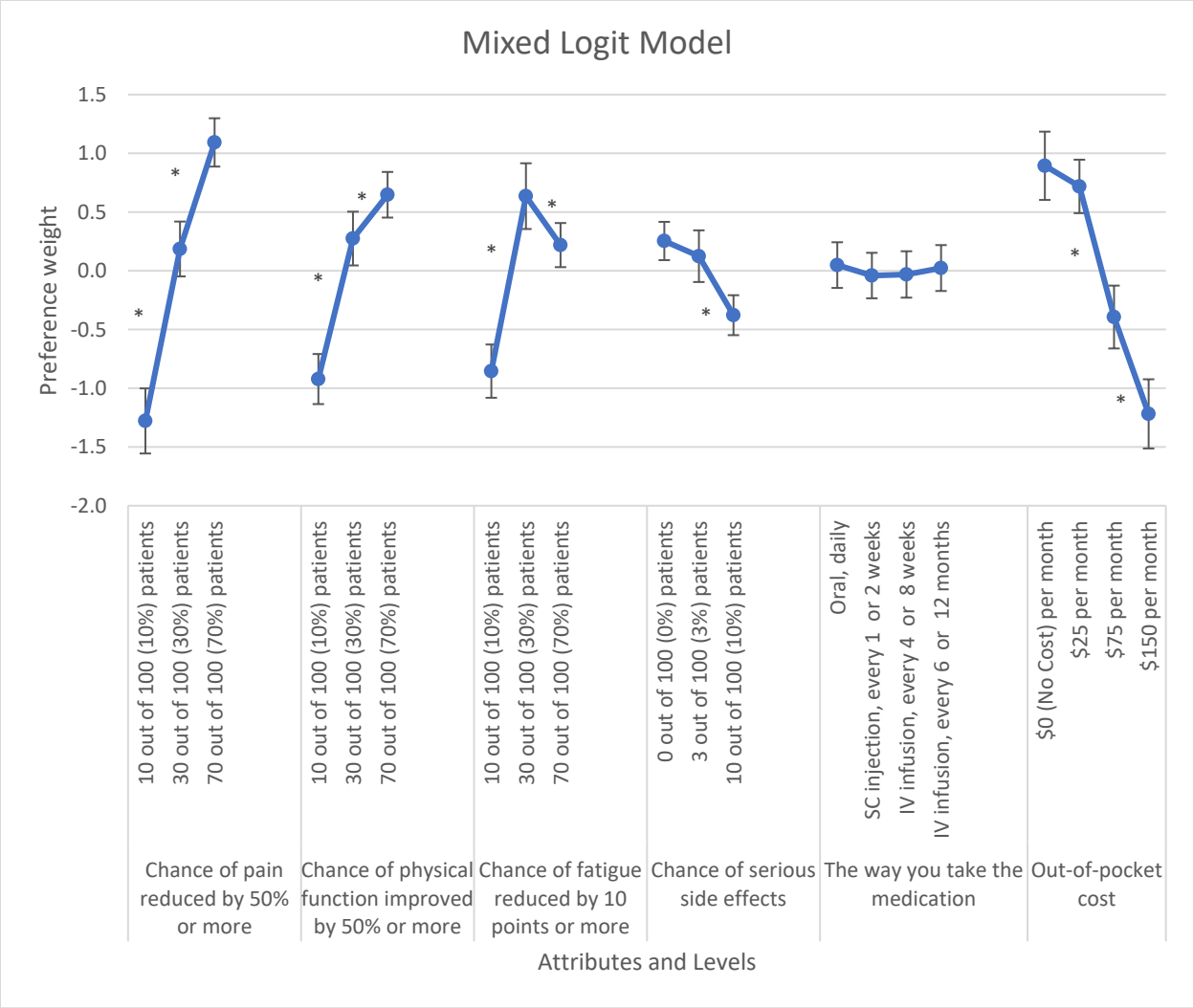
This study had several implications for making treatment decisions. First, even though most RA patients had health insurance coverage, the out-of-pocket cost remained one of the most important factors influencing treatment preferences. Thus, while making a treatment decision, a clinician should provide patients with comparative out-of-pocket cost information.[71] Second, the RA patients weighed the importance of the chance of fatigue higher than the chance of serious side effects and the route and frequency of administration. This implied that clinicians should assess the impact of DMARDs on the fatigue of their patients to provide individualized care and improve the quality of life[221] Furthermore, the existence of diverse preferences among patients implied that the importance of DMARD attributes might vary depending on individual patient characteristics and underlying conditions. Therefore, treatment decisions should be tailored to individual patients considering their preferences through a shared decision-making process.

Our study should be interpreted in light of the following limitations. First, the patients in this study included the overrepresentation of white, female, and highly educated patients with RA

and might not represent the RA patients in the US. Second, the study relied on patient preferences for hypothetical treatment options, which might not correspond to their actual treatment choices that could be influenced by various emotional, financial, and clinical factors. However, this study used real-world treatment attributes and levels to construct hypothetical treatment options. Third, the study used a self-administered web-based questionnaire, which could be subject to response bias due to the potential for misinterpreting attribute levels. However, the study employed various measures, such as an expert review and a validity check choice set, to minimize this bias. Fourth, the study only included six treatment attributes, and while they were chosen carefully, other treatment factors could still influence patient preferences. Fifth, apart from the route and frequency of administration, this study assumed that all attributes had linear continuous specifications, which might not be a valid assumption when WTPs were calculated. Finally, although it is a best practice also to include RA patients who did not correctly respond to the validity choice question and perform a sensitivity analysis, given the lack of availability of data of these patients from Qualtrics^{XM}, only those RA patients who provided a valid response were included in the analyses.

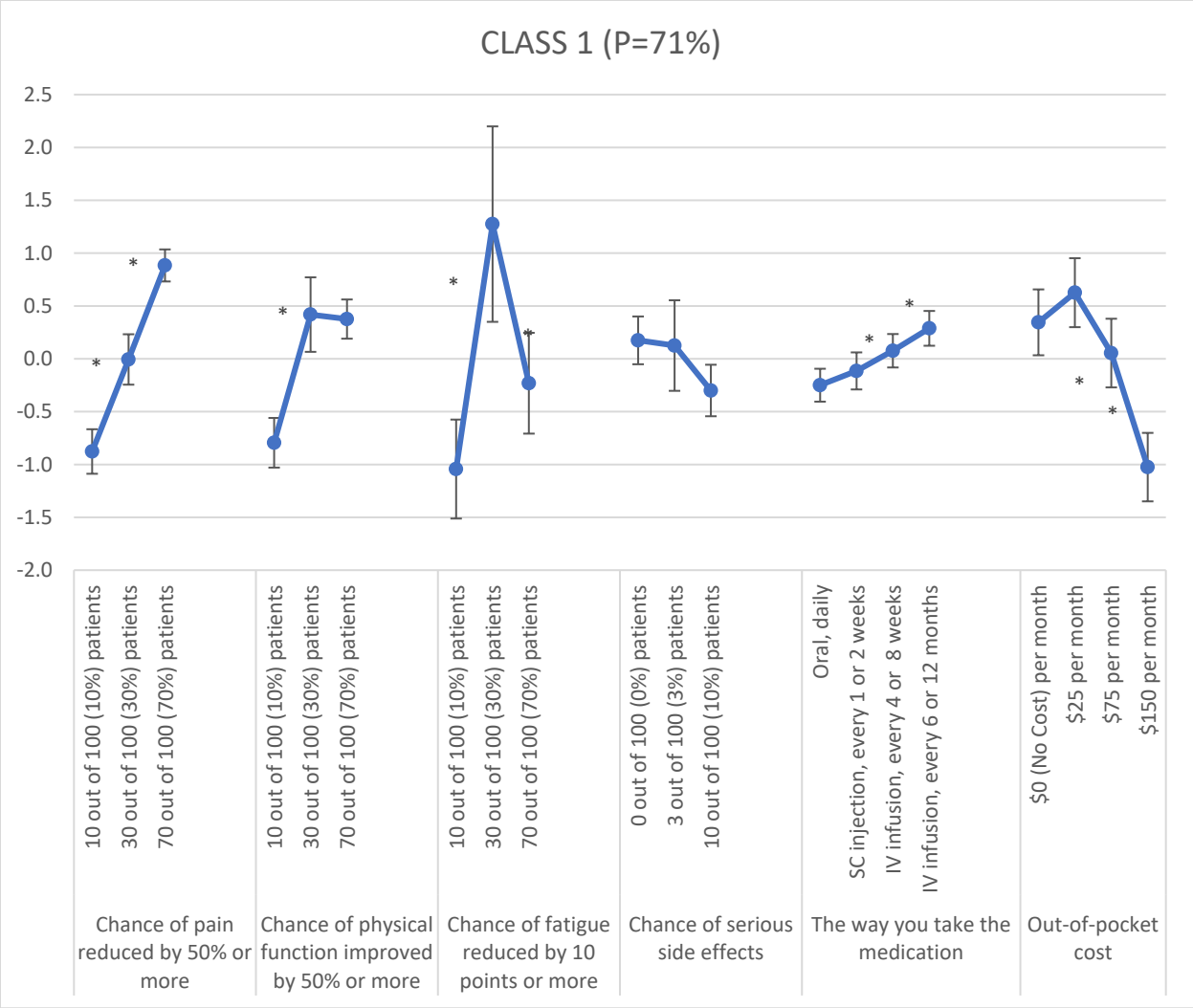
5.6 Conclusion

The chance of pain reduced by 50% or more, the chance of physical function improved by 50% or more, the chance of fatigue reduced by 10 points or more, the chance of serious side effects, the route and frequency of administration, and out-of-pocket cost per month were important to patients with RA. Patients with RA tended to weigh the importance of the benefits, including the reduction of fatigue, and out-of-pocket cost higher than the serious side effects and the route and frequency of administration of DMARDs. However, preference heterogeneity was present, implying the need for individualized treatment for each patient.



* = Significance at 5% level

Figure 4. Preference weights of attributes of DMARDs from the mixed logit model


CLASS 1 (P=71%)
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
10 out of 100 (10%) patients
30 out of 100 (30%) patients
70 out of 100 (70%) patients
Chance of pain reduced by 50% or more
10 out of 100 (10%) patients
30 out of 100 (30%) patients
70 out of 100 (70%) patients
Chance of physical function improved by 50% or more
10 out of 100 (10%) patients
30 out of 100 (30%) patients
70 out of 100 (70%) patients
Chance of fatigue reduced by 10 points or more
0 out of 100 (0%) patients
3 out of 100 (3%) patients
10 out of 100 (10%) patients
Chance of serious side effects
Oral, daily
SC injection, every 1 or 2 weeks
IV infusion, every 4 or 8 weeks
IV infusion, every 6 or 12 months
The way you take the medication
$0 (No Cost) per month
$25 per month
$75 per month
$150 per month
Out-of-pocket cost

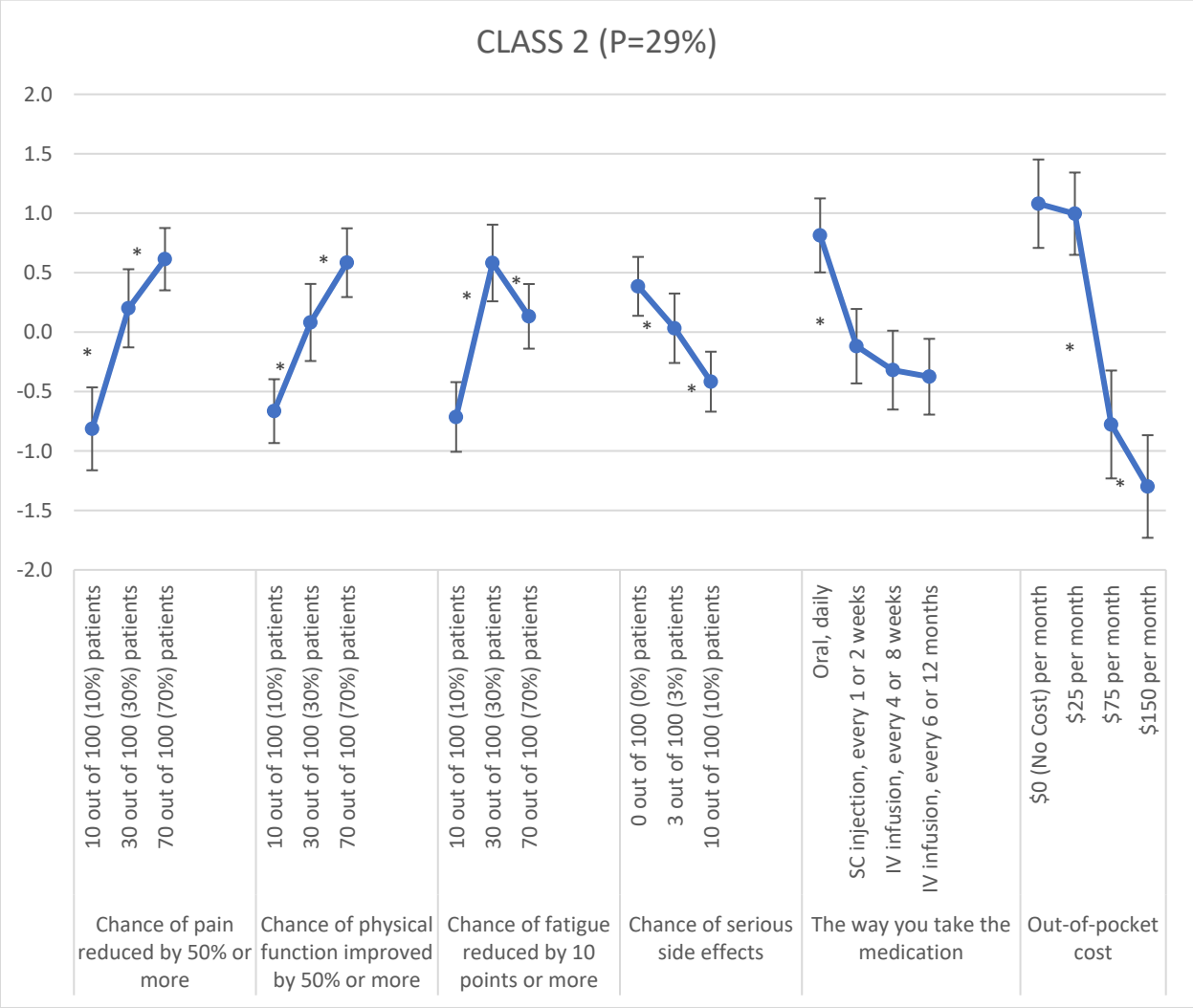


Figure 5. Preference weights of attributes of DMARDs from the latent class model

Table 12. Demographic characteristics of the RA patients

Age in years, mean (SD), N=228	50.3 (13.70)
Duration of Rheumatoid Arthritis (years), mean (SD)	33.2 (9.20)
DMARD used N (%)	
Actemra® (Tocilizumab)	6 (2.63)
Cimzia® (Certolizumab pegol)	2(0.88)
Enbrel® (Etanercept)	42(18.42)
Humira® (Adalimumab)	61(26.75)
Kevzara® (Sarilumab)	1(0.44)
Olumiant® (Baricitinib)	0 (0.00)
Orencia® (Abatacept)	11 (4.82)
Remicade® (Infliximab)	9 (3.95)
Rinvoq® (Upadacitinib)	11 (4.82)
Rituxan® (Rituximab)	6 (2.63)
Simponi®/Simponi Aria® (Golimumab)	5 (2.19)
Xeljanz® (Tofacitinib citrate)	11 (4.82)
Hydroxychloroquine (For example: Plaquenil®)	39 (17.11)
Leflunomide (For example: Arava®)	10 (4.39)
Methotrexate (For example: Otrexup®)	51 (22.37)
Sulfasalazine (For example: Azulfidine®)	10 (4.39)
Other (Please specify):	26 (11.40)
Not sure	22 (9.65)
None of the above	0 (0.00)
Willing to pay more than $150 per month (?)	
Yes	64 (28.07)
No	164 (71.93)
Sex, N (%)	

Male	40 (17.54)
Female	188 (82.46)
Race, N (%)	
White	200 (87.72)
Black or African American	15 (6.58)
American Indian / Alaska Native	2 (0.88)
Asian / Native Hawaiian / Other Pacific Islander	4 (1.75)
Others	1 (.044)
Two or more race	6 (2.63)
Marital Status, N (%)	
Married or domestic partnership	113 (49.56)
Single, never married	40 (17.54)
Divorced or separated/Widowed/Others	75 (32.89)
Household Income, N (%)	
$200,000 or more per year	7 (3.07)
$150,000 to $199,999 per year	4 (1.75)
$100,000 to $149,999 per year	20(8.77)
$50,000 to $99,999 per year	57 (25.00)
Less than $50,000 per year	132 (57.89)
Prefer not to say	8 (3.51)
Education, N (%)	
Graduate or professional degree (e.g., MBA, MS, MD, PhD)	13 (5.70)
4-year college degree (e.g., BA, BS)	30 (13.16)
2-year college degree (associate degree)	38 (16.67)
Technical / vocational training	19 (8.33)
Some college but no degree	61 (26.75)
High school or less than high school	67 (29.39)
Employment Status, N (%)	

Employed full-time	60 (26.32)
Employed part-time	19 (8.33)
Self-employed	18 (7.89)
Stay-at-home spouse	15 (6.58)
Student	3 (1.32)
Retired	42 (18.42)
Unemployed	14 (6.14)
Disabled	55 (24.12)
Others (Please specify)	2 (0.88)
Health Insurance, N (%)	
Medicare	80 (35.09)
Medicaid	88 (38.60)
Veterans Affairs	6 (2.63)
Tricare	8 (3.51)
Health insurance through my workplace or employer	51 (22.37)
Health insurance purchased directly from marketplace	18 (7.89)
I do not have health insurance	8 (3.51)
Others (Please specify)	15 (6.58)
Comorbidities, N (%)	
High blood pressure	98 (42.98)
Heart diseases	21 (9.21)
High blood lipid levels e.g., cholesterol, triglyceride	48 (21.05)
Cancer	15 (6.58)
Ulcer or stomach diseases	27 (11.84)
Blood diseases	9 (3.95)
Kidney diseases	8 (3.51)
Lung diseases	22 (9.65)
Liver diseases	7 (3.07)

Diabetes	35 (15.35)
Back pain	149 (65.35)
Depression	133 (58.33)
Obesity	63 (27.63)
Others (Please specify)	45 (19.74)
None	13 (5.70)
Health Status, N (%)	
Excellent	1 (0.44)
Very good	32 (14.04)
Good	90 (39.47)
Fair	86 (37.72)
Poor	19 (8.33)

Table 13. Willingness to pay (WTP) estimates for the DMARDS currently available in the US market

	DMARDs	Chance of pain reduced by 50% or more	Chance of physical function improved by 50% or more	Chance of fatigue reduced by 10 points or more	Chance of serious side effects	Oral, daily	SC injection, every 1 or 2 weeks	IV infusion, every 4 or 8 weeks	IV infusion, every 6 or 12 months	WTP estimates
1	Abatacept IV	40	40	60	4			1		173
2	Abatacept SC	40	40	60	3		1			200
3	Adalimumab	40	40	55	5		1			187
4	Baricitinib	47	47	65	4	1				208
5	Certolizumab	30	30	55	7		1			146
6	Etanercept	45	45	50	5		1			198
7	Golimumab IV	30	30	60	3			1		144
8	Golimumab SC	30	30	60	6		1			155
9	Hydroxychloroquine	20	20	35	3	1				91
10	Infliximab	30	30	40	7		1			131
11	Leflunomide	20	20	35	3	1				91
12	Methotrexate oral	20	20	41	3	1				97
13	Methotrexate SC	20	20	41	3					97

14	Rituximab	25	25	60	6					1	112
15	Sarilumab	45	45	40	4		1				192
16	Sulfasalazine	20	20	35	3	1					91
17	Tocilizumab	47	47	55	3			1			195
18	Tofacitinib	32	32	58	3	1					155
19	Upadacitinib	55	55	65	5	1					231

Abbreviations: IV, Intravenous infusion, SC, Subcutaneous injection, WTP, Willingness to pay. **Note** Benefit and risk of each DMARDs was based on the information obtained from the Institute for Clinical and Economic Review on targeted immune modulators for rheumatoid arthritis: effectiveness and value, Janus Kinase Inhibitors and Biosimilars for Rheumatoid Arthritis: Effectiveness and Value, and other best available literatures. WTP estimates should be interpreted based on the value of benefit and risk used in this study as they may vary with a different source of literature.

Chapter 6 Conclusion and Implications

6.1 Conclusions and Study Implications

In summary, we observed that expenditure for patients with RA, who used DMARDs, increased over the five study periods (2008-2009, 2010-2011, 2012-2013, 2014-2015, and 2018-2019) in the U.S. The RA costs notably increased between the 2010-2011 to 2012-2013 periods. The upward trend of the RA costs was largely driven by prescription drug costs, especially the costs of DMARDs, which also continued to rise over time. The increasing costs strain healthcare resources in the country, impacting its ability to provide adequate care to patients. While absenteeism had a relatively small contribution to the overall expenditure of RA in this study, the impact of DMARDs on absenteeism was observed. The costly DMARDs could reduce patient adherence, resulting in poorer health outcomes, e.g., decreased productivity, increased disability, and decreased quality of life.

While market competition through new product entry could be one of the possible solutions to curve rising prices for DMARDs, this study observed that the new within-class brand-name DMARD entries had variable effects on the prices of the existing DMARDs. However, the price trends after entries tended to be upward due to the market adjustment. As a result, payers could face the increasing costs of DMARDs and require patients with RA to share more costs. Subsequently, patients with RA could have limited access to DMARDs since they could not afford DMARDs, given the higher out-of-pocket costs. These findings highlighted the complex nature of the U.S. pharmaceutical market and suggested that addressing the issue of rising DMARD prices required a multifaceted approach besides the market competition. For instance, clinicians might need to consider patient affordability when choosing DMARDs. Also, there was a need for

policymakers to explore strategies other than the market competition to address high DMARD prices, such as implementing value assessment frameworks to evaluate the costs and benefits of DMARDs.

This study also assessed the preference-based value of DMARDs, which could be used to supplement the widely used CEA with QALYs. Among various attributes of DMARDs, the benefits of DMARDs, including the reduction in fatigue that was never examined or taken into account when making treatment decisions, and out-of-pocket cost tended to be important factors when choosing DMARDs. However, preference heterogeneity was observed among RA patients. Therefore, clinicians should tailor treatment decisions for individual patients based on their characteristics and underlying conditions. Based on patient preferences, this study also showed the RA patients' WTPs for DMARDs varied from $91 to $231 per month. These WTPs reflected how patients valued different DMARDs due to their preference weights on the attributes and levels of DMARDs. Besides the clinical evidence and CEA with QALY, clinicians, payers, and policymakers could use these WTPs to guide their decision making. However, it was noteworthy that these WTPs were the maximum amount of money patients with RA were willing to forfeit from their out-of-pocket money based on the DMARD attributes. They should not be interpreted as fair prices or WTP amounts in real life.

6.2 Limitations

The expenditure study included various limitations. First, we could not control the severity and duration of RA, which might influence the direct medical and absenteeism-related costs. Second, the self-report bias in the MEPS surveys might affect disease prevalence and costs. Third, the study only included non-institutional individuals. Fourth, the indirect costs were based solely

on absenteeism-related costs, excluding other productivity losses and quality of life impacts. Therefore, the true indirect cost estimates might not be accurately reflected.

There were three primary considerations regarding the study of the new brand-name DMARD entries on price trends. First, the estimation of monthly acquisition costs using AWP might be inflated, and they might not reflect the actual costs to the payers due to discounts and rebates. Secondly, biosimilar entries and within-molecule competitions, which were not captured in this study, might also affect price trends. Additionally, data availability restricted the analysis to a small number of brand-name DMARDs.

The study on the preference-based value of DMARDs for RA also included various limitations. First, the study population overrepresented white, female, and highly educated patients with RA. Secondly, hypothetical bias and response bias might exist. Thirdly, the study only included six treatment attributes, and other factors might influence patient preferences. Fourth, the assumptions of linear continuous specifications for all attributes might not hold when calculating WTP. Finally, the analysis excluded RA patients who did not correctly respond to the validity choice question.

6.3 Future Research

While the impact of absenteeism-related costs was relatively minor in this study, it was important to note that our findings were limited to observations from MEPS data, where absenteeism-related costs were the only measure of indirect costs. Therefore, future research should aim to comprehensively explore the trends in the economic burden of RA by incorporating multiple data sources to estimate indirect costs. This could involve examining the impact of RA on reduced productivity while at work (presenteeism), loss of employment, caregiver burden, and decrease in quality of life. Moreover, future studies with larger sample sizes of RA patients and

more detailed information on the severity and duration of their illness would allow a more accurate assessment of the impact of RA on both direct and indirect costs. It was also noteworthy that most RA patients in our study did not use DMARDs because of potential self-reported bias or misclassification. Therefore, future studies could benefit from using real-world data, such as medical records, to verify self-reported information.

Furthermore, we observed that overall prices of brand-name cDMARDs, bDMARDs, and tDMARDs used for the RA treatments increased over time, as estimated using the WAC. However, WAC is generally the manufacturer's list price before prompt pay or other discounts, rebates, or price reduction and may not be the actual acquisition cost. Thus, future research could explore the impact of discounts and rebates on estimating the trends in monthly acquisition costs. This might include investigating the effects of brand-brand competition in the rebate and discount space on DMARD prices. Future research could also examine the impact of biosimilars on DMARD prices since more biosimilars are anticipated to enter the market, and the competition should increase.

Last, our study was the first rigorous study that quantitively showed that RA patients considered fatigue reduction a significant attribute of DMARDs while making a treatment decision. This highlighted the importance of eliciting patients' unmet needs, such as living a normal life and maintaining independence, in future preference studies. In addition, there was a need to explore practical methods for incorporating preference-based values of DMARDs into policy decisions. This might involve considering when and how to incorporate patient preferences into decision-making processes.

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APPENDIX

Appendix I: Brand-name disease-modifying antirheumatic drugs (DMARDs) approved by U.S. FDA for RA treatments.

Brand Name	Generic name	Manufacturer	Route of administration	Group	FDA Approval
Actemra®	Tocilizumab subcutaneous	Genentech	Subcutaneous	BO	10/21/2013
Actemra®	Tocilizumab IV infusion	Genentech	IV infusion	BO	1/8/2010
Arava®	Leflunomide	Sanofi Aventis Us	Oral Tablet	CS	9/10/1998
Azulfidine EN-Tabs®	Sulfasalazine delayed release	Pharmacia And Upjohn	Oral Tablet	CS	8/18/2000
Azulfidine EN-tabs®	Sulfasalazine delayed release	Pharmacia And Upjohn	Oral Tablet ER	CS	6/20/1950
Azulfidine®	Sulfasalazine	Pharmacia And Upjohn	Oral Tablet	CS	6/20/1950
Cimzia®	Certolizumab Pegol	Ucb Inc	Subcutaneous	BO	5/13/2009
Enbrel®	Etanercept	Immunex	Subcutaneous	BO	11/2/1998
Humira®	Adalimumab	Abbvie Inc	Subcutaneous	BO	12/31/2002
Kevzara®	Sarilumab	Sanofi Synthelabo	Subcutaneous	BO	5/22/2017
Methotrexate Sodium	Methotrexate sodium	Hospira	Oral/Injectable*	CS	8/10/1959
Olumiant®	Baricitinib	Eli Lilly And Co	Oral Tablet	TS	5/31/2018
Orencia®	Abatacept	Bristol Myers Squibb	Subcutaneous	BO	7/29/2011
Orencia®	Abatacept IV	Bristol Myers Squibb	IV infusion	BO	12/23/2005
Otrexup®	Methotrexate	Antares Pharma Inc	Subcutaneous	CS	10/11/2013
Plaquenil®	Hydroxychloroquine	Concordia	Oral Tablet	CS	4/18/1955
Rasuvo®	Methotrexate	Medexus	Subcutaneous	CS	7/10/2014
Reditrex®	Methotrexate	Cumberland Pharms	Subcutaneous	CS	11/27/2019
Remicade®	Infliximab	Centocor Inc	IV infusion	BO	4/1/1999

Rinvoq®	Upadacitinib	Abbvie Inc	Oral Tablet ER	TS	8/16/2019
Rituxan®	Rituximab	Genentech	IV injection	BO	2/28/2006
Simponi Aria®	Golimumab	Janssen Biotech	IV infusion	BO	7/18/2013
Simponi®	Golimumab	Centocor Ortho Biotech Inc	Subcutaneous	BO	4/24/2009
Xeljanz Xr®	Tofacitinib Citrate	Pfizer	Oral Tablet ER	TS	2/23/2016
Xeljanz®	Tofacitinib Citrate	Pf Prism Cv	Oral tablet	TS	11/6/2012
Xeljanz®	Tofacitinib Citrate	Pfizer	Oral Solution	TS	9/25/2020

Abbreviations: BO, Biological Original; CS, Conventional Synthetic; TS, Targeted synthetic

Appendix II: Details of search strategy and literature reviewed.

Literature search Data: 11/1/2022

PubMed

Qualitative studies

	Mesh Terms	**Number of articles**
1	"Arthritis, Rheumatoid"[Mesh]	123,013
2	"Patient Preference"[Mesh] OR Stated preference methods OR Preference	417,045
3	Patient AND (experience OR satisfaction OR center* OR value* OR Perce* OR perspective)	3,362,906
4	Unmet need	20,694
5	#2 OR #3 OR #4	3,709,037
6	"Qualitative Research"[Mesh] OR Qualitative* OR "Focus Groups"[Mesh]	387,350
7	#5 AND #6	492

Discrete choice experiment/Conjoint analysis studies

	Mesh Terms	**Number of articles**
1	"Arthritis, Rheumatoid"[Mesh]	123,013
2	"Patient Preference"[Mesh] OR Stated preference methods OR Preference	417,045
3	Discrete Choice Experiment OR Conjoint OR Choice Model* OR "Choice Behavior"[Mesh]	123,864
4	#1 AND #2 AND #3	55

Table 1. List of studies that identified RA related experience/outcome domain (n=25).

Author (year)	Number of patients (Country)	Important experience/outcome domains	Reference
Carandang et.al., 2020	37 (U.S.)	➢ Experience pain, stiffness, or fatigue ➢ Emotional distress and/or anxiety ➢ Impact physical function o Reduced quality of activity engagement, require additional time to complete task, avoid certain part of the activity	[222]
Serban et.al., 2019	60 (U.S.)	➢ Frustration, anxiety, and depression ➢ Acceptance of treatment ➢ Impact on work life ➢ Impact on social life (hobbies and social activities) ➢ Flare ups ➢ Interaction with other medication and side effects ➢ Numerous hospital appointment as burden ➢ Coping strategy	[223]
Barton et.al., 2018	19 (U.S.)	➢ Sadness surrounding the loss of ability to fully engage in everyday activities because of pain or fatigue ➢ Treatment goals involving pain reduction and increased energy, while minimizing side effects ➢ Negative impact on the quality of life	[224]
Taylor et.al., 2010	2039 (U.S.)	➢ Pain, depression	[225]
Iaquinta et.al., 2005	(U.S.)	➢ Pain ➢ Anger, fear, frustration, self-consciousness, depression ➢ Adverse effects of medications, duration of onset of action, need to switch due to medication ineffectiveness ➢ Future outcomes of the disease process ➢ Possible physical deformity and forced dependency ➢ Inability to assume usual personal and professional responsibilities ➢ Being self-conscious, has to change to new lifestyle	[226]
Chen et.al., 2022	30 (Taiwan)	➢ Physical suffering o Always living with pain and stiffness, uncertainty about deformities ➢ Limitation of abilities o Loss of performing daily activities, loss of social life, loss of physical activities ➢ Coexisting with the disease o Making changes, comparing with other	[227]

Pedraz-Marcos et.al, 2020	19 (Spain)	➢ Helplessness, Life goes on, coping with daily life, home adaptation, self-image, planning	[228]
Loyola et.al, 2020	13 (Canada)	➢ Relationship with healthcare providers (Trust) ➢ Perception of medications effects (Benefits and harms) ➢ Understanding of medications mechanism (Alignment with biomedical model, Indigenous knowledge) ➢ Medications administration (Interfering with lifestyle, Invasiveness to the body) ➢ Support and influence from family ➢ Fear and stigma of drug dependency ➢ Affordability and availability (Cost, availability)	[229]
Walter et.al., 2017	29 (Dutch)	➢ Perceived stress (associated with pain and functional disability) ➢ Balancing the activities and rest ➢ Medication intake had a negative influence on their general well being ➢ Social stress ➢ Relationship with professionals ➢ Higher disease burden due to comorbidity ➢ Negative impact on the wellbeing, both physically and mentally	[230]
Pho et.al., 2017	16 (Singapore)	➢ Altered physical activity and well being o Severe pain and fatigue o Struggling to perform activities o Restriction in basic daily movements ➢ Psychological and emotional challenges o Anger and frustration o Sadness, despair, and helplessness o Worry and fear o Embarrassment and low self-esteem ➢ Changes in social life o Interruption to working life o Disruption of roles and relationships ➢ Various coping strategies o Medications o Alternative treatments o Adaptation and behavioral strategies o Cognitive strategies ➢ Support received and further support needs o Support from family, friends, and society o Support from health care professionals	[231]

		○ Financial counseling and support ○ Access to health care services	
Flurey et.al., 2017	22 (UK)	➢ Challenges to masculinity ○ Reduction in strength and abilities ○ Challenges to masculine identity and role ○ Loss of power and control ➢ Getting through life with RA ○ Just get on with it ○ Information seeking ○ Destructive behaviors ○ Social withdrawal ○ Source of support ➢ What type of support is acceptable ○ Styles of acceptable support packages ○ Who should attend and run a support package	[232]
Bala et.al., 2016	10 (Sweden)	➢ An existence dominated by painful symptoms and treatment ➢ Radical changes and limitations in one's life ➢ A continual struggle to cope with one's life and to master the illness ➢ A dependency on those who are close by and the world around	[233]
Van Der Elst et.al., 2016	26 (Belgium)	➢ Return to being normal ➢ Aspect of disease control ○ Proof of disease control ○ Prevention or stabilization of joint damage ○ Less medication ➢ Physical aspect ○ Relief of pain and other physical symptoms ○ Improve joint function and mobility ○ Limited side effect ○ Improve sleep ➢ Aspect of participation ○ Performing activities of daily living ○ Engaging in work and/or leisure ○ Fulfilling family, social, and/or societal roles ○ Vitality ➢ Mental aspect ○ Emotional well being ○ Self and identity ○ Life enjoyment ○ Not feeling ill	[234]

Ter Wee et.al., 2016	18 (Dutch)	➢ Performing or maintaining their job ➢ Difficulty in coping with the disease (fluctuation) ➢ Influence of the disease on relationship with others, such as partners, children, and friends ➢ Performing activity in daily life and in spare time ➢ Pain, fatigue, emotion	[235]
Ebbevi et.al., 2016	22 (Sweden)	➢ Survival o Mortality ➢ Degree of recovery or health o Avoiding physical symptoms o Avoiding aesthetic symptoms o Ability to perform ADL and exercise o Control of chronic disease complications ➢ Time to recovery or return to normal activities o Time to treatment/remission o Time to definitive diagnosis o Time to access specialist treatment o Time spent accessing treatment o Workdays missed ➢ Disutility of care or treatment process o Pain and anxiety before and during treatment o Care complications ➢ Health over time o Sustainability ➢ Long term consequences of care o Avoid long-term side effect	[236]
Van Tuyl et.al., 2015	47, (Amsterdam, The Netherlands, Vienna, Austria, UK)	➢ Symptom o Reduction of pain, stiffness, fatigue, and swelling were mentioned frequently, but also recovery of strength and improved sleep ➢ Impact o Physical functioning, activity of daily living, and being independent ➢ Normality o Reduction in symptom and impact o Being able to work o Family role o Perception of others	[237]
Östlund et.al., 2014	48 (Sweden)	➢ Feelings of grief, aggressiveness, fear and shame are emotions closely related to participation restrictions of RA in everyday life.	[238]

Flurey et.al., 2014	15 (UK)	➢ Mediating the impact of RA on daily life o Physical impact of RA and its mediation o Emotional impact of RA and its mediation ➢ Redefining me o Retaining independence o Adapting normality's o Incorporating RA into identity o Cognitive adjustment ➢ Unwelcome reminders o The unpredictable nature of RA o Perception ➢ Trying to make sense of fluctuations o Uncertainty o Avoiding seeking help ➢ Trying to regain control o Crisis management o Social withdrawal o Attributing fluctuation to luck ➢ Losing control o Unimaginable impact o Seeking medical help	[239]
Sanderson et.al., 2011	26 (UK)	➢ Pain ➢ Joint damage ➢ Fatigue ➢ Activities of daily living ➢ Mobility	[217]
Buitinga et.al., 2012	16 (Dutch)	➢ Dependency on others ➢ Increasing dependency on medication ➢ Inability to walk ➢ Activity limitations ➢ Worsening fatigue	[240]
Lacaille et.al., 2007	36 (Canada)	➢ Fatigue ➢ Pain ➢ Physical limitations ➢ Invisibility of arthritis ➢ Variability/fluctuations of symptoms ➢ Unpredictability of flares ➢ Unpredictability of future arthritis progression	[241]

		➢ Problems related to disease management o Treatment side effects interfering with work performance o Concern about taking time off work for medical appointments o Limited access to multidisciplinary arthritis services outside of working hours o Lack of time/energy for comprehensive arthritis care o Lack of information, resources, and services to help cope with arthritis on daily basis o Lack of help from health care team for dealing with work-related issues o Not using splints/aids/devices useful to manage arthritis at work to maintain invisibility ➢ Self-preserving strategies to cope with pain and fatigue limit potential for advancement, job satisfaction, and personal fulfillment	
Ahlmen et.al., 2005	25 (Sweden)	➢ Normal life o Be looked upon as before. Feel no limitations. Manage normal social roles ➢ Physical capacity o Reduce pain, stiffness, and fatigue. Increase mobility, grip force and muscle strength ➢ Independence o Manage daily activities. Care for oneself and family. Manage work and leisure time ➢ Well-being o Be able to enjoy life. Regain self-confidence. Get psycho-social support ➢ Benefit from treatments o Experience improvement in symptom severity. Increase levels of ability and activity ➢ Communication with the rheumatology staff o Obtain good mutual relationship with the rheumatology staff. Receive satisfactory expert treatment ➢ 'Taking charge' o Be accepted as experts on living with rheumatoid arthritis. Take own responsibility for their situation ➢ Resources of and access to rheumatology care facilities o Get resources of rheumatology care. Have access to rehabilitation facilities	[242]
Hwang et.al., 2003	5 (Korea)	➢ Severe pain o Limited physical activities o Experience of severe pain o Abruptly decreased physical strength o Deformed body appearance ➢ Self-esteem o Concealment of distorted body o Pretend nothing is amiss ➢ Negative feelings o Sad, Regretful, Annoyed, Anxious, Sensitive, Shameful, Suffering, Resentful, Unfair, Confused, Fearful, Guilty ➢ Reflect the past life o Miss past healthy life	[243]

		○ Resent and feel empty to sacrifice themselves to their family ○ Think about cause of the disease ➢ Concentrate on recovery from disease ○ Attempt to overcome the disease by self ○ Try almost every effective treatment ○ Rely on religion ➢ A comfortable mind in pain ○ Try to keep comfortable ○ Try to get out anxiety about the disease ○ Accept the disease as 'my life' ➢ Support of family and others ○ Thankful for energy gained from support of family ○ Strengthen will for life through support from others ➢ New life ○ Desire to live only for self from now ○ Satisfaction with present physical condition ○ Desire to give service to the public	
Carr et.al., 2003	39 (UK)	➢ What outcomes are important? ○ Physical (pain, disability, deformity) ○ General wellbeing (fatigue, feeling well) ○ Independence ○ Return to normality ○ Emotional impact ○ Fear of the future ○ The relative importance of outcomes changes over time and depending on circumstances ➢ What makes you satisfied or dissatisfied with treatment? ○ Treatment efficacy ○ Side effects ○ Patient-health professional communication ○ Access to care ➢ How do you decide that treatment is working? ○ Symptom reduction ○ "Forgetting you have RA" ○ Change in priorities for outcome over time ○ Magnitude of improvement/change varies with disease duration	[244]
McPherson et.al., 2001	10	➢ Personal factors ○ Limitation and restrictions ➢ External factors ○ Impeded/undermined ➢ Future issue	[245]

		○ Negative or limitation restrictions ➢ Perception of normality ○ Lack of limitation or restriction ➢ Tacking charge ○ Active engagement in control	

Table 2. List of reviews that identified RA related experience/outcome domain (n=9).

Author (year)	Type of study	Important experience/outcome domains	Reference
Bekker et.al., 2021	Review + focus group	➢ Medication Adherence o Timing, dosing, accuracy of injection technique, medication knowledge, medication adherence knowledge, medication beliefs, medication concerns, support form healthcare professional, family support, community support, general emotional support, memory forgetfulness, medication effectiveness, medication side effects, safe efficacy ➢ Pathophysiology o Physical: Physical functioning, range of motion, mobility, disease activity, pain, inflammation, organ function, biomarkers, fitness, sexual function o Psychological: Well-being, Fatigue, Anger/irritability, Depression, Helplessness, Satisfaction, Morale, Confidence o Medication side effects ➢ Life impact o Quality of life, ability to work, sleep disruption, social roles, Independence ➢ Economic impact o Cost of disease and treatment, healthcare utilization, productivity loss	[246]
Van der Elst et.al, 2020	Meta synthesis	➢ A normal life despite RA o Disease control: Relief of symptoms, finding the right treatment, staying stable o Physical performance: Functional ability, performing activities o Self-accomplishment: Self-management, Role fulfillment, Self, and identity o Wellbeing: Emotional wellbeing, positive outlook, vitality	[247]
Parenti et.al, 2020	Meta synthesis	➢ Physical domain o Symptomatology, treatments, functionality, sexual health ➢ Social domain o Relationships o Healthcare system o Work ➢ Psychological domain o Identity o Power and control o Negative emotions	[248]
Donnelly et.al., 2020	Systematic review	➢ Cognitive emotional (what we think and feel) o Acceptance, lack of, anger, frustration, irritability, blame, cause, social comparison, depression, sadness, despair, suicide, hope and fears, optimism, positivity, humor, religion and spirituality, self (concept, esteem, efficacy), shame, guilt, embarrassment ➢ Behavioral (What we do; action taken)	[249]

		○ Adjustment and adaptation, planning, pacing, self-care, help-seeking ➢ Social (interaction with others and roles) ○ Invisible illness, domestic roles, employment, economic, gender, loss, loneliness, isolation, personal and social relationships ➢ Environmental (setting in which we manage) ○ Access and built environment, weather, and temperature) ➢ Physical (the body in which we manage) ○ Body as ill, deformed, disabled, symptoms ➢ Technological (technologies used to manage) ○ Assistive devices and aids, Health care professionals and services ○ Medical treatment	
Michaud et.al., 2021	Systematic review	➢ Functional disability, ➢ Tender or swollen joints, ➢ Pain, ➢ Patient global assessment ➢ Fatigue	[75]
Kelly et.al, 2018	Systematic review	➢ Intensifying disease identity ○ Severity of sudden pharmacotherapy ○ Signifying deteriorating health ○ Daunting lifelong therapy ➢ Distressing uncertainties and consequences ○ Poisoning the body ○ Doubting efficacy ○ Conflicting and confusing advice ○ Prognostic uncertainty with changing treatment regimens ➢ Powerful social influence ○ Swayed by other's experiences ○ Partnering with physicians ○ Maintaining roles ○ Confidence in comprehensive and congoing care ○ Valuing peer support ➢ Privilege and right of access to biologic agents ○ Expensive medications must be better ○ Right to receive a biologic ○ Fearing dispossession ➢ Maintaining control ○ Complete ownership of decision ○ Taking extreme risks ○ Minimizing lifestyle intrusion ➢ Negotiating treatment expectation	[250]

		○ Miraculous recovery ➢ Mediocre benefit ○ Reaching the end of the line	
Hulen et.al.,	Systematic review	➢ Bodily experience of RA ○ Functionality, pain reduction, lessening of joint swelling and stiffness, increase in energy levels, mitigation of undesired impact of medications, prevention of disease progression, sexuality, and reproduction ➢ Achieving normalcy and maintaining wellness ○ Freedom, normalcy, general wellbeing, self-efficacy, mood improvement ➢ Social connectedness and support ○ Social support and social connections ➢ Interpersonal and healthcare system interactions ○ Effective patient provider communication, ability of support services, access to rheumatologist, RA education, patient centered care, sensitive healthcare delivery, care coordination, primary care access, cost-effective RA care, and trust in healthcare providers	[251]
Rendas-Baum et.al, 2014	Review	➢ Pain ➢ Fatigue ➢ Physical health (functioning) ➢ Mental health (emotional wellbeing) ➢ Social functioning ➢ Sleep ➢ Work	[252]
Hoving et.al., 2013	Review	➢ Symptoms and disease and effects on work ○ Fatigue and energy, pain and stiffness, physical limitations, unpredictability and invisibility activity arthritis and flares, concentration ➢ Managing arthritis and consequences ○ Help, information, access and treatment of arthritis from health care Optimal medical care and importance of healthy lifestyle Importance of disease activity Coping, understanding, adapting and managing disease Awareness of limitations and abilities, balancing work and leisure activities Importance of assertiveness, importance of planning Desire of contact or information from others with disease ➢ Socioeconomic factors ○ Job insecurity and financial concerns Support from society, regulations and aid for persons with arthritis Opportunities for part-time work or disability benefits ➢ Work condition and adaptations ○ Support or help from employer and/or supervisor: such as active help with looking for solutions, providing adequate work conditions, work accommodation Employer help/advocacy/policies regarding career planning, (re)training, accommodation psychological help: understanding, acceptance, considering needs of the patient Providing flexibility regarding work arrangements, and	[253]

		working time schedules, medical appointments and taking of time Ergonomic assessment and ergonomic adjustments to workplace ➢ Emotional challenges o Setting boundaries, self-confidence Dealing with feeling like a burden, dealing with reactions colleagues Managing fear and anxiety, guilt, sadness, stress Feelings of dependency or helplessness Impact on personal fulfilment ➢ Interpersonal issues and choices affecting work and family life o Role of understanding and social support from all actors such as colleagues, supervisors, health care professionals and patient organizations Difficulty with/lack of communication, mistrust and acceptance Relationship with colleagues Dealing with negative comments at work, asking for help, dealing with unsolicited help Reluctance to disclose (consequences of having) arthritis and being honest to colleagues Family and work life balance: challenges and negative effects that occur as a result of maintaining work for family life and in communicating with family ➢ Meaning of work o Perceptions and meaning of work Desire, value and motivation to work Importance of worker role and identity Work important to well-being Value of work in social environment/friends Diverting attention away from disease Work as rehabilitative factor	

Table 3: List of studies that identified DMARD related outcome domain (n=11).

Author	Number of RA patient	Important domains/Experience	Reference
Singh et.al., 2021	47 (U.S.)	➢ Efficacy/effectiveness with regard to joint pain, joint destruction, fatigue, energy, sleep, joint stiffness, mobility, quality of life and the ability to function in daily lives ➢ Time to onset of action/mode of action ➢ Side effects/fear of side effects ➢ Cost including out of pocket ➢ Co-payments and patient responsibility ➢ Convenience of use/frequency of use ➢ Doctor opinion ➢ Other drugs/comorbidity/ other patient's experience/effect on other people, ➢ Fear of needles ➢ Newness of the medication	[76]
Barton et.al, 2018	19 (U.S.)	➢ Treatment goals involving pain reduction and increased energy, while minimizing side effects ➢ Quality of life	[224]
Binder-Finnema et.al., 2019	156 (U.S.)	➢ Treatment cost and the ability to pay	[254]
Andersen et.al., 2019	39 (U.S.)	➢ Side effect seen as the price you pay for improvement ➢ Day to day physical and social function matter more ➢ Patients have difficulty sorting outside effect from other factors ➢ Different DMARDs elicit different safety concern ➢ Concerns are influenced by disease and medication experience, and individual and social factors	[255]
Shaw et.al., 2018	48 (U.S.)	➢ Emotional motivation to accept treatment o Desire to return to the normal life (relief from pain and fatigue, and improve physical functioning), fear of future disability to the RA ➢ Emotional barriers to accept treatment o Fear of medication (life threatening adverse events), maintaining control over health, denial of sick identity, disappointment with treatment, feeling overwhelmed by the cognitive burden of deciding	[140]
Bekker et.al, 2021	38 (Canada, Australia, Netherland)	➢ Protecting and enhancing emotional, physical, and social well being ➢ Medication adherence: (timing, dosing, accuracy of injection technique) o Motivation to maintain mental and physical fitness so that they were able to maintain their social function and ability to work o Feel the medication were futile and left them anxious and depressed	[246]
Pasma et.al,	24	➢ Symptom severity o Pain, fatigue, disability	[256]

2015	Netherland	➢ Experiences with medication o Previous experience with medication for other diseases or current experience with DMARD, side effects ➢ Perception about medication and the illness o Expectations about medication, confrontation with having a chronic illness by the use of medication. ➢ Information about medication/knowledge acquisition o In the early phase, patients started gathering information. o Information obtained from the rheumatologist, the medication information leaflet, or by searching the Internet. ➢ Communication style and trust in the rheumatologist o The rheumatologist should build toward a trustful relationship, for instance by acknowledging fears about medication and explaining the treatment plan in detail.	
Sanderson et.al, 2010	23 (UK)	➢ RA under control o Reduction in symptoms, commonly including a reduction in the magnitude or quality of pain, swelling, and fatigue, avoidance of joint damage ➢ Doing things o Ability to carry out everyday activities and to plan them o Doing leisure activities o Mobility o Ability to work ➢ Emotional health o Less stigmatizing, mood fluctuation, positive psychological functioning ➢ Coping with illness o Personal control ➢ Feeling well, return to/maintain a normal life	[257]
Sanderson et.al, 2010	23 (UK)	➢ Less pain ➢ Doing everyday things ➢ No more visible joint damage ➢ More mobility ➢ Enjoy life ➢ More independent ➢ Less fatigue ➢ Doing everything you want	[258]
Scarpato et.al, 2009	802 (Italy)	➢ Dissatisfied with the current treatments, owing to inefficacy, side effects and inconvenience of administration ➢ Reasons for the choice of i.v. administration were the safety of treatment at the hospital and the reassuring effect of physician presence. ➢ The s.c. administration was chosen for the convenience of treatment and in particular for home treatment.	[259]

Chilton et.al, 2008	109 UK	➢ Lack of control, convenience and technical issues as influencing treatment choice ➢ Lack of confident about self-administering treatment, thus prefer regular hospital attendance.	[260]

Table 4. List of reviews that identified DMARD related outcome domain (n=5).

Author	Number of RA patient	Important domains/Experience	Reference
Simons et.al, 2022	Systematic Review	➢ Most important determinants of treatment choice: o Benefits o Risks o Administration method o Cost (when included) ➢ For detailed list of attributes see paper	[191]
Bywall et.al, 2022	Review	➢ The highest ranked attributes were o Improved functional capacity o Reduced inflammation o Reduced pain and fatigue and o Risk of getting a severe side effect ➢ The framework analysis revealed two overarching themes for further exploration: treatment goals and side effects. ➢ 'Treatment goals' emerged from functional capacity, revealing two dimensions: physical functional capacity and psychosocial functional capacity. ➢ 'Side effects' revealed that mild and severe side effects were the most important to discuss in shared decision-making. ➢ For detailed list of attributes see paper	[190]
Zartab et.al, 2021	Systematic review	➢ The most common attributes that were used in surveys were efficacy, adverse effect, route of administration, frequency of administration, and cost ➢ For detailed list of attributes see paper	[192]
Durand et.al, 2020	Systematic review	➢ Despite the heterogeneity of attributes in DCE studies, o Treatment benefits (disease improvement) were usually more important than both non-serious (6 of 8 studies) and serious adverse events (5 of 8), and route of administration (7 of 9) ➢ Subcutaneous therapy was often but not always preferred over intravenous therapy. ➢ For detailed list of attributes see paper	[65]
Hsiao et.al, 2019	Review	➢ Members of the largest group most concerned with the cost of medications ➢ For detailed list of attributes see paper	[220]

Table 5. List of attributes identified from previous Discrete choice experiment/Conjoint analysis for RA patients in U.S. (n=8)

Author	Number of RA patient	Important domains/Experience	Reference
Fraenkel et.al., 2018	1273	Route of administration, onset of action, bothersome side effects, serious Infection, very rare side effects, amount of information available, cost	[71]
Husni et.al., 2017	510	Reduction in the number of swollen joints, Reduction in pain, Improvement in physical function, Abnormal laboratory results, Cancer, Serious infection, Route of administration, Dose frequency, Out-of-pocket cost per month	[66]
Louder et al., 2016	380	Route of administration, Frequency of administration, Chance of serious side effects, Monthly cost to you (commercial), Medication burden (taken with another medication), Ability to reduce daily joint pain and joint swelling, Improvement in ability to perform daily tasks and activities	[72]
Fraenkel et al., 2015	156	Decreased joint pain and swelling, Ability to get around and participate in social or leisure activities outside of the house, Slowing or stopping joint damage seen on X-rays, Ability to work, Risk of injection or infusion reaction, Risk of infection, Risk of tuberculosis, Risk of neurologic disease.	[70]
Poulos et al., 2014	901	Change of medicine working, Mode of administration, Time needed for infusion, how often injection/infusions are taken, chance of immediate serious treatment reaction, chance of immediate mild treatment reaction	[67]
Constantinescu et.al, 2009	136	Remission, Improvement, Radiographic progression, Route, Injection site reaction, Reversible adverse events, Risk of lung injury, Risk of tuberculosis, extremely rare adverse events, Risk of cancer	[68]
Özdemir et al., 2009	463	Change of efficacy, Onset of effect, Mode/frequency, Irritation, Serious infection, and Cost	[61]
Fraenkel et al., 2004	120	Route, Physician experience, Onset, Chance of benefit, Bone erosions, Injection site reaction, Rash, Oral ulcers, Alopecia, Nausea/vomiting, Diarrhea, Cancer, Nephrotoxicity, Pneumonitis, Cost	[69]

Appendix III: Evidence for the attribute level for DMARDs

Table 1. Attributes and levels incorporated in prior U.S. based DCE studies.

Author	Attributes	Levels	Reference
Fraenkel et.al, 2018	Route of administration	Pills	[71]
		Injection	
		Infusion	
	Onset of action	2 weeks	
		6 weeks	
		12 weeks	
	Bothersome side effects	0%	
		10%	
		30%	
	Serious infection	1%	
		3%	
		5%	
	Very rare side effects	Stomach or intestinal tear (0.2%)	
		Neurologic disease like multiple sclerosis (0.05%)	
		Permanent eye problems (0.3%)	
		Life threatening brain infection (0.005%)	
	Amount of information available	A lot (on the market for 27 years)	
		Some (on the market for 10 years	
		A little (on the market for 3 years)	
	Cost	Easy to afford	
		Somewhat affordable	
		Hard to afford	
Husni et.al, 2017	Reduction in the number of swollen joints	No reduction	[66]

		25% reduction	
		50% reduction	
		75% reduction	
	Reduction in pain	No reduction	
		25% reduction	
		50% reduction	
		75% reduction	
	Improvement in physical function	No improvement	
		20% improvement	
		40% improvement	
		60% improvement	
	Abnormal laboratory results	10%	
		20%	
		30%	
	Cancer	0%	
		1%	
		2%	
	Serious infection	0%	
		2%	
		4%	
	Route of administration	Oral	
		Subcutaneous injection	
		Intravenous infusion	
	Dose frequency	Daily	
		Every two weeks	
		Monthly	
	Out-of-pocket cost per month	$0	
		$50	

		$100	
Louder et.al, 2016	Route of administration	Oral	[72]
		By self-injection	
		By infusion	
	Frequency of administration	Twice daily	
		Once weekly	
		Every other week	
		Once every 8 weeks	
	Chance of serious side effects	4 of 100 people	
		6 of 100 people	
		8 of 100 people	
	Monthly cost to you (commercial)	$25 copay	
		$50 copay	
		$75 copay	
	Ability to reduce daily joint pain and joint swelling	50 of 100 people	
		52 of 100 people	
		54 of 100 people	
		58 of 100 people	
	Improvement in ability to perform daily tasks and activities	32%	
		33%	
		34%	
		36%	
	Medication burden (take with other medication)	No	

		Yes	
Fraenkel et.al, 2015	Decreased joint pain and swelling	70 in 100 people feel much better, but occasionally have some joint pain and swelling	[70]
		40 in 100 people feel much better, but occasionally have some joint pain and swelling	
		People continue to have the same joint pain and swelling	
	Ability to get around and participate in social or leisure activities outside of the house	70 in 100 people can get around much easier and participate in social and leisure activities outside of the house	
		40 in 100 people can get around much easier and participate in social and leisure activities outside of the house	
		People continue to have the same problems getting around and participating in social and leisure activities outside of the houses	
	Slowing or stopping joint damage seen on x-rays	80 in 100 people have no further bone damage seen on x-ray	
		30 in 100 people have no further bone damage seen on x-rays	
		Bone damage seen on x-rays continues to progress at same rate	
	Ability to work	80 in 100 people are able to keep working	
		60 in 100 people are able to continue working	
		People continue to have the same problems being able to work	
	Risk of injection/infusion reaction	No risk of an injection reaction	
		3 in 100 people get an infusion reaction (headache, nausea, fever)	
		20 in 100 people get a rash or burning at the injection site	
	Risk of infection	No increased risk of infection	
		20 in 100 people get bronchitis or sinusitis	
		3 in 100 people get a serious infection (like pneumonia) requiring hospitalization	
	Risk of TB	No increased risk of TB	
		Very rare risk of TB (1 in 10,000 people)	
		Very rare risk of TB (5 in 10,000 people)	

	Risk of neurologic disease	No increased risk of neurologic disease	
		Extremely rare risk (a few reported cases) of a neurologic disease like MS	
		Extremely rare risk (a few reported cases) of a neurologic disease that usually causes death	
Poulos et al., 2014	Change of medicine working	75 of 100 patients (75%)	[67]
		60 of 100 patients (60%)	
		40 of 100 patients (40%)	
	Mode of administration	Injection at home	
		Infusion at a doctor's office or clinic	
	Time needed for infusion	No time (Injection at home)	
		30 minutes (0.5 hours)	
		1 hours	
		2 hours	
		4 hours	
	How often injection/infusions are taken	2 treatments every week (104 times per year)	
		1 treatment every 2 weeks (26 times per year)	
		1 treatment every month (12 times per year)	
		2 treatments 2 week apart every 6 months (4 times a year)	
	Chance of immediate serious treatment reaction	1 of 100 patients (1%)	
		10 of 100 patients (10%)	
		25 of 100 patients (25%)	
	Chance of immediate mild treatment reaction	1 of 100 patients (1%)	
		10 of 100 patients (10%)	
		25 of 100 patients (25%)	

Constantinescu, et.al, 2009	Chance of remission	45 out of 100 patients go into remission	[68]
		25 out of 100 patients go into remission	
		15 out of 100 patients go into remission	
	Symptom improvement	70 out of 100 patients feel much better, but occasionally have some joint pain or swelling	
		50 out of 100 patients feel much better, but occasionally have some joint pain or swelling	
		40 out of 100 patients feel much better, but occasionally have some joint pain or swelling	
	Radiographic progression	No further bone damage seen on X-rays in 80 out of 100 patients	
		No further bone damage seen on X-rays in 50 out of 100 patients	
		No further bone damage seen on X-rays in 30 out of 100 patients	
	Route of administration	Pill you take once a week	
		Injection you give yourself once every 1–2 weeks	
		Intravenous infusion you get every 6–8 weeks	
	Injection reaction	No injection reactions	
		30 in 100 patients get a rash or local burning at the site of injection	
		3 in 100 patients will get a reaction during the infusion (headache, nausea, fever)	
	Reversible adverse events	No increased risk of nausea, dizziness or unusual tiredness	
		10 in 100 people will have nausea, dizziness or unusual tiredness	
	Risk of lung injury	No increased risk of lung or liver injury	
		Rare risk of lung injury (2 in 100 patients) or liver injury (about 1 in 1000 patients)	
	Risk of tuberculosis	No increased risk of tuberculosis	
		Extremely rare risk of tuberculosis (about 1 in 10,000 patients)	
	Extremely rare adverse events	No increased risk of neurologic disease or heart failure.	

		Extremely rare risk of neurologic disease or heart failure (about 1 in 10,000 patients)	
	Risk of cancer	No increased risk of cancer	
		Possible increased risk of cancer (about 1 in 1000 patients)	
Özdemir et.al, 2009	Chance the medicine will work well	Works well in 25% of patients	[61]
		Works well in 50% of patients	
		Works well in 75% of patients	
		Works well in 100% of patients	
	If it works, how long it takes to work after taking the medicine	1 week	
		2 weeks	
		4 weeks	
		10 weeks	
	Way you take the medicine	1 injection every week at home	
		1 injection every 2 weeks at home	
		1 injection every 4 weeks at home	
		1 infusion in every 8 weeks that takes 2 hours in your doctor's office or clinic	
		1 infusion in every 12 weeks that takes 30 minutes in your doctor's office or clinic	
	How long the injection site is irritated after taking the medicine	You have injection site irritation for 15 minutes	
		You have injection site irritation for 1 hour	
		You have injection site irritation for 3 hours	
	Chance of serious infection	None	
		5 out of 100 (5%)	
	Personal cost to you per month not	$50	

	covered by insurance		
		$150	
		$300	
		$600	
		$1,000	
Fraenkel et.al., 2004	Route	One pill taken once a day	[69]
		Subcutaneous injection given by you or a partner at home twice a week	
		Intramuscular injection given by a nurse in a clinic once a week	
	Physician experience	Drug used to treat arthritis for more than 20 years	
		New drug with unknown long term safety profile	
	Onset	The drug starts working in 2 weeks	
		The drug starts working in 4 weeks (1 month)	
		The drug starts working in 8 weeks (2 months)	
	Chance of benefit	75% (75 in 100) of people receiving this drug will feel much better	
		60% (60 in 100) of people receiving this drug will feel much better	
		45% (45 in 100) of people receiving this drug will feel much better	
	Bone erosions	75% (75 in 100) do not develop any new bone damage at 1 year	
		60% (60 in 100) do not develop any new bone damage at 1 year	
	Injection site reaction	0% (no one) get a skin reaction at the injection site	
		40% (40 in 100) get a skin reaction at the injection site	
	Rash	0% (no one) gets an uncomfortable itchy rash	
		10% (10 in 100) get an uncomfortable itchy rash	
		40% (40 in 100) get an uncomfortable itchy rash	
	Oral ulcers	0% (no one) gets painful mouth sores	
		10% get painful mouth sores	

	Alopecia	0% (no one) gets hair thinning	
		10% (10 in 100) get hair thinning	
	Nausea/vomiting	0% (no one) gets nausea	
		10% (1 in 100) get nausea	
		30% (30 in 100) get nausea	
	Diarrhea	0% (no one) gets diarrhea	
		10% (1 in 100) get diarrhea	
		30% 30 in 100) get diarrhea	
	Cancer	The risk of cancer is not increased with this drug	
		Theoretical, but unproven, increased risk of cancer	
	Nephrotoxicity	0% (no one) gets kidney damage from this drug	
		1% (1 in 100) get kidney damage	
	Hepatotoxicity	0% (no one) gets liver damage	
		0.1% (1 in 1000) get liver damage	
	Pneumonitis	0% (no one) gets lung damage	
		0.1% (1 in 1000) get lung damage	
		1% (1 in 100) get lung damage	
	Cost	Free	
		$5.00 co-pay per month	
		$15.00 co-pay per month	
		$30.00 co-pay per month	

Table 2: DMARDs attributes level derived from clinical trials from product labels acquired through Drugs@FDA

Molecule (Name)	Study	Active and comparators	ACR 50 (Pain and mobility)			Route	Frequency	SSE (%)	Reference
			Week 12	Week 24	Week 52				
Methotrexate (RASUVO)	-	-	-	-	-	Subcutaneous injection	7.5 mg once per week	-	https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/205776s004lbl.pdf
						Oral Tablet			
Methotrexate (OTREXUP)	-	-	-	-	-	Subcutaneous injection	7.5 mg once per week	-	https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/204824s010lbl.pdf
Hydroxychloroquine (PLAQUENIL)	-	-	-	-	-	Oral Tablet	400 mg to 600 mg single daily dose or two divided dose (dosage form available 200 mg)	-	https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/009768s056lbl.pdf
Sulfasalazine (AXULFIDINE)	-	-	-	-	-	Oral Tablet	2 g daily (dosage form available 500 mg tablet, take in two equally divided doses i.e., 1gm each)	-	https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/007073s129lbl.pdf
Leflunomide (ARAVA)	Study I	ARAVA			34%	Oral Tablet	20 mg per day (dosage form available 10 mg, 20 mg, and 100 mg)	-	https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020905s031lbl.pdf
		Placebo			8%				
		Methotrexate			23%				
	Study II	ARAVA		33%					
		Placebo		14%					
		Sulfasalazine		30%					
	Study III	ARAVA			10%				
		Methotrexate			16%				
	Study I	Placebo	8%	5%	NA			Placebo=0.8%, MTX=3.6%,	https://www.accessdata.fda.gov/drugsatfda_d

Etanercept (ENBREL)		Enbrel	41%	40%	NA	Subcutaneous injection	50 mg once weekly with or without methotrexate	Enbrel+MTX=1.4%, Enbrel+Anakinra=7%	ocs/label/2022/103795s5591lbl.pdf
	Study II	MTX/Placebo	0%	3%	NA				
		MTX/Enbrel	42%	39%	NA				
	Study III	MTX	24%	32%	43%				
		Enbrel	29%	40%	49%				
Adalimumab (HUMIRA)	Study I	Placebo		8%		Subcutaneous injection	40 mg every other week.	Placebo=2.9 per 100 patient years, Humira=4.3 per 100 patient year, serious opportunistic infections=0.05 per 100 patient year, Less than 5%	https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125057s417lbl.pdf
		HUMIRA (40 mg every other week)		22%					
		HUMIRA (40 mg every week)		35%					
	Study II	Placebo/MTX		10%	10%				
		HUMIRA/MTX (40 mg every other week)		39%	42%				
Certolizumab (CIMZIA)	Study I	Placebo + MTX		8%	8%	Subcutaneous injection	400 mg initially and at Weeks 2 and 4, followed by 200 mg every other week; for maintenance dosing, 400 mg every 4 weeks can be considered	Serious adverse reaction, Placebo=9%, CIMZIA=10%, CIMZIA=6%, 4.7%, 3% Placebo=4.5%, 2%,1%	https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125160s293lbl.pdf
		CIMZIA(a) 200 mg + MTX q 2 weeks		37%	38%				
		CIMZIA(a) 200 mg + MTX Placebo + MTX		30% (24%, 37%)	30% (24%, 37%)				
	Study II	Placebo		4%					
		CIMZIA(b) 400 mg q 4 weeks		23%					
		CIMZIA(b) 400 mg -Placebo		19% (10%, 28%)					
Golimumab (SIMPONI)	Study I	Placebo+ DMARDs	7%	4%		Subcutaneous injection (prefilled autoinjector)	50 mg Once a month	SIMPONI=1.4%, Placebo=1.3%, SIMPONI=5.7 (3.8,8.2) infection per 100 patient years,	https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125289s146lbl.pdf
		SIMPONI+DMARDS	15%	16%					
	Study II	Background MTX	10%	14%					

		SIMPONI + Background MTX	35%	37%				Placebo=4.2 (1.8,8.2) infection per 100 patient years	
	Study III	MTX	N/A	29%					
		SIMPONI+MTX	N/A	40%					
Golimumab (SIMPONI ARIA)		Placebo + MTX	9%	13%		Intravenous infusion over 30 min	0, 4 and every 8 weeks	SIMPONI ARIA=0.9%, Placebo=0%, SIMPONI ARIA=2.2 (0.61, 5.71), 4.07 (2.09, 5.57) per 100 patient years, Placebo=0 (0.00, 3.79) per 100 patient year	https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125433s032lbl.pdf
		SIMPONI ARIA+MTX	30%	35%					
Infliximab (REMICADE)	Study I	Placebo + MTX		5% (30 weeks)	9% (54 weeks)	Intravenous infusion for at least 2 hours	0,2,6 weeks, then every 8 weeks	Serious infusion reaction=5.3%, 4%, <1% , Placebo=3.7%, 1.7%	https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/103772s5401lbl.pdf
		Infliximab (3mg/kg)+MTX (q8)		27% (30 weeks)	21% (54 weeks)				
		Infliximab (3mg/kg)+MTX (q4)		29% (30 weeks)	34% (54 weeks)				
		Infliximab (10mg/kg)+MTX (q8)		31% (30 weeks)	40% (54 weeks)				
		Infliximab (10mg/kg)+MTX (q4)		26% (30 weeks)	38% (54 weeks)				
	Study II	Placebo + MTX		N/A (30 weeks)	32% (54 weeks)				
		Infliximab (3mg/kg)+MTX (q8)		N/A (30 weeks)	46% (54 weeks)				
		Infliximab (6mg/kg)+MTX (q8)		N/A (30 weeks)	50% (54 weeks)				
Abatacept (ORENCIA)	Study I	ORN	16%	N/A	N/A	Intravenous infusion for at least 2 hours	0,2,6 weeks, then every 8 weeks	Serious infusion reaction=5.3%, 4%, <1% , Placebo=3.7%, 1.7%	https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125118s240lbl.pdf
		PBO	6%	N/A	N/R				

	Study III	ORN+MTX	32%	40%	48%	Intravenous infusion over 30 min	0, 2, 4 weeks and Every 4 weeks thereafter	Serious infections (4.4% vs. 0.8%), (3% vs 1.9%)	
		PBO+MTX	8%	17%	18%				
	Study IV	ORN+DMARDs	18%	20%	N/A				
		PBO+DMARDs	6%	4%	N/A				
	Study VI	ORN+MTX	40%	53%	57%				
		PBO+MTX	23%	38%	42%				
	Study SC-1	ORN SC+MTX	33%	52%	N/A				
Rituximab (RITUXAN)	Study I	Placebo + MTX		5%		Intravenous infusion administered by a healthcare professional with appropriate medical support	Two-1,000 mg intravenous infusions separated by 2 weeks (one course) every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks.	Serious infection <5%	https://www.accessdata.fda.gov/drugsatfda_docs/label/1997/ritugen112697-lab.pdf
		RITUXAN+MTX		27%					
	Study II	Placebo + MTX		27%	26% (48 week)				
		RITUXAN+MTX		21%	29% (48 week)				
Tocilizumab (ACTEMRA)	Study I	MTX		34%	N/A	Intravenous drip infusion over 1 hour	4/8 mg per kg every 4 weeks	4.4 and 5.3 events per 100 patient-years (5%)	https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125276s134lbl.pdf
		Actemra (8 mg per kg)		44%	N/A				
	Study II	Placebo + MTX		10%	10%				
		Actemra (4mg per kg)+MTX		25%	29%				
		Actemra (8 mg per kg + MTX		32%	36%				
	Study III	Placebo + MTX		11%	N/A				
		Actemra (4mg per kg) +MTX		32%	N/A				
		Actemra (8 mg per kg) +MTX		44%	N/A				
	Study IV	Placebo + DMARDs		9%	N/A				
		Actemra (8 mg per kg) + DMARDs		38%	N/A				

	Study V	Placebo + MTX		4%	N/A				
		Actemra (4mg per kg) +MTX		17%	N/A				
		Actemra (8 mg per kg) +MTX		29%	N/A				
	Study I	TCZ SC 162 mg every week + DMARD		47%		Subcutaneous injection (prefilled syringe/prefilled pen)	Less than 100kg: Every other week Above 100 kg: Every week		
		TCZ IV 8mg/kg + DMARD		49%					
	Study II	TCZ SC 162 mg every other week + DMARD		40%					
		Placebo + DMARD		12%					
Sarilumab (KEVZARA)	Study I	Placebo + MTX	12%	17%	18%	Subcutaneous injection	200 mg once every two weeks	3.8 and 4.4 events per 100 patient-years	https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761037s001lbl.pdf
		KEVZARA 150 mg+MTX	26.50%	37%	40%				
		KEVZARA 200 mg+MTX	36.30%	46%	42.90%				
	Study II	Placebo + DMARD	13.30%	18%					
		KEVZARA 150 mg+DMARD	30.40%	37%					
		KEVZARA 200 mg+DMARD	33.20%	41%					
Tofacitinib (XELJANZ/XR)	Study I	PBO	12%	N/A		Oral tablet	5 mg twice daily	1.7-2.7 events per 100 years	https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/203214s028,208246s013,213082s003lbl.pdf
		XELJANZ 5 mg Twice Daily	31%	42%		Oral solution			
	Study IV	PBO+MTX	8%	9%		Oral extended-release tablet	11 mg once daily		
		XELJANZ 5 mg Twice Daily + MTX	29%	32%					
		PBO + MTX	8%	N/A					

		XELJANZ 5 mg Twice Daily + MTX	26%	37%					
Baricitinib (OLUMINAT)	Study III	Placebo + cDMARDs	13%	21%		Oral tablet	2 mg once daily	3.6 events per 100 patient year	https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/207924Orig1s000lbl.pdf
		OLUMIANT 2 mg/day + cDMARDs	34%	41%					
	Study IV	Placebo + cDMARDs	8%	13%					
		OLUMIANT 2 mg/day + cDMARDs	20%	23%					
Upadacitinib (RINVOQ)	Study I	MTX	28%	33%		Extended-release oral tablet	15 mg once daily	2.3-8.4 events per 100 patient years	https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/211675s010lbl.pdf
		RINVOQ 15 mg	52%	60%					
	Study II	MTX	15%						
		RINVOQ 15 mg	42%						
	Study III	PBO	15%						
		RINVOQ 15 mg	38%						
	Study IV	PBO	15%	21%					
		RINVOQ 15 mg	45%	54%					
	Study V	PBO	12%						
		RINVOQ 15 mg	34%						