

Relative Importance of Disease-Modifying Antirheumatic Drug Attributes for Patients with Rheumatoid Arthritis

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Purpose: The significance of fatigue reduction in rheumatoid arthritis (RA) is well recognized. However, prior patient preference studies on disease-modifying antirheumatic drugs (DMARDs) have not adequately explored the relative importance of fatigue reduction compared to other DMARD attributes or accounted for preference heterogeneity. The objective of this study is to determine the relative importance of DMARD attributes, including fatigue reduction, from the patient perspective.

Patients and Methods: We conducted a web-based discrete choice experiment (DCE) survey among RA patients in the US. Six DMARD attributes were included: 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, the route and frequency of administration, and out-of-pocket cost per month. Choice sets were constructed using a Bayesian efficient design. Mixed logit (ML) and latent class (LC) models were developed to determine preference weights and to calculate the conditional relative importance of each attribute.

Results: Of 228 patients, the ML model showed that the chance of pain reduction had the highest conditional relative importance (2.4), followed by out-of-pocket cost (2.1), the chance of physical function improvement (1.6), the chance of fatigue reduction (1.5), the chance of experiencing serious adverse events (0.6), and the route and frequency of administration (0.09). Preference heterogeneity was observed. The LC model identified two patient classes. The chance of fatigue reduction and the out-of-pocket cost were the most important attributes for class 1 and class 2, respectively.

Conclusion: Pain reduction, physical function improvement, fatigue reduction, and out-of-pocket cost were relatively important DMARD attributes for RA patients. However, the presence of preference heterogeneity underscores the need for individualized treatment. Future studies should explore fatigue preferences and generalizability in the broader RA population.

Keywords: discrete choice experiment, fatigue, patient preference, preference heterogeneity

Introduction

Rheumatoid arthritis (RA) management involves disease-modifying antirheumatic drugs (DMARDs).^{1–3} Methotrexate, a conventional synthetic DMARDs (cDMARDs), is often used as the first-line treatment and can lead to low disease activity or remission in 25–50% of patients.^{3,4} However, given the progressive nature of RA, biological DMARDs (bDMARDs), and targeted synthetic DMARDs (tDMARDs) may be required as monotherapy or combination therapy for patients with RA.¹

American College of Rheumatology (ACR) recommends shared treatment decisions between clinicians and patients, considering patient preferences.^{5–7} A systematic review summarized the findings from eight studies on patients' preferences for DMARDs in the US.^{8–15} Overall results showed that patients with RA valued treatment benefits (eg,

functional improvement) over other treatment attributes (eg, side effects). African American patients placed more emphasis on the risk of toxicity and less on the potential benefits, indicating preference heterogeneity for DMARDs.^{8,16} However, five of these studies relied on conjoint analysis (CA), potentially lacking the ability to capture human preference.^{8–11,13,15} Additionally, two studies used a discrete choice experiment (DCE) to examine patient preferences but did not account for preference heterogeneity.^{12,14} Another study, using a DCE to evaluate the preference-based value of DMARDs and preference heterogeneity, was conducted in 2009 prior to the introduction of various DMARDs, such as subcutaneous and intravenous tocilizumab, intravenous golimumab, and oral upadacitinib.¹⁵

Recent studies indicated that fatigue was a crucial outcome for patients with RA in the US.^{16–18} Specifically, the Innovation and Value Initiative (IVI) and Arthritis Foundation-led studies qualitatively interviewed patients with RA and reported that the patients factored fatigue into their choices of DMARDs. The introduction of fatigue as one of the patient-valued domains has been a landmark in RA in multiple European countries.¹⁹ However, to the best of our knowledge, previous patient preference studies never examined the relative importance of fatigue reduction as compared to other attributes from the perspective of patients with RA in the US.¹⁶ Thus, the objective of this study was to determine the relative importance of DMARD attributes, including fatigue reduction, based on the patient perspective.

Materials and Methods

A cross-sectional, web-based, DCE questionnaire survey was used in this study.²⁰ The design of this study followed the User's DCE guide and the Good Research Practices Task Force report from The Professional Society for Health Economics and Outcomes Research (ISPOR).^{21–23} The study protocol was approved by the Auburn University Institutional Review Board (IRB). Before commencing the survey, all participants granted their consent online and complied with the Declaration of Helsinki.

Study Samples

A purposive sample of RA patients were recruited through a national online Qualtrics^{XM} research panel, a market research company, between January 29 and February 10, 2023. The Qualtrics research panel consists of survey respondents who have been pre-recruited and have agreed to participate in surveys on an ongoing basis. We defined our target respondents as RA patients in the US who were 18 years and older, proficient in English and used DMARDs. Additionally, to further ensure the accuracy of the RA diagnosis, we included only patients who met our screening criteria, those who reported a physician diagnosed RA and had taken DMARDs at any point prior to the survey. Qualtrics^{XM} distributed the survey hosted on the Qualtrics platform, exclusively to panelists whose self-reported profile information matched the study's inclusion criteria, until we met our target sample size. This targeted recruitment approach helped ensure relevance while introducing some selection limitations due to reliance on a pre-existing panel. Based on the best research practices, at least 200 patients were deemed appropriate for the study sample size.^{21,24,25} The final dataset, including responses from over 200 participants, was delivered in an anonymized format for analysis. Participants were compensated for their time by Qualtrics^{XM}.

Study Attributes and Levels

Supplemental materials [Appendix I \(Table S1–Table S5\)](#) lists important DMARD-related attributes generated from the systematic literature search process. Prior DCE/conjoint analysis studies ([Supplemental materials Appendix II Table S1](#)) also informed our attribute selection. Based on the literature review and one-on-one interview with five purposely sampled RA patients (no new information was generated from the fifth patient) and a rheumatologist, six important attributes were selected. Essentially, these attributes included the benefits, risks, route and frequency of administration, and the cost of DMARDs. Clinical knowledge, literature, and qualitative interviews (ie, one-on-one interviews) were used to ensure independence of attribute. The levels of all attributes, except cost, were obtained from the clinical trials of DMARDs gathered from the Drugs@FDA.²⁶ The levels of the cost attribute were based on the willingness-to-pay estimates obtained from our pilot study. [Table 1](#) lists the attributes and levels included.

Table 1 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

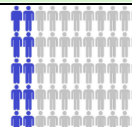





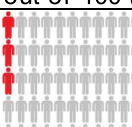
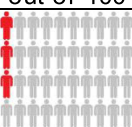


The survey was built on a Qualtrics^{XM} web-based platform. A Bayesian efficient design was used to draw 36 choice tasks from all possible combinations of the selected attributes and levels.^{22,27} Prior parameters were obtained from a pilot study with 30 patients with RA. These 36 choice tasks were 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 1. The survey incorporated two validity check choice tasks: a within-task dominant alternative (a medication with the highest benefits, lowest risks, and lowest cost) and a repeated choice task to assess the stability of patient responses. Questions on patient characteristics and RA experiences were also added to the survey instrument.

To ensure the patient understood the study attributes, lay language was used, and a tutorial with clear explanations and practice questions was provided. The effectiveness of the lay language and tutorial was assessed using follow-up questions administered after the explanation of each attribute level. If a respondent answered incorrectly, the correct response was displayed along with a brief explanation to reinforce comprehension. A “cheap talk” script (non-binding communication between the researcher and respondents to encourage greater effort and attention to the preference-elicitation task) was incorporated to enhance survey response validity.¹⁵ The survey was reviewed by a clinical expert and two social scientists and then validated with five RA patients using the think-aloud method until no new insights emerged. Finally, the survey was piloted-tested with 30 patients recruited through the Qualtrics^{XM} panel. Based on pilot study feedback, adjustments were made, such as setting the maximum cost attribute to \$150 per month and reducing the number of practice questions for each attribute from three to two to reduce cognitive burden.

Data Analysis

The demographic characteristics of the patients were descriptively analyzed. Mixed logit (ML) and latent class (LC) models were developed to examine preference weights and preference heterogeneity. Effect coding was applied, and participants who chose neither Medication A nor Medication B were treated as selecting a third, opt-out alternative. The general form of the utility function (U_{nsj}) of the ML model was: $U_{nsj}^n = \sum_{k=1}^K (\beta_k + i_k) X_{sjk}^n + \tau_j^n$ and for the LC model was

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 1 An example DCE choice set.

Notes: Preference weights on the y-axis represent the relative utility or importance of each attribute level shown on the x-axis. Higher weights indicate greater preference. Preference weights were derived from β estimates of the mixed logit model. A Wald test assessed statistical differences between attribute levels; *Denotes statistical significance at the 5% level. For example, preferences for \$75 per month were significantly lower than \$25 per month, while there was no difference in preferences for \$0 and \$25 per month. The strongest drivers of patient choice were treatment benefits, particularly pain reduction followed by cost and physical function improvement, indicating a strong desire for improved quality of life. While serious side effects were a concern, patients were willing to accept higher risks for more effective or affordable treatments. Fatigue reduction also emerged as a meaningful driver, underscoring the need to consider broader impacts of RA on daily functioning. Preference heterogeneity (not displayed in the figure) was assessed by evaluating the significance of the random parameter (see [Supplemental Material, Appendix III, Table S1](#)). Model fit statistics: Akaike Information Criterion (AIC) = 3190.2, McFadden Pseudo R-squared = 0.31.

Abbreviations: IV, Intravenous Infusion; SC, Subcutaneous Injection.

$U_{sj|c}^n = \sum_{k=1}^K \beta_k X_{sjk}^n + \varepsilon_{sj|c}^n$. For ML model, U_{sj}^n is a utility function relating to individual n and alternative j on the choice set s . X_{sjk}^n is a full vector of observed attributes relating to individual n and alternative j on the choice set s , and β_k is a vector of individual-specific coefficients of attribute k . η_{jk}^n is a random error term whose distribution depends on alternative j and individual n . τ_j^n is an error distribution that did not depend on underlying parameters or data. The variation in the estimated mean of the coefficients across individuals reflected preference heterogeneity.²⁸ Each individual was assumed to have their own set of preferences, which were modeled as random coefficients. Similarly, for the LC model, in addition to the previously defined notations, c represents the number of classes (unknown to the researchers) defined by using various model fit parameters, eg, Akaike Information Criteria (AIC). $\varepsilon_{sj|c}^n$ is a class-specific error term whose distribution depended on alternative j and individual n . The LC model assumed that individual behavior depended on observable attributes and latent heterogeneity that differed from factors unobserved by researchers.²⁹ As the focus of this study was to identify distinct preference pattern across subgroup without underlying decision variability, scale adjustment was not performed for the LC analysis for simplicity. The conditional relative importance for each attribute was determined by comparing the change in preference weights between its most and least favorable levels.

Results

The responses from 228 patients were included in the analysis. These patients correctly responded to the validity choice tasks. Table 2 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 had less than a 4-year college degree (81.4%). All participants used at least one DMARD. Most patients correctly answered

Table 2 Demographic characteristics of the RA patients

Characteristics		N (%)
Age in years, mean (SD)		50.3 (13.70)
Duration of Rheumatoid Arthritis (years), mean (SD)		33.2 (9.20)
Sex	Male	40 (17.54)
	Female	188 (82.46)
Race	White	200 (87.72)
	Black or African American	15 (6.58)
	Multiracial	6 (2.63)
	Asian / Native Hawaiian / Other Pacific Islander	4 (1.75)
	American Indian / Alaska Native	2 (0.88)
	Others	1 (.044)
	Marital Status	Married or domestic partnership
	Single, never married	40 (17.54)
	Divorced or separated/Widowed/Others	75 (32.89)
Household Income	\$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	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)

(Continued)

Table 2 (Continued).

Characteristics		N (%)	
Employment Status	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	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	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)	
Health Status		None	13 (5.70)
		Excellent	1 (0.44)
		Very good	32 (14.04)
	Good	90 (39.47)	
	Fair	86 (37.72)	
	Poor	19 (8.33)	

the practice questions assessing their understanding of the attributes and levels, including attributes and levels of pain (85.1%), physical function (74.6%), fatigue (93.4%), serious side effects (87.3%), and the method of DMARD administration (95.2%), indicating that respondents comprehended the survey content.

Preference Weights of the DMARD Attributes from the ML Model

Figure 2 illustrates the preference weights for the study attributes from the ML model. The preference weights of all attributes and their levels, except the chance of fatigue reduced by 10 points or more, were in the expected directions. Higher chances of pain reduced, and physical function improved by 50% or more, along with the lower chance of serious side effects and lower out-of-pocket cost, had higher preference weights. The adjacent levels of the chances of pain reduced and physical function improved by 50% or more were significantly different. The differences in the preference weights for the chances of serious side effects at 0% and 3%, as well as for the out-of-pocket cost at \$0 (no cost) and \$25

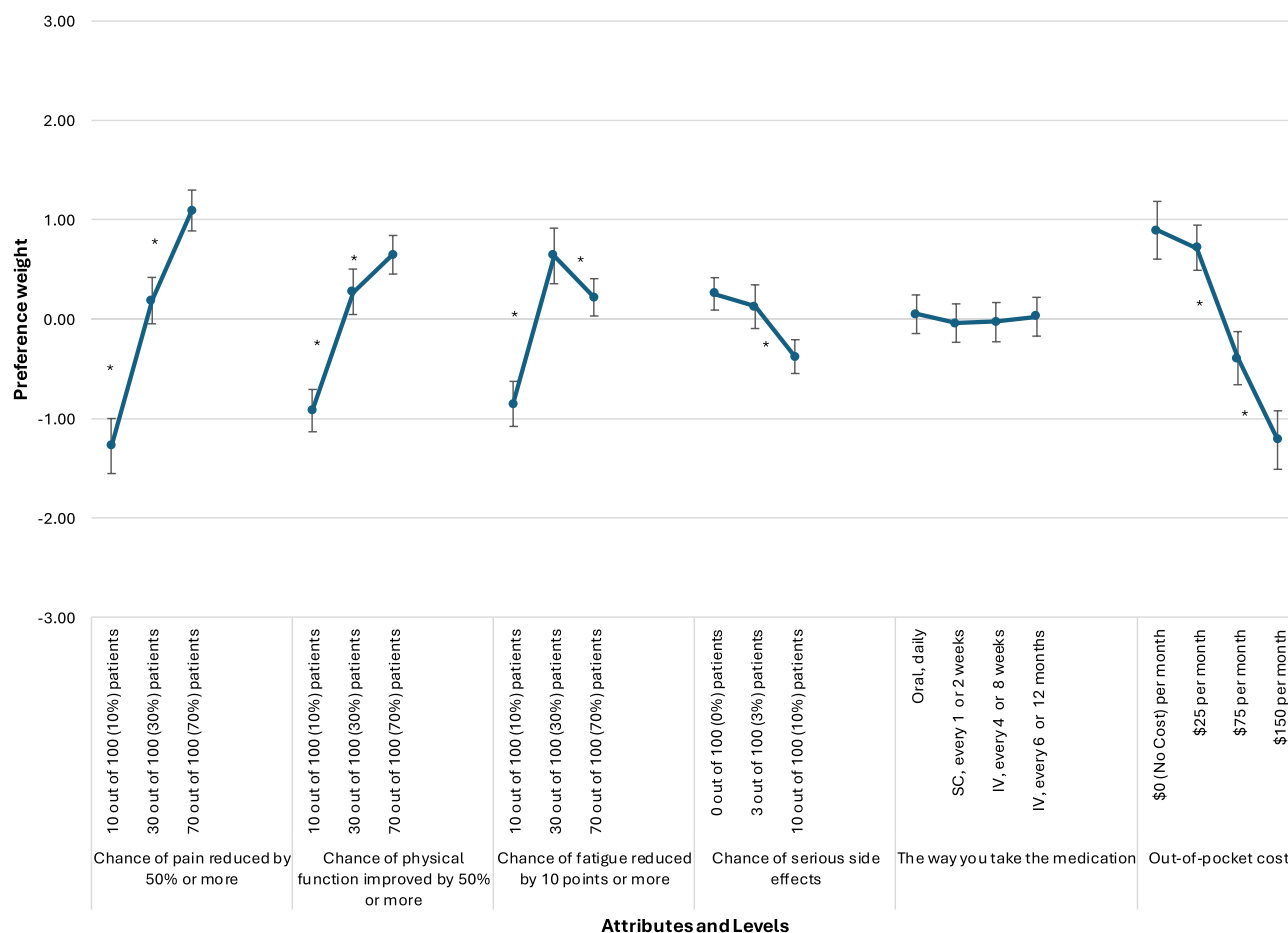


Figure 2 Preference weights of attributes of DMARDs from the mixed logit model.

Note: Latent class analysis identified two distinct patient classes based on model fit statistics (Akaike Information Criterion (AIC)) and interpretability. Preference weights on the y-axis represent the relative utility or importance of each attribute level shown on the x-axis. Higher weights indicate greater preference. Preference weights were derived from β estimates of a latent class model. A Wald test assessed statistical differences between attribute levels; * denotes statistical significance at the 5% level. For example, for class 1 (A), preferences for \$75 per month were significantly lower than \$25 per month, while there was no difference in preferences for \$0 and \$25 per month. Both Class 1 (A) and Class 2 (B) prioritized pain reduction and lower out-of-pocket costs. However, Class 1 patients emphasized the importance of a lower risk of serious side effects and favored IV infusion, while Class 2 (B) patients preferred lower risk of serious side effects and preferred oral versus injectable DMARDs. These differences in preferences across class highlight preference heterogeneity and the need for shared decision-making regarding the efficacy, affordability and administration of DMARDs. Model fit statistics: Akaike Information Criterion (AIC) = 2960, McFadden Pseudo R- squared = 0.36.

Abbreviations: IV, Intravenous Infusion, SC, Subcutaneous Injection.

per month, were not significant. No adjacent level of the route and frequency of administration attribute was significantly different. A kink (unexpected sharp change) in preferences for increasing the chance of fatigue reduction was observed. Patients showed a significant preference for a 30% chance of fatigue reduction over a 10% chance. However, the preference weight for a 70% chance of fatigue reduction was lower than a 30% chance.

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 (1.5), the chance of experiencing severe adverse events (0.6), and the administration of the medication (0.09). The standard deviations of the preference weights of all attributes were statistically significant, indicating the presence of preference heterogeneity for these study attributes. For details, see [supplemental material Appendix III \(Table S1\)](#).

Preference Weights of the DMARDs Attributes from the LC Model

Based on the AIC values, the best LC model suggested two distinct classes. [Figure 3](#) displays the preference weights of DMARD attributes for RA patients in both classes. 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, all adjacent levels of the chance of pain reduction differed significantly. Only the difference between the preference weights of medications offering a 10% chance and a 30% chance of physical function improved by 50% or more was significant. 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. Adjacent level of 3% and 10% chance of serious side effects was significantly different. IV infusion every six- or 12-month or every four- or eight week had significantly higher preference weights than subcutaneous injection every 1 or two weeks. In class 2, all adjacent levels of the chance of pain reduction, physical function improvement, and serious side effects differed significantly. 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. Oral, daily medications had a significantly higher preference weight than the subcutaneous injection of every one- or two-week. A kink in preferences for increasing the chance of fatigue reduction for this class mirrored the ML results. Compared with a 10% chance of fatigue reduction, patients significantly preferred a 30% chance. There was a significant reduction in the preference weight between medications, offering a 70% chance of fatigue reduction compared to a 30% chance.

In class 1, the conditional relative importance estimate of the chance of fatigue reduced by 10 points or more was the highest (2.5), followed by the chance of pain reduced by 50% or more (1.8), the out-of-pocket cost (1.6), the chance of physical function improved by 50% or more (1.3), the administration of 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 (2.3), the chance of pain reduced by 50% or more (1.4), the chance of fatigue reduced by 10 points or more (1.3), the chance of

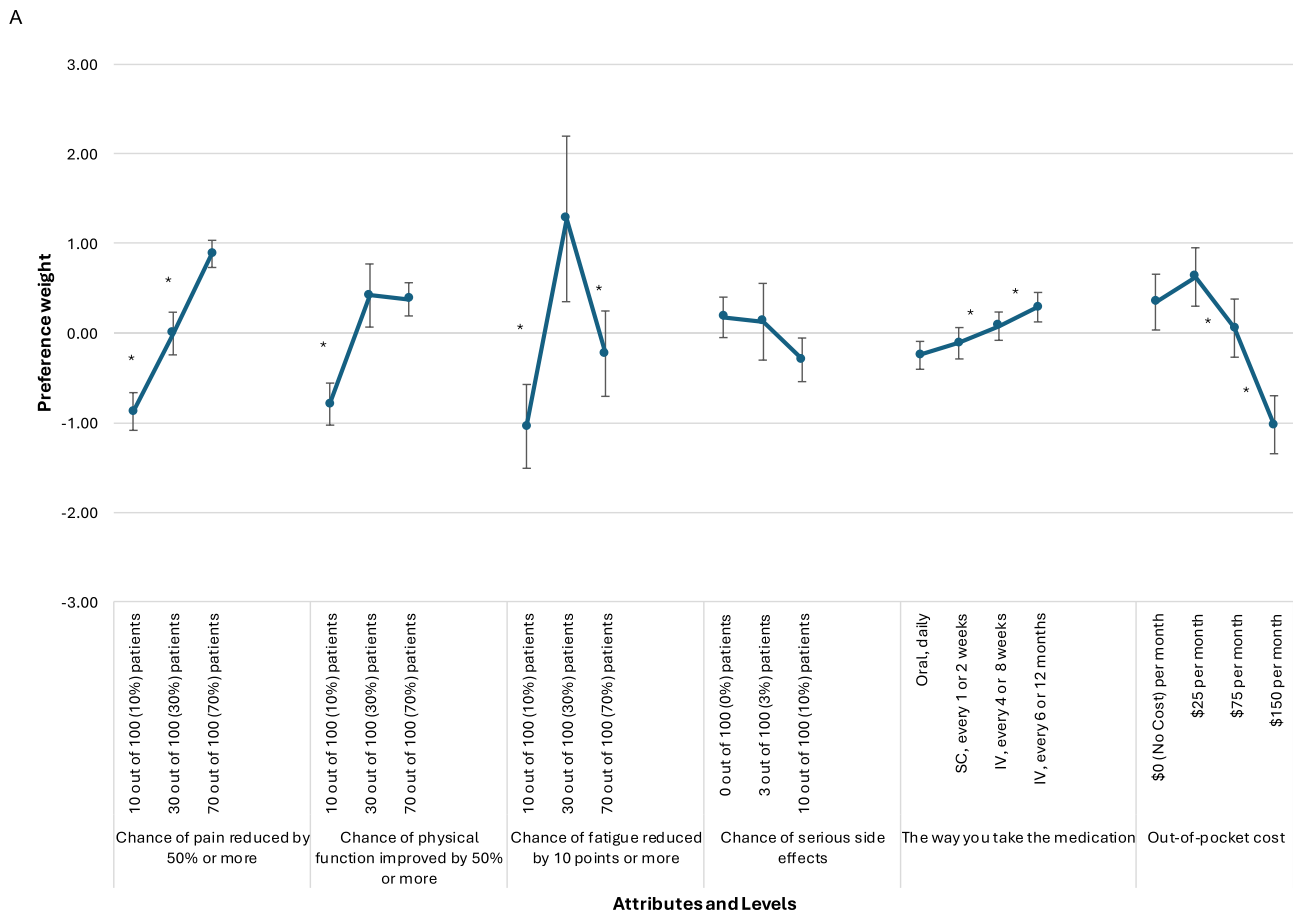


Figure 3 Continued.

B

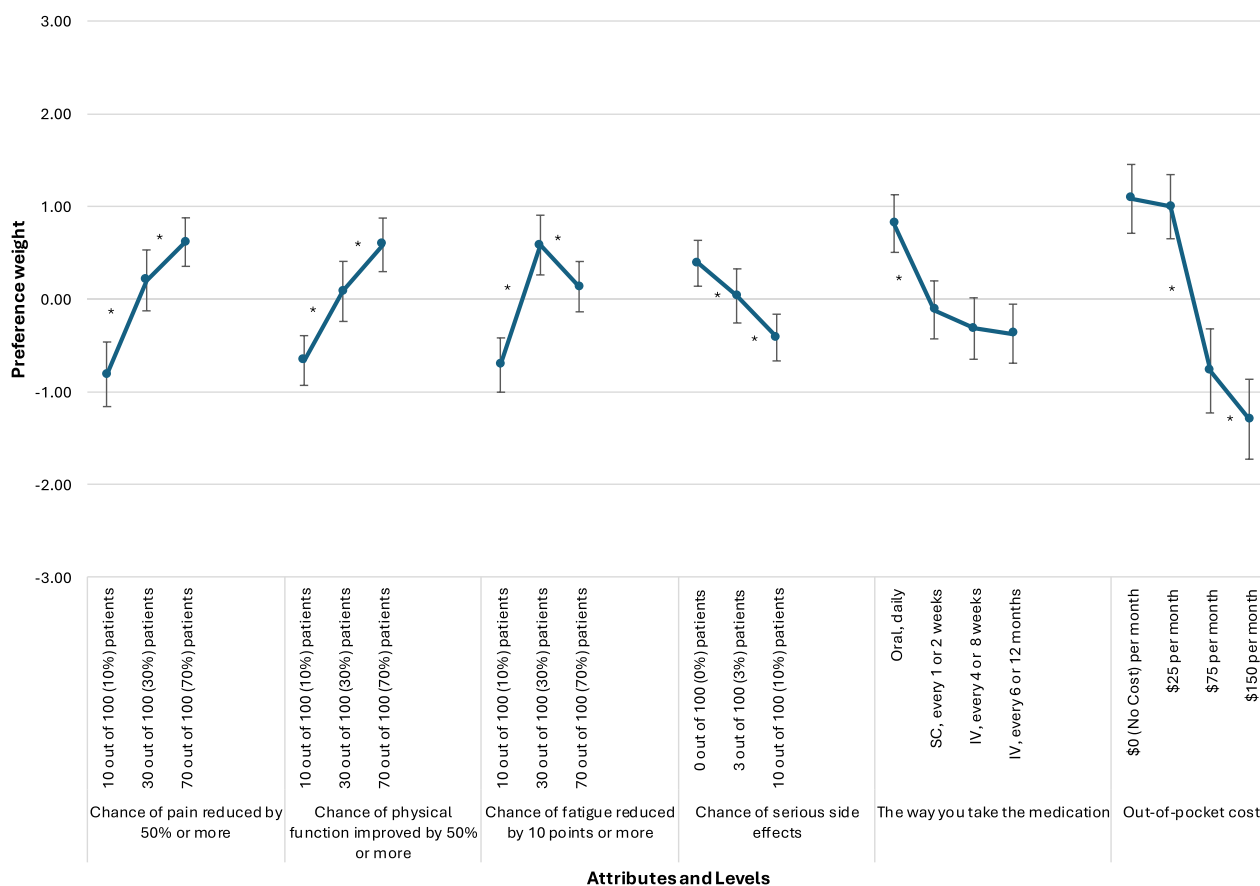


Figure 3 Preference weights of attributes of DMARDs from the latent class model.

physical function improved by 50% or more (1.3), the administration of medication (1.1), and the chance of serious side effects (0.8). For details, see [supplemental material Appendix III \(Table S2\)](#).

Discussions

RA patients preferred DMARDs that provided greater chances of pain reduction and physical function improvement (treatment benefits), a lower chance of severe side effects, and a lower out-of-pocket cost. These findings were consistent with the findings of previous studies.^{30–32} Interestingly, although patients with RA assigned a greater preference weight to a 30% chance of fatigue reduction compared to a 10% chance, their lower preference weight for a 70% chance of fatigue reduction compared to a 30% chance was counterintuitive. This pattern may reflect a diminishing marginal value of fatigue reduction with additional units of fatigue reduction.³³ Given the long disease duration among our study participants (mean duration of RA = 33 years), it is possible that many had adapted to living with chronic fatigue. As a result, once fatigue levels are perceived as manageable, additional reductions may not significantly enhance quality of life. Additional analyses, exploring the interaction between the chance of physical function improvement and the chance of reduction in fatigue (see supplemental material Appendix IV: Figures S1 and S2), revealed that, for each of the three levels of chance of physical function improvement, a 30% chance of reduction in fatigue had a higher preference weight than a 10% chance. Only for a 30% chance of physical function improvement, the preference weight was marginally significant for a 70% chance of reduction in fatigue compared to a 30% chance of reduction. These results suggested that patients with RA exhibited similar preferences for a 30% chance and a 70% chance of reduction in fatigue when DMARDs provided either a low or high chance of physical function improvement. It was plausible that when DMARDs

performed well and improved physical function, patients might view the reduction in fatigue as just only an additional benefit, and this benefit might no longer be a priority. Conversely, a high chance of fatigue reduction might not be important for RA patients if DMARDs performed poorly in improving physical function since the patients might focus more on the effects of DMARDs on physical activity. This could likely explain the counterintuitive shift in the preference weight from a 30% to a 70% chance of a reduction in fatigue in the main ML model.

The ML results revealed a statistically significant and positive alternative-specific constant, suggesting that, on average, respondents exhibited a preference for taking medication over choosing neither option. There was no variation in preference weights across different levels of the route and frequency of administration. Previous studies, despite heterogeneity, suggested that patients with RA in the US generally favored oral treatments over SC injections or IV infusions and preferred less frequent administration over more frequent administration.^{9,12–14} Although our findings could not be directly compared to the findings of these previous US-based DCE studies—since the levels of the route and frequency of administration differed across these studies—one possible reason might be that RA patients might trade between convenience resulting from a lower frequency of administration and inconvenience from the injection for this study attribute.

Several choice-based studies investigated the conditional relative importance of DMARD attributes in the US.^{8–15} The conditional relative importance of the chance of pain reduction, followed by out-of-pocket cost, physical function improvement, and serious side effects, in this study was in line with the previous study findings. A strong preference for treatment benefits might stem from a patient's desire to attain a normal life by experiencing symptom relief and enhanced capacity to engage in daily activities.³⁴ This sentiment was also captured in the current treatment guidelines with a strong recommendation for a treat-to-target to achieve low disease activity or remission.³⁵ Although patients favored a lower chance of a serious side effect, this attribute was relatively less important to treatment benefits or cost, implying patients' willingness to accept a treatment with a higher risk for greater treatment for higher benefits or lower cost of treatment. Notably, we used a generic term for the serious side effects (chance of serious side effects). However, previous studies suggested that the level of details of risk descriptions (eg, chance of cancer) did not affect the hierarchical order of the attribute importance.^{12,30} Additionally, we observed a heterogeneity of preference, which indicated the presence of RA patients with varying degrees of risk tolerance. This heterogeneity underscored that RA treatments should be customized to meet individuals' risk-taking levels and align with their preferences.

The chance of fatigue reduction significantly impacted the patients' choices of DMARDs. 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.^{16,36–39} Previous qualitative studies suggested that fatigue could be as important as improving pain and physical function.^{32,34,40–42} Its importance was slightly lower than physical function improvement, aligning with a UK study where pain and mobility were prioritized over fatigue.⁴³

For LC analysis, two distinct patient classes were identified based on model fit statistics (Akaike Information Criterion (AIC)) and interpretability. Patients in class 1 demonstrated a general preference for initiating treatment, favoring taking medication over opting out of treatment altogether. In contrast, individuals in class 2 showed a tendency to avoid treatment, preferring neither of the available medication options. Both classes considered pain reduction and out-of-pocket costs among the most important attributes. According to previous studies, greater importance was expected for the treatment benefits, such as the chance of pain reduction.^{32,44} 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%) in this study might be the reasons for the greater importance given by the patients to the cost attribute. These results suggested the need for shared decision-making among the patients and providers regarding the affordability of DMARDs.⁴⁵

Interestingly, the relative importance of fatigue reduction was highest for class 1. It was possible that persistent fatigue might limit their ability to work, engage in social activities, or maintain independence. Additionally, statistically non-significant, consistent with prior studies, patients in this class preferred lower levels of serious side effects.¹³ They might be aware of side effect of medication given higher education level among these group ([Supplemental materials Appendix III Table S3](#)). 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 and less frequent dosing requirements.⁴⁶ For patients in class 2, the preference weights significantly decreased with the increased chance of serious side effects. These

findings suggested that patients in class 2 were more sensitive to the serious side effects. Similar to some previous studies, they were reluctant to use injectable DMARDs.^{8,11,47} It was possible that these patients might have different levels of awareness and experience with DMARDs, and therefore, they were concerned about the side effects and the treatment injection. Additionally, it is important to note that variation across classes may be influenced not only by true differences in preferences but also by differences in response consistency among two subgroups. Therefore, observed heterogeneity in this study should be interpreted in light of potential differences in how consistently individuals engage with the choice tasks.

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, clinicians should provide patients with comparative out-of-pocket cost information while making a treatment decision.¹¹ Second, this study confirmed that the RA patients weighed the importance of the chance of fatigue improvement, so clinicians should assess the impact of DMARDs on the fatigue of their patients to improve their quality of life.⁴⁸ Third, risk-benefit trade-offs may be more acceptable to patients who are educated and informed in their treatment choices, highlighting the importance of patient education. Furthermore, the existence of diverse preferences among patients reinforced that treatment decisions should be tailored to individual patients, considering their preferences through a shared decision-making process.

Our study had limitations. First, the patients were recruited from Qualtrics^{XM} panel, primarily white, female, highly educated, and had RA for approximately 32 years potentially limiting the generalizability to the broader RA population in the US. The dynamic effects of disease duration, racial differences, prior DMARD exposure, and disease activity on patient preferences for RA treatments should be considered while interpreting our results.⁸ Second, patient preferences were derived from hypothetical treatment options, which might not fully reflect real-world behavior. Third, the use of a self-administered, web-based questionnaire to identify RA patients might also introduce the possibility of response bias due to misdiagnosis and misinterpreting attribute levels. However, various measures, such as an expert review and the inclusion of validity check choice sets, were implemented to minimize this bias. Fourth, only six treatment attributes were included, although other treatment attributes could influence patient preferences. Finally, although it is the best practice to also include RA patients who did not correctly respond to the validity choice questions and perform analysis using statistical control,⁴⁹ given the lack of availability of data on these patients from Qualtrics^{XM}, only those RA patients who provided a valid response were included in the analyses.

Conclusions

This study provided a deeper understanding of the DMARD attributes that were important to patients with RA. Patients with RA tended to weigh the importance of the benefits, including fatigue reduction, 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 each patient's need for individualized treatments. Future studies should further investigate the counterintuitive preferences for improvements in fatigue, as well as examine preference and scale heterogeneity across diverse groups of RA patients to enhance generalizability.

Data Sharing Statement

All data are available upon reasonable request.

Ethics

This study was approved by the Auburn University Institutional Review Board (IRB). Protocol number 22-372 EX 2210.

Acknowledgments

This paper is based on the dissertation of [Poudel N]. It has been published on the institutional website: <https://auetd.auburn.edu/handle/10415/8889>

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure

JRC declare to receive grants/contracts from AbbVie, Amgen, BMS, Janssen, Lilly, Novartis, Pfizer, Sanofi, Setpoint, and UCB. JRC declare to receive consulting fees from AbbVie, Amgen, AQTUAL, Janssen, Lilly, Novartis, Moderna, Pfizer, Sanofi, Setpoint, and UCB. KBG and JRC receive support from NIH P30AR072583. All other authors declare no conflict of interest.

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