Patient preferences on rheumatoid arthritis second-line treatment: A discrete choice experiment of Swedish patients

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Abstract

Background

Preference assessments of patients with rheumatoid arthritis (RA) help inform clinical therapeutic decisions for including biologic and targeted synthetic drugs to use. This study assesses patient preferences for biologics or Janus kinases (JAK) inhibitors and heterogeneity within these preferences to estimate the relative importance of treatment characteristics and to calculate the minimum benefit levels patients require to accept higher levels of side effects.

Methods

Between November 2018 to August 2019, patients were recruited to participate in a survey containing demographic and disease-related questions as well as a Discrete Choice Experiment to measure their preferences for second-line therapies using biologics or JAK inhibitors. Treatment characteristics (attributes) included in the DCE were mode of administration, frequency of use, probability of mild short-term side effects, probability of side effects affecting appearance, probability of psychological side effects, probability of severe side effects, and effectiveness of treatment.

Results

A total of 358 patients were included in the analysis. Latent class analysis revealed three preference patterns. When choosing treatment, the respondents found either effectiveness of treatment, mode of administration, or probability of severe side effects as most important. In addition, disease duration and mild side effects influenced the patients' choices.

Conclusion

Respondents found either effectiveness, severe side effects, or mode of administration as the most important attribute. Patients noting effectiveness as most important were more willing than other patients to accept higher risks of side effects.

Key Points

- There are multiple treatments available for patients with RA and patients' preferences for these treatments vary significantly.
- Compared to previous research, this study measured patient preferences for more specific side effects and their probabilities and therefore may better fit into the European health care perspective.
- This study could support shared decision making in recognising the different preference patterns of patients and the minimum acceptable benefit patients require to make certain DMARD treatment decisions.
- Results from this study have the potential to support evaluations regarding the approval of new RA treatments.

1. Introduction

Information about patient preferences has long been considered important for supporting patient-centeredness in clinical decisions [1]. Over the past decade, measuring patient preferences has evolved to use methods that quantify preferences in the clinical context [2–5]. Today, rheumatology uses quantitative assessment of patient preferences to inform clinical decisions [6]. Recently, the interest in quantifying preferences of patients with rheumatic diseases has been expanded to f new regulatory marketing authorisation decisions of new rheumatic disease

medicines [7, 8]. Patient preference assessment is important in regulatory marketing approvals in order to adjust decision making to patient opinions on the meaning and significance of treatment attributes such as the balance between estimated effects and adverse reactions. A better adjustment to patient preferences may also have a positive impact on patient adherence [9].

Patients with rheumatoid arthritis (RA) are often treated with multiple disease-modifying anti-rheumatic drugs (DMARD). DMARDs have different modes of action and characteristics, such as method and frequency of administration and probability of adverse events or monitoring requirements. Newly-diagnosed patients with RA usually start with conventional synthetic DMARDs as first-line therapy. If first-line therapy is not tolerated or is ineffective, biologics or Janus kinases (JAK) inhibitors are recommended [10]. An advantage of JAK inhibitors is that they are given orally rather than subcutaneously or intravenously as is required for biologics) [11].

Previous research has shown that cost, efficacy, and administration strongly influence patient preferences for second-line therapy – i.e., biologics or JAK inhibitors [2, 3, 12]. However, both biologics and JAK inhibitors are associated with side effects such as infections, nausea, anxiety, and skin rash [11]. Therefore, clinicians should provide patients with specific information about treatments with these drugs, including the extent and probability of experiencing side effects, so patients can make informed decisions about their treatment that align with their preferences. Although treatment costs can be an important determinant of preference, they are less relevant in countries with universal health care systems, as is the case for most of Europe.

Clinicians need to understand their patients' preferences and perspectives when informing their patients about potential RA treatments so their patients can make decisions about their treatment that are aligned with their preferences [9, 13, 14]. Quantitative assessments of patient preferences have the potential to support both clinicians and regulators when they consider patient perspective [7, 11]. However, currently there is a lack of evidence on the extent to which patients feel that risk for a wide range of possible side effects are acceptable for new treatments with JAK inhibitors or biologics. This study assesses preferences regarding treatment with biologics and JAK inhibitors and heterogeneity within these preferences for patients with RA. These preferences are used to estimate the relative importance of different treatment characteristics and to calculate the minimum benefit levels patient require in order to accept higher levels of potential side effects.

2. Methods

2.1 Recruitment

Treatment preferences of patients with RA were assessed using a discrete choice experiment (DCE). An invitation to participate in the study was advertised to members of the Swedish Rheumatism Association via email, newspaper, newsletter, social media, mobile application, and the association's website. The invitation to participate was also distributed to patients attending ten rheumatology clinics in Sweden and via an online research panel of patients with RA. A printed copy of the survey was distributed by the Rheumatology clinic at Uppsala University hospital. All participants received information about the study and provided their informed consent before completing the survey. The following inclusion criteria were used: established RA diagnosis, 18–80 years of age, and the ability to understand and answer the questions themselves. Data were collected from November 2018 to August 2019. The survey was approved by the regional ethics review board in Uppsala, Sweden (Reg no. 2017/521, 2018/156). Data generation, storage and sharing were governed by the General Data Protection Regulation (GDPR) Act, Uppsala University data protection and security policies and ethical consent provided.

2.2 Methodology of discrete choice experiment

DCEs, a cross-sectional survey method used to assess preferences, allows for quantitative assessment of patient

, and interventions [15]. DCEs, which uses random utility theory (RUT), aims to

quantify the relative importance of one treatment characteristic over another treatment characteristic. RUT assumes that the value (utility) of a product can be determined by the value (utility) of the characteristics of that product (i.e., attributes) and their levels. Participants in a DCE are presented with hypothetical scenarios (choice questions) with varying attributes and levels. Participants are asked to choose their preferred option for each question [16]. The utility can be estimated by modelling the choices that respondents make between alternatives of treatments that are described by different choice questions [17]. DCEs can also be used to measure and explain heterogeneity within the preferences of patients [18].

2.3 Attributes and levels

Using a step-wise approach, we identified attributes and levels for inclusion in the DCE. First, the analysis of a literature review of previous studies of patient preferences for DMARDs resulted in 12 potential treatment attributes [2, 3, 5, 14, 19–24]. Second, the attributes and levels identified in the literature review were discussed with a rheumatologist to make sure that they reflected current clinical practice. Third, three focus groups using the nominal group technique (NGT) were conducted with patients with RA (n = 7); these patients were asked to identify new attributes and rank all potential attributes from most to least important [25]. The focus groups were audio recorded, lasted for about 90 minutes, and conducted using an interview guide. Fourth, results from the focus groups were discussed during several validation meetings with one rheumatologist, the research team, and two patient research partners. These meetings revealed seven attributes: mode of administration, frequency of use, probability of mild short-term side effects, probability of side effects affecting appearance, probability of psychological side effects, probability of severe side effects, and effectiveness of treatment. Each attribute was revealed to have three levels based on current clinical knowledge of existing biologics and JAK inhibitors. Detailed information regarding the selection and description of the attributes and levels is available in the Supplementary material. All attributes and levels included in the DCE are displayed in Table 1.

Table 1
Attributes and levels

Attribute	Level 1	Level 2	Level 3
Route of administration	Tablet	Injection	Drip
Frequency of use	Daily	Weekly	Monthly
Probability of mild short-term side effects (nausea, vomiting or headache)	Common, 1 in 10	Uncommon 1 in 100	Rare 1 in 1000
Probability of side effects changing appearance (hair loss, weight changes or skin rash)	Common, 1 in 10	Uncommon 1 in 100	Rare 1 in 1000
Probability of psychological side effects (anxiety, mood changes, depression or sleep disturbance)	Common, 1 in 10	Uncommon 1 in 100	Rare 1 in 1000
Probability of severe side effects that requires hospitalisation such as severe infections or allergic reactions	Common, 1 in 10	Uncommon 1 in 100	Rare 1 in 1000
Effectiveness (the ability to decrease inflammation and swelling of the joints, also pain and other symptoms)	30% improvement So out of 100 persons taking the treatment, 30 will get enough improvement, the rest will get a small or no improvement	50% improvement So out of 100 persons taking the treatment, 50 will get enough improvement, the rest will get a small or no improvement	70% improvement So out of 100 persons taking the treatment, 70 will get enough improvement, the rest will get a small or no improvement

2.4 Experimental design and survey

The survey started with information about RA and available treatment options before entering the DCE. The last section of the survey consisted of demographic and disease-related questions, health literacy [26], and numeracy [27]. The DCE had an attribute-based experimental design. Each respondent answered 15 hypothetical choice questions characterised by varying attribute levels. Participants were asked to choose their preferred treatment from two alternatives (treatment A or treatment B).

The survey was pilot tested with a subgroup (n = 22) of patients with RA and RA research partners. Six of the pilot tests were ‘think aloud’ interviews. The participants were encouraged to articulate their thoughts while completing the survey. The language and the layout of the survey were slightly changed after the pilot test. Using the pilot test data, we fitted a Multinomial logit (MNL) model and used the beta estimates as priors for the final experimental DCE design generated by NGene 1.0 (ChoiceMetrics, 2011), which is a *d*-efficient (Bayesian) design [28]. A constraint was posed on the design: mode of administration and frequency of use (e.g., if the drug was a pill, the frequency could not be ‘monthly’). A total of 60 unique choice questions were divided into four blocks. Each respondent had to make 15 decisions. We applied the decision-making scenario ‘think of yourself in a situation where your treatment is not working, your joints are swollen, you have pain or unbearable side effects and need to change to a second-line treatment’.

2.5 Statistical analysis

SPSS® Statistics 20 and Nlogit® were used for analyses. Demographic data were analysed using descriptive statistics. Results were considered statistically significant if $P<0.05$. Latent class analysis (LCA) models were used for the analysis of the DCE data. Such models account for the multilevel structure of the data (i.e., every respondent answered multiple choice questions) and account for the investigation of preference heterogeneity. LCA models assume that there are two or more latent classes of data with different preferences. The classes are characterised by unobserved latent variables that can be related to a set of choice patterns. Once choice patterns have been stratified into classes, it is possible for the model to determine the probability that a participant with certain characteristics will be assigned to each class [29]. The 'likelihood ratio test', the Akaike information criterion (AIC), and the Bayesian information criterion (BIC) were used to determine the most appropriate model. The attributes were dummy coded and the utility equation used for the analysis is shown below:

$$V_{\text{rta\&b}|c} = \beta 0|c + \beta 1|c \text{ Mode of administration}_{\text{Pill rta\&b}|c} + \beta 2|c \text{ Mode of administration}_{\text{Injection rta\&b}} + \beta 3|c \text{ Frequency of use}_{\text{Daily rta\&b}} + \beta 4|c \text{ Frequency of use}_{\text{Weekly rta\&b}} + \beta 5|c \text{ Mild side effects}_{\text{1 in 10 rta\&b}} + \beta 6|c \text{ Short term side effects}_{\text{1 in 100 rta\&b}} + \beta 7|c \text{ Appearance side effects}_{\text{1 in 10 rta\&b}} + \beta 8|c \text{ Appearance side effects}_{\text{1 in 100 rta\&b}} + \beta 9|c \text{ Psychological side effects}_{\text{1 in 10 rta\&b}} + \beta 10|c \text{ Psychological side effects}_{\text{1 in 100 rta\&b}} + \beta 11|c \text{ Severe side effects}_{\text{1 in 10 rta\&b}} + \beta 12|c \text{ Severe side effects}_{\text{1 in 100 rta\&b}} + \beta 13|c \text{ effectiveness}_{\text{rta\&b}}$$

The utility component (V) describes the utility that respondent 'r' belonging to class 'c' reported for alternative 'a' in choice question 't'. β0 represents the constant of the model. The attribute level estimates of each attribute level is represented by β1 – β13. A significant attribute estimate within a certain class indicates that this attribute contributes to the decision-making process of respondents who belong to that class. The sign of the beta indicates whether the attribute level has a positive or negative effect on the utility.

Several demographic and disease-related variables were tested for their potential impact on class membership in the LCA: age, gender, numeracy, health literacy, education level, disease duration, occupational status, and experience with DMARD treatment and side effects. To calculate the relative importance of the attributes, the difference between the highest and lowest estimates of the attribute level was calculated for each attribute. The largest difference value was given a 1, representing the attribute that was deemed most important by respondents. The other difference values were divided by the largest difference value, resulting in a relative distance between all other attributes and the most important attribute.

A minimum acceptable benefit (MAB) for changes in attribute levels was calculated. The MAB is interpreted as the minimum change in effectiveness that respondents would require (on average) to accept changes to a less desirable level in another attribute (probability of getting a certain side effect by 10%, 1%, and 0.1%). MAB was estimated as the difference between the preference weights (parameters) for two levels of an attribute divided by the preference weight:

$$MAB = -\frac{(\beta_{k,l=2} - \beta_{k,l=1})}{\left(\beta_{k=effectiveness,}\right)}$$

3. Results

3.1 Participants

In total, 422 patients completed the full survey although 29 were removed after testing for flat-lining (choosing option A at least 13 out of 15 times) and 35 were removed because they answered the survey in under five minutes. Most of the participants were female (77%). The participants represented all age categories between 18–80 years of age. The level of education was categorised into low (n = 105), medium (n = 86), or high (n = 162). A full overview of patient and disease characteristics is presented in Table 2.

Table 2
Patient and disease characteristics

Item		*N*	*N* in %
Total		358	100
Gender			
	Female	272	77
	Male	83	23
Age			
	18–24	15	4
	25–34	42	12
	35–44	31	9
	45–54	64	18
	55–64	99	28
	65–80	105	30
Education level			
	Low (elementary school, primary school, real school, or similar, 2-year high school or vocational school, 3–4 year high school)	105	30
	Medium (college or university shorter than 3 years)	89	25
	High (college or university 3 years or longer)	162	45
Occupational status			
	Full time employee, part time employee, parental leave/occupational leave	154	43
	Work part time since RA, long-term sick leave, sick pension	79	22
	Age pensioner/unemployed	177	33
	Other	6	2
Health literacy			
	Sufficient	197	55
	Problematic	134	38
	Lacking	24	7
Numeracy			
	High	28	8
	Medium	212	60
	Low	113	32

Item		*N*	*N* in %
Disease duration			
	1–12 months	22	6
	1–5 years	88	25
	5–10 years	67	19
	More than 10 years	179	50
Time till onset of drug effect			
	0–3 months	121	34
	3–12 months	87	25
	1–2 years	33	9
	2–5 years	37	11
	More than 5 years	32	9
	Still not working	43	12
Experience with treatment			
	First line treatment only (csDMARDs)	182	51
	Second line treatment	116	32
	Biologics		
	JAK inhibitors	12	3
Experience with side effects			
	Mild short term	205	57
	Appearance	154	43
	Psychological	137	38
	Severe	80	22
	No side effects	89	24

3.2 Preferences and relative importance

On average, all of the respondents preferred a pill over an injection or drip. The respondents also preferred monthly over weekly or daily medication. A strong disutility for the highest frequency of side effects was found in all classes. Finally, respondents preferred the medicine with the highest effectiveness. The directions of the effects of the attributes on utility were as expected, which confirms that respondents understood the choice questions. On average, the most important attribute for respondents was the probability of severe side effects. Treatment effectiveness was the second most important attribute, closely followed by the probability of psychological side effects. Mode of administration came in fourth place followed by frequency of use, probability of mild short-term side effects, and side effects changing appearance (Table 3).

Table 3
Preferences of patients based on latent class analysis

		Class 1 Estimate	SE	RI	Class 2 Estimate	SE	RI	Class 3 Estimate	SE	RI
Mode of administration										
	Pill	1.22***	0.27	0.25	0.92***	0.20	1.00	1.14***	0.19	0.31
	Injection	0.37**	0.17		0.51***	0.15		0.64***	0.16	
	Drip (ref)									
Frequency of use										
	1 a day	-1.00***	0.18	0.22	-0.75***	0.16	0.82	-0.59***	0.14	0.16
	1 a week	-0.47***	0.17		-0.23	0.14		-0.02	0.16	
	1 a month (ref)									
Probability of mild short-term side effects										
	1 in 10	-0.30*	0.17	0.06	-0.27*	0.14	0.29	-0.44**	0.17	0.12
	1 in 100	-0.15	0.13		-0.08	0.12		-0.06	0.14	
	1 in 1000 (ref)									
Probability of side effects changing appearance										
	1 in 10	-0.87***	0.20	0.18	-0.34**	0.16	0.11	-1.55***	0.21	0.42
	1 in 100	-0.04	0.17		-0.10	0.14		-0.48***	0.15	
	1 in 1000 (ref)									
Probability of psychological side effects										
	1 in 10	-1.11***	0.23	0.23	-0.75***	0.18	0.82	-2.61***	0.28	0.72
	1 in 100	-0.01	0.18		-0.62***	0.15		-0.34**	0.17	
	1 in 1000 (ref)									
Probability of severe side effects										
	1 in 10	-1.75***	0.27	0.36	-0.21	0.18	0.23	-3.65***	0.39	1.00
	1 in 100	-0.82***	0.16		-0.08	0.12		-0.79***	0.16	

and 10%, respectively.

		Class 1 Estimate	SE	RI	Class 2 Estimate	SE	RI	Class 3 Estimate	SE	RI
	1 in 1000 (ref)									
Effectiveness (linear)		0.12***	0.01	1.00	0.01**	0.00	0.43	0.04***	0.00	0.44
Class probability model										
Constant		1.32	0.96		2.51***	0.96		-	-	
Disease duration		-0.16	0.12		-0.32***	0.12		-	-	
Experience with mild side effects		-0.46	0.36		-0.99**	0.39		-	-	
Average class probability		0.33			0.27			0.38		
Note: ***, **, and * significance at 1%, 5%, and 10%, respectively.										

3.3 Preference heterogeneity

Considerable heterogeneity was found in the preferences. Respondents were divided into three classes (patterns), representing differences in preferences. The average probability of respondents belonging to one of the classes was 34%, 28%, and 38%, respectively (Table 3). The model fit significantly improved when including disease duration and experience of mild short-term side effects (loglikelihod = -2495 and − 2491, $P < 0.05$) to the class assignment model.

Although the directions of the impact of the attribute levels on utility were the same in all classes, high levels of heterogeneity were observed with respect to the importance of the attribute levels. The relative importance (RI) score of the attributes was separately calculated for the three classes of the latent class analysis (Fig. 1). Class 1 respondents found treatment effectiveness most important, class 2 respondents found mode of administration most important, and class 3 respondents found probability of severe side effects most important. Respondents with newly-diagnosed RA and no experiences of mild short-term side effects were more likely to belong to class 2, whereas respondents with longer disease duration and previous mild short-term side effects were more likely to belong to class 3.

3.4 Minimum acceptable benefit

Table 4 shows the minimum acceptable benefit (MAB) levels required (in percentage point increases in effectiveness) to compensate respondents for worsening levels of probability of certain side effects. Due to preference heterogeneity, large differences were found in the MAB across the three classes. In class 1, only a small benefit was needed to accept a switch to a less favourable frequency of side effects. In the other two classes, respondents would require a larger increase in effectiveness to accept an increase in risk of side effects. The highest MAB levels were seen in class 3 respondents for moving from a 0.1% probability of severe side effects to a 10% probability, which required a 91.3 percentage point increase in treatment effectiveness. The second highest MAB level was seen in class 2 for moving from a 0.1% probability of psychological side effects to a 10% probability, which required a 75.0 percentage point increase in treatment effectiveness.

Table 4
Minimum acceptable benefit for changes in attribute levels

Attribute	Change	Minimum acceptable benefit in percentage		
		Class 1	Class 2	Class 3
Probability of mild short-term side effects				
	Moving from 0.1–10%	2.5	27.0	11.0
	Moving from 0.1–1%	1.3	-	1.5
	Moving from 1–10%	1.3	35.0	9.5
Probability of side effects changing appearance				
	Moving from 0.1–10%	7.3	34.1	38.8
	Moving from 0.1–1%	-	10.0	12.0
	Moving from 1–10%	7.6	24.0	26.8
Probability of psychological side effects				
	Moving from 0.1–10%	9.3	75.0	65.3
	Moving from 0.1–1%	-	62.0	8.5
	Moving from 1–10%	9.3	13.0	56.8
Probability of severe side effects				
	Moving from 0.1–10%	14.6	21.0	91.3
	Moving from 0.1–1%	-	8.0	18.8
	Moving from 1–10%	21.4	13.0	71.5

4. Discussion

This study assesses preferences regarding treatment with biologics and JAK inhibitors and heterogeneity within these preferences among patients with RA as well as estimates of the relative importance of different treatment characteristics. In addition, this study calculates the minimum benefit levels patient require in order to accept higher levels of potential side effects. Respondents found either effectiveness of treatment, mode of administration, or probability of severe side effects to be most important. This study also reveals that disease duration and experience with mild side effects had an impact on patients' choices. For newly-diagnosed patients with no experience of mild side effects, mode of administration (with oral administration being most preferred) was the most important treatment attribute. This preference might be due to wanting a treatment that fits with current lifestyle, since taking a pill is less invasive and more convenient than a self-administered injection or having a daily infusion [23]. In addition, participants might find it easier to understand the impact of mode of administration on daily life, whereas relatively small changes in side effects may be more complicated to understand.

Findings from this study are in line with previous research reporting on different patterns of preferences of patients with RA, as the importance of effectiveness and severe side effects [2, 3, 12]. However, the attributes and levels for this study address more side effects in the choice questions, such as the probability of psychological side effects or side effects affecting appearance and the probabilities of these side effects.

For patients whose choices were most influenced by treatment effectiveness, the impact of side effects on decision making was marginal. These patients might be recognised as a subgroup with increased willingness to accept higher risk of side effects for an increase in effectiveness. Such patients might be willing to try a new orally-administered treatment even though there is uncertainty regarding long-term outcomes. Newly-diagnosed patients preferred an oral medication over all other attributes; however, they did not accept an increased risk of severe side effects. Similarly, patients with longer disease duration and experience with mild side effects were less willing to accept a treatment with a higher risk of severe side effects.

Previous studies have revealed that rheumatologists and patients with RA have different treatment preferences [14, 30]. This study could support rheumatologists and patients in shared-decision making by identifying which attributes should be the focus of treatment discussions. This study has also revealed the trade-offs that patients with RA are willing to make, a finding that may help patients recognise what is most important from an individual perspective. Tailoring treatment according to patients' preferences may increase treatment satisfaction and compliance, which could improve treatment outcomes in patients with RA [3].

For regulatory decision-making, considering preference heterogeneity in marketing authorisations or in post authorisations may lead to decisions that are more acceptable to the end users. Treatment satisfaction may increase for patients with a higher acceptance of side effects if the prospect of effectiveness is higher [31, 32].

There are some limitations of this study. First, several sources were used to recruit patients with RA and there was limited control over patient selection, it was not possible to calculate the response rate. However, respondents were only able to participate at one time and no duplicates were found in the patient sample. The patient characteristics (age, gender, education and treatment experience) suggest a representative sample of the Swedish RA population [33]. This article provides a useful addition to the literature by assessing the Swedish population. The results may not be generalizable to other European countries as the health care systems are different. However, there are some concordance between the results of similar, previous studies in a range of countries [34].

Future research should focus on other important disease-related characteristics such as disease activity and risk propensity, characteristics that may influence respondents' preferences. Research needs to develop methods and guidelines to bring in the results of patient preference assessments in both regulatory marketing approval decisions and in the clinical context of shared decision making.

Conclusions

Respondents' choices were most influenced by either mode of administration, effectiveness of treatment, or probability of severe side effects. Patients who found effectiveness of treatment to be most important only reported a marginal impact of side effects; these patients might be recognised as a subgroup of patients more willing to accept higher risk of side effects for increased effectiveness. Other patients may not accept a switch associated with increased risk of severe side effects. This study could support personalisation of treatment with biologics and JAK inhibitors by recognising the different preference patterns of patients and the minimum acceptable levels of benefit. Consideration of preference heterogeneity in marketing authorisations or in post authorisations may lead to decisions more acceptable to the end users.

Declarations

Ethics approval and consent to participate

The study was approved by the regional ethics review board in Uppsala, Sweden (Reg no. 2017/521, 2018/156). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Availability of data and materials

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interest

KR is supported by the Birmingham NIHR Biomedical Research Centre and is a member of the Research into Inflammatory Arthritis Centre Versus Arthritis and the MRC Versus Arthritis Centre for Musculoskeletal Ageing Research.

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Author's contributions

All authors have made substantial contributions to the conception, design of the work, the analysis and interpretation of data. All authors contributed to drafting of the work and substantively revised it. All authors read and approved the final manuscript.

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References

1. Charles C, Gafni A. The vexing problem of defining the meaning, role and measurement of values in treatment decision-making. Journal of comparative effectiveness research. 2014;3(2):197–209.

2. Alten R, Kruger K, Rellecke J, Schiffner-Rohe J, Behmer O, Schiffhorst G, Nolting HD. Examining patient preferences in the treatment of rheumatoid arthritis using a discrete-choice approach. Patient Prefer Adherence. 2016;10:2217–28.
3. Fraenkel L, Nowell WB, Michel G, Wiedmeyer C. **Preference phenotypes to facilitate shared decision-making in rheumatoid arthritis**. *Ann Rheum Dis* 2017.
4. Augustovski F, Beratarrechea A, Irazola V, Rubinstein F, Tesolin P, Gonzalez J, Lencina V, Scolnik M, Waimann C, Navarta D, et al. Patient preferences for biologic agents in rheumatoid arthritis: a discrete-choice experiment. Value Health. 2013;16(2):385–93.
5. Louder AM, Singh A, Saverno K, Cappelleri JC, Aten AJ, Koenig AS, Pasquale MK. Patient Preferences Regarding Rheumatoid Arthritis Therapies: A Conjoint Analysis. Am Health Drug Benefits. 2016;9(2):84–93.
6. Meara A, Crossnohere NL, Bridges JFP. Methods for measuring patient preferences: an update and future directions. Curr Opin Rheumatol. 2019;31(2):125–31.
7. Patient. **Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling: Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders** http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm446680.pdf.
8. **The patient's voice in the evaluation of medicines**. In., 18 October 2013 edn: European Medicines Agency, Stakeholders and Communication Division; 2013.
9. Ho M, Saha A, McCleary KK, Levitan B, Christopher S, Zandlo K, Braithwaite RS, Hauber AB. A Framework for Incorporating Patient Preferences Regarding Benefits and Risks into Regulatory Assessment of Medical Technologies. Value Health. 2016;19(6):746–50.
10. Aletaha D, Smolen JS. Diagnosis and Management of Rheumatoid Arthritis: A Review. JAMA. 2018;320(13):1360–72.
11. European. **Medicines Agency** http://www.ema.europa.eu/ema/.
12. van Heuckelum M, Mathijssen EG, Vervloet M, Boonen A, Hebing RC, Pasma A, Vonkeman HE, Wenink MH, van den Bemt BJ, van Dijk L. Preferences of patients with rheumatoid arthritis regarding disease-modifying antirheumatic drugs: a discrete choice experiment. Patient Prefer Adherence. 2019;13:1199–211.
13. Muhlbacher AC, Juhnke C, Beyer AR, Garner S. Patient-Focused Benefit-Risk Analysis to Inform Regulatory Decisions: The European Union Perspective. Value in health: the journal of the International Society for Pharmacoeconomics Outcomes Research. 2016;19(6):734–40.
14. Nolla JM, Rodriguez M, Martin-Mola E, Raya E, Ibero I, Nocea G, Aragon B, Lizan L, Prades M. Patients' and rheumatologists' preferences for the attributes of biological agents used in the treatment of rheumatic diseases in Spain. Patient Prefer Adherence. 2016;10:1101–13.
15. Clark MD, Determann D, Petrou S, Moro D, de Bekker-Grob EW: **Discrete choice experiments in health economics: a review of the literature**. *PharmacoEconomics* 2014, **32**(9):883–902.
16. Ryan M, Gerard K. Using discrete choice experiments to value health care programmes: current practice and future research reflections. Appl Health Econ Health Policy. 2003;2(1):55–64.
17. Viney R, Savage E, Louviere J. Empirical investigation of experimental design properties of discrete choice experiments in health care. Health Econ. 2005;14(4):349–62.
18. Lancsar E, Louviere J. Conducting discrete choice experiments to inform healthcare decision making: a user's guide. PharmacoEconomics. 2008;26(8):661–77.
19. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis rheumatism. 2010;62(9):2569–81.

20. van Tuyl LH, Sadlonova M, Hewlett S, Davis B, Flurey C, Goel N, Gossec L, Heegaard Brahe C, Hill CL, Hoogland W, et al. The patient perspective on absence of disease activity in rheumatoid arthritis: a survey to identify key domains of patient-perceived remission. Ann Rheum Dis. 2017;76(5):855–61.
21. Husni ME, Betts KA, Griffith J, Song Y, Ganguli A. Benefit-risk trade-offs for treatment decisions in moderate-to-severe rheumatoid arthritis: focus on the patient perspective. Rheumatol Int. 2017;37(9):1423–34.
22. Hazlewood GS, Bombardier C, Tomlinson G, Thorne C, Bykerk VP, Thompson A, Tin D, Marshall DA. Treatment preferences of patients with early rheumatoid arthritis: a discrete-choice experiment. Rheumatology. 2016;55(11):1959–68.
23. van der Elst K, Meyfroidt S, De Cock D, De Groef A, Binnard E, Moons P, Verschueren P, Westhovens R. Unraveling Patient-Preferred Health and Treatment Outcomes in Early Rheumatoid Arthritis: A Longitudinal Qualitative Study. Arthritis Care Res (Hoboken). 2016;68(9):1278–87.
24. Harrison M, Marra C, Shojania K, Bansback N. Societal preferences for rheumatoid arthritis treatments: evidence from a discrete choice experiment. Rheumatology. 2015;54(10):1816–25.
25. Hiligsmann M, van Durme C, Geusens P, Dellaert BG, Dirksen CD, van der Weijden T, Reginster JY, Boonen A. Nominal group technique to select attributes for discrete choice experiments: an example for drug treatment choice in osteoporosis. Patient Prefer Adherence. 2013;7:133–9.
26. Wangdahl JM, Martensson LI. The communicative and critical health literacy scale–Swedish version. Scand J Public Health. 2014;42(1):25–31.
27. McNaughton CD, Cavanaugh KL, Kripalani S, Rothman RL, Wallston KA. Validation of a Short, 3-Item Version of the Subjective Numeracy Scale. Med Decis Making. 2015;35(8):932–6.
28. Bridges JF, Hauber AB, Marshall D, Lloyd A, Prosser LA, Regier DA, Johnson FR, Mauskopf J. Conjoint analysis applications in health-a checklist: a report of the ISPOR Good Research Practices for Conjoint Analysis Task Force. Value Health. 2011;14(4):403–13.
29. Zhou M, Thayer WM, Bridges JFP. Using Latent Class Analysis to Model Preference Heterogeneity in Health: A Systematic Review. Pharmacoeconomics. 2018;36(2):175–87.
30. Scalone L, Sarzi-Puttini P, Sinigaglia L, Montecucco C, Giacomelli R, Lapadula G, Olivieri I, Giardino AM, Cortesi PA, Mantovani LG, et al. Patients', physicians', nurses', and pharmacists' preferences on the characteristics of biologic agents used in the treatment of rheumatic diseases. Patient Prefer Adherence. 2018;12:2153–68.
31. Johnson FR, Beusterien K, Ozdemir S, Wilson L. Giving Patients a Meaningful Voice in United States Regulatory Decision Making: The Role for Health Preference Research. The patient. 2017;10(4):523–6.
32. Hsiao B, Binder-Finnema P, Benjamin Nowell W, Michel G, Wiedmeyer C, Fraenkel L. **Preference phenotypes can be used to support shared decision-making at point-of-care for patients with rheumatoid arthritis: A proof of concept study**. *Arthritis Care Res (Hoboken)* 2018.
33. Eriksson JK, Neovius M, Ernestam S, Lindblad S, Simard JF, Askling J. Incidence of rheumatoid arthritis in Sweden: a nationwide population-based assessment of incidence, its determinants, and treatment penetration. Arthritis Care Res (Hoboken). 2013;65(6):870–8.
34. Durand C, Eldoma M, Marshall DA, Bansback N, Hazlewood GS. Patient Preferences for Disease-modifying Antirheumatic Drug Treatment in Rheumatoid Arthritis: A Systematic Review. J Rhuematol. 2020;47(2):176–87.

Figures

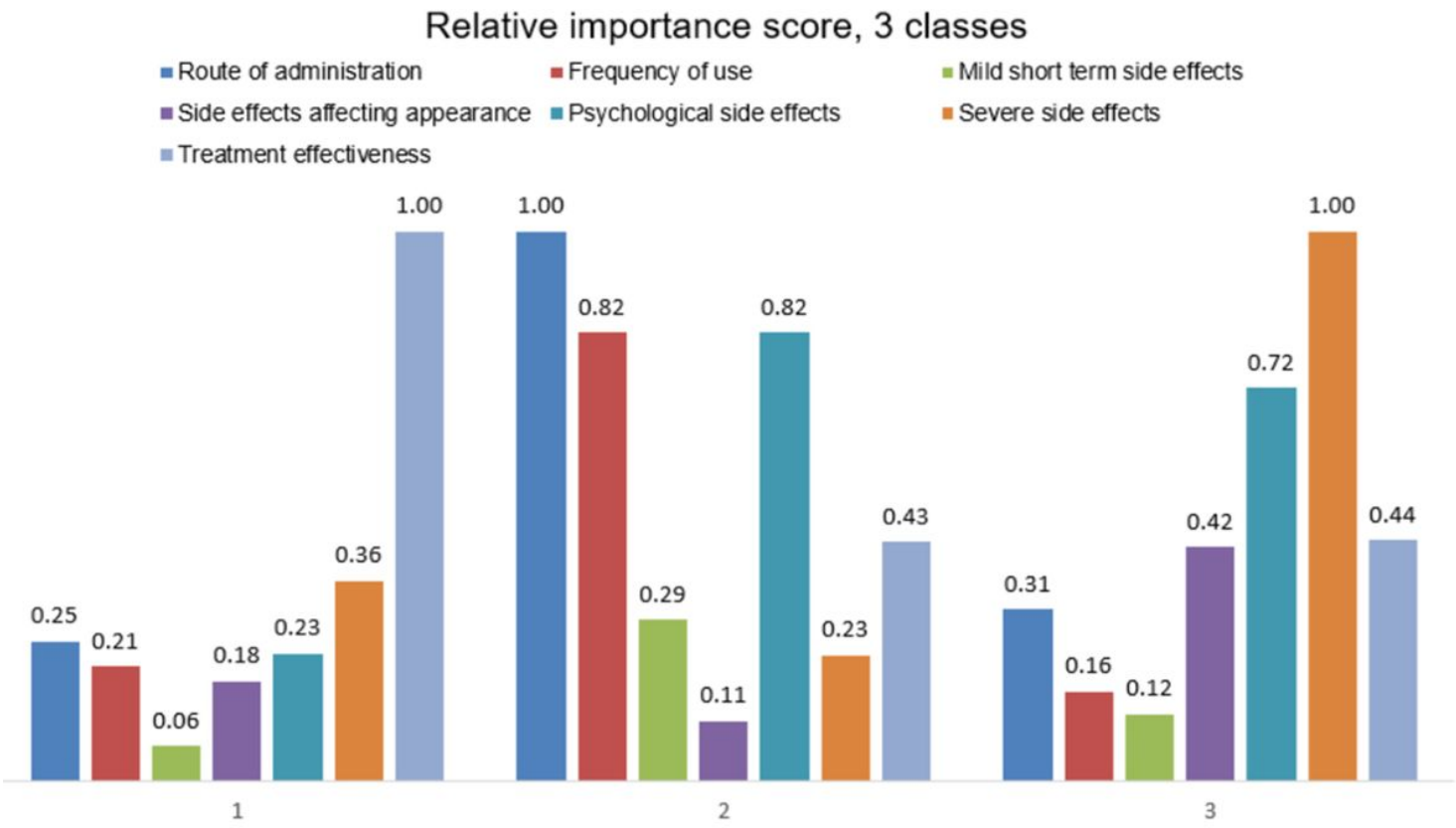

Figure 1

Relative importance score of attributes

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