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ORIGINAL RESEARCH

What benefit–risk trade-offs are acceptable to rheumatoid arthritis patients during treatment selection? Evidence from a multicountry choice experiment

Rieke Alten ,[1] Juan Carlos Nieto-Gonzalez ,[2] Peggy Jacques ,[3] Carlomaurizio Montecucco,[4] Robert Moots,[5,6] Helga Radner,[7] Harald E Vonkeman,[8,9] Sebastian Heidenreich,[10] Chiara Whichello,[10] Nicolas Krucien,[10] Katrien Van Beneden[11]

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For numbered affiliations see end of article.

Correspondence to
Dr Rieke Alten;
rieke.alten@schlosspark-klinik.de

ABSTRACT

Objective Understanding preferences of patients with rheumatoid arthritis (RA) can facilitate tailored patient-centric care. This study elicited trade-offs that patients with RA were willing to make during treatment selection.

Methods Patients with RA completed an online discrete choice experiment, consisting of a series of choices between hypothetical treatments. Treatment attributes were selected based on literature review and qualitative patient interviews. Eligible patients were ≥18 years old, diagnosed with RA, receiving systemic disease-modifying antirheumatic drug therapy, and residents of Europe or USA. Male patients were oversampled for subgroup analyses. Data were analysed using a correlated mixed logit model.

Results Of 2090 participants, 42% were female; mean age was 45.2 years (range 18–83). Estimated effects were significant for all attributes ($p<0.001$) but varied between patients. Average relative attribute importance scores revealed different priorities ($p<0.001$) between males and females. While reducing pain and negative effect on semen parameters was most important to males, females were most concerned by risk of blood clots and serious infections. No single attribute explained treatment preferences by more than 30%. Preferences were also affected by patients' age: patients aged 18–44 years placed less importance on frequency and mode of treatment administration ($p<0.05$) than older age groups. Patients were willing to accept higher risk of serious infections and blood clots in exchange for improvements in pain, daily activities or administration convenience. However, acceptable trade-offs varied between patients ($p<0.05$).

Conclusion Treatment preferences of patients with RA were individual-specific, but driven by benefits and risks, with no single attribute dominating the decision-making.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with rheumatoid arthritis and their prescribers face challenging trade-offs during treatment selection. To accommodate patients' circumstances in comprehensive disease management, current recommendations for management emphasise the need to recognise patient preferences.

WHAT THIS STUDY ADDS

⇒ Results of this study show that preferences of patients with rheumatoid arthritis were driven by multiple benefits and risks of treatments, with no single attribute dominating the decision making. The trade-offs that patients were willing to make were heterogeneous and varied both between both individuals and subgroups.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings emphasise the importance of considering the entire treatment profile, including benefits, risks and administration, to support shared decision-making between providers and patients.

INTRODUCTION

Disease modification is the guiding principle for the management of rheumatoid arthritis (RA), with treatments aiming to control the inflammatory cascade and to improve symptoms, physical function, quality of life and work capacity, while inhibiting long-term complications from structural damage.[1] With the increasing number of efficacious disease-modifying agents and the rise of precision medicine,[2] recommendations on the development of patient-centric treatment targets can help inform RA management to achieve comprehensive disease care. For instance, the European Alliance of Associations for Rheumatology (EULAR) recommendations state that treatment selection should be based on

shared decision-making between patient and rheumatologist.[1] This shared decision-making implies the recognition of patient preferences, and involves all aspects of the disease, including information on RA and its potential consequences, the modalities of disease assessment, decisions on the therapeutic target and the potential means to reach the target, as well as the development of a management plan and discussions on the benefits and risks of individual therapies.

Considering the complexity of the RA treatment landscape and the diverse treatment targets, engaging in shared decision-making is key to understanding patients' treatment priorities and the trade-offs they are willing to make, as this is important for delivering tailored care.[1] For example, sulfasalazine and methotrexate are effective first-line conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), but have been linked to adverse events, including gastrointestinal complications, infections, skin reactions, neurotoxicity, malignancies, infertility, and negative effects on sperm that may or may not be reversible.[3–7]

Treatment selection is especially challenging among advanced therapies. While the American College of Rheumatology and EULAR align on recommendations for first-line therapies, approximately one-third of patients have an inadequate response to conventional csDMARDs, such as methotrexate and sulfasalazine, and often progress to one of multiple available advanced treatments.[1 8 9] These may be biological (bDMARDs), such as tumour necrosis factor alpha (TNFα) inhibitors, T cell costimulation modulators, CD20, and interleukin-6R inhibitors, or targeted synthetic (tsDMARDs), such as Janus kinase (JAK) inhibitors.[10] Preventive effects of authorised advanced therapies and undesirable effects, including potential changes in laboratory parameters and increased risk of infections, malignancies and gastrointestinal disorders, have been well characterised.[11 12] Therefore, when making a specific treatment decision, risks and benefits can be compared. To facilitate the interpretation of benefit–risk comparisons, patient preference information can provide insights into the trade-offs that patients are willing to make when selecting an advanced therapy for RA. In addition, understanding how acceptable trade-offs may vary in different patient populations can help guide individual shared-decision making processes in doctor–patient interactions. Patient preference information is also increasingly used by decision-makers, such as regulators or health technology assessment agencies, to help interpret clinical data from patients' perspectives.[13–15]

The objective of this study was to elicit benefit–risk trade-offs that patients with RA in Europe and the USA are willing to make. For this purpose, an online discrete choice experiment (DCE) was conducted, in which patients with RA made trade-offs between multiple benefits and risks of various DMARDs, with a focus on advanced therapies. While previous preference research has been undertaken in RA, insights are limited, because these studies grouped adverse events into unclear, overarching categories, outcomes did not relate to clinical endpoints, or studies were conducted in a specific small setting or population that limits insights into preference heterogeneity.[16–22]

METHODS

Study design

An online DCE was conducted from September to October 2021 in adults with RA to elicit the benefit–risk trade-offs they were willing to make. Patients were eligible if they were ≥18 years old, resident of the USA, the UK, France (FR), Germany (DE), Italy (IT) or Spain (ES), and had a RA diagnosis for which they were currently receiving systemic therapy (csDMARDs, bDMARDs, tsDMARDs). Patients were excluded if they reported diagnosis with psoriatic arthritis, axial spondyloarthritis, ankylosing spondylitis or psoriasis, without RA, or were enrolled in a clinical trial at the time of the study. All patients had to provide online informed consent prior to taking part in the study. Male patients were oversampled with a target quota of 50% to allow for subgroup analysis and exploring their willingness to accept the risk of negative effects on semen parameters. All patients were recruited via nationally representative online access panels, physician referrals, patient organisations and social media. Participants were recruited by sending an invitation with information about the study, with contact details or a URL link. Participants who expressed interest and consented to participate were screened for eligibility. On completion of study participation, participants were remunerated either as a direct bank transfer, gift card or panel points.

Survey design

A multiphase approach was used to design and test the DCE in compliance with best-practice guidance.[23 24] The study was conducted in five phases: first, a targeted literature review identified 26 concepts (ie, 11 benefits, 10 risks, 5 other) potentially relevant for explaining patients' treatment preferences (online supplemental A.1, table A.1). Second, concepts identified from the literature were discussed in 30 semistructured 60-min virtual interviews that were conducted with patients across the six target countries (online supplemental A.2, tables A.2, A.3 and figure A.1). Third, an initial DCE design was tested and iteratively refined in 30 web-assisted 60-min pretesting interviews with patients across the six target countries (online supplemental A.3, table A.4). The aim of the qualitative pretesting was to ensure that the survey and DCE were clear and that patients were willing and able to make trade-offs between the different attributes of DMARDs.[25] Fourth, a quantitative pilot study (online supplemental A.4 and A.5) was conducted with 712 patients (FR: n=111; DE: n=92; IT: n=144; ES: n=114; UK: n=93; USA: n=158). The purpose of the quantitative pilot was to explore the expected data quality and to

Table 1 Attributes and levels

Attribute	Description	Levels
How and how often the treatment is taken	How the treatment is taken can differ between medicines. While some medicines are taken every day via an oral pill, others may require regular injections or infusions.	1. Oral pill every day 2. Injection every other week 3. Injection once a week 4. Injection twice a week*
Difficulty with daily activities	RA treatments aim to improve your symptoms—and therefore, your level of difficulty with daily activities. However different medicines have different effectiveness levels, and thus result in different difficulty levels with daily activities. Examples of daily activities include going up stairs, showering/bathing, grocery shopping, walking outside and/or doing typical house chores.	1. Mild or no difficulty with daily activities with treatment 2. Moderate difficulty with daily activities with treatment 3. Severe difficulty with daily activities with treatment*
Amount of pain	Many patients with RA suffer from pain. This may get better or worse over time, depending on your treatment and how your RA develops. RA treatments also differ in effectiveness, and your pain level depends on your treatment.	1. 10 out of 100 2. 40 out of 100 3. 80 out of 100*
Risk of blood clots	RA treatments may have a warning for risk of causing blood clots. Signs of blood clots in the veins include a painful swollen leg, chest pain or shortness of breath. In some cases, you may have to stay in the hospital for the duration of the treatment. In rare instances, blood clots can result in life-threatening complications.	1. 0 out of 100 (0%) 2. 3 out of 100 (3%) 3. 6 out of 100 (6%)*
Risk of serious infections	The risk of serious infections for 1 year on treatment is shown. Serious infections, such as pneumonia, require hospitalisation and may become life-threatening. Different treatments have different risks of causing serious infections.	1. 0 out of 100 (0%) 2. 3 out of 100 (3%) 3. 6 out of 100 (6%)*
Risk of negative effects on sperm (males only)	Some RA treatments may affect the quality of your sperm or reduce the number of sperms per ejaculation. This does not mean that your overall sexual health is impacted. The changes to sperm may be partially reversible after 13 weeks of stopping the medication.	1. 0 out of 100 (0%) 2. 15 out of 100 (15%) 3. 30 out of 100 (30%)*

*Reference level.
RA, rheumatoid arthritis.

assess whether patients were able to distinguish between the different risk levels included in the DCE. No changes were made to the instrument following the quantitative pilot and the data were subsequently merged with the main dataset. Fifth, the final data were collected between September and October 2021 (approximately 6 weeks).

The DCE was part of a wider survey that included a screening questionnaire, an informed consent form, patient information material, the DCE, numeracy and health literacy questions,[26–28] and clinical and demographics questionnaires (online supplemental B).

DCE design

The final set of DMARD attributes, their definitions and corresponding levels considered in the DCE are shown in table 1.

A D-efficient design was generated in Ngene V.1.2.1 (ChoiceMetrics Sydney, Australia) and included 45 experimental DCE choice tasks that were split equally across 5 blocks.[29] The design was optimised using Bayesian priors obtained from the quantitative pilot.[30] Within each DCE choice task, patients were asked to choose between two hypothetical DMARDs described by the attributes and levels as determined by the experimental design. An example choice task is shown in figure 1. The order of choice tasks was randomised across patients to reduce the risk of ordering effects.[31] A first practice choice task and two tasks for testing the internal validity of responses were added to the experimental choice tasks.[32] The first validity test repeated the 10th choice task as seen by patients to explore choice consistency. The second validity test was a dominance test in which one of the two DMARDS outperformed the alternative on all attributes (ie, administration was identical). In line with best-practice, no patient was excluded from the analysis based on the internal validity tests to avoid introducing selection bias.[33] Overall, each patient completed 12 choice tasks.

Analysis

The experimental choice tasks were used for the analysis of the DCE data. All statistical tests were two-sided and used a significance level of 0.05. Comparison of statistical performance across models was based on Bayesian information criterion and the adjusted McFadden R^2.[34] All analyses were conducted in the statistical software R V.4.0.2.

A correlated mixed logit model was used to analyse the DCE data within a random utility maximisation framework that estimated the effect of changes in attributes

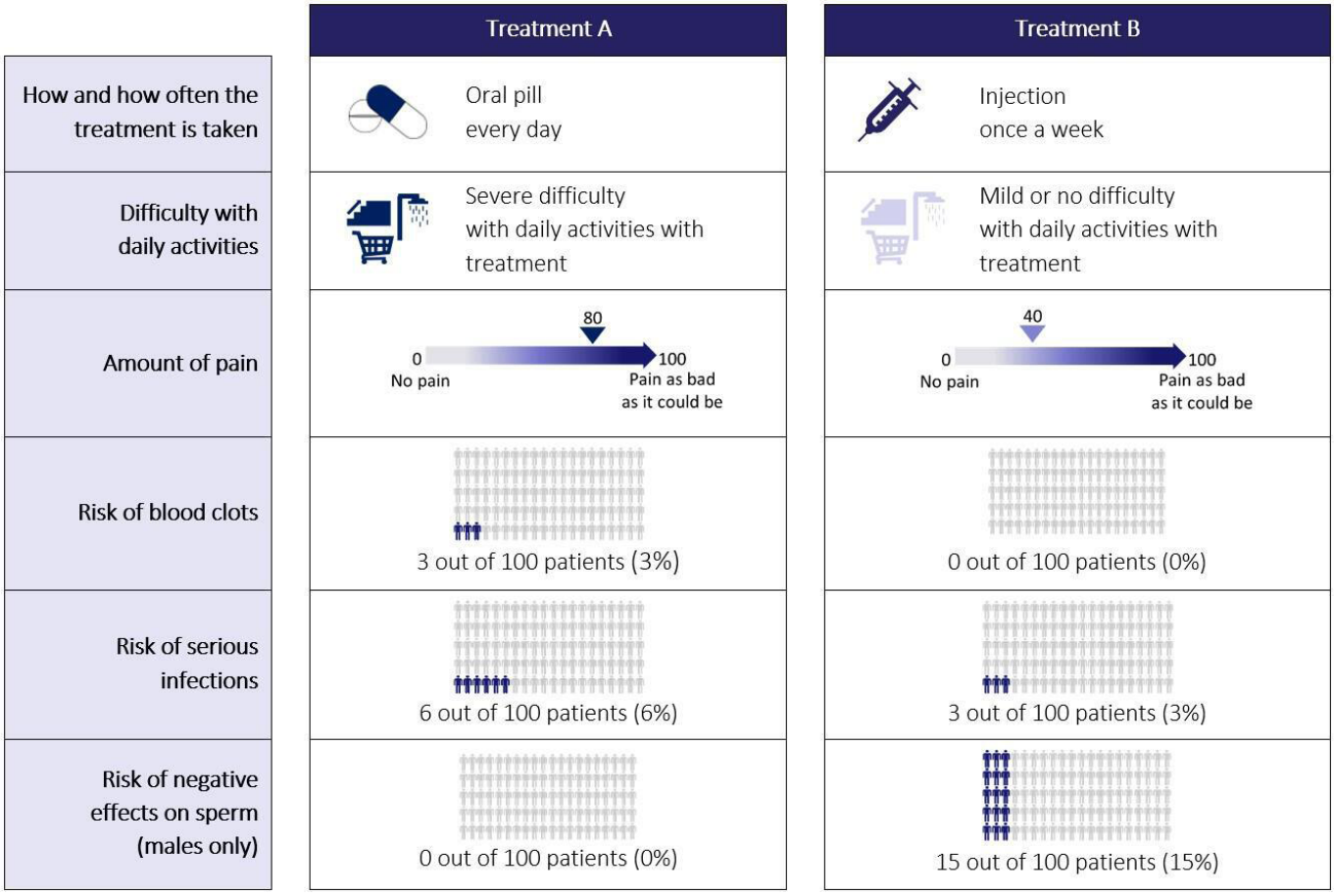

Figure 1 Example choice task asking participants to select one of two hypothetical treatments.

on preferences as part-worth utilities.[35 36] Compared with classical multinomial logit models, the estimated model implicitly accounted for panel effects, heterogeneity in preferences and variations in choice consistency.[37] Two behavioural outputs were obtained from the estimates for the overall sample and by gender: first, relative attribute importance (RAI) scores were calculated to measure the maximal contribution of each attribute to a treatment choice. Second, trade-offs that patients with RA were willing to make between attributes were quantified as maximum acceptable risks (MAR) of blood clots, serious infections and negative effects on sperm. Delta method was used to obtain the SEs and 95% CIs of MAR estimates.[38] In addition, subgroup analyses were conducted by estimating RAI scores by age and country using interaction effects included in the mixed logit model. More details on the analysis are included in online supplemental D.

RESULTS

Participants

A total of 44 221 potential participants were invited across the six countries, with 2090 eligible patients (table 2; Online supplemental figure C.1) consenting and completing the survey.

In line with the sampling quota, 42% of the patients were female (n=878), with an overall mean age of 45.2 years (SD=11.3, range 18–83). Female patients were slightly older (mean 46.3 years, SD 12.2) than males (mean 44.4 years, SD 10.4). Most patients had high numeracy (ie, adequate facility with numbers; 79%; n=1656), but fewer patients had high health literacy (ie, adequate facility with reading; 47%; n=973). Half of patients (n=1038, 49%) had been diagnosed 3 or more years ago and most reported 0 to 10 tender or swollen joints (62%; n=1279). The three most reported current symptoms by patients were joint pain (57%; n=1189), joint tenderness (53%; n=1104), and joint swelling (47%; n=988).

Most patients had children (87%; n=1828) and had not conceived children after their diagnosis (79%; n=1448). The majority were not planning on having more children in the future (77%; n=1602). Of male participants, 29% (n=352) were planning to have more children.

Preferences

Within the DCE, most patients passed both the dominance (76%; n=1588) and stability (75%; n=1576) tests, with observed failure rates comparable to other health DCEs in the literature (online supplemental table C.1).[32] The mean survey completion time was 17 min (SD=12.5; median=14 min). The data fit for the mixed logit model

Table 2 Sociodemographic and clinical characteristics

	Overall (N=2090)	Male (N=1212, 58%)	Female (N=878, 42%)
Age			
Mean (SD)	45.2 (11.2)	44.4 (10.4)	46.3 (12.2)
18–44 years	1141 (55%)	689 (57%)	452 (51%)
45–64 years	802 (38%)	459 (38%)	343 (39%)
65–74 years	120 (6%)	49 (4%)	71 (8%)
75+ years	27 (1%)	15 (1%)	12 (1%)
Are there other people in your family who also have rheumatoid arthritis?			
Yes	501 (24%)	310 (26%)	191 (22%)
No	1524 (73%)	871 (72%)	653 (74%)
Unsure	65 (3%)	31 (3%)	34 (4%)
Have had children			
No	262 (13%)	145 (12%)	117 (13%)
Yes	1828 (87%)	1067 (78%)	761 (77%)
Have you had children after being diagnosed with rheumatoid arthritis?			
Yes	364 (20%)	261 (24%)	103 (14%)
No	1448 (79%)	799 (75%)	649 (85%)
Unsure	16 (1%)	7 (1%)	9 (1%)
Not applicable	262 (13%)	145 (12%)	117 (13%)
Planning to have children in the future			
Yes	488 (23%)	352 (29%)	136 (15%)
No	1602 (77%)	860 (71%)	742 (85%)
Racial background (USA or UK)			
White	321 (98%)	159 (99%)	162 (97%)
Black/African/Caribbean	4 (1%)	1 (1%)	3 (2%)
Asian/Asian British	1 (0%)	0 (0%)	1 (1%)
Other	1 (0%)	0 (0%)	1 (1%)
Prefer not to say	1 (0%)	1 (1%)	0 (0%)
Not applicable	1762 (84%)	1051 (87%)	711 (81%)
Education			
Elementary school	45 (2%)	37 (3%)	8 (1%)
High school	541 (26%)	278 (23%)	263 (30%)
Some college/university	272 (13%)	114 (9%)	158 (18%)
College/university degree	1017 (49%)	612 (50%)	405 (46%)
Postgraduate degree	88 (4%)	73 (6%)	15 (2%)
Other	6 (0%)	3 (0%)	3 (0%)
Employment status			
Employed, full time	1432 (69%)	918 (76%)	514 (59%)
Employed, part time	240 (11%)	120 (10%)	120 (14%)
Self-employed	65 (3%)	45 (4%)	20 (2%)
Voluntary work	14 (1%)	8 (1%)	6 (1%)
Homemaker	35 (2%)	5 (0%)	30 (3%)
Student	11 (1%)	6 (0%)	5 (1%)
Unemployed	37 (2%)	14 (1%)	23 (3%)
Retired	182 (9%)	81 (7%)	101 (12%)
On sick leave	23 (1%)	4 (0%)	19 (2%)

Continued

Table 2 Continued

	Overall (N=2090)	Male (N=1212, 58%)	Female (N=878, 42%)
Maternity/paternity leave	2 (0%)	1 (0%)	1 (0%)
Not able to work due to disability	49 (2%)	10 (1%)	39 (4%)
Insurance status			
Private insurance	1026 (49%)	636 (52%)	390 (44%)
National health insurance	1409 (67%)	794 (66%)	615 (70%)
Veterans Affairs	17 (1%)	10 (5%)	7 (4%)
Medicare	178 (9%)	92 (48%)	86 (50%)
Medicaid	42 (2%)	27 (14%)	15 (9%)
None	3 (0%)	2 (1%)	1 (1%)

was good (adjusted McFadden R^2=0.583), suggesting it was able to explain the choices that patients made in the DCE. Estimated effects were significant for all attributes (p<0.001), implying that they all influenced patient preferences for DMARDs (online supplemental table C.2).

On average, patients tended to prefer an oral pill every day over an injection every other week (overall: p<0.001; male: p<0.001; female: p<0.001; figure 2, online supplemental table C.3), or an injection once a week (overall: p<0.001; male: p<0.1; female: p<0.001). Patients valued all reductions in pain and avoiding any of the considered risks (overall: p<0.001; male: p<0.001; female: p<0.001). In addition, treatment preferences of male patients were significantly affected by the risk of negative effects on semen parameters (p<0.001). All estimates were found to vary (p<0.001) between patients, indicating the presence of preference heterogeneity.

RAI scores implied by the model estimates are presented in figure 3. While reducing pain was the largest driver of male patients' treatment preferences (RAI 25%; 95% CI 20% to 30%; Online supplemental table C.4), female patients placed the highest importance on avoiding blood clots (RAI 30%; 95% CI 28% to 32%). Further, while the risk of serious infections was the second most important attribute to female patients (RAI 23%; 95% CI 21% to 25%), it ranked as the fourth most important attribute for male patients (RAI 14%; 95% CI 11% to 17%). Avoiding negative effects on semen parameters was the second most important driver of male patients' preferences (RAI 23%; 95% CI 19% to 26%). Furthermore, while female patients placed a higher importance on reducing difficulties with daily activities (male RAI 10%; 95% CI 7% to 13%; female RAI 16%; 95% CI 14% to 19%) than they placed on treatment administration (male RAI 10%; 95% CI 8% to 13%; female RAI 9%; 95% CI 7% to 11%), male patients placed a comparable importance on both attributes (p>0.05). Overall, no treatment attribute contributed with more than 30% to treatment preferences of male or female patients.

The RAI scores can be used to gain insights into differences and similarities of treatment priorities of male and female patients. For example, reducing the risk of blood clots was 1.4 (=19%/14%) times and 1.3 (=30%/23%) times more important than the risk of serious infections to male and female patients, respectively. Reducing pain was 2.6 (=25%/10%) times and 1.3 (=21%/16%) times more important than reducing difficulties with daily activities to male and female patients, respectively. Furthermore, while male patients considered reducing pain as 1.3 (=25%/19%) times more important than reducing the risk of blood clots, female patients considered reducing the risk of blood clots as 1.4 (=30%/21%) times more important than reducing pain.

Trade-offs

The MAR estimates obtained from the analysis are presented in table 3 and provide insights into the benefit–risk trade-offs patients were prepared to make.

For example, patients were willing to accept higher risks of blood clots (male MAR 1.8%, 95% CI 0.9% to 2.8%; female MAR 0.8%, 95% CI 0.4% to 1.2%), serious infections (male MAR 2.5%, 95% CI 1.0% to 4.0%; female MAR 1.0%, 95% CI 0.5% to 1.6%) or negative effects on sperm (male MAR 7.4%, 95% CI 4.2% to 10.7%) for being able to take an oral pill every day instead of receiving an injection once a week. Similarly, patients were willing to accept higher risks of blood clots (male MAR 2.3%, 95% CI 1.7% to 3.0%; female MAR 1.2%, 95% CI 1.0% to 1.5%), serious infections (male MAR 3.2%, 95% CI 2.1% to 4.2%; female MAR 1.6%, 95% CI 1.2% to 2.0%) or negative effects on sperm (male MAR 10.4%, 95% CI 7.9% to 13.0%) in exchange for reducing the amount of pain from 30 to 10 on a scale of 0–100. Similar observations were made for improved performance of daily activities. MAR estimates also provided insights into trade-offs between risks. For example, patients were willing to accept an extra risk of blood clots in exchange for reduced risk of serious infections from 3% to 0% (male MAR 2.2%, 95% CI 1.6% to 2.9%; female MAR 2.3%, 95% CI 2.0% to 2.6%) or from 6% to 0% (male MAR 4.5%, 95% CI 3.2% to 5.7%; female MAR 4.6%, 95% CI 4.0% to 5.2%).

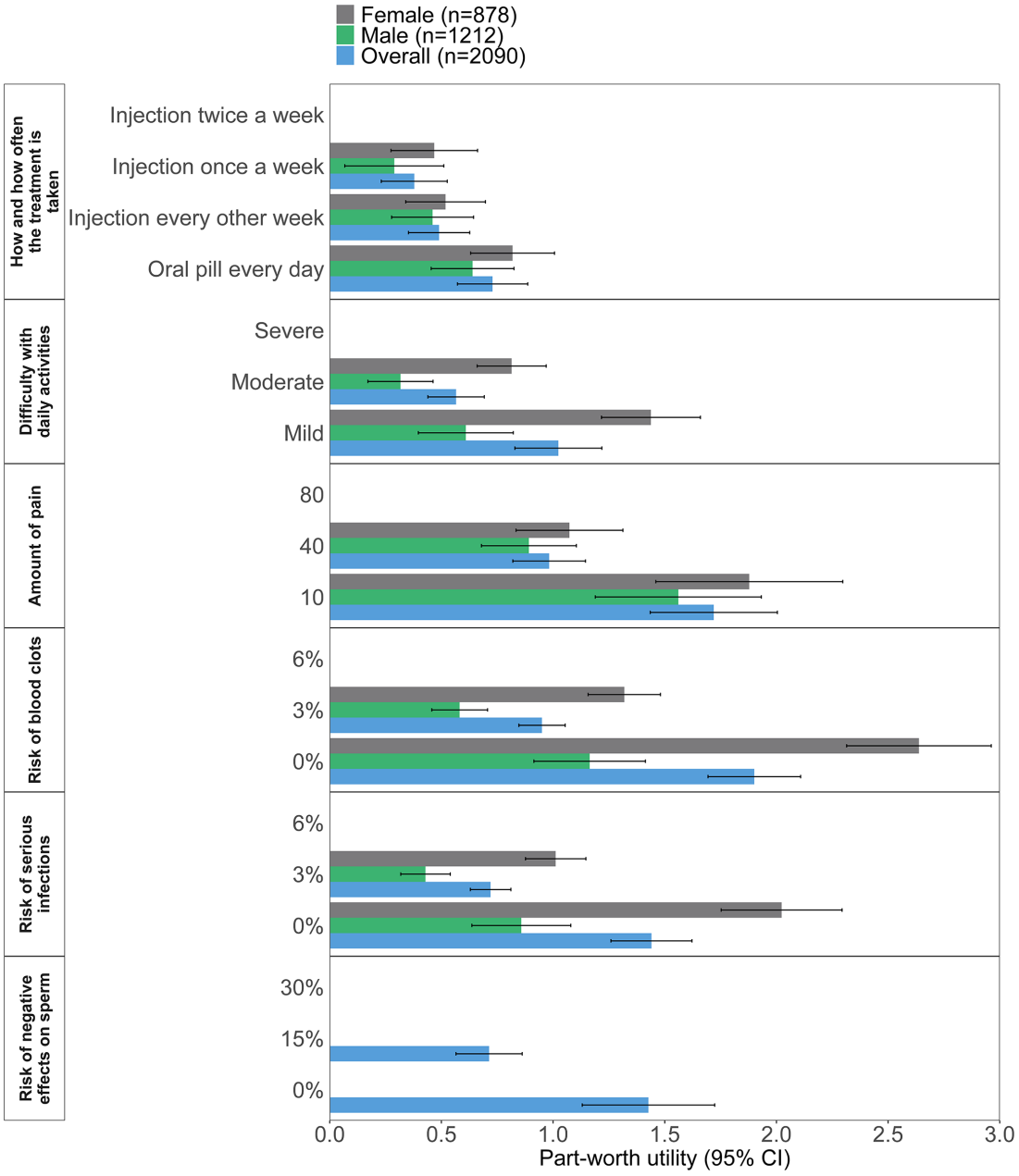

Figure 2 Main estimates: the effect of changes in attributes on preferences.

Subgroup analyses

In subgroup analyses by age, patients older than 65 were less (p<0.05) concerned with the risk of serious infections (RAI 16%, 95% CI 12% to 20%) than patients aged 18–44 (online supplemental figure C.2). Conversely, younger patients aged 18–44 (RAI 5%, 95% CI 2% to 7%) placed less importance on frequency and mode of treatment administration (p<0.05) than patients aged 45–64 (RAI=12%, 95% CI 10% to 14%) or those older than 65 (RAI 12%, 95% CI 10% to 13%). Similarly, patients aged 18–44 (RAI 10%, 95% CI 7% to 14%) were less (p<0.05) concerned about difficulties with daily activities than patients aged 45–64 (RAI 13%, 95% CI 10% to 16%) or those older than 65 (RAI 15%, 95% CI 12% to 18%).

Some similarities and differences were observed between countries. Patients from Spain, Italy, the UK and France placed more importance on amount of pain than on difficulty with daily activities, whereas patients from the USA and Germany indicated almost similar importance for amount of pain and daily difficulties (online supplemental table C.5). Patients from France (RAI 32%, 95% CI 25% to 38%) and the UK (RAI 25%, 95% CI 19% to 32%) placed more importance on avoiding pain (p<0.05) than those from Spain (RAI 19%, 95% CI 14% to 25%), the USA (RAI=15%, 95% CI 9% to 21%), Italy (RAI=17%, 95% CI 11% to 24%), or Germany (RAI=13%, 95% CI 2% to 23%). Conversely, participants from Germany (RAI=27%, 95% CI 20% to 33%) and Spain (RAI=27%, 95% CI 23% to 30%) placed higher importance on the risk of blood clots (p<0.05) than patients from France (RAI=14%, 95% CI 10% to 19%), Italy (RAI=22%, 95% CI 18% to 30%), the UK (RAI=22%,

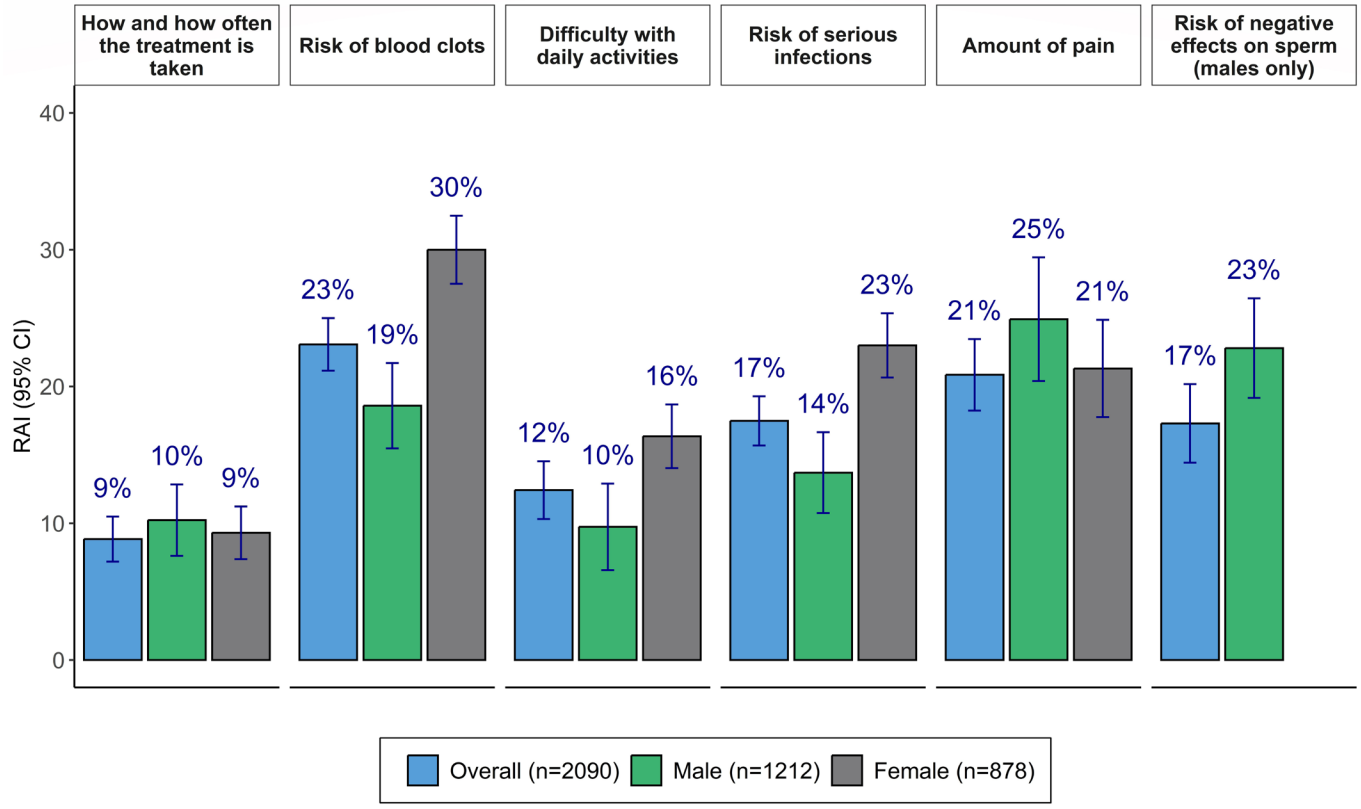

Figure 3 RAI in the overall population and by sex. Respondents: 2090. Observations: 18 810. Parameters: 64. Null log-likelihood: −13 038.1. Model log-likelihood: −5404.4. Note: The relative importance of negative effects on sperm is based on male responses only. RAI, relative attribute importance.

95% CI 18% to 25%) and the USA (RAI=20%, 95% CI 17% to 23%). Patients from Italy and the USA placed more importance on the risk of negative effects on semen parameters than other countries. No differences in RAI were found (p>0.05) when comparing preferences between European (pooled) and US patients.

Patients without prior experience with advanced therapies placed a higher relative importance on treatment administration (RAI=13%, 95% CI 11% to 15%) and difficulty with daily activities (RAI=18%, 95% CI 16% to 20%) than the average patient in the sample. Patients with prior experience of ≥3 advanced therapies placed a higher relative importance on the risk of negative effects on sperm (RAI=30%, 95% CI 22% to 38%) and a lower relative importance on difficulty with daily activities (RAI=3%, 95% CI 0% to 7%) than the average patient in the sample.

DISCUSSION

Summary

To the best of our knowledge, this is the largest study concerned with the treatment preferences of patients with RA, and specifically designed to capture benefit–risk trade-offs relevant to healthcare decision-making; it is also the first study to include potential impacts on semen parameters. This patient preference study contributed to the literature by offering specific and applicable insights into the benefit–risk trade-offs that patients with RA are willing to make, while accounting for preference heterogeneity. We found that the trade-offs patients were willing to make were heterogeneous and varied both between and within subgroups. A central finding of this study is that none of the considered treatment attributes was a dominant driver for treatment preferences for patients with RA. This highlights the need for a careful consideration of the entire profile of suitable DMARDs, with the aim of weighing relevant benefits, risks and administration aspects.

While administration contributed less than 10% to treatment preference, patients with RA were also willing to make trade-offs between convenience, benefits and risks. Specifically, male patients were prepared to accept an extra 1.3% and female patients an extra 0.9% risk of serious infections for being able to take an oral pill once daily instead on relying on an injection that is administered every other week. Preferences also varied significantly between age groups and countries. Patients with RA aged 18–44 placed less importance on treatment administration than older patients. Overall, the relative importance that patients placed on difficulties with daily activities tended to increase with age, while the importance that male patients with RA placed on the risk of negative effects on semen parameters decreased with age. The amount of pain was more important to

Table 3 Maximum acceptable risk of serious infections, blood clots and negative sperm effects

	Attribute change		MAR of blood clots (95% CI)			MAR of serious infections (95% CI)			MAR of negative effects on sperm (95% CI)
Attribute	**From**	**To**	**Overall**	**Male**	**Female**	**Overall**	**Male**	**Female**	**Male**
How and how often the DMARD is taken	Injection weekly	Oral daily	1.1%	1.8%	0.8%	1.5%	2.5%	1.0%	7.4%
			(0.7%; 1.6%)	(0.9%; 2.8%)	(0.4%; 1.2%)	(0.9%; 2.1%)	(1.0%; 4.0%)	(0.5%; 1.6%)	(4.2%; 10.7%)
	Injection biweekly	Oral pill daily	0.8%	0.9%	0.7%	1.0%	1.3%	0.9%	5.1%
			(0.3%; 1.2%)	(<0.1%; 1.8%)	(0.3%; 1.1%)	(0.4%; 1.6%)	(<−0.1%; 2.6%)	(0.4%; 1.4%)	(2.0%; 8.2%)
Difficulty with daily activities	Moderate	Mild	1.5%	1.5%	1.4%	1.9%	2.1%	1.9%	21.8%
			(1.0%; 1.9%)	(0.6%; 2.4%)	(1.0%; 1.8%)	(1.3%; 2.5%)	(0.8%; 3.3%)	(1.3%; 2.4%)	(15.7%; 27.8%)
	Severe	Mild	3.2%	3.2%	3.3%	4.3%	4.3%	4.3%	12.0%
			(2.6%; 3.9%)	(1.9%; 4.4%)	(2.7%; 3.9%)	(3.4%; 5.2%)	(2.5%; 6.2%)	(3.5%; 5.1%)	(8.4%; 15.6%)
	Severe	Moderate	1.8%	1.6%	1.9%	2.4%	2.3%	2.4%	9.7%
			(1.4%; 2.2%)	(0.8%; 2.5%)	(1.5%; 2.2%)	(1.8%; 2.9%)	(1.1%; 3.5%)	(1.9%; 3.0%)	(6.2%; 13.2%)
Risk of serious infections	2%	0%	1.5%	1.5%	1.5%	–	–	–	10.2%
			(1.3%; 1.7%)	(1.1%; 1.9%)	(1.3%; 1.7%)	–	–	–	(7.9%; 12.5%)
	3%	0%	2.3%	2.2%	2.3%	–	–	–	15.3%
			(2.0%; 2.6%)	(1.6%; 2.9%)	(2.0%; 2.6%)	–	–	–	(11.8%; 18.8%)
	6%	0%	4.6%	4.5%	4.6%	–	–	–	30.6%
			(4.0%; 5.1%)	(3.2%; 5.7%)	(4.0%; 5.2%)	–	–	–	(23.6%; 37.6%)
Amount of pain	30	10	1.6%	2.3%	1.2%	2.0%	3.2%	1.6%	10.4%
			(1.3%; 1.8%)	(1.7%; 3.0%)	(1.0%; 1.5%)	(1.7%; 2.4%)	(2.1%; 4.2%)	(1.23%; 2.0%)	(8.0%; 13.0%)
	60	10	3.9%	5.8%	3.06%	5.1%	7.9%	4.0%	26.1%
			(3.2%; 4.5%)	(4.2%; 7.4%)	(2.4%; 3.7%)	(4.2%; 6.1%)	(5.3%; 10.5%)	(3.1%; 4.9%)	(19.7%; 32.4%)
	60	30	2.3%	3.5%	1.8%	3.1%	4.8%	2.4%	15.6%
			(1.9%; 2.7%)	(2.5%; 4.5%)	(1.4%; 2.2%)	(2.5%; 3.6%)	(3.2%; 6.3%)	(1.8%; 3.0%)	(12.0%; 19.4%)
Risk of blood clots	0.20%	0%	–	–	–	0.3%	0.3%	0.3%	1.4%
			–	–	–	(0.2%; 0.3%)	(0.2%; 0.4%)	(0.2%; 0.3%)	(1.1%; 1.6%)
	0.50%	0%	–	–	–	0.7%	0.7%	0.6%	3.4%
			–	–	–	(0.6%; 0.7%)	(0.5%; 0.9%)	(0.6%; 0.7%)	(2.6%; 4.1%)
	1%	0%	–	–	–	1.3%	1.4%	1.3%	6.7%
			–	–	–	(1.2%; 1.5%)	(1.0%; 1.8%)	(1.1%; 1.5%)	(5.3%; 8.2%)
Respondents			2090						
Observations			18810						

Continued

Table 3 Continued

Attribute	Attribute change From	To	MAR of blood clots (95% CI) Overall	Male	Female	MAR of serious infections (95% CI) Overall	Male	Female	MAR of negative effects on sperm (95% CI) Male
Parameters			55						
Null log-likelihood			−13 038.1						
Model log-likelihood			−5385.1						

DMARD, disease-modifying antirheumatic drug; MAR, maximum acceptable risk.

patients from Spain, Italy, the UK and France than difficulty with daily activities, whereas patients from the USA and Germany placed similar importance on pain and daily difficulties. Additionally, patients from Spain and Germany were most concerned about blood clots, and patients from Italy and the USA placed highest importance on risk of negative effects on semen parameters compared with other countries. These spatial differences indicate the need for reflecting on local perceptions and needs when evaluating new treatments and developing treatment guidelines. However, no significant differences were found when comparing a pooled European sample to a pooled US sample.

Preferences were found to vary significantly in the patient population, at both individual and subgroup levels. Overall, no treatment attribute contributed with more than 30% to treatment preferences of male or female patients. The study demonstrated that patients tended to prefer an oral pill every day over an injection and valued all reductions in pain and avoiding any of the considered risks. At the gender level, female patients placed a higher importance on reducing difficulties with daily activities than they placed on treatment administration, while male patients placed a comparable importance on both attributes. In addition, while pain relief had the largest average impact on male patients' treatment preferences, female patients placed on average the highest importance on the risk of blood clots. This resulted in differences in the average trade-offs that male and female patients were willing to make. For instance, female patients accepted an extra 1.2% risk of blood clots for reducing their pain score from 30 to 10, compared with male patients who would be willing to accept an extra 2.3% risk of blood clots for the level of pain relief. Thus, women required a higher benefit to compensate for a given level of blood clot risks than men.

This was also the first study to explore the relative importance that male patients with RA placed on a potential risk of negative effects on sperm from DMARDs. While only 29% of males were still planning to have children, avoiding the risk of negative effects on sperm was valued by male patients. However, male patients were willing to accept higher risks of negative impacts on sperm for additional treatment benefits. For instance, they were willing to accept an extra 17.3% additional risks of negative effects on sperm for reducing pain from 80 to 40 or an additional 9.9% risk of negative effects on sperm for reducing difficulties with daily activities from severe to moderate. While few data on the effects of advanced treatments for inflammatory rheumatic diseases on semen parameters are available, recent data indicated that filgotinib, a preferential JAK1 inhibitor, does not appear to have a negative impact on this aspect of health based on data from the recent MANTA and MANTA/RAy clinical trials.[39]

While a number of studies have examined preferences of rheumatologists for DMARDs,[21 22 40 41] patient preference data that is suitable for characterising bDMARDs and tsDMARDs is limited. However, findings of this study complement existing evidence. For example, Mathijssen *et al* conducted a DCE among patients with RA and found that their treatment preferences were affected by route of administration, frequency of administration, and risk of serious infections.[42] Similarly, in a DCE conducted by Alten *et al*, patients were found to prefer 'oral administration' over 'intravenous infusion'.[43] Results from two recent systematic reviews evaluating patient preference studies in RA showed variability in preferences across different populations.[21 22] Results of the current study align with these findings.

Strengths and limitations

This was the largest patient preference study in RA to date, providing a sample size large enough to conduct robust subgroup analyses, with a diverse composition in terms of socioeconomic and clinical characteristics. The study contributes to understanding preferences of patients with RA for DMARDs, with a particular focus on bDMARDs and tsDMARDs (ie, 86% of patients were taking an advanced therapy at the time of the study). The DCE was developed based on best-practice mixed-methods research and provides unique insights into patients' treatment priorities.

Despite the advantages of the studies, results must be considered within the context and limitations of the applications. First, by the nature of DCEs, all results are

contingent on the considered attributes, which were selected based on qualitative research, clinical data and questions about the effect on semen parameters on treatment decisions. While the consideration of additional attributes may provide a more comprehensive overview of treatments, it may result in overburdening respondents and potential bias from simplifying choice behaviours. Similarly, not all quality-of-life dimensions were captured, as DCEs may specifically not be suitable for assessing psychological elements due to their hypothetical nature (ie, it would require telling participants how to feel). Second, as with most patient preference studies, clinical data were based on self-reports and were not verified by chart reviews. Third, the average age of the sample was lower than that of the general RA population.[44] However, the large sample size allowed for a detailed analysis by age group. Fourth, male patients were oversampled in this study to allow for eliciting the relative importance of potential negative effects on semen parameters from DMARD exposure. To test the effect of the oversampling, a model that reweighted the sample composition to one-third male and two-thirds female did not find significant differences in estimates (online supplemental table C.6). Fifth, the data collection was conducted during the COVID-19 pandemic, with unknown effects on patients' perspectives. For example, blood clot risks were widely discussed in the media as an adverse event of COVID-19 and vaccinations. Sixth, it remains unknown if preferences of patients who participated in this research differed from patients who decided not to take part in the study. Seventh, the risk of negative effects on sperm was specifically included to test its potential impact on treatment decisions in the RA population. Finally, cost was not assessed as willingness-to-pay was considered out of scope for this study.

CONCLUSION

Preferences of patients with RA were driven by multiple benefits and risks of RA treatments, with no single attribute dominating the decision making. Patients were willing to accept higher risks of serious infections and blood clots in exchange for administration convenience, pain relief or improvements in daily functioning. The trade-offs that patients were willing to make were however heterogeneous and varied among individuals and subgroups. Our findings underline the EULAR recommendations on engaging in a shared decision-making process that implies understanding patient preferences and considers patient characteristics as well as the entire treatment profile, including benefits, risks and administration. This comprehensive approach to disease management is essential for optimising patient care. To enable and improve such shared decision-making in routine clinical practice, further research is needed and should consider the development of an engagement process as well as preference-based shared decision-making aids.

Author affiliations
[1]Schlosspark Klinik, University Medicine Berlin, Berlin, Germany
[2]Servicio de Reumatología, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[3]Department of Rheumatology and VIB Inflammation Research Center, University Hospital Ghent, Ghent, Belgium
[4]Division of Rheumatology, University of Pavia and Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[5]Department of Rheumatology, Aintree University Hospital, Liverpool, UK
[6]Faculty of Health, Care and Medicine, Edge Hill University, Ormskirk, UK
[7]Department of Internal Medicine III, Division of Rheumatology, Medical University Vienna, Vienna, Austria
[8]Department of Rheumatology and Clinical Immunology, Medisch Spectrum Twente, Enschede, The Netherlands
[9]Department of Psychology, Health & Technology, University of Twente, Enschede, The Netherlands
[10]Evidera Inc, London, UK
[11]Galapagos NV, Mechelen, Belgium

Twitter Juan Carlos Nieto-Gonzalez @JCNietoGon

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ORCID iDs
Rieke Alten http://orcid.org/0000-0002-3395-4412
Juan Carlos Nieto-Gonzalez http://orcid.org/0000-0002-5971-4185
Peggy Jacques http://orcid.org/0000-0001-9227-257X

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