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Benefit-risk trade-offs for treatment decisions in moderate-to-severe rheumatoid arthritis: focus on the patient perspective

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Abstract Given the increasing number of available treatments for rheumatoid arthritis (RA) with varying efficacy and safety profiles, it is critical to understand the level of trade-offs that patients are willing to make between benefits and risks. Adult patients with moderate to severe RA were invited to participate in a discrete choice experiment that solicited their preferences for hypothetical RA treatments. Each participant was presented with 14 choice cards asking about their preference between two hypothetical RA treatments with varying levels of efficacy, adverse events, and process-related attributes. A multivariable logistic regression model assessed the association between the attributes and the patient's decision and risk-increases were calculated. 510 eligible patients with moderate to severe RA completed the study. The average age of the participants was 56.4 years, 64.7% were female, and 45.1% received biologic agents. To achieve a 50% improvement in physical function, patients were willing to accept risk-increases of 91.1, 4.7, and 18.4% for abnormal laboratory results, cancer, and serious infection, respectively. Similarly, to achieve a 50% reduction in RA-related pain, patients were willing to accept risk-increases of 70.6, 3.7, and 14.2% for each AE. Moreover, patients were willing to trade risk-increases of 42.0, 2.2, and 8.5% for each AE to obtain a 50% reduction in the number of swollen joints. Patients with moderate to severe RA are willing to accept increased treatment risks to achieve improved physical function and disease control. These attributes are helpful to clinicians to make informed treatment choices.

keywords Rheumatoid arthritis · Patient preference · Treatment options · Discrete choice experiment · Benefit-risk

Introduction

Rheumatoid arthritis (RA) is a long-term, debilitating autoimmune disease that occurs in 0.5–1.0% of the adult population [1]. It is characterized by joint inflammation (swelling and pain) and the erosion of cartilage and bones, which lead to deformity [2]. Symptoms of active RA include tender or swollen joints, reduction of physical function, fatigue, lack of energy, and muscle and joint pain. Traditional treatment options include glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs) such as methotrexate [3].

A major advance in the treatment of RA occurred with the development of biologic agents. The first biologic agents approved for the treatment of RA were tumor necrosis factor (TNF)-α inhibitors, including adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab. Over the past few years, biologic agents with different targets have been approved, including interleukin inhibitors (anakinra and tocilizumab), T cell co-stimulation modulators (abatacept), CD20 inhibitors (rituximab), and small molecules including janus kinase (JAK) inhibitors (tofacitinib).

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Studies have shown that biologic therapies control inflammation, minimize joint damage, and preserve physical function when compared against traditional DMARDs [4, 5]. The 2015 American College of Rheumatology (ACR) guidelines for the treatment of RA recommend biologic agents for patients with moderate or high disease activity despite treatment with DMARD monotherapy [3]. Real-world evidence suggests that patients who cycled fewer conventional DMARDs before switching to a biologic therapy experience a lower economic burden than those who cycled more conventional DMARDs [6]. In addition, TNF-α inhibitors were shown to be associated with better efficacy and less frequent healthcare resource use compared with other biologic agents in the treatment of RA [7–10].

While biologic agents are proven effective for the treatment of RA, the US Food and Drug Administration (FDA) has issued black-box warnings for several of the treatments, indicating that these agents may lead to severe adverse events such as serious infections and malignancies [11–18]. However, the incidence rates of these severe adverse events are low, and it is unknown what benefit-risk thresholds RA patients are willing to accept in potential efficacy gains compared to the potential risks of adverse events in the US. Additionally, biologic treatments are administered via subcutaneous injection or intravenous infusion, which may be less convenient for patients and have been shown to influence patient decision-making [19]. Data from the CORRONA registry study show an average time of over 4 years from patient initiation of a conventional DMARD to initiation of biologic therapy [20], which suggests that patients may delay biologic initiation for the treatment of RA.

Due to the increasing number of RA treatments and their varied efficacy and safety profiles, patient preferences for different profiles of treatment options play an increasingly important role in the clinical decision-making process. It is crucial to understand preferences from the patient perspective because studies have shown discrepancies in patients' and physicians' health perceptions [21] and opinions from potential treatment recipients should also be valued during the disease journey. Therefore, it is important to understand how treatment attributes affect patient preferences for RA treatments and the level of trade-offs patients are willing to make between potential benefits and risks. The objectives of this study were to quantify the thresholds of benefit-risk trade-offs that patients are willing to accept in the treatment of RA in the US.

Methods

A discrete choice experiment was conducted among patients with moderate to severe RA. Discrete choice experiments are a rigorous method for eliciting preferences. This method assumes that any product or service can be described by a number of attributes and that the extent to which an individual values a product or service depends on the level of those features. It allows for the estimation of the relative importance of different attributes and the trade-offs between those attributes. This method is considered valuable for patient-centered evaluations of health products and services [22, 23].

Patients with RA from an existing patient panel were invited to participate in this study. Eligible participants were required to be at least 18 years of age at the time of the survey, have a confirmed diagnosis of moderate to severe RA for at least 6 months, and be willing to participate in the study. This study was exempted from a full ethics review by the New England Institutional Review Board.

Identification of treatment attributes and levels

Nine attributes associated with RA treatments were selected based on a targeted literature review in combination with expert opinion. These attributes describe efficacy, safety, and process-related measures associated with RA treatment. The efficacy attributes include (1) reduction in the number of swollen joints, (2) reduction in RA-related pain, and (3) improvement in physical function. The safety attributes include (1) risk of having abnormal laboratory results (including abnormal liver function tests [such as increased levels of alanine transaminase or aspartate transaminase] or abnormal blood counts [such as neutropenia, leukopenia, or thrombocytopenia]), (2) risk of malignancies (including skin cancers, lymphoma, breast cancer, and colon cancer), and (3) risk of serious infection (including tuberculosis, pneumonia, and sepsis). The process-related attributes include (1) route of administration (oral, intravenous infusion, or subcutaneous injection), (2) dose frequency (daily, biweekly, or monthly), and (3) out-of-pocket treatment cost per month. The levels of each attribute were selected based on their observed ranges in the literature for different RA treatments such that they reflected the realistic conundrum that patients were facing for treatment selection and were distinguishable enough from each other for patients to make a meaningful choice [24–36]. Table 1 presents the list of attributes and their levels included in the study.

Experimental design

Hypothetical treatment profiles were generated with random combinations for the levels of each treatment attribute. With three four-level attributes and six three-level attributes (46,656 possible combinations), a full factorial design was not feasible. A smaller orthogonal design with 144 pairs of treatment profiles was adopted in the study. Each pair of treatment profiles composed

Table 1 Choice card attributes and levels for RA treatments

Attributes	Level 1	Level 2	Level 3	Level 4
Reduction in the number of swollen joints	No reduction	25% reduction	50% reduction	75% reduction
Reduction in pain	No reduction	25% reduction	50% reduction	75% reduction
Improvement in physical function	No improvement	20% improvement	40% improvement	60% improvement
Abnormal laboratory results[a]	10%	20%	30%	–
Cancer[b]	0%	1%	2%	–
Serious infection[c]	0%	2%	4%	–
Route of administration	Oral	Subcutaneous injection	Intravenous infusion	–
Dose frequency	Daily	Every two weeks	Monthly	–
Out-of-pocket cost per month	$0	$50	$100	–

RA rheumatoid arthritis, *DMARDs* disease-modifying anti-rheumatic drugs

Attribute levels for efficacy and safety measures were determined based on clinical trial results for both biologic and non-biologic DMARDs for RA. The number of levels for each attribute was determined based on the range of possibilities seen in the literature and are not meant to be compared across attributes

[a] Abnormal laboratory results include elevated liver function tests (elevated alanine transaminase or aspartate transaminase) and hematological tests (neutropenia, leukopenia, and/or thrombocytopenia)

[b] Cancers include skin cancers, breast cancer, lymphoma, and colon cancer, among others

[c] Serious infections include tuberculosis, pneumonia, and sepsis, among others

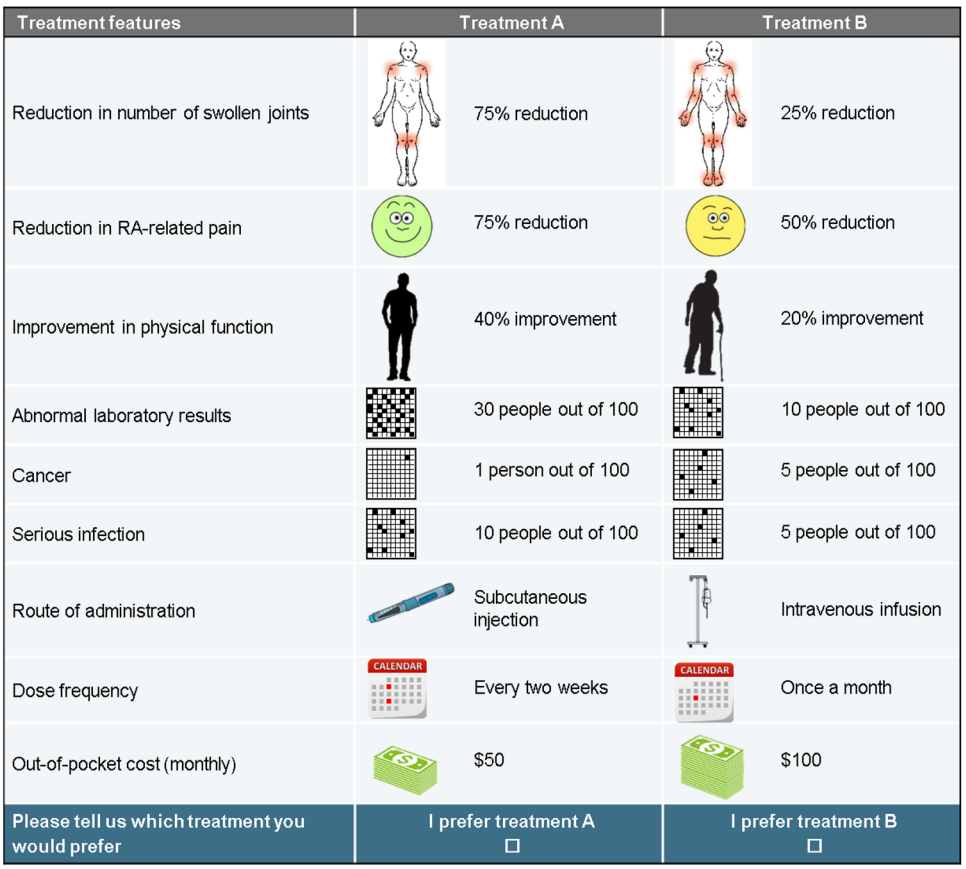

Fig. 1 Example choice card used in the study

one choice card. The experimental design guarantees an optimal combination of attribute levels with the highest statistical efficiency [37]. To make the questionnaire manageable, the 144 choice card pairs were randomly grouped into 16 versions of questionnaires. Each version had nine choice cards per design. In addition, four

extra choice cards were randomly included in each questionnaire to test the internal validity of the responses. Each participant was presented with a randomly selected version of questionnaire. Figure 1 presents an example choice card used in the study.

Participants and survey process

Participants were recruited from the Harris Panel (owned by Nielsen Opinion Quest), which consists of individuals who had voluntarily registered and agreed to regularly complete research surveys on a variety of topics. Adult RA patients were randomly selected to participate in the survey based on pre-registered medical history information. These patients received invitations to participate in the survey by Nielsen Opinion Quest, a well-established market research firm. The survey started with a brief introduction of the study and asked the respondents whether they would like to participate in the study. In the case of non-response, reminders were sent to individuals to increase the overall response rate. If patients gave consent to take the survey, they would proceed to the main survey and were screened for eligibility. Eligible participants were first presented with a tutorial that explained the study process and the treatment attributes involved. An example choice card was shown to each participant. Patients were then presented a randomly selected version of questionnaire from the 16 versions generated from the experimental design. The participants were asked to select the preferred treatment profile from each choice card presented to them. Moreover, the survey also collected basic demographic information and RA-related medical history of the participants. No personally identifiable data were collected in the survey and the identities of the participants are anonymous to the researchers of this study.

It has been recommended that the sample size of the discrete choice experiment should include at least 300 respondents, and when planning to study subgroups the sample size should comprise of at least 200 respondents per group [38]. Therefore, a sample of 500 respondents was planned for this study to allow for subgroup analyses of patients who had not received any biologic agents for the treatment of RA. This strategy has been endorsed by the Good Research Practices for Conjoint Analysis Task Force of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [39].

Statistical methods

Baseline characteristics were summarized for all eligible participants. Furthermore, patient preferences for the RA treatment features were assessed using a multivariable logistic regression model by regressing the patient's choice decision on the level of change in RA treatment features between the two treatment profiles of a choice card. Coefficients obtained from this regression analysis indicated the relative importance of attributes in determining patient preferences, and the associated p values showed whether these features affected patients' decisions in a statistically significant manner. Odds ratios were calculated based on the regression coefficients from the logistic regression model. An odds ratio greater than one indicates that patients prefer a profile with this level of a particular attribute, while an odds ratio less than one indicates that patients prefer a profile without this level of a particular attribute. Benefit-risk thresholds were presented as willingness to trade (WTT) and were calculated as the absolute value of the ratio between the regression coefficient of one efficacy measure and the regression coefficient of one adverse event. The WTT indicates how much risk-increase of an adverse event an average RA patient is willing to accept to gain an increase in efficacy. Patient preferences were further expressed as willingness to pay (WTP) and were calculated as the absolute value of the ratio between the regression coefficient of an attribute and the regression coefficient of out-of-pocket treatment cost. The WTP indicates how much money per month an average RA patient is willing to pay to achieve higher efficacy or avoid higher risk of adverse events. Subgroup analysis was conducted among patients who had not received any biologic agents for the treatment of RA. All analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Out of 859 patients who responded to the survey invitation, 510 patients from all census regions in the US met the eligibility criteria and completed the survey for a 59.4% completion rate. Table 2 presents the characteristics of the respondents. The respondents were 56.4 years old on average, and approximately two-thirds were female. A majority of the respondents (77.3%) had education beyond high school, and 38.4% of the sample was employed at the time of the survey. A total of 62.4% of respondents reported being in excellent, very good, or good health, and 43.1% of patients had RA for more than 10 years. Approximately 12% of patients had severe RA. In terms of treatment experience, 45.1% respondents had used prior biologic DMARDs, with the most common being etanercept (22.4%) and adalimumab (21.8%). 48.2% respondents had used non-biologic DMARDs, with the most common being methotrexate (39.6%) and hydroxychloroquine (24.3%). In

Table 2 Baseline characteristics of RA patients

	All patients ($N = 510$)	Biologic-naïve ($N = 280$)
Demographics		
Age (years), mean (SD)	56.4 (13.8)	58.6 (13.3)
Female, *n* (%)	330 (64.7%)	180 (64.3%)
Years of school completed, *n* (%)		
Less than high school	8 (1.6%)	7 (2.5%)
Completed high school	99 (19.4%)	62 (22.1%)
Some college	122 (23.9%)	66 (23.6%)
Associate's degree	80 (15.7%)	42 (15.0%)
Bachelor's degree or higher	192 (37.6%)	99 (35.4%)
Other	9 (1.8%)	4 (1.4%)
Employment status, *n* (%)		
Employed	196 (38.4%)	89 (31.8%)
Unemployed	40 (7.8%)	28 (10.0%)
Retired	204 (40.0%)	126 (45.0%)
Student	8 (1.6%)	6 (2.1%)
Homemaker	41 (8.0%)	18 (6.4%)
Other	21 (4.1%)	13 (4.6%)
Income level, *n* (%)[a]		
Missing	81 (15.9%)	51 (18.2%)
Not missing	429 (84.1%)	229 (81.8%)
Less than $35,000	120 (28.0%)	76 (33.2%)
$35,000 to $74,999	164 (38.2%)	84 (36.7%)
$75,000 to $149,999	122 (28.4%)	60 (26.2%)
$150,000 or above	23 (5.4%)	9 (3.9%)
Disease characteristics		
Current health, *n* (%)		
Excellent	12 (2.4%)	7 (2.5%)
Very good	96 (18.8%)	46 (16.4%)
Good	210 (41.2%)	112 (40.0%)
Fair	152 (29.8%)	93 (33.2%)
Poor	40 (7.8%)	22 (7.9%)
Time since RA diagnosis, *n* (%)		
Less than 5 years	192 (37.6%)	106 (37.9%)
5 to less than 10 years	98 (19.2%)	52 (18.6%)
10 to less than 20 years	117 (22.9%)	66 (23.6%)
More than 20 years	103 ((20.2%)	56 (20.0%)
RA disease severity, *n* (%)		
Moderate	250 (49.0%)	161 (57.5%)
Moderate to severe	200 (39.2%)	93 (33.2%)
Severe	60 (11.8%)	26 (9.3%)
Medications used for RA, *n* (%)		
Biologic DMARDs	230 (45.1%)	–
Adalimumab	111 (21.8%)	–
Etanercept	114 (22.4%)	–
Infliximab	52 (10.2%)	–
Tocilizumab	18 (3.5%)	–
Abatacept	38 (7.5%)	–
Rituximab	25 (4.9%)	–
Golimumab	9 (1.8%)	–
Tofacitinib	20 (3.9%)	–

Table 2 continued

	All patients ($N = 510$)	Biologic-naïve ($N = 280$)
Certolizumab	10 (2.0%)	–
Non-biologic DMARDs	246 (48.2%)	105 (37.5%)
Methotrexate	202 (39.6%)	72 (25.7%)
Leflunomide	37 (7.3%)	9 (3.2%)
Sulfasalazine	51 (10.0%)	11 (3.9%)
Azathioprine	14 (2.7%)	3 (1.1%)
Hydroxychloroquine	124 (24.3%)	55 (19.6%)
Any DMARDs	335 (65.7%)	105 (37.5%)
Fewer than 2 DMARDs[b]	139 (41.5%)	70 (66.7%)
2 DMARDs or more[b]	196 (58.5%)	35 (33.3%)
Fewer than 3 DMARDs[b]	218 (65.1%)	95 (90.5%)
3 DMARDs or more[b]	117 (34.9%)	10 (9.5%)
Received treatment, but did not remember name	57 (11.2%)	49 (17.5%)
Other[c]	101 (19.8%)	80 (28.6%)
None	63 (12.4%)	63 (22.5%)

RA rheumatoid arthritis, *SD* standard deviation, *DMARDs* disease-modifying anti-rheumatic drugs, *NSAIDs* non-steroidal anti-inflammatory drugs

[a] Percentages were calculated out of respondents whose income information was available

[b] Percentages are calculated out of respondents who had any DMARDs

[c] The most frequently used other drugs included NSAIDs, narcotic pain medications, and steroids

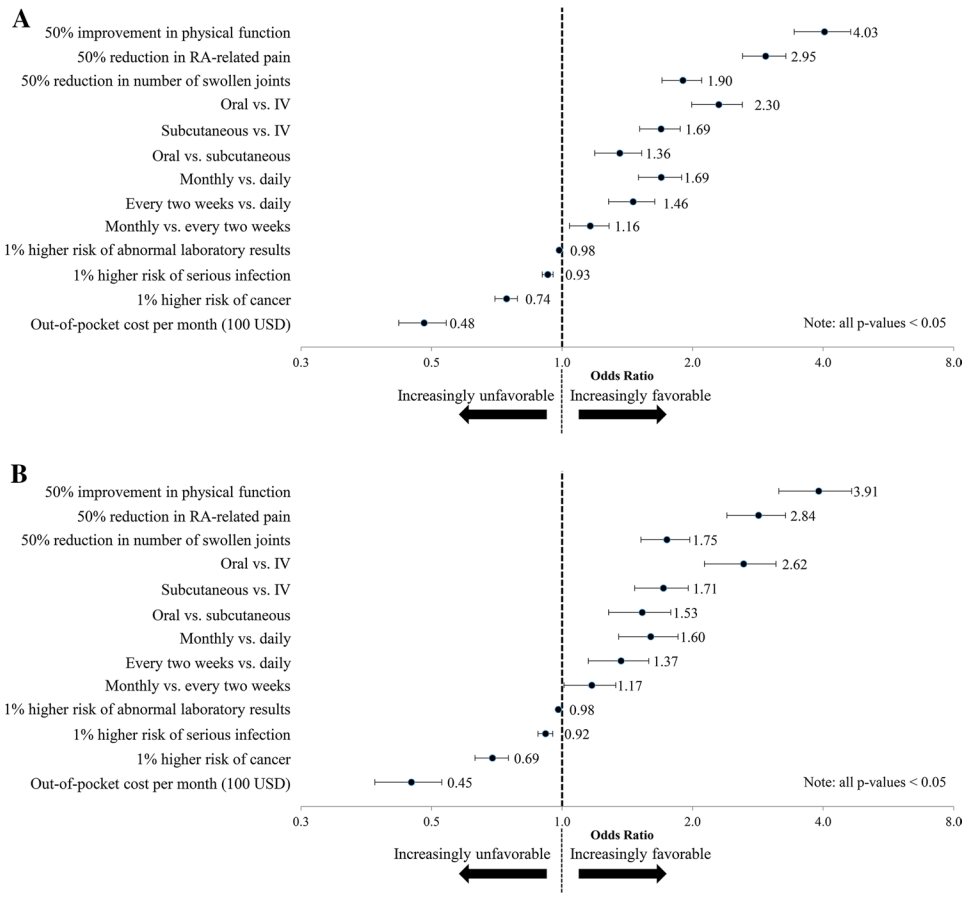

Fig. 2 Importance of treatment attributes to patients with RA. **a** Overall RA patients; **b** biologic-naive RA patients

addition, 58.5% of respondents had previously used two or more different biologic or non-biologic DMARDs.

Patient preferences

Figure 2 presents the odds ratios for each treatment attribute obtained from the logistic regression model. For all efficacy measures (50% reduction in the number of swollen joints, 50% reduction in RA-related pain, and 50% improvement in physical function), the odds ratios were greater than one, indicating that patients preferred treatments with these attributes (all p values <0.01). Physical function affected patients' preference for treatments the most (OR 4.03 for 50% improvement), followed by RA-related pain (OR 2.95 for a 50% reduction) and number of swollen joints (OR 1.90 for a 50% reduction). Patients also preferred oral treatments to intravenous infusion, subcutaneous injection to intravenous infusion, and oral to subcutaneous injection (all p values <0.01). They also favored treatments with lower dosing frequencies, including monthly dosing over daily dosing, every two weeks over daily, and monthly over every two weeks (all p values <0.01). Patients avoided treatments with higher risks of adverse events—increased risk of cancer affected patients' avoidance of treatment the most (OR 0.74 for a 1% increase, p value <0.01), followed by serious infections (OR 0.93 for a 1% increase, p value <0.01).

Figure 3 presents patients' thresholds of benefit-risk trade-off. Patients were most willing to trade off to achieve a 50% improvement in physical function, as they were willing to accept risk-increases of 91.1% in abnormal laboratory results, 18.4% in serious infection, and 4.7% in cancer. In comparison, to achieve a 50% reduction in RA-related pain, patients were willing to accept risk-increases of 70.6% in abnormal laboratory results, 14.2% in serious infection, and 3.7% in cancer. Patients were slightly less willing to trade off to achieve a 50% reduction in swollen joints, as they were willing to accept risk-increases of 42.0% in abnormal laboratory results, 8.5% in serious infection, and 2.2% in cancer.

Table 3 presents patients' willingness to pay for each of the treatment attributes. Among efficacy measures, patients placed the highest value on improvement in physical function (willing to pay $190 per month for a

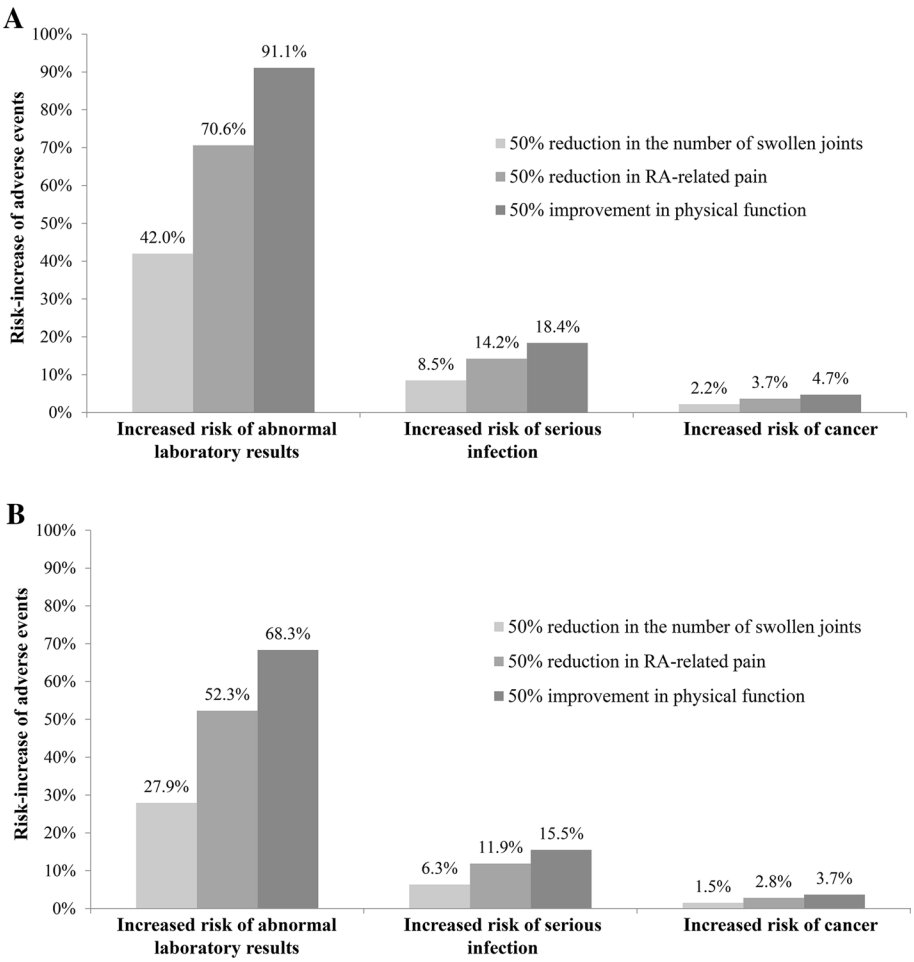

Fig. 3 Thresholds of benefit-risk trade-off of patients with RA. **a** Overall RA patients; **b** biologic-naive RA patients

Table 3 Marginal willingness to pay for features of RA treatment

	Willingness to pay (monthly out-of-pocket cost)[a]	
	All patients ($N = 510$)	Biologic-naïve ($N = 280$)
Efficacy measures		
50% reduction in the number of swollen joints	$87.57	$69.57
50% reduction in RA-related pain	$147.36	$130.29
50% improvement in physical function	$190.12	$170.26
Adverse events		
1% decrease in abnormal laboratory results	$2.09	$2.49
1% decrease in cancer	$40.23	$46.15
1% decrease in serious infection	$10.35	$10.99
Process-related measures		
Route of administration		
To get oral instead of intravenous infusion	$113.47	$120.39
To get subcutaneous injection instead of intravenous infusion	$71.70	$67.19
To get oral instead of subcutaneous injection	$41.77	$53.20
Dose frequency		
To get monthly instead of daily	$71.85	$58.78
To get every two weeks instead of daily	$51.42	$39.12
To get monthly instead of every two weeks	$20.42	$19.66

RA rheumatoid arthritis

[a] Willingness to pay was calculated using formula $-(\beta_{\text{attribute}}/\beta_{\text{out-of-pocket cost}})$. The number indicates how much money per month an average RA patient is willing to pay to achieve or avoid an attribute

50% increase), followed by reduction in RA-related pain ($149 per month for a 50% decrease), which is consistent with the benefit-risk thresholds. Patients also valued the convenience of a treatment and were willing to pay high amounts for oral treatment instead of intravenous infusion ($113 per month) and monthly dosing instead of daily ($72 per month).

Subgroup analysis

A subgroup analysis was conducted among biologic-naïve patients ($n = 280$). The baseline characteristics were largely consistent with the overall sample (Table 2). The average age of the naïve subgroup was 58.6 years, 64.3% were female, and 43.6% had RA for more than 10 years. Biologic-naïve patients were slightly less severe than the overall sample—9.3% had severe RA (vs. 11.8% in the overall sample), and 81.1% reported being in excellent, very good, or good health (vs. 62.4% in the overall sample).

The subgroup results were largely consistent with the results in the overall sample (Figs. 2, 3); the benefit-risk thresholds were slightly lower among biologic-naïve patients. Physical function affected their preference for treatments the most (OR 3.91 for 50% improvement, p value <0.05), followed by RA-related pain (OR 2.84 for a 50% reduction, p value <0.05) and number of swollen joints (OR 1.75 for a 50% reduction, p value <0.05). Among adverse events, increased risk of cancer affected biologic-naïve patients' avoidance of treatment the most (OR 0.69 for a 1% increase, p value <0.05), followed by serious infections (OR 0.92 for a 1% increase, p value <0.05), consistent with the overall sample. Among efficacy measures, the biologic-naïve patients placed the highest value on improvement in physical function (willing to pay $170 per month for a 50% increase), followed by reduction in RA-related pain ($130 per month for a 50% decrease), which is consistent with the benefit-risk thresholds for the overall sample (Table 3).

Data validity

In the entire sample, 93.9% of the responses passed validity tests—2.2% of respondents failed test–retest validity, meaning they did not consistently respond to two choice cards with the same pair of profiles, but in different orders; 5.5% failed transitivity validity, meaning they did not consistently respond when presented with three choice cards of an apparent ranking of superiority/inferiority. The failure rates in this study are below what was reported in the literature. Based on recommendations from previous discrete choice experiment research, these

responses that did not pass the validity tests were not excluded from the analysis [40].

Discussion

The ACR guidelines recommend biologic treatments to RA patients with moderate to high disease activity after failing an initial conventional synthetic DMARD [3]. While biologic DMARDs are able to bring significant clinical benefits, these drugs are associated with risks of adverse events including serious infections and malignancies. These potential adverse events may prevent physicians from prescribing the clinically beneficial biologic DMARDs to patients, albeit the actual willingness of patients to accept these slightly increased risks to get better efficacy is uncertain. Since treatment decision is a mutual agreement between physicians and patients, it is important to understand if patients would accept increased risk of adverse events against efficacy benefits. As the time a physician has with a patient may be limited, attributes that are the most meaningful to a patient will be important for physician awareness during this limited time to improve conversations around treatment options that may result in improved acceptance by the patient.

The results from our study suggested that patients were willing to accept increased risk of adverse events including abnormal laboratory results, serious infection, and cancer for improved efficacy (reduction in the number of swollen joints, reduction in RA-related pain, and improvement in physical function). Among the three adverse events investigated, cancer risk is the most impactful attribute that the patients try to avoid when making decisions on treatment selection. Nonetheless, patients are still willing to accept 2–4% increased risk of cancer to obtain better physical function and disease control. For other risks including abnormal laboratory results and serious infection, patients showed higher benefit-risk thresholds than for cancer, ranging from 42 to 91 and 9 to 18%, respectively.

Discrete choice experiments are a rigorous method for eliciting preferences and quantifying benefit risk thresholds. They have recently been applied to healthcare research and are considered valuable for patient-centered evaluations of health products and services [22, 23]. Discrete choice experiments generate and rank hypothetical product profiles mimicking real-world use of drugs, and allow patient preferences for both the individual treatment features and the overall treatment profiles to be elicited.

A number of studies have used discrete choice experiments to evaluate patient preferences for treatments in various disease areas, including RA [19, 41–48]. Previous discrete choice experiments in RA have found that patients expressed strong preference for improved efficacy and avoidance of adverse events; oral treatments and treatments with lower frequency of administration were valued [19, 41, 43, 45–47]. One study also recognized a higher willingness to pay for a treatment with improved efficacy and more convenient features [19]. The results of the current study corroborate the existing literature on patient preferences in RA treatments [19, 41, 43, 45–47].

While there are a number of studies that evaluated patients' preference for RA treatments, few have established the thresholds of benefit-risk. Thresholds of benefit-risk from a patient-based survey can clearly inform physicians and decisions makers of the degrees of trade-offs that patients are willing to accept. One Canadian study has identified a threshold of 15% increase in major symptom improvement for possible increased risk of cancer and small risk of serious infection. However, the precise level of the increased risk of cancer and serious infection was not evaluated [45]. To our knowledge, the current study was the first US study to assess the thresholds of benefit-risk in the treatment of RA. The thresholds identified from the current study can help physicians better communicate risks and benefits in clinical practice to improve patient acceptance of recommended treatments. For instance, patients were willing to accept up to 18.4% increased risk of serious infection for increased efficacy, while the rate of serious infection in one pivotal trial of adalimumab was only 2.3% [24]. Similarly, patients are willing to accept up to 4.7% increased risk of cancer for increased efficacy, but the reported rates of malignancies for adalimumab are below 1% [24]. This study can help physicians better identify how patients value the benefits of treatment compared to the risks.

The current study also separately evaluated the thresholds of benefit-risk of RA treatments of biologic-naïve patients. Compared to the overall population, biologic-naïve patients were less willing to accept increased risk of adverse events to achieve greater efficacy. A potential reason is that the patients with less severe RA have more treatments still available to them and hope to achieve efficacy results without experiencing adverse events. In addition, biologic-experienced patients already have drug exposure and familiarity with benefit and risks and may be more willing to accept additional risks.

The current study evaluated preferences from the patient perspective. Since preferences of patients may differ from those of physicians, understanding what is truly important in patients' opinions in terms of risk and benefit of a treatment helps physicians come up with a treatment plan that is tailored toward patients' needs. The Outcome Measures in Rheumatology (OMERACT) group endorsed the necessity

to have treatment of RA target on patient-relevant outcomes and has been working toward incorporating more patients' opinions in RA outcome measures [49]. One study that compared patients' and physicians' perceptions of RA disease activities found that pain was the most important determinant for patients while for physicians it was mostly joint swelling. The results of the current study showed a consistent story that patients preferred treatments that could relieve pain more than those that could mitigate joint swelling [50].

The current study has some limitations. First, even though the data for this study came from a patient population from all census regions in the US, the use of a panel-based survey may present a generalizability issue. The panel population may not be completely representative of the broader RA population. In addition, other factors could potentially affect a respondent's preference, such as cultural or socioeconomic differences. These effects were not evaluated in the current study. However, because this is a randomized experiment, the cultural or socioeconomic differences are not likely to confound the results of the benefit-risk measures. Second, to be considerate of the response burden, only a limited number of features that were considered most impactful were included in the study. Some features of interest were not included in the product profiles, such as other adverse events. Future studies are encouraged to investigate the impact of different features of RA treatment on preference and thresholds of benefit-risk.

In conclusion, efficacy, safety, and process-related features significantly affect patient preferences in RA treatment. Patients with moderate to severe RA are willing to accept increased risks of adverse events to achieve improved physical function and disease control. The current study findings can help physicians and decision makers customize patient-oriented treatment plans and facilitate physician–patient conversations around treatments to improve patient acceptance of recommended treatment plans.

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Compliance with ethical standards

Conflict of interest Dr. M. Elaine Husni has served as a consultant to AbbVie and on advisory boards for AbbVie, Bristol-Meyers Squibb, Genentech, Novartis, Pfizer, and Janssen. Keith A. Betts and Yan Song have served as consultants to AbbVie. Jenny Griffith and Arijit Ganguli are employees of AbbVie and may own company stock.

Research involving human participants and or animals 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 Informed consent was obtained from all individual participants included in the study.

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