Patient preferences for disease modifying anti-rheumatic drug treatment in rheumatoid arthritis: A systematic review

Caylib Durand, Maysoon Eldoma, Deborah A Marshall, Nick Bansback, Glen S Hazlewood

This is a pre-copyediting, author-produced PDF of an article accepted for publication in *The Journal of Rheumatology* following peer review. The definitive publisher-authenticated version [Durand C, Eldoma M, Marshall DA, Bansback N, Hazlewood GS. Patient Preferences for Disease-modifying Antirheumatic Drug Treatment in Rheumatoid Arthritis: A Systematic Review. Journal of Rheumatology. 2020;47(2):176-87] is available online at: https://www.jrheum.org/content/47/2/176.long.

Patient preferences for disease modifying anti-rheumatic drug treatment in rheumatoid arthritis: A systematic review

Caylib Durand, Maysoon Eldoma, Deborah A Marshall, Nick Bansback,
Glen S Hazlewood (ORCID ID: 0000-0001-7709-3741)

Keywords: Patient preference, rheumatoid arthritis, disease modifying anti-rheumatic drugs, systematic review

Attribution: From the Department of Medicine and Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta; Arthritis Research Canada; Centre for Health Evaluation and Outcome Sciences, Providence Health Care, St Paul's Hospital, Vancouver, British Columbia

Support: The work was supported in part by a Canadian Initiative for Outcomes in Rheumatology Care grant and a Canadian Institute of Health Research (CIHR) Grant (MOP - 142441). Dr. Hazlewood is supported by a Canadian Institute of Health Research (CIHR) New Investigator Salary Award and The Arthritis Society Young Investigator Salary Award. Dr. Marshall is supported by a CIHR Canada Research Chair in Health Services and Systems Research and the Arthur J.E. Child Chair Rheumatology Outcomes Research.

Conflict of interest: The authors declare that they have no competing interests.

Affiliations and Degrees:

C Durand, MD, PhD, FRCP(C), Rheumatology Fellow, University of Calgary; M Eldoma, MD, FRCP(C), Rheumatology Fellow, University of Calgary; DA Marshall, Professor of Medicine, University of Calgary; N Bansback, Associate Professor, University of British Columbia; GS Hazlewood, MD, PhD, FRCP(C), Assistant Professor, University of Calgary

Correspondence to:

Dr. Glen Hazlewood

3330 Hospital Dr NW, Calgary, Alberta, Canada, T2N 4N1

Tel: (403) 220-5903, Fax: (403) 210-7367

Email: gshazlew@ucalgary.ca

Running head: Patient preference DMARD RA

Word count: 3669

ABSTRACT

OBJECTIVE: To summarize patients' preferences for disease modifying anti-rheumatic drug (DMARD) therapy in rheumatoid arthritis (RA).

METHODS: We conducted a systematic review to identify English-language studies in adult RA patients that measured patients' preferences for DMARDs or health states and treatment outcomes relevant to DMARD decisions. Study quality was assessed using a published quality assessment tool. Data on the importance of treatment attributes and associations with patient characteristics was summarized across studies.

RESULTS: From 7951 abstracts, we included 36 studies from a variety of countries. Most studies were in patients with established RA and were rated as medium (n=19) or high quality (n=12). The methods to elicit preferences varied, with the most common being discrete choice experiment (DCE) (n=13). Despite the heterogeneity of attributes in DCE studies, treatment benefits (disease improvement) were usually more important than both non-serious (6 of 8 studies), and serious adverse events (5 of 8), and route of administration (7 of 9). Amongst the non-DCE studies, some found patients placed high importance on treatment benefits, while others (in patients with established RA) found patients were quite risk averse. Subcutaneous therapy was often, but not always preferred over intravenous therapy. Patient preferences were variable and commonly associated with sociodemographics.

CONCLUSION: Overall, the results showed that many patients place a high value on treatment benefits over other treatment attributes including serious or minor side effects, cost or route of administration. The variability in patient preferences highlights the need to individualize treatment choices in RA.

INTRODUCTION

Expanding treatment options for rheumatoid arthritis (RA) has led to increased choices for patients and physicians. These choices come with trade-offs in risks and benefits, and there is growing recognition of the importance of including patient preferences in treatment decision-making. With individual patients, shared decision-making is regarded as the preferred approach to achieve evidence-informed decisions consistent with a patient's values (1). Within clinical practice guidelines, understanding patient preferences for key trade-offs is a necessary step in the evidence-to-decision process (2). Under the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach, strong recommendations are reserved for situations in which most patients would choose a treatment based on the balance of benefits and harms (3). Summarizing the existing literature on patient preferences is a critical step in developing patient-centered guidelines.

Evidence on patient preferences can come from a variety of sources (4). Researchers may record patients' choices when presented with an informed choice, typically with a patient decision aid. Alternatively, the importance of outcomes or health states can be assessed either individually in absolute terms (uni-dimensional) or relative to each other (multi-dimensional) (5). The absolute importance of a health state is usually expressed on a 0 (equivalent to death) to 100 (full health) scale. This can be derived through a simple visual analog scale or utility elicitation techniques, where patients are asked to trade-off between continued existence in a given health state, or a return to full health but with a

small chance of immediate death (standard gamble) or shortened life-expectancy (time trade-off) (6).

Alternatively, the relative importance of health states can be elicited through multi-dimensional methods like a discrete-choice experiment (DCE) that ask patients to rate, rank or choose between treatment alternatives (4). In a DCE, patients complete a series of choice tasks, in which they are presented with a choice of 2 or more treatments that differ in their attributes (e.g. characteristics like dosing, cost, side effects, route of administration) (7). The value patients place on each attribute is then estimated using statistical models, assuming that patients chose the treatment with the highest overall value.

The primary objective of this systematic review was to summarize the available quantitative evidence regarding the preferences of patients with RA for DMARD therapy. The secondary objective was to identify any associations between patient characteristics and preferences. The aim was to provide knowledge that can help inform treatment recommendations and clinical decision making for RA. By aligning treatment recommendations and decisions with patient preferences, patient adherence to DMARD therapy may increase (8, 9).

MATERIALS AND METHODS

Study Design and Inclusion Criteria

We performed a systematic review to identify English-language studies in adults (age > 18) with a diagnosis of RA that assessed patients' preferences for different DMARDs, or treatment attributes relevant to a choice between DMARDs. DMARDs included any conventional synthetic DMARD (csDMARD) (e.g. methotrexate), biologic originator or biosimilar DMARD (boDMARD, bsDMARD) (e.g. adalimumab), targeted synthetic DMARD (tsDMARD) (e.g. tofacitinib), or corticosteroids. We included any study that provided a quantitative assessment of patient preferences, which was defined according to the MeSH definition in the National Library of Medicine as an "individual's expression of desirability or value of one course of action, outcome, or selection in contrast to others" (10). This included studies that: 1) examined the choices patients made when presented with a decision aid for alternate DMARDs; 2) measured patient preferences for alternative treatment options or attributes relevant to a choice between DMARDs.

We excluded studies reporting health related quality of life (HR-QOL), as HR-QOL measures the value a patient places on their current health state, not their preference for potential treatment outcomes or attributes. We also excluded studies with mixed rheumatic disease populations, unless the data for RA patients were reported separately. As we were interested in information regarding patients' preferences for attributes relevant to DMARD therapy, we excluded studies that measured patient preferences for an unrealistic outcome such as a complete cure. Finally, we also excluded studies that measured preferences for components of a single attribute (e.g. relative importance of questions within a functional status outcome, or specific mechanisms of an auto-injector);

these trade-offs were felt to less relevant to treatment decision-making in clinic or within guidelines. The study protocol was registered with Prospero (PROSPERO 2015 CRD42015027528).

Search Strategy and Data Sources

We conducted a database search for studies on or before January 2018 in the following databases: Medline In Process and Other Non-indexed Citations, CENTRAL (Cochrane Central Registry of Controlled Trials), EMBASE (Excerta Medica Database), Psychinfo, and HealthStar. The MEDLINE search strategy is included in Supplementary Table 1. Briefly, the search combined keywords and subject headings for RA with terms for patient preferences or methods used to assess patient preferences. The MEDLINE and EMBASE RA filters were derived from Cochrane reviews and adapted for the other databases (11). The patient preference filter was informed by a published systematic review of patient preferences (12). We also reviewed the reference lists of all eligible studies.

Study Selection

Two reviewers independently screened articles. Any article included by either reviewer in the title or abstract screen proceeded to full-text review, where disagreements were resolved by consensus or with a third reviewer if necessary.

Assessment of Study Quality

To assess for study quality and to identify potential biases, two reviewers used a methodological assessment tool previously developed by other investigators (13). The checklist includes 31 questions to assess for potential biases across 5 domains: 1) external validity (i.e. is the population studied representative of the target population); 2) quality of construct representation (i.e. are the health states considered appropriate, comprehensive and meaningful); 3) construct-irrelevant variance (i.e. were there factors outside of the measurement, such as task complexity, that may have impacted responses); 4) quality of reporting and analyses (i.e. was the data complete and analyzed appropriately); 5) other aspects that strengthen or weaken the study. After each of the 5 domains were evaluated, an overall quality rating (high/medium/low) was assigned to the study. The overall quality rating included a judgment across all domains for that outcome, although not all domains were equally weighted (13). The quality rating was done by two independent reviewers, with disagreements resolved by consensus.

Data Extraction and Analysis

For each included study, two reviewers extracted the study method and attributes considered, the setting in which the study took place, number of patients involved, patient characteristics, treatment(s) of interest, and funding sources into a standardized form. The results of the studies were not combined into a meta-analysis because of the heterogeneity of the methodologies, patient populations and treatment options evaluated. Instead, we summarized data into tables based on the type of study method used and highlighted overall themes across the body of evidence. For DCEs, we summarized results across studies in a table of pairwise comparisons of attribute importance, as described below.

Results for the association between patient characteristics and preferences were summarized descriptively.

For DCE studies, we calculated the proportion of times an attribute was preferred out of the total number of comparisons. For example, if remission and route of administration were both included as attributes in 3 different studies, and remission was more important in all 3, this would be presented as 3/3, favoring remission. If the number of studies in which each of the 2 attributes was favoured was the same, then the word "neither" was placed above the ratio to reflect the fact that there was no overall direction of the preference. For these comparisons, we grouped similar attributes into 9 categories representing treatment benefits (remission/low disease activity, symptom/ functional improvement, avoiding joint damage), adverse events (serious and non-serious), dosing (onset/duration, route, frequency) and cost. If a study included more than 1 attribute in a given category (e.g. multiple serious adverse events (AE)), we considered the attribute category to be more important in that study if it was favoured in the majority of pairwise comparisons. When drawing conclusions from these analyses, we were careful to consider that the attributes and levels varied considerably across studies. Thus, as a secondary summary, we also extracted the attributes and levels considered in each study along with their utility values, scaling the results (multiplying by a constant term) such that they summed to 100 within each study.

RESULTS

Search Results and Study Characteristics

From 7951 records, we included 36 unique studies (Figure 1). The included studies were published between 1990 and 2018, across multiple countries and had sample sizes ranging from 10 to 1588 (Table 1). Most studies included patients with established RA (mean disease duration 7 to 17 years), except 2 that examined the preferences of patients with early RA (14, 15). Most (n=22) were focused on health states relevant to advanced therapeutics (biologic or targeted synthetic therapy), and in most studies, patients had previously or were currently taking one or more of the treatments that the study was focused on. For funding, 15 of the studies were funded partially or entirely by industry. The methods used to elicit preferences included: DCE (n=13); standard gamble (SG), time trade-off (TTO) or visual analogue scale (VAS) (n=3); willingness to pay (n=2); and willingness to accept risk (n=5) (Table 1). Fourteen other studies used various rating or ranking tasks to evaluate patient preferences for different routes of delivery (n=5), different treatment outcomes (n=6) or different treatment options (n=3) (Table 1 with full details in Table 4). The attributes considered in each study varied considerably, and are presented and discussed alongside the results of the studies (see below).

Quality Assessment of Included Studies

Overall, 12 studies were rated as high quality, 19 were medium, and 5 were low quality (Supplementary Table 2). Low quality studies typically had poor external validity with small sample sizes that did not reflect typical rheumatology RA patients, and/or had complex surveys without adequate pre-testing or piloting to ensure comprehension, leading to low ratings for the construct-irrelevant variance domain (i.e. understanding of the task). Most studies were rated as medium or high quality for construct representation

and quality of reporting and analysis. Ratings of overall study quality were similar between DCE (4 high, 8 medium, 1 low) and non-DCE studies (8 high, 11 medium, 4 low).

Summary of findings

Discrete Choice Experiments (DCE)

The summary of pairwise comparisons of attribute importance across DCE studies is presented in Table 2, with additional details and calculated relative importance of attributes in Supplementary Table 3. For each pairwise comparison in Table 2, the attribute that was preferred most often is listed in each cell, along with the ratio of the number of times it was preferred over the total number of times those 2 attributes were compared across all studies. While the DCE studies were heterogeneous in their attributes and levels, some overall trends can be observed. Treatment benefits were often more important than both serious and non-serious adverse events across the ranges of levels considered in the studies. In particular, symptom/functional improvement was rated as more important than serious but rare AE in 5 of 8 studies (Table 2). Serious but rare AE were more important than more common, but less serious 'nuisance' side effects in 5 of 6 studies (2 ties). Cancer in particular, even when described as a 'theoretical risk' was often the most important AE (14, 16, 17). In the only study in patients with early RA, treatment benefits were the most important attribute (14).

Dosing and administration considerations were typically less important than benefits, but again this varied across studies (Table 2 and Supplementary Table 3). The route and

frequency were often more important than adverse events, both serious and non-serious. Most studies that included cost found that patients would be willing to pay at least $100 USD/month for the most desirable treatment attributes including treatment benefits or avoiding side effects.

Standard gamble, time-trade-off, visual analogue scale

Three studies measured the absolute importance of health states on a 0 (death) to 1 (full health) scale using a standard gamble, time-trade-off or visual analogue scale (Table 3). Chiou et. al. found ACR50 and ACR70 responses were similar in importance and considerably higher than ACR20 response, which would support the use of the former in outcome evaluation in RA trials (18). The greatest distinction in side effects was between 'severe' and 'moderate' with relatively little difference between moderate and mild (Table 3). Ferraz et. al. found patients were risk-tolerant and valued the described benefits of 15 mg prednisone (well controlled disease but a high risk of side effects) considerably more than treatments with no prednisone (severe disease but no risk of side effects) (19). Suarez-Almazor et. al. found mild arthritis had relatively little loss in utility compared to severe arthritis (20). From a measurement perspective, both Ferraz and Suarez-Almazor had considerably lower values when using a VAS versus other utility-based methods (20, 21), which is consistent with the broader literature.(22)

Willingness to pay (WTP)

Two studies valued various health states directly using the WTP approach (Table 3). Slothuus et. al. found patients were willing to pay approximately 3X their current

monthly drug expenditure for a treatment with anti-TNF properties (maximal improvement and small risk of mild infection) (23, 24). Tuominen et. al. found that the severity of AM stiffness (which is not commonly measured in trials) was approximately 1.5X more important than its duration (25).

Willingness to accept risk

Three studies measured patient's willingness to accept risk used very different approaches and had quite different findings (Table 3). Fraenkel et. al. found many patients with established RA were completely unwilling to accept even very rare (1/1000, or 1/100,000) risks associated with DMARD therapy for a beneficial treatment (26, 27). Similarly, Ho et. al. found patients were very unwilling to accept even a small risk of death for improvement in arthritis symptoms (28). In contrast, O'Brien et. al. found patients were willing to accept a considerable risk of death for specific health benefits, which was highest for relief of pain (29). The quality of these later 2 studies was, however, rated as low (Supplementary Table 2).

Other studies

The remainder of studies utilized other rating or ranking methods to assess patient preferences for different modes of administration, treatment outcomes, or treatment options (Table 4). In 3 of the 5 studies examining patients preferred route of delivery, more patients preferred subcutaneous over intravenous therapy, although 2 of these found 22% and 21% of patients expressed no preference (30, 31). The final study found preferences to be split (50%) between subcutaneous (SC) and intravenous (IV) (32).

In the studies that evaluated the importance of treatment outcomes, reduction in pain and improvement in function (particularly hand/finger function and walking) and fatigue were consistently identified as highly important (33-35). An additional study identified 'being dependent on others' as the worst-case scenario for patients (36). In the RA-Patient Priorities for Pharmacologic Intervention (RA-PPI) questionnaire, developed through an iterative process, the 6 most important outcomes to evaluate when assessing treatment efficacy were: pain, activities of daily living, joint damage, mobility, life enjoyment, independence, fatigue, and valued activities (35).

Finally, 2 studies assessed patient preferences for different treatment options in the context of guidelines (37), or a randomized trial (15), Fraenkel et. al. trained a patient panel in the GRADE approach for developing recommendations (37). In 3/16 recommendations, the patient panel recommended a different treatment than the traditional physician-dominated panel, due to differences in how patients valued treatment attribute trade-offs. Patients were generally more willing to prefer the treatment with the highest chance of benefit. Similarly, in a post-hoc study of patients with early RA from the BeST trial, more patients expressed a preference to be randomized to the methotrexate and infliximab arm (with the higher perceived chance of benefit) than the other trial arms. Patients also expressed a preference not to be randomized to the arm with corticosteroids (15). Finally, Van Overbeeke et. al. found most patients (60%) expressed no preference and trusted their physician for the decision whether to start a biosimilar or originator biologic DMARD (38).

Associations Between Patient Characteristics and Treatment Preferences

The observed associations between patient characteristics and preferences across studies are summarized in Supplementary Table 4. Overall, sociodemographic variables including age, education, ethnicity, and income were found to be associated with preferences more frequently than variables related to RA disease severity or treatment history. Two studies found younger RA patients placed higher importance on treatment benefits (39, 40) and 3 studies found more educated RA patients were more risk tolerant and preferred more intense treatments (14, 41, 42). In 2 of 3 studies that examined an association between income and preferences, higher incomes were associated with greater risk tolerance.(14, 41, 42) Both studies that explored an association between ethnicity and risk tolerance found greater risk aversion in black patients compared to non-black patients (41) and black patients compared to white patients (42).

DISCUSSION

This systematic review identified 36 studies that used various methods to investigate patient preferences for RA therapy and treatment outcomes. Amongst studies that compared treatment attributes, the benefits of treatment were generally more important than most risks. However, some studies found patients to be quite risk averse and there was important variability in preferences. Taken together, these results support current intensive treatment strategies, but highlight the critical need to individualize treatment decision-making. For guideline developers, it suggests that many decisions may be preference sensitive. Under the GRADE approach, this would mean that for these

treatment decisions, a conditional, rather than a strong recommendation may be more appropriate (3). Decision tools linked to these recommendations would then be encouraged to support shared decision-making, which has been shown to improve decision-making quality (43), and may also improve adherence (44).

When grading the strength of treatment recommendations, guideline developers require an understanding of the relative importance of treatment outcomes and other attributes. With this in mind, we believe there are some general statements that are supported by the evidence:

- Treatment benefits were usually more important than adverse events, but not always. In particular, some studies in patients with established RA, found patients to be quite risk averse.
- Serious but rare AE, including a hypothetical risk of cancer, were usually more important than more common but less serious AE.
- Dosing regimens and monitoring requirements with therapy were generally less important than the benefits of treatment.
- Patient preferences were variable and frequently associated with sociodemographic characteristics.

RA treatment approaches have moved towards a treat-to-target paradigm, with treatment escalation recommended until patients are in remission, or if not possible, low disease activity (45-47). Implicit in this recommendation is that patients generally value the benefits of improved disease control more than any risks or undesirable aspects of

treatment escalation. Overall, our findings support this, but with some caveats. Several studies showed that patients with established RA place a high importance of avoiding rare but serious AE. These patients may prefer to maintain on their current treatment rather than escalate therapy in the setting of active disease that is well tolerated. This is recognized in guidelines, which support that a less intensive treatment target, such as low disease activity, for some patients with established disease (45-47). It is critical, however, that patients adequately understand both the risks of treatment and the risks of active disease. A reluctance to escalate treatment may be related to a misunderstanding of risks, particularly rare AE, which are difficult for patients to understand (48). Although the evidence was not robust, three studies suggested patients with early RA are relatively risk tolerant and would prefer early intensive treatment approaches with the greatest chance of benefit (45-47). This may suggest that patients' preferences change over time, as patients adapt to their condition, which is supported by qualitative research (49). It is also possible that patients with early RA in the studies were less well-informed of the risks and benefits of treatment. Longitudinal studies could help clarify this.

The above conclusions must keep in mind the limitations of the available evidence. Several studies were judged to be of low or moderate quality, and the majority of the studies were in patients with established RA. The studies were often conducted in academic centres. Patients without access to these centres, including marginalized patient populations, may therefore be underrepresented. The majority of the studies were also industry funded, which may have introduced bias. Most of the studies included patients

currently on RA treatment and as such, are not reflective of the preferences of people who refuse or discontinue DMARD therapy.

Strengths of our review include the registered protocol, comprehensive search terms and quality assessment, although the later 2 are also sources of potential limitations. Systematic reviews of patient preferences are quite new. We were over-inclusive with our search terms, but it is possible we missed relevant studies. A search filter for patient preference studies has recently been proposed and is in the process of being validated (50). Similarly, the quality assessment of patient preference studies is not as well standardized as with other types of evidence. A recent systematic review identified 6 different quality rating systems, including the one we used (51). Summarizing findings across studies is also challenging, given the study heterogeneity. We were careful in considering the study context in the interpretation of our findings, but it is possible others may have a somewhat different interpretation of the same evidence. Qualitative studies were also excluded; they may provide a better understanding of patient preferences but are even more challenging to summarize.

To the best of our knowledge, this is the first systematic review on patient preferences for DMARD treatment in RA. The results highlight the variability in preferences between patients, providing further rationale for efforts to promote shared decision-making. For guideline developers, our review provides evidence to inform the risk/benefit trade-offs that are required when developing and grading treatment recommendations. Guideline developers using our findings should judge whether the available evidence on patient

preferences is sufficient to understand the balance of benefits and harms for their target patient population. If not, further research should be prioritized. It is hoped that this work can help inform the risk benefit trade-offs required when deciding between RA treatments.

REFERENCES

1. Elwyn G, Frosch D, Thomson R, Joseph-Williams N, Lloyd A, Kinnersley P, et al. Shared decision making: a model for clinical practice. J Gen Intern Med. 2012;27:1361-7.
2. Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66:726-35.
3. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol. 2013;66:719-25.
4. Ryan M, Scott DA, Reeves C, Bate A, van Teijlingen ER, Russell EM, et al. Eliciting public preferences for healthcare: a systematic review of techniques. Health technology assessment (Winchester, England). 2001;5:1-186.
5. Hazlewood G. Measuring patient preferences: An overview of methods with a focus on discrete-choice experiments. Rheumatic Disease Clinics of North America. 2018;[in press].
6. Froberg DG, Kane RL. Methodology for measuring health-state preferences--II: Scaling methods. J Clin Epidemiol. 1989;42:459-71.
7. Bridges JFP. Stated preference methods in health care evaluation: an emerging methodological paradigm in health economics. Appl Health Econ Health Policy. 2003;2:213-24.
8. van den Bemt BJ, van Lankveld WG. How can we improve adherence to therapy by patients with rheumatoid arthritis? Nat Clin Pract Rheumatol. 2007;3:681.
9. Barton JL. Patient preferences and satisfaction in the treatment of rheumatoid arthritis with biologic therapy. Patient Prefer Adherence. 2009;3:335-44.
10. Medical Subject Headings (MeSH) [database on the Internet]. US National Library of Medicine. 2018 [cited 3 Apr 2018]. Available from: https://meshb.nlm.nih.gov/record/ui?ui=D057240.
11. Hazlewood GS, Barnabe C, Tomlinson G, Marshall D, Devoe DJ, Bombardier C. Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis: A network meta-analysis. Cochrane Database Syst Rev. 2016:CD010227.
12. Purnell TS, Joy S, Little E, Bridges JF, Maruthur N. Patient preferences for noninsulin diabetes medications: a systematic review. Diabetes care. 2014;37:2055-62.
13. Eiring O, Landmark BF, Aas E, Salkeld G, Nylenna M, Nytroen K. What matters to patients? A systematic review of preferences for medication-associated outcomes in mental disorders. BMJ open. 2015;5:e007848.

14. Hazlewood GS, Bombardier C, Tomlinson G, Thorne C, Bykerk VP, Thompson A, et al. Treatment preferences of patients with early rheumatoid arthritis: a discrete-choice experiment. Rheumatology (Oxford). 2016;55:1959-68.
15. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, Kerstens PJ, Grillet BA, de Jager MH, et al. Patient preferences for treatment: report from a randomised comparison of treatment strategies in early rheumatoid arthritis (BeSt trial). Ann Rheum Dis. 2007;66:1227-32.
16. Constantinescu F, Goucher S, Weinstein A, Smith W, Fraenkel L. Understanding why rheumatoid arthritis patient treatment preferences differ by race. Arthritis Rheum. 2009;61:413-8.
17. Fraenkel L, Bogardus S, Concato J, Felson D, Wittink D. Patient preferences for treatment of rheumatoid arthritis. Ann Rheum Dis. 2004;63:1372-8.
18. Chiou CF, Weisman M, Sherbourne CD, Reyes C, Dylan M, Ofman J, et al. Measuring preference weights for American college of rheumatology response criteria for patients with rheumatoid arthritis. J Rheumatol. 2005;32:2326-9.
19. Ferraz MB, Quaresma MR, Goldsmith CH, Bennett K, Atra E. Corticosteroids in patients with rheumatoid arthritis: utility measurements for evaluating risks and benefits. Rev Rhum Engl Fr. 1994;61:240-44.
20. Suarez-Almazor ME, Conner-Spady B. Rating of arthritis health states by patients, physicians, and the general public. Implications for cost-utility analyses. J Rheumatol. 2001;28:648-56.
21. Ferraz MB, Quaresma MR, Goldsmith CH, Bennett K, Atra E. [Estimation of benefits and risks of the treatment of rheumatoid polyarthritis with glucocorticoids using the health-related quality of life measurements]. Rev Rhum Ed Fr. 1994;61:255-9.
22. Dolan P, Sutton M. Mapping visual analogue scale health state valuations onto standard gamble and time trade-off values. Soc Sci Med. 1997;44:1519-30.
23. Slothuus U, Brooks RG. Willingness to pay in arthritis: a Danish contribution. Rheumatology (Oxford). 2000;39:791-9.
24. Slothuus U, Larsen ML, Junker P. Willingness to pay for arthritis symptom alleviation. Comparison of closed-ended questions with and without follow-up. International journal of technology assessment in health care. 2000;16:60-72.
25. Tuominen R, Tuominen S, Mottonen T. How much is a reduction in morning stiffness worth to patients with rheumatoid arthritis? Scand J Rheumatol Suppl. 2011;125:12-6.
26. Fraenkel L, Bogardus S, Concato J, Felson D. Unwillingness of rheumatoid arthritis patients to risk adverse effects. Rheumatology (Oxford). 2002;41:253-61.
27. Fraenkel L, Bogardus S, Concato J, Felson D. Risk communication in rheumatoid arthritis. J Rheumatol. 2003;30:443-8.

28. Ho M, Lavery B, Pullar T. The risk of treatment. A study of rheumatoid arthritis patients' attitudes. Br J Rheumatol. 1998;37:459-60.
29. O'Brien BJ, Elswood J, Calin A. Willingness to accept risk in the treatment of rheumatic disease. J Epidemiol Community Health. 1990;44:249-52.
30. Bolge SC, Goren A, Brown D, Ginsberg S, Allen I. Openness to and preference for attributes of biologic therapy prior to initiation among patients with rheumatoid arthritis: patient and rheumatologist perspectives and implications for decision making. Patient Prefer Adherence. 2016;10:1079-90.
31. Navarro-Millan I, Herrinton LJ, Chen L, Harrold L, Liu L, Curtis JR. Comparative Effectiveness of Etanercept and Adalimumab in Patient Reported Outcomes and Injection-Related Tolerability. PloS one. 2016;11:e0149781.
32. Scarpato S, Antivalle M, Favalli EG, Nacci F, Frigelli S, Bartoli F, et al. Patient preferences in the choice of anti-TNF therapies in rheumatoid arthritis. Results from a questionnaire survey (RIVIERA study). Rheumatology (Oxford). 2010;49:289-94.
33. da Silva JA, Ramiro S, Pedro S, Rodrigues A, Vasconcelos JC, Benito-Garcia E. Patients- and physicians- priorities for improvement. The case of rheumatic diseases. Acta Reumatol Port. 2010;35:192-9.
34. Heiberg T, Kvien TK. Preferences for improved health examined in 1,024 patients with rheumatoid arthritis: pain has highest priority. Arthritis Rheum. 2002;47:391-7.
35. Sanderson T, Morris M, Calnan M, Richards P, Hewlett S. Patient perspective of measuring treatment efficacy: the rheumatoid arthritis patient priorities for pharmacologic interventions outcomes. Arthritis Care Res (Hoboken). 2010;62:647-56.
36. Buitinga L, Braakman-Jansen LM, Taal E, van de Laar MA. Worst-case future scenarios of patients with rheumatoid arthritis: a cross-sectional study. Rheumatology (Oxford). 2012;51:2027-33.
37. Fraenkel L, Miller AS, Clayton K, Crow-Hercher R, Hazel S, Johnson B, et al. When Patients Write the Guidelines: Patient Panel Recommendations for the Treatment of Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2016;68:26-35.
38. van Overbeeke E, De Beleyr B, de Hoon J, Westhovens R, Huys I. Perception of Originator Biologics and Biosimilars: A Survey Among Belgian Rheumatoid Arthritis Patients and Rheumatologists. BioDrugs. 2017;31:447-59.
39. Skjoldborg US, Lauridsen J, Junker P. Reliability of the discrete choice experiment at the input and output level in patients with rheumatoid arthritis. Value Health. 2009;12:153-8.
40. Augustovski F, Beratarrechea A, Irazola V, Rubinstein F, Tesolin P, Gonzalez J, et al. Patient preferences for biologic agents in rheumatoid arthritis: a discrete-choice experiment. Value Health. 2013;16:385-93.
41. Fraenkel L, Cunningham M, Peters E. Subjective numeracy and preference to stay with the status quo. Med Decis Making. 2015;35:6-11.

42. Constantinescu F, Goucher S, Weinstein A, Fraenkel L. Racial disparities in treatment preferences for rheumatoid arthritis. Med Care. 2009;47:350-5.
43. Stacey D, Legare F, Col NF, Bennett CL, Barry MJ, Eden KB, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev. 2014;1:CD001431.
44. Lofland JH, Johnson PT, Ingham MP, Rosemas SC, White JC, Ellis L. Shared decision-making for biologic treatment of autoimmune disease: influence on adherence, persistence, satisfaction, and health care costs. Patient Prefer Adherence. 2017;11:947-58.
45. Bykerk VP, Akhavan P, Hazlewood GS, Schieir O, Dooley A, Haraoui B, et al. Canadian Rheumatology Association recommendations for pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs. J Rheumatol. 2012;39:1559-82.
46. Singh JA, Saag KG, Bridges SL, Jr., Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis & rheumatology. 2016;68:1-26.
47. Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017;76:960-77.
48. Paling J. Strategies to help patients understand risks. BMJ. 2003;327:745-8.
49. Goodacre LJ, Goodacre JA. Factors influencing the beliefs of patients with rheumatoid arthritis regarding disease-modifying medication. Rheumatology (Oxford). 2004;43:583-6.
50. Selva A, Sola I, Zhang Y, Pardo-Hernandez H, Haynes RB, Martinez Garcia L, et al. Development and use of a content search strategy for retrieving studies on patients' views and preferences. Health Qual Life Outcomes. 2017;15:126.
51. Yepes-Nunez JJ, Zhang Y, Xie F, Alonso-Coello P, Selva A, Schunemann H, et al. Forty-two systematic reviews generated 23 items for assessing the risk of bias in values and preferences' studies. J Clin Epidemiol. 2017;85:21-31.
52. Fraenkel L, Nowell WB, Michel G, Wiedmeyer C. Preference phenotypes to facilitate shared decision-making in rheumatoid arthritis. Ann Rheum Dis. 2017.
53. 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;37:1423-34.
54. Alten R, Kruger K, Rellecke J, Schiffner-Rohe J, Behmer O, Schiffhorst G, et al. Examining patient preferences in the treatment of rheumatoid arthritis using a discrete-choice approach. Patient Prefer Adherence. 2016;10:2217-28.

55. Hazlewood GS, Bombardier C, Tomlinson G, Marshall D. A Bayesian model that jointly considers comparative effectiveness research and patients' preferences may help inform GRADE recommendations: an application to rheumatoid arthritis treatment recommendations. J Clin Epidemiol. 2018;93:56-65.
56. Louder AM, Singh A, Saverno K, Cappelleri JC, Aten AJ, Koenig AS, et al. Patient Preferences Regarding Rheumatoid Arthritis Therapies: A Conjoint Analysis. Am Health Drug Benefits. 2016;9:84-93.
57. Nolla JM, Rodriguez M, Martin-Mola E, Raya E, Ibero I, Nocea G, et al. 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.
58. Poulos C, Hauber AB, Gonzalez JM, Turpcu A. Patients' willingness to trade off between the duration and frequency of rheumatoid arthritis treatments. Arthritis Care Res (Hoboken). 2014;66:1008-15.
59. Ozdemir S, Johnson FR, Hauber AB. Hypothetical bias, cheap talk, and stated willingness to pay for health care. J Health Econ. 2009;28:894-901.
60. Bacalao EJ, Greene GJ, Beaumont JL, Eisenstein A, Muftic A, Mandelin AM, et al. Standardizing and personalizing the treat to target (T2T) approach for rheumatoid arthritis using the Patient-Reported Outcomes Measurement Information System (PROMIS): baseline findings on patient-centered treatment priorities. Clin Rheumatol. 2017;36:1729-36.
61. van Tuyl LH, Sadlonova M, Hewlett S, Davis B, Flurey C, Goel N, 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;76:855-61.
62. Desplats M, Pascart T, Jelin G, Norberciak L, Philippe P, Houvenagel E, et al. Are abatacept and tocilizumab intravenous users willing to switch for the subcutaneous route of administration? A questionnaire-based study. Clin Rheumatol. 2017;36:1395-400.
63. Huynh TK, Ostergaard A, Egsmose C, Madsen OR. Preferences of patients and health professionals for route and frequency of administration of biologic agents in the treatment of rheumatoid arthritis. Patient Prefer Adherence. 2014;8:93-9.
64. Martin RW, Enck RD, Tellinghuisen DJ, Eggebeen AT, Birmingham JD, Head AJ. Comparison of the Effects of a Pharmaceutical Industry Decision Guide and Decision Aids on Patient Choice to Intensify Therapy in Rheumatoid Arthritis. Med Decis Making. 2017;37:577-88.
65. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum. 2005;52:3381-90.

FIGURE LEGENDS

Figure 1. Flowchart of literature search results

Table 1: Characteristics of included studies

Study ID	Setting	N	Patient characteristics (median/mean)	Treatments of interest	Patient experience with Rx of interest	Funding
Discrete Choice Experiments						
Fraenkel 2017 (52)	Online panel (self-reported RA), USA	1101	Age: 51 years Female: 90% Years RA: NR	csDMARDs, bDMARDs, tofacitinib	NR (all on at least 1 DMARD)	Public
Husni 2017 (53)	Patient registry, USA	510	Age: 56 years Female: 65% Years RA: 43% > 10 years	csDMARDs, bDMARDs, tofacitinib	45% prior bDMARD	Industry
Alten 2016 (54)	Outpatient clinics, Germany	1588	Age: 48% > 60 years Female: 74% Years RA: 44% > 10 years	bDMARDs and tofacitinib	NR (all on at least 1 DMARD)	Industry
Hazlewood 2016 (14, 55)	Outpatient clinics, Canada	152	Age: 53 years Female: 63% Years RA: 0.7	csDMARDs, anti-TNF	97% csDMARD, 5% bDMARDs	Public

Louder 2016 (56)	Insurance database, USA	380	Age: 55 years Female: 82% Years RA: 9	bDMARDs and tofacitinib	Naïve	Industry
Nolla 2016 (57)	Outpatient clinics, Spain	165	Age: 56 years Female: 74% Years RA: 13	bDMARDs	100% currently taking bDMARDs	Industry
Fraenkel 2015 (41)	Outpatient clinics, USA	156	Age: 59 Female: 85% Years RA: 9	bDMARDs	48% currently taking bDMARD	Public
Poulos 2014 (58)	Online panel (self-reported RA), USA	849	Age: 61% ≥ 55 years Female: 74% Years RA: NR	bDMARDs	NR (34% prior SC, 30% prior IV)	Industry
Augustovski 2013 (40)	Outpatient clinics, Argentina	240	Age: 56 years Female: 87% Years RA: 9	bDMARDs	Naïve	Industry
Constantinescu 2009 (16, 42)	Outpatient clinics, USA	136	Age: 55 years Female: 83% Years RA: 8	Methotrexate, bDMARDs	Median DMARDs: 2	Public

Ozdemir 2009 (59)	Online panel (self-reported RA), USA	463	Age: 53 years Female: 64% Years RA: 8	bDMARDs	16% receive SC or IV	Public
Skjoldborg 2009 (39)	Outpatient clinic, Denmark	178	NR	Anti-TNF	Prior treatment not reported	Public
Fraenkel 2004 (17)	Outpatient clinics, USA	120	Age: 70 years Female: 76% Years RA: 8	csDMARDs, etanercept	60% currently using a DMARD	Public
Standard gamble (SG), time trade-off (TTO), visual analogue scale (VAS)						
Chiou 2005 (18)	Outpatient clinics, USA	484	Age: 59 years Female: 79% Years RA: 13	No specific Rx*	Prior treatment not reported	Industry
Suarez-Almazor 2001 (20)	Outpatient clinics, Canada	51	Age: 60 years Female: 72% Years RA: NR	No specific Rx*	Prior treatment not reported	NR
Ferraz 1994 (19)	Outpatient clinic, Brazil	25	Age (range): 34-70 years Female: 20% Years RA: 8	Prednisone	95% ever taken steroids	NR

Willingness to pay						
Tuominen 2011 (25)	Patient registry, Finland	166	Age: 64 years Female: 69% Years RA: NR	No specific Rx*	Prior treatment not reported	Partial industry
Slothuus 2000 (23, 24)	Outpatient clinic, Denmark	115	Age: 56 years Female: 71% Years RA: 15	Anti-TNF (infliximab)	Naïve	NR
Willingness to accept risk						
Fraenkel 2002 (26, 27)	Outpatient clinics, USA	100	Age: 68 years Female: 73% Years RA: NR	NSAIDs, prednisone, csDMARDs	Current use: 39% NSAIDs; 68% prednisone; 81% csDMARDs	Public
Ho 1998 (28)	Outpatient clinic, UK	67	Age: 57 years Female: 73% Years RA: 10	No specific Rx*	Prior treatment not reported	Public
O'Brien 1990 (29)	Outpatient clinic and inpatients, UK	50	Age: 51 years Female: 84% Years RA: 13	No specific Rx*	Prior treatment not reported	Public

Rating or ranking of treatment outcomes						
Bacalao 2017 (60)	Outpatient clinic, USA	119	Age: 57 years Female: 91% Years RA: 11	No specific Rx*	Prior treatment not reported	Public and industry
van Tuyl 2017 (61)	Clinics and online panel in 5 countries	274	Age: 57 years Female: 75% Years RA: 12	No specific Rx*	Prior treatment not reported	Public
Buitinga 2012 (36)	Outpatient clinic, Netherlands	74	Age: 58 years Female: 62% Years RA: 7	No specific Rx*	Current use: 70% csDMARDs; 30% bDMARD	Public
Sanderson 2010 (35)	Mix outpatient clinics and registries, UK	254	Age: 61% > 60 years Female: 76% Years RA: 76% > 5	No specific Rx*	Current use: 52% csDMARD; 39% bDMARD	Public
Da Silva 2010 (33)	Outpatient clinics (self-reported RA), Portugal	667	NR	No specific Rx*	Prior treatment not reported	Public
Heiberg 2002 (34)	Patient registry, Norway	1024	Age: 63 years Female: 79% Years RA: 13	No specific Rx*	Prior treatment not reported	Public

Preference for different routes of delivery						
Desplats 2017 (62)	Outpatient clinics, France	201	Age: 58 years Female: 81% Years RA: 17	bDMARDs	100% on IV bDMARDs (ABA or TCZ)	Industry
Bolge 2016 (30)	Online panel (self-reported RA), USA	243	Age: 53 years Female: 85% Years RA: 13	bDMARDs	Naïve	Industry
Navarro-Millan 2016 (31)	Patient registry, USA	242	Age: 54 years Female: 73% Years RA: 8	Anti-TNF	100% currently taking anti-TNF	Public
Huynh 2014 (63)	Outpatient clinics, Denmark	142	Age: 57 years Female: 77% Years RA: NR	bDMARDs	75% taking bDMARD, 25% bDMARD naïve	Industry
Scarpato 2010 (32)	Outpatient clinics, Italy	802	Age: 56 years Female: 77% Years RA: 9	Anti-TNF	Naïve	Industry
Preference for different treatment options						

Martin 2017 (64)	Outpatient clinic, USA	402	Age: 64 years Female: 67% Years RA: 10.4	Etanercept	Biologic naïve	Public and industry***
Van Overbeeke 2017 (38)	Broad recruitment including social media, Belgium	121	Age: 57% 40-60 years Female: 87% Years RA: NR	bDMARDs and biosimilars	55% prior DMARD, all naïve to biosimilars	Public
Fraenkel 2016 (37)	Patient panel, USA	10	Age: 38 years Female: 70% Years RA: 11	All DMARDs	Current use: 40% csDMARD only; 60% bDMARD	Public
Goekoop-Ruiterman 2007 (15)	Patients enrolled in BeST RCT(65)	440	Age: 55 years Female: 68% Years RA: 0.4 (at entry of BeST)	4-arms of BeST**	All patients exposed to one of 4 trial arms	Industry

*These studies valued health states relevant to DMARD treatment decisions, without a specific DMARD of interest. **The 4 arms of the BeST trial were (1) Sequential csDMARD monotherapy; (2) Step-up csDMARD combination therapy; (3) Initial csDMARD combination therapy with prednisone; (4) Initial combination therapy with infliximab. ***In-kind contribution from industry, who provided decision aid booklets at no cost. RA: rheumatoid arthritis; NR: not reported; DMARD: disease-modifying antirheumatic drug; csDMARD: conventional synthetic DMARD; bDMARD: biological DMARD; anti-TNF: antitumor necrosis factor; SC:

subcutaneous; IV: intravenous; NSAID: nonsteroidal antiinflammatory drug; RCT: randomized controlled trial; ABA: abatacept; TCZ: tocilizumab.

Table 2: Relative importance of treatment attributes across discrete choice experiment studies

	Attribute ranked as most important (number of times ranked as most important/ total number of comparisons)							
	Benefits			**Dosing and administration**			**Adverse events (AE)**	
	Remission or low disease activity	Symptom or Functional Improvement	Avoid joint Damage	Onset or Duration of Effect	Route	Frequency	Serious	Non-Serious
Benefits								
Symptom or functional improvement	Remission 1/1	--						
Avoid joint damage	Remission 1/1	Improvement 2/3	--					
Administration								
Onset or duration of effect		Improvement 2/3	Onset 1/1	--				
Route (alone or combined with frequency)	Route 1/1	Improvement 7/9	Avoid JD 2/3	Route 4/5	--			

Frequency		Similar		Frequency	Route	--		
		2/4		1/1	3/5			
Adverse events (AE)								
Serious AE*	Remission	Improvement	Avoid JD	Serious AE	Route	Frequency	--	
	1/1	5/8, 1 tie	2/3	4/4, 1 tie	5/9, 2 ties	2/3, 2 ties		
Non-serious AE**	Remission	Improvement	Avoid JD	Non-serious	Route	Frequency	Serious	--
	1/1	6/8	2/3	2/3	5/8	3/3	5/6, 2 ties	
Cost ($USD/month)								
$50		Improvement		Onset	Route	Frequency	Serious	Non-serious
		4/5		1/1	4/4	3/3	3/3, 1 tie	4/4
$100		Improvement		Onset	Route	Neither	Serious	Similar
		3/4		1/1	3/3	1/2	2/2, 1 tie	2/4
$250		Improvement		Cost	Neither	Frequency	Neither	Cost
		2/3		1/1	1/2	1/1	1/2	2/3

*Serious AE: allergy, infection, abnormal labs (54); infection, possible risk of cancer (14); possible rare lung or liver reaction (14); serious side effects (56); high risk of adverse events (57); risk of TB, risk of neurological disease (41); immediate serious reaction (58); generalized AE, serious infection (40); tuberculosis, lung injury, extremely rare AE, possible increased risk cancer (16); serious

infection (59); nephrotoxicity, cancer, hepatotoxicity, pneumonitis (17); serious infection, very rare side effects (levels: stomach/ intestinal tear, neurological disease, permanent eye problems, brain infection (52); serious infection, cancer (53)

**Minor AE: side effect requiring medication to be stopped (14); risk of infection (0 to 20%) (41); risk of IV/SC reaction (41); immediate mild reaction (58); local AE (40); injection reaction, reversible AE (16); slightly higher risk minor infection (39); alopecia, oral ulcers, nausea/vomiting, injection site reaction, rash, diarrhea (17); bothersome side effects (52); abnormal lab results (53). JD: joint damage; SC: subcutaneous; IV: intravenous.

Table 3: Summary of uni-dimensional studies assessing the absolute importance of health states and outcomes

Study ID	Measure	Health states (ranked from most to least preferred)	Value	Summary
Standard gamble (SG), time-trade-off (TTO), visual analogue scale (VAS)				
Chiou 2005 (18)	VAS	ACR response (with no adverse events)		Biggest difference between ACR20 and ACR50 (ACR50/70 similar), and moderate and severe AE (mild/moderate similar)
		ACR70	0.84	
		ACR50	0.80	
		ACR20	0.68	
		Adverse events (and ACR50 response)		
		Mild (e.g. headache)	0.76	
		Moderate (e.g. URTI)	0.70	
		Severe (e.g. GI bleed)	0.53	
Suarez-Almazor 2001 (20)	SG, TTO, VAS	Mild (some problems walking, moderate pain)	0.95, 0.95, 0.75	Mild arthritis activity well tolerated as measured by SG/TTO. Large differences between VAS and other methods.
		Severe (problems with self-care, extreme pain)	0.82, 0.72, 0.42	
Ferraz 1994 (19)	TTO, VAS	15 mg prednisone (able to fulfil all duties, but high likelihood mod-severe side effects)	0.77, 0.73	Benefits of disease control more important than risk of side effects with 15 mg prednisone
		5 mg prednisone	0.68, 0.52	

		No prednisone (no side effects, but unable to fulfil most duties at home, work, ADLs)	0.44, 0.23	
Willingness to pay				
Tuominen 2011 (25)	Euro/day	Improvement in AM stiffness duration 50% 100% Improvement in AM stiffness severity 50% 100%	 8 17 11 24	Severity of morning stiffness ~ 1.5X more important than duration, but over a small range of costs
Slothuus 2000 (23, 24)	Danish Krone/month	'Maximal improvement' (morning stiffness to 5 min, pain to 1.9/10, swollen joints to 5/66) and small risk of mild infection	581-650 (83-93 USD)	Patients willing to pay ~3X their current drug expenditure (186 DKK/month) for a drug with properties of an anti-TNF agent
Willingness to accept risk				
Fraenkel 2002 (26, 27)	Proportion patients unwilling to accept 1/1000 risk of AE (for beneficial treatment)*	Major toxicity Temporary discomfort	60% (cancer) to 34% (hip fracture) 45% (severe N/V) to 30% (mild N/V)	Patients very risk averse. Results similar even when risk dropped to 1/100,000.(27)

		Cosmetic changes	37% (hirsutism) to 29% (acne)	
Ho 1998 (28)	Median maximum acceptable risk of mortality (log scale)	30% improvement in symptoms	$1/10^6$	Patients very unwilling to accept any risk of death
		No deterioration in symptoms	$1/10^6$	
O'Brien 1990 (29)	Mean acceptable risk of mortality	Relief of pain	23%	Relief of pain most important
		Relief of stiffness	20%	
		Return to normal functioning	15%	

*Assessed using a VAS that ranged from 0 (not willing under any circumstances) to 100 (definitely willing). ACR: American College of Rheumatology; URTI: upper respiratory tract infection; GI: gastrointestinal; AE: adverse events; ADL: activities of daily living; AM: morning; TNF: tumor necrosis factor; N/V: nausea/vomiting; VAS: visual analog scale.

Table 4: Other studies

Study ID	Measure	Health states	Summary
Rating or ranking of different routes of delivery			
Desplats 2017 (62)	Stated preference	Route (SC versus IV)	46% preferred to remain on IV therapy. Patients preferring SC were more likely to have experience with other SC treatments
Bolge 2016 (30)	Likert scale	Route (SC versus IV; frequency not specified)	More patients somewhat or strongly preferred SC (49%) than IV (29%), with 22% of patients expressing no preference
Navarro-Milan 2016 (31)	Stated preference	SC every 1-2 weeks versus IV every 8 weeks	More patients preferred SC (57%) over IV (22%), with 21% expressing no preference
Huynh 2014 (63)	Stated preference	Various options that differed in terms of route (SC vs IV) and frequency of administration	77% of biologic-naïve patients preferred SC. Amongst patients currently taking biologic therapy, strong preference for current route (71% taking SC preferred SC; 85% currently taking IV preferred IV).
Scarpato 2010 (32)	Stated preference	Route (SC versus IV; frequency not specified)	50% of patients preferred SC and 50% preferred IV
Rating or ranking of treatment outcomes			

Bacalao 2017 (60)	Ranking of importance of PROMIS domains on impact on quality of life	Pain, fatigue, depression, physical function, social function	In order of priority: Physical function (39%), pain (37%), fatigue (16%), social function (3%), depression (5%)
van Tuyl 2017 (61)	Rating of outcome importance	26 domains relevant to a definition of remission	Domains chosen as top 3 in importance: Pain (67%), fatigue (33%) and independence (19%)
Buitinga 2012 (36)	Percent of patients choosing health state as worst-case scenario	Being dependent on others No longer being able to walk Being dependent on medication Being extremely fatigued Being indifferent No longer being able to do any leisure activities	Twice as many participants chose 'being dependent on others' as the worst (35%), relative to other options (11 to 18%)
Sanderson 2010 (35)	Iterative process of item reduction, including ranking and Likert scales of outcome importance	32 potential outcomes initially identified in nominal groups	Patients top 6 priority outcomes for treatment were: pain, activities of daily living, joint damage, mobility, life enjoyment, independence, fatigue, valued activities

Da Silva 2010 (33)	AIMS2 question 60 (top 3 priorities for improvement)	12 different priorities for improvement*	The highest rated priorities for improvement were pain (selected as a top 3 priority area by 69%), hand/finger function (51%) and walking/bending (48%)
Heiberg 2002 (34)	AIMS2 question 60 (top 3 priorities for improvement)	12 different priorities for improvement*	The highest rated priorities for improvement were pain (selected as a top 3 priority area by 69%), hand/finger function (45%) and walking/bending (33%)
Preference for different treatment options			
Martin 2017 (64)	Decision aid (patients randomized to 3 different versions)	Hypothetical choice between added etanercept versus not. Patients instructed to assume RA had become 'more active than you want to tolerate'.	Percentage of patients who chose to add etanercept varied according to information received: 31% (Pharma pamphlet) versus 15% and 14% for short and long versions of a decision aid (P<0.001).
Van Overbeeke 2017 (38)	Stated preference	Stated preference for biosimilar if a) cheaper than originator; b) equal price	Most patients (~60%) expressed no preference and trusted physician; ~30% preferred originator and 10% preferred biosimilar if it was cheaper.
Fraenkel 2016 (37)	Judgement of strength/direction of GRADE recommendations by patient panel	18 recommendations for treatment of early or late RA with mild, moderate, or high disease activity with different combinations of DMARDs	Patients disagreed with physician-dominated panel on direction of recommendation for 3 recommendations (due to value placed on benefits/harms. All were for MTX/DMARD-naïve patients with mod-high disease activity:

			1) Patients preferred triple therapy over single therapy 2) Patients preferred 2/3 DMARDs over single DMARD 3) Patients preferred tofacitinib over methotrexate
Goekoop-Ruiterman 2007 (15)	Stated preference for randomization (post-hoc)	4 arms of the BeST trial: 1) sequential monotherapy; 2) step-up combination therapy; 3) initial combination therapy with high-dose prednisone; 4) initial combination therapy with infliximab	33% expressed preference for arm 4 (4-8% for other groups; 44% expressed no preference) 38% expressed preference NOT to be randomized to group 3 (1-6% for other groups; 46% expressed no aversion)

*The 12 priority areas for improvement considered in AIMS-2 question 60 are: mobility, walking/bending, hand/finger function, arm function, self-care, household tasks, social activity, support from family, arthritis pain, work, level of tension, mood. SC: subcutaneous; IV: intravenous; AIMS: Arthritis Impact Measurement Scales; PROMIS: Patient Reported Outcomes Measurement Information System; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; RA: rheumatoid arthritis; DMARD: disease-modifying antirheumatic drug; MTX: methotrexate.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. MEDLINE Search Strategy

1. exp arthritis, rheumatoid/
2. ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat* or reumat* or revmarthrit*) adj3 (arthrit* or artrit* or diseas* or condition* or nodule*)).tw.
3. or/1-2
4. qualitative stud*.tw.
5. exp Qualitative Research/
6. survey*.tw.
7. exp Data Collection/
8. questionnaire*.tw.
9. focus group*.tw.
10. conjoint analysis.tw.
11. discrete choice experiment*.tw.
12. rating task*.tw.
13. ranking task*.tw.
14. choice experiment*.tw.
15. decision aid*.tw.
16. risk attitude*.tw.
17. risk aversion.tw.
18. discrete choice*.tw.
19. standard gamble.tw.
20. willingness to pay.tw.
21. willingness-to-pay.tw.
22. decision support technique*.tw.
23. decision support system*.tw.
24. decision making.tw.
25. time trade*.tw.
26. exp Questionnaires/
27. trade off*.tw.
28. stated preference*.tw.
29. contingent valuation.tw.
30. choice experiment.tw.
31. or/4-30

32. exp Consumer Satisfaction/
33. exp Consumer Participation/
34. exp Patient Satisfaction/
35. patient perspective*.tw.
36. exp "Attitude of Health Personnel"/
37. exp Health Knowledge, Attitudes, Practice/
38. exp "Delivery of Health Care"/
39. patient compliance.tw.
40. patient participation.tw.
41. patient satisfaction.tw.
42. treatment refusal.tw.
43. patient preference*.tw.
44. patient opinion*.tw.
45. patient belief*.tw.
46. patient concern*.tw.
47. patient perspective*.tw.
48. patient choice*.tw.
49. patient value*.tw.
50. patient priorit*.tw.
51. exp Health Priorities/
52. patient perception*.tw.
53. choice behavio*.tw.
54. patient consensus.tw.
55. exp Consensus/
56. (dissent and dispute*).tw.
57. uncertaint*.tw.
58. (utility or utilities).ti,ab.
59. discrete choice*.tw.
60. ((patient$ or participant$) adj3 (participation or satisfaction or perspective$ or compliance or preference$ or opinion$ or belief$ or concern$ or choice$ or value$ or priorit$ or perception$ or request$)).tw.
61. or/32-60
62. 3 and 31 and 61
63. exp animals/ not humans.sh.
64. 62 not 63

Supplementary Table 2. Study quality assessment

Study ID	Was the patient population representative of patients with RA? (external validity)	Did the task(s) appropriately represent the choice being evaluated? (quality of construct representation)	Did participants understand the tasks as intended? (construct-irrelevant variance)	Was the data complete and analyzed appropriately? (quality of reporting and analysis)	Other	Overall study quality
Alten 2016(54)	High	High	Moderate	High	No difference	High
Augustovski 2013(40)	High	Medium	High	High	Strengthen	High
Bacalao 2017(60)	Medium	High	High	High	No difference	High
Bolge 2016(30)	Low	Medium	Low	High	No difference	Low
Buitinga 2012(36)	Medium	High	High	High	No difference	High
Chiou 2005(18)	Medium	Medium	Moderate	High	No difference	Medium
Constantinescu 2009(16, 42)	High	Medium	Moderate	High	No difference	Medium
Da Silva 2010(33)	High	High	High	High	No difference	High
Desplats 2017(62)	High	Medium	Moderate	High	No difference	Medium
Ferraz 1994(19)	Low	Low	Low	High	No difference	Low
Fraenkel 2002(26, 27)	Medium	Medium	Moderate	High	No difference	Medium
Fraenkel 2004(17)	Medium	Medium	Moderate	High	No difference	Medium
Fraenkel 2015(41)	High	Medium	Moderate	High	No difference	High
Fraenkel 2016(37)	Low	High	High	High	No difference	Medium
Fraenkel 2017(52)	Medium	Medium	Moderate	Medium	No difference	Medium
Goekoop-Ruiterman 2007(15)	High	Medium	Moderate	High	No difference	Medium
Hazlewood 2016(14, 55)	High	Medium	High	High	Strengthen	High
Heiberg 2002(34)	Medium	High	High	High	No difference	High
Ho 1998(28)	Medium	Low	Low	Low	Weaken	Low
Husni 2017(53)	Medium	Medium	Moderate	High	No difference	Medium
Huynh 2014(63)	Medium	High	High	High	No difference	Medium
Louder 2016(56)	Low	Medium	High	High	Weaken	Low
Martin 2017(64)	Medium	Medium	Moderate	Medium	No difference	Medium
Navarro-Millan 2016(31)	Medium	High	High	High	No difference	Medium
Nolla 2016(57)	Medium	Medium	Moderate	High	No difference	Medium
O'Brien 1990(29)	Low	Medium	Moderate	High	No difference	Low

Ozdemir 2009(59)	Medium	Low	High	High	No difference	Medium
Poulos 2014(58)	Low	Medium	High	High	No difference	Medium
Sanderson 2010(35)	High	High	High	High	No difference	High
Scarpato 2010(32)	High	High	High	High	No difference	High
Skjoldborg 2009(39)	Medium	Low	Low	High	Strengthen	Medium
Slothuus 2000(23, 24)	Medium	Medium	High	High	Strengthen	Medium
Suarez-Almazor 2001(20)	Medium	High	High	High	Strengthen	High
Tuominen 2011(25)	High	Medium	Moderate	Medium	Weaken	Medium
Van Overbeeke 2017(38)	Low	High	Moderate	High	No difference	Medium
van Tuyl 2017(61)	High	High	High	High	No difference	High

Supplementary Table 3. Relative importance of treatment attributes from Discrete Choice Experiment studies

Study ID	Attributes	Levels (best to worst, from left to right)	Relative Importance	Summary
Fraenkel 2017(52)	Cost	Easy, somewhat, hard to afford	24.7	No benefits considered. Of the AE, bothersome side effects more important than rare or very rare AE.
	Bothersome side effects	0 to 30%	20.7	
	Very rare side effects	GI tear, neuro disease like MS, permanent eye problems, life-threatening brain infection	13.7	
	Onset of action	2 to 12 weeks	11.5	
	Serious infection	1 to 5%	11.0	
	Route of administration	Oral, SC, IV	10.7	
	Time on the market	27 to 3 years	7.8	
Husni 2017(53)	Improvement in physical function	0 to 60%	21.4	Treatment benefits most important
	Reduction in pain	0 to 75%	20.7	
	Reduction in number of swollen joints	0 to 75%	12.3	
	Route	Oral, SC, IV	10.6	
	Risk of cancer	0 to 2%	9.5	
	Monthly co-pay	$0 to $100	9.4	
	Dose frequency	Monthly, Q2W, daily	6.7	
	Abnormal lab results	10 to 30%	5.2	
	Risk of serious infection	0 to 4%	4.3	
Alten 2016(54)	Route of administration	Oral, SC, IV	31.6	Practical aspects of dosing (route of administration with order from best to worst: oral>SC>IV) more important than side effects (benefits not considered)
	Combination therapy with MTX	No, Yes	22.8	
	Frequency	Q12M to BID	19.2	
	Possible side effects	allergy, infection, abnormal labs	17.5	
	Onset of benefit	1 to 3 months	9.0	
Hazlewood 2016(14)	Major symptom improvement	70 to 30%	30.2	Treatment benefits most important (symptom improvement, avoiding joint damage). Patients wanted to avoid IV therapy, but other dosing options less important.
	Serious joint damage	2 to 30%	23.2	
	Dosing	SC vs IV (plus weekly pills)	10.9	
		Daily pills vs 5 non-IV options	7.3	
	Infection, possible risk of cancer	No, Yes	11.5	
	Stopping due to side effect	2 to 20%	7.3	
	Possible rare lung or liver reaction	No, Yes	6.0	

	Limit alcohol	No, Yes	2.4	
	Regular eye exams	No, Yes	1.2	
Louder 2016(56)	Route	SC vs IV	18.9	Dosing considerations more important than side effects and benefits (across the marginal range of benefits considered).
		Oral vs SC	15.2	
	Frequency	Q8W to twice daily	16.4	
	Serious side effects	4% to 8%	12.0	
	Monthly co-pay	$25 to $75 USD	10.1	
	Take with another DMARD	No, Yes	9.8	
	Reduction in joint pain/swelling	58% to 50%	8.9	
	Improvement in function	36% to 32%	8.8	
Nolla 2016(57)	Pain relief/ functional improvement	Yes, None	37.5	Benefits most important, although magnitude of benefit not well defined in survey.
	Risk of AE	Low, High	24.3	
	Route	SC vs IV	21.0	
	Duration of effect	4 to 1 weeks	17.2	
Poulos 2014(58)	Immediate serious reaction	1% to 25%	34.6	Serious infusion reactions most important across a very wide range levels (1 to 25%). Benefits more important than other considerations. Route (sc versus IV) least important.
	Medication working well	75% to 40%	24.2	
	Frequency	4 per year to Q2W	20.1	
	Time for infusion	0 (home) to 4 hours	13.0	
	Immediate mild reaction	1% to 25%	6.2	
	Route	SC vs IV	1.9	
Augustovski 2013(40)	Monthly co-pay	$0 to $1500 USD	21.9	Frequency and AE more important than benefit, but benefit considered relatively small. Patients wanted to avoid IV therapy, but little difference between SC and oral. Costs considered were over a wide range, as goal was to estimate willingness to pay.
	Generalized AE	0 to 30%	18.3	
	Frequency	Q10M to daily	16.9	
	Improvement in patient global	-40 to -20 mm on VAS	12.4	
	Route	SC vs IV	11.4	
		Oral vs SC	<0.1	
	Local AE	0 to 40%	10.9	
	Serious infection	1 to 5%	8.2	
Constantinescu 2009*(16, 42)	Remission	45 to 15%	13.4	Overall, treatment benefits more important than dosing and most AEs, except a ‘possible increased risk of cancer, which was of similar importance.
	No joint damage on x-rays	80 to 30%	12.6	
	Symptom improvement	70 to 40%	12.2	
	Rare, but serious AE (various: cancer, neurologic disease, TB, lung injury)	None to increased	6.5 (TB) to 11.9 (cancer)	
	Route	Oral, SC, IV	9.0	
	Injection reaction	0 to 30%	7.4	

	Reversible AE	0 to 10%	6.6	
Ozdemir 2009(59)**	Monthly co-pay	$50 to $1000	44.4	Benefits more important than harms and dosing, although wide range of levels for benefits considered. Costs considered were over a wide range, as goal was to estimate willingness to pay.
	Medication works well	100% to 25%	23.0	
	Dosing	5 sc and IV options	10.5	
	Serious infection	0% to 5%	9.1	
	Onset of effect	1 to 10 weeks	6.8	
	Duration of injection site irritation	15 min to 3 hrs	6.2	
Skjoldborg 2009(39)	Monthly co-pay	0 to 5000 DKK ($841 USD***)	78.8	Of benefits, reducing fatigue most important (twice as important as a large change in pain), but similar to slightly higher risk minor infection, suggesting patients quite risk averse.
	Feeling of being tired	Reduced, unchanged	8.8	
	Slightly higher risk minor infection	No, Yes	8.3	
	Pain level	0 to 10	3.6	
	Number swollen joints	0 to 25	0.3	
	Duration morning stiffness	0 to 120 min	<0.1	
Fraenkel 2004(17)	Less common, but serious AE (various: kidney, liver, cancer, lung)	None to increased	6.6 (kidney) to 7.8 (lung)	Common, reversible AE and less common but serious AE more important than treatment benefits.
	Common, but reversible AE (various: alopecia, oral ulcers, nausea, injection reaction, rash, diarrhea)	None to increased	5.0 (alopecia) to 7.6 (diarrhea)	
	Route	Oral vs SC vs IM	6.5	
	Drug onset	2 to 8 weeks	5.9	
	Monthly co-pay	Free to $30	5.8	
	Physician experience	Available >20 years, new	5.4	
	Chance of benefit	45 to 75% improvement	4.6	
	Bone erosions	60% to 75% do *not* get	4.0	

*Relative importance values are a weighted average of White and Black subgroups, which were reported separately in paper.
**Patient sample split into 2 groups, one of which received 'cheap-talk' text introducing the survey; these estimates from this sample are reported (n=233).
***conversion rate 2009: 1USD=5.95DKK

Supplementary Table 4. Association between patient characteristics and preferences.

The table summarizes the results of studies that examined a potential relationship between patient variables and preferences. The arrow indicates the direction of the effect, with a sideways arrow (↔) indicating the association was explored and found to not be statistically significant.

		Higher importance placed on				Risk tolerant: prefer more intensive Rx (higher benefit with higher AE)	Willingness to pay	
Characteristic	**Direction of effect**	**Treatment benefits**	**Adverse events**	**Treatment costs**	**Route (SC > IV)**		**Benefits**	**Avoid side effects**
Sociodemographics								
Age	Younger	↑↑↔ (17, 39, 40)	↔↔↔↔↔ (17, 26, 39, 40, 52)	↓↔↔↔ (17, 39, 40, 52)	↔↔↔↔↔ (17, 32, 40, 52, 63)	↔↔↔ (14, 41, 42)	↔ (59)	↓ (59)
Sex	Female	↔ (39)	↓↔↔ (26, 39, 52)	↑↔ (39)	↔↔ (32)	↔↔↔ (14, 41, 42)		
Marital status	Married		↔ (26)			↑↔ (41, 42)		
Number children	More	↔ (28)						
Smoking	Current	↔ (28)				↑ (14)		
Ethnicity	Black					↓↓ (41, 42)		
	Hispanic		↔ (52)	↔ (52)	↑ (52)	↔ (41)		
	Causcasian		↔ (52)	↔ (52)	↓ (52)			
Income	Higher	↔↔ (39, 40)	↔↔↔ (39, 40, 52)	↓↓↔ (39, 40, 52)	↔↔ (40, 52)	↑↑↔ (14, 41, 42)	↑ (59)	↑ (59)
Employment status	Employed	↑ (39)	↔↔↔ (26, 39)	↓↔ (39, 52)	↔ (52)	↑↔ (41, 42)		
Insurance coverage	Public (vs other)					↔ (42)		
Education	Higher		↔↔ (26, 52)	↔ (52)	↔↔ (26, 52)	↑↑↑ (14, 41, 42)	↔ (59)	↑ (59)
Subjective numeracy	Higher					↑ (41)		
RA disease status and history								
Disease duration	Shorter	↔↔ (28, 39)	↔ (39)	↔ (39)	↔ (32)	↔↔↔ (14, 41, 42)	↑ (24)	
Disease activity (global or composite measures)	Higher					↔↔ (14, 41)		
Arthritis-related health status	Better	↔ (17)	↔↔↔ (17, 26, 52)	↔↔ (17, 52)	↔↔ (17, 52)	↔ (42)		
Functional status	Greater disability	↔ (28)				↔ (42)		
Pain	Higher	↔↔ (28, 39)	↔ (39)	↔ (39)	↓ (32)		↑ (24)	
Fatigue	Higher	↔ (39)	↔ (39)	↔ (39)				
Swollen joints	More	↔ (39)	↔ (39)	↔ (39)				
Morning stiffness	Higher	↔ (39)	↔ (39)	↔(39)			↑ (25)	
RA treatment history								
Satisfaction with current Rx	Dissatisfied due to side effects				↑ (32)			

Prior treatment	(Unclear)						↔ (59)	↔ (59)
Current RA treatment	Biologic vs not		↔ (52)	↔ (52)	↔ (52)	↑ ↔ (41, 42)		
	SC vs IV				↑ (63)			
	More intensive vs single					↑ (14)		
	Greater number prior DMARDs				↔ (32)			
	Unclear	↔ (28)						
History of AE	Prior AE	↔ (39)	↓ ↔ (26, 39)	↔ (39)				
Current drug costs	Monthly drug expenditures	↔ (39)	↓(39)	↔ (39)			↑ (24)	
Other medical history								
Comorbidities	More					↔ (14)		
Clinic characteristics								
Travel time to clinic	Greater				↔ (63)		↑ (24)	
Clinic location	Public (vs private)	↔ (40)	↔ (40)	↔ (40)	↔ (40)			

7