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

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

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Support: The work was supported in part by a Canadian Initiative for Outcomes in Rheumatology Care (CIORA) grant. 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.

This article has been accepted for publication in The Journal of Rheumatology following full peer review. This version has not gone through proper copyediting, proofreading and typesetting, and therefore will not be identical to the final published version. Reprints and permissions are not available for this version. Please cite this article as doi 10.3899/jrheum.181165. This accepted article is protected by copyright. All rights reserved.

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Running head: Patient preference DMARD RA

Word count: 3669

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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.

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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.

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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

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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

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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);

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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

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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.

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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

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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

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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

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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 higher than those 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

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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 that 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).

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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).

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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

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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

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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

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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, which 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

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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.

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FIGURE LEGENDS

Figure 1. Flowchart of literature search results

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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

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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

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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

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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

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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

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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

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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

***The VAS ranged from: 0=not willing under any circumstance; to 100= definitely willing

****In-kind contribution from industry, who provided decision aid booklets at no cost

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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 2/4		Frequency 1/1	Route 3/5	--		

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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)

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**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)

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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	

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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 Cosmetic changes	60% (cancer) to 34% (hip fracture) 45% (severe N/V) to 30% (mild N/V) 37% (hirsutism) to 29% (acne)	Patients very risk averse. Results similar even when risk dropped to 1/100,000.(27)
Ho 1998 (28)	Median maximum acceptable risk of mortality (log scale)	30% improvement in symptoms No deterioration in symptoms	$1/10^6$ $1/10^6$	Patients very unwilling to accept any risk of death

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O'Brien	Mean acceptable risk	Relief of pain	23%	Relief of pain most important
1990 (29)	of mortality	Relief of stiffness	20%	
		Return to normal functioning	15%	

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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%)

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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			

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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;	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)

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	4) initial combination therapy with infliximab

*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

**Assessed using a VAS that ranged from: 0=not willing under any circumstance; to 100= definitely willing

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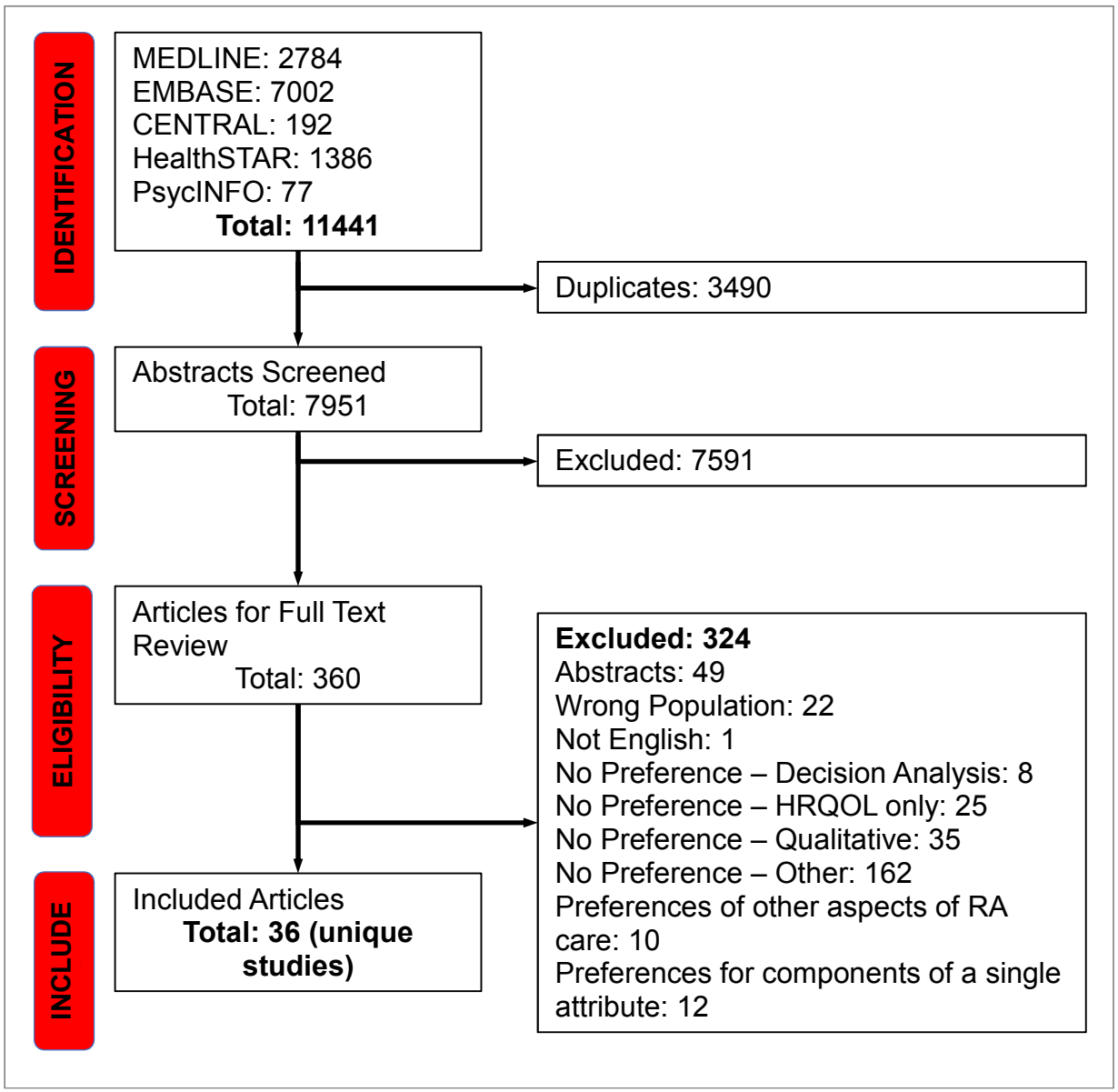

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