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Systematic Literature Review of Economic Evaluations of Biological Treatment Sequences for Patients with Moderate to Severe Rheumatoid Arthritis Previously Treated with Disease-Modifying Anti-rheumatic Drugs

Salah Ghabri¹ · Laurent Lam¹ · François Bocquet² · Hans-Martin Spath³

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Abstract

Objective This systematic literature review (SLR) had two objectives: to analyse published economic evaluations of biological disease-modifying anti-rheumatic drugs (bDMARDs) for patients with moderate to severe rheumatoid arthritis (RA) previously treated with DMARDs and to assess the quality of those that included sequences of treatments.

Methods We performed an SLR on PubMed, Central, Cochrane, and French databases from January 2000 to December 2018. The search focused on cost-effectiveness/utility/benefit analyses. We extracted data on treatment sequences, outcomes (e.g. quality-adjusted life year) and choices of economic evaluation methods (e.g. model type, type of analysis, and method of utility estimation). We analysed the improvement of methods by comparing two sub-periods (2000–2009 and 2010–2018). The quality of reporting and the quality of the methods were assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) and a set of eight key aspects for a reference case for economic evaluation of bDMARDs based on the Outcome Measures in Rheumatology (OMERACT) and Drummond checklists. Data extraction and study assessment were performed independently by two health economists.

Results From the 824 records identified in the initial search, 51 publications were selected. Of these, 31 included sequences. Individual models such as discrete-event simulations were used in over two-fifths (22/51, 43%) of the selected studies. Few studies (7/51, 14%) used utility scores based on generic instruments (e.g. EQ-5D). Estimation of hospitalization costs was described in only approximately one-third of studies (19/51). Loss of quality of life (QoL) related to adverse events such as tuberculosis and pneumonia was included in one-tenth (5/51, 10%) of the studies. It was difficult to compare the results of the economic evaluations (i.e. incremental cost-effectiveness ratios) due to the high heterogeneity of studies in terms of disease stage, data sources, inputs, and methods of health outcome assessment used. For identified studies including sequences, the CHEERS assessment of reporting quality showed insufficient reporting of uncertainty analyses and utility weights in more than a third of the studies (11/31, 35%; 9/25, 36%). An in-depth assessment of the quality of the studies revealed that only seven, mostly conducted during the sub-period 2010–2018, addressed the majority of methodological quality assessment issues such as the simulation of patient sequence pathways, the use of systematic reviews and meta-analyses of comparative effectiveness, the choice of treatment sequence, and rules for switching.

Conclusion Our SLR identified a lack of high-quality evaluations assessing bDMARD sequences, although some improvements were made in the reporting and modelling of patients' pathways in studies published after 2010. In order to improve economic evaluations of RA, clear health technology assessment guidance on RA health-related QoL instruments must be provided, and data including long-term disease progression must be made available.

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s40273-020-00887-6>) contains supplementary material, which is available to authorized users.

Extended author information available on the last page of the article

Key Points for Decision Makers

Despite abundant literature focusing on the burden of rheumatoid arthritis and some recent improvements in economic modelling of treatments for this disease, few high-quality economic evaluations assessing sequences of biological and/or targeted synthetic disease-modifying anti-rheumatic drugs were identified. Few sequences have been compared, as most publications compare individual biological drugs rather than drug sequences.

Clinical trials comparing second-line biological treatments as well as utilities estimated using health-related quality of life instruments are needed to improve the validation of rheumatoid arthritis decision analytic models and to improve the usefulness of these models as a tool for health decision making.

Clear guidelines for the inclusion of adverse events and their consequences (costs and loss of quality of life) in economic models of treatment sequences are needed.

1 Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that causes painful swelling of the peripheral joints (e.g. wrists, hands, and feet) and gradually destroys those joints. RA affects the patient's quality of life and leads to functional disability. The prevalence of RA varies from 0.3 to 1% worldwide [1, 2]. Several types of disease-modifying anti-rheumatic drugs (DMARDs), such as conventional synthetic (csDMARDs), biological (bDMARDs), and targeted synthetic DMARDs (tsDMARDs), can be prescribed to achieve low disease activity or even remission. Methotrexate (MTX) is the most frequently prescribed csDMARD [3, 4].

Since the 2000s, an abundant body of literature has focused on the cost-effectiveness of DMARDs, but most publications compared individual drugs rather than treatment sequences [5, 6]. The inclusion of treatment sequences enables the tracking of patients' pathways, including switches to further lines in a selected sequence [7, 8].

In 2017, the French National Authority for Health (HAS) conducted a systematic literature review (SLR) of economic evaluations of bDMARDs. The SLR covered RA patients previously treated with either csDMARDs (i.e. MTX) or bDMARDs (e.g. tumour necrosis factor alpha (TNF- α) inhibitors). This SLR had two objectives: to assess published economic evaluations of bDMARDs for patients with moderate to severe RA previously treated with DMARDs and to

assess the quality of those that include sequences of treatments. Critiques related to sophisticated technical aspects of treatment-sequence modelling are beyond the scope of this SLR.

2 Methods

This SLR was conducted in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [9]. A protocol was developed and validated by the HAS RA working group (two rheumatologists, two pharmacists, two health economists, and a representative of an RA patient association). The first step covered all economic evaluations including bDMARDs. Wherever possible, the improvement of methods over time was analysed by comparing two decades (2000–2009 and 2010–2018), given a sufficient number of studies from each decade. Only studies addressing treatment sequences were included in the quality assessment process. The scope of the SLR was extended to publications on tsDMARDs assessed by health technology assessment (HTA) agencies during the period of the literature search. Detailed information on databases sources and search strategy is provided in the Tables S1 and S2 of the electronic supplementary material.

2.1 Eligibility Criteria

This review included all studies that reported cost-effectiveness analyses (CEAs), cost-utility analyses (CUAs), or cost-benefit analyses (CBAs) of bDMARDs or sequences of treatments including bDMARDs for adult patients with moderate to severe RA who had been treated unsuccessfully with a csDMARD, such as MTX, or a bDMARD. Cost-minimization studies, cost studies, and budget-impact studies were excluded. Economic evaluations of bDMARDs for MTX-naïve patients were not included because bDMARDs are rarely prescribed in that population [3].

2.2 Search and Study Selection

Systematic searches were undertaken in PubMed, Central, Cochrane Library, and the French databases Pascal and Lissa, as well as in HTA websites for papers reporting CEA, CUA, or CBA of RA treatments and published in French or English from January 2000 to December 2018, a period in line with the objectives of the HAS economic evaluation. Studies reported only in a poster or abstract were excluded because those formats present incomplete information.

2.3 Data Extraction and Analysis

Four categories of data (listed in the appendices of the HAS RA report [10]) were extracted. The first summarizes the characteristics of the studies (e.g. indication, objective, characteristics of the population at model entry, strategies compared). The second summarizes the sources of data considered in the development of model inputs (e.g. efficacy, safety, mortality, quality of life). The third describes the methodological choices: type of analysis (e.g. CUA or CEA), model type (e.g. Markov, discrete-event simulation), model characteristics (cohort vs. individual, deterministic vs. stochastic), time horizon and discounting, methods of outcome estimation (e.g. costs, life years gained, quality-adjusted life years [QALYs] gained). The fourth included results such as the incremental cost-effectiveness ratio (ICER) and sensitivity analyses.

2.4 Assessment of Reporting and Quality of Studies

The reporting quality of the selected studies was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement checklist [11]. This instrument is a 24-item checklist verifying whether important aspects of economic evaluation (e.g. compared strategies, analysis population, perspective) and the results of such evaluation are described.

Because the CHEERS statement checklist is not sufficient to assess all issues related to the methods of conduct of economic evaluations, we carried out an in-depth assessment of the quality of the economic evaluations after defining “key aspects” of a reference case for economic evaluation of bDMARD sequences based on the Outcome Measures in Rheumatology (OMERACT) [12] and the general checklist of Drummond et al. [13] (both provided in the electronic supplementary material). The process of defining these key aspects was approved by the HAS RA working group [10]. The selected aspects were as follows:

- Providing the rationale behind the choice of clinical criteria for describing disease activity
- Providing the rationale behind the clinical criteria for describing disease severity
- Conducting at least an adequate systematic review and meta-analysis
- Justifying the choice of treatment sequences and structural assumptions considered in the modelling (e.g. clear definition of the sequences and the rules for switching)
- Providing the rationale and technical details relevant to the estimation of outcomes and their data sources (e.g. utilities)

- Verifying whether the modelled treatments adhered to guidelines on RA management (e.g. the National Institute for Health and Care Excellence (NICE) guidelines)
- Providing the rationale for the inclusion of adverse events (AEs) related to DMARDs (the occurrence and the incidence rate of AEs)
- When possible, conducting an analysis of low- and high-risk sub-populations stratified by RA risk factors or comorbidities.

The assessment used an ordinal scale: – not considered, – unsatisfactory; (+/–) fair, + good, and ++ very good.

2.5 Quality Process

Studies were independently selected and assessed by two authors (SG and LL). Any discrepancies were resolved by discussion within the HAS RA group until a consensus was reached.

3 Results

3.1 Search Results

A total of 824 records were identified through the initial search. The reasons for exclusion of studies are given in Fig. 1. Fifty-one studies that fulfilled all eligibility criteria were included in the quality assessment step [3, 4, 9–57]. Forty studies focused on patients with moderate to severe RA previously treated with csDMARDs [7, 8, 14, 16–19, 21–23, 25–31, 33, 38–49, 52–57, 59–61]. Eleven studies focused on the treatment of adult patients with active, severe RA previously treated with DMARDs, including at least one TNF- α antagonist [15, 20, 24, 32, 34–36, 50, 51, 58, 62]. Thirty-one studies included bDMARD and tsDMARD sequences. For more than half of the studies (30/51), at least one author declared a conflict of interest.

3.2 Literature Analysis

A synthesis of the literature is provided in the electronic supplementary material (Table S6). Details on the fourth category of extracted data (as described in Sect. 2.3) are given in the appendices of the HAS RA report [10].

3.2.1 Data Sources

Approximately one-third of the studies (31%, 16/51) included meta-analyses, which were carried out mainly on American College of Rheumatology (ACR) response (e.g. ACR 20, ACR 50). These studies were published after 2010.

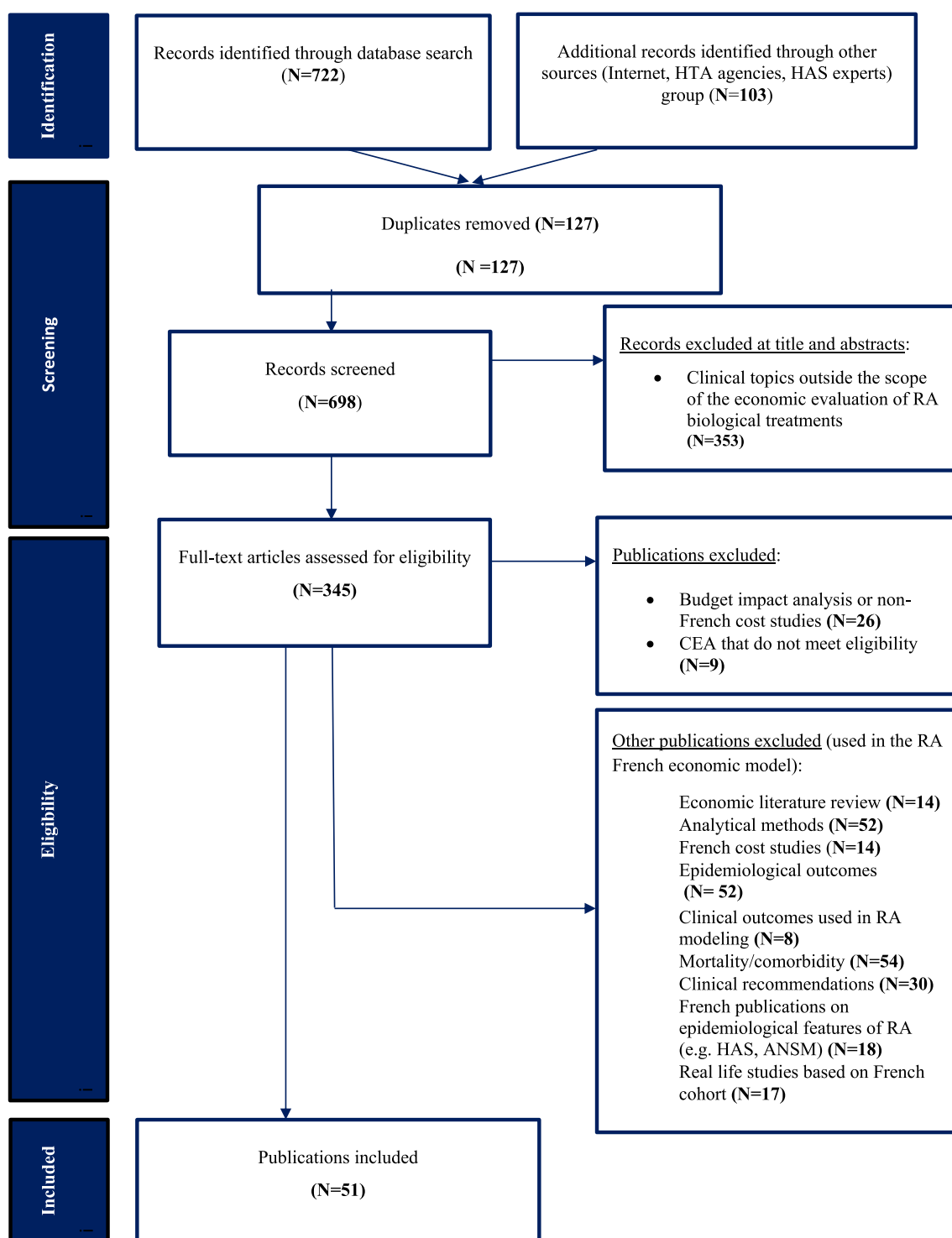


Fig. 1 PRISMA diagram showing the flow of publications identified in the systematic review. ANSM Agence nationale de sécurité du médicament et des produits de santé, CEA cost-effectiveness analysis, HAS French National Authority for Health (*Haute Autorité de Santé*),

HTA health technology assessment, PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RA rheumatoid arthritis

Only recent network meta-analyses (NMAs) [7, 8, 49] used European League Against Rheumatism (EULAR) response measures. Sources of AEs were reported in 24% (12/51)

of the studies, and 8% (4/51) performed meta-analyses of AE data. With regard to survival data, country-specific life tables were used in three-quarters of the studies (38/51).

Sources of cost data were generally on the country level and included claims databases as well as national lists of tariffs and drug prices. National income statistics were used to estimate productivity losses or disability pensions related to RA for economic evaluations that included indirect costs. Under half of the studies (19/51) used literature on mapping utility based on patient Health Assessment Questionnaire (HAQ) scores and socio-demographic characteristics such as gender and age [7, 19, 63].

3.2.2 Choice of Model and Analytical Methods

Type of economic analysis A majority of the studies (45/51, 88%) were CUAs. Fewer (6/51, 12%) were solely CEAs.

Type of modelling A wide range of model types were identified. More than two-fifths (22/51, 43%) of the selected studies used individual models: discrete-event simulation or Markov micro-simulation. Individual models have been used increasingly since 2010. One-third (17/51, 33%) were based on multi-state cohort Markov models, and 12% (6/51) were based solely on decision trees. In the remaining six studies, no decision analytic model was proposed (i.e. outcomes were obtained using linear regression or bootstrap methods). The following assumptions were made: (1) HAQ scores returned to the initial value upon discontinuation of treatment (i.e. “rebound effect”); (2) mortality was either adjusted by HAQ score or stratified according to HAQ classes [64, 65]; and (3) treatment switching was justified by RA management in the country considered in the economic evaluation. Patient preferences and adherence to treatment were not specified as reasons for treatment switching.

Population at entry The main characteristics of the population, such as age, sex, RA history, initial disease activity score (DAS28), and HAQ, were reported in three-quarters of the studies (39/51).

Perspective Two-thirds of the included studies (33/51, 65%) considered the payer perspective, and one-third (18/51, 35%) considered the societal perspective.

Comparators Approximately two-fifths (20/51, 39%) of the studies compared single treatments, among which MTX monotherapy was the most common comparator (11/20, 55%). Treatment sequences were considered in 61% (31/51) of studies, with the most frequent reference strategies including csDMARDs (14/31, 45%).

Time horizon and discounting Approximately one-half of the studies (26/51) used a lifetime horizon. For the other half, the time horizons ranged from 1 to 20 years. Costs

and QALYs were discounted in 80% (41/51) of the studies. The discount rates were country-specific and ranged from 1.5 to 6%.

Estimation and valuation of costs The direct costs of DMARDs (acquisition, administration, monitoring, and hospitalization) and the valuation of those costs were reported in almost all studies. Estimation of hospitalization costs (e.g. based on days of hospitalization) was described in only approximately one-third of studies (19/51, 37%) and was frequently stratified by HAQ category. One-third of studies (18/51, 35%) included disability costs.

Estimation and valuation of outcomes The most common outcome was QALYs (45/51, 88%). Remission and low disease activity were considered in only a few studies (6/51, 12%). Utilities were mostly estimated via linear or non-linear mapping that included HAQ score, age, and sex. A few studies (7/51, 14%) used utility scores based on generic instruments [e.g. EQ-5D, Health Utilities Index (HUI)] and relied on country-specific value sets. Loss of quality of life related to infections (e.g. tuberculosis, pneumonia) was included in 10% (5/51) of the studies.

3.2.3 Results of the Studies

The ICER ranged from €9000 to €1,948,919 per QALY gained for first-line comparison of a bDMARD to continued csDMARDs. ICERs were greater than €50,000/QALY gained in two-thirds of the CUAs for patients with inadequate response to TNF- α inhibitors. The economic evaluations included in this review differed in population, perspective, analytical methods, and sources of inputs. For these reasons, it is difficult to compare the results, even among studies focusing on the same treatment (or sequence).

Despite the growing number of methodological publications on model validation (e.g. face validity, cross-model validation) in the last decade [66, 67], external validation was documented poorly or not at all in almost all the studies, excluding two recent studies [7, 8].

3.2.4 Sensitivity Analyses

Deterministic sensitivity analyses (including one-way and scenario analyses) were performed in 71% (36/51) of the studies. Probabilistic sensitivity analyses were carried out in almost half (25/51). The key drivers were the scenarios of progression or severity of the disease defined using the HAQ and its long-term change (20/51, 39%), bDMARD acquisition prices (13/51, 25%), utilities (12/51, 24%), and treatment responses such as ACR responses (7/51, 14%).

3.3 Assessment of the Quality of the Studies

The assessment of quality was performed on the 31 studies [7, 8, 14–16, 19, 21, 22, 24, 28, 32, 34–37, 39, 41–45, 47–51, 58–62] comparing treatment sequences.

3.3.1 Compliance with CHEERS Statement Reporting Standards

The reporting quality of 31 studies including treatment sequences was assessed using the CHEERS statement. The results are shown in Table 1. The level of compliance with CHEERS reporting standards was especially high for the general items (e.g. title, abstract, objectives) and those related to the methodological aspects (e.g. discount rate, time horizon, perspective). All studies were defined as either a CUA or CEA. About a quarter of studies did not adequately report the target population and subgroups (8/31, 26%). Effectiveness data (e.g. full description of synthesis-based estimates) were fairly reported (20/31, 65%).

Studies failed to report relevant aspects of uncertainty analyses (e.g. structural uncertainty) and utility weights in

more than a third of the studies (11/31, 35%; 9/25, 36%). The heterogeneity was not assessed for almost all the selected studies as no study included subgroups, whereas conflicts of interest were fully reported in the majority of the studies (26/31, 84%).

3.3.2 Quality Assessment of the Studies

The results of the quality assessment of the selected studies using the key aspects for a reference case for economic evaluation of bDMARD sequences based on the OMERACT and the Drummond checklist are summarized in Table 2. Only seven studies [3, 4, 17, 44, 53, 55, 57] that have been conducted since 2012 have suitably addressed at least six issues of RA modelling (inclusion of progression of disease activity in the model, inclusion of disease severity in the model, use of systematic review or at least of relevant clinical trials, clear rationale for sequences and structural assumptions, description of health outcomes methods and use of guidelines for RA management). Some improvements in modelling after 2011 were identified. For instance, the rationale for treatment sequences was provided in the UK assessments [7, 62], which proposed the following: (1) discrete-event

Table 1 Assessment of the reporting quality of selected studies including sequences using CHEERS statement ($n=31$)

Item	Reported, n (%)	Not reported, n (%)
Title	31 (100)	0 (0)
Abstract	31 (100)	0 (0)
Background and objectives	31 (100)	0 (0)
Target population and subgroup	23 (74)	8 (26)
Setting and location	31 (100)	0 (0)
Perspective	28 (90)	3 (10)
Comparators	28 (90)	3 (10)
Time horizon	31 (100)	0 (0)
Discount rate (on analyses with a time horizon longer than 2 years; $n=25$)	25 (100)	0 (0)
Choice of health outcome	27 (87)	4 (13)
Measurement of effectiveness	20 (65)	11 (35)
Measurement and valuation of preference-based outcomes (on analyses of CUA, $n=25$)	16 (64)	9 (36)
Estimation resources and costs	26 (84)	5 (16)
Currency, price, date, and conversion	31 (100)	0 (0)
Choice of models	25 (81)	6 (19)
Assumptions	22 (71)	9 (29)
Analytical methods	22 (71)	9 (29)
Study parameters	20 (65)	11 (35)
Incremental costs and outcomes	25 (81)	6 (19)
Characterizing uncertainty	20 (65)	11 (35)
Characterizing heterogeneity	1 (3)	30 (97)
Study finding, limitations, generalizability, and current knowledge	23 (74)	8 (26)
Source of finding	28 (90)	3 (10)
Conflicts of interest	26 (84)	5 (16)

CHEERS Consolidated Health Economic Evaluation Reporting Standards, CUA cost-utility analysis

Table 2 Assessment of the quality of studies including treatment sequences according to the criteria extracted from OMERACT and Drummond checklists

Author, year (classified by reference number)	Country	Providing the rationale behind the choice of clinical criteria for describing disease activity	Providing the rationale behind the clinical criteria for describing disease severity	Conducting at least an adequate systematic review and meta-analysis	Justifying the choice of treatment sequences and structural assumptions considered in the modelling	Providing the rationale and technical details relevant to the estimation of outcomes and their data sources	Verifying whether the modelled treatments adhered to guidelines on RA management	Providing the rationale for the inclusion of AEs related to DMARDs	Conducting an analysis of low- and high-risk sub-populations stratified by RA risk factors or comorbidities
Stevenson et al., 2016 [7]	United Kingdom	++	++	++	++	++	++	+	--
ICER, 2017 [8]	USA	++	+	++	++	+	+	+	--
Athanasakis et al., 2015 [14]	Greece	(+/-)	-	--	(+/-)	(+/-)	(+/-)	--	--
Beresniak et al., 2013 [15]	Germany	+	-	--	(+/-)	(+/-)	-	--	--
Brennan et al., 2004 [16]	United Kingdom	+	+	--	+	(+/-)	+	--	--
Bansback et al., 2005 [19]	Sweden	+	+	--	+	(+/-)	+	(+/-)	-
Carlson et al., 2015 [21]	USA	+	+	(+/-)	-	+	(+/-)	--	-
Diamantopoulos et al., 2014 [22]	United Kingdom	+	+	+	+	+	+	+	--
Hallinen et al., 2010 [24]	Finland	-	-	--	-	(+/-)	+	--	-
Kvamme et al., 2015 [28]	Norway	-	-	--	+/-	+	+	--	--
Merkedal et al., 2010 [32]	Germany	+	+	(+/-)	(+/-)	+	+	-	--
Puolakka et al., 2012 [34]	Finland	(+/-)	-	--	-	(+/-)	+	--	--
Saraux et al., 2010 [35]	France	+	-	--	(+/-)	(+/-)	-	--	--
Russell et al., 2009 [36]	Canada	+	-	--	(+/-)	(+/-)	-	--	--
Soimi et al., 2012 [37]	Finland	(+/-)	-	-	-	-	+	--	--
Tanno et al., 2006 [39]	Japan	-	-	--	(+/-)	-	+	(+/-)	--
Wu et al., 2012 [41]	China	(+/-)	(+/-)	(+/-)	+	-	+	--	--

Table 2 (continued)

Author, year (classified by reference number)	Country	Providing the rationale behind the choice of clinical criteria for describing disease activity	Providing the rationale behind the clinical criteria for describing disease severity	Conducting at least an adequate systematic review and meta-analysis	Justifying the choice of treatment sequences and structural assumptions considered in the modelling	Providing the rationale and technical details relevant to the estimation of outcomes and their data sources	Verifying whether the modelled treatments adhered to guidelines on RA management	Providing the rationale for the inclusion of AEs related to DMARDs	Conducting an analysis of low- and high-risk sub-populations stratified by RA risk factors or comorbidities
Hashemi-Meshkini et al., 2016 [42]	Iran	(+/-)	-	-	+	-	+	--	--
Alemao et al., 2018 [43]	United Kingdom	+	+	--	+	+	+	--	+
Park et al., 2016 [44]	South Korea	(+/-)	(+/-)	(+/-)	-	(+/-)	+	(+/-)	--
Jalal et al., 2016 [45]	USA	(+/-)	(+/-)	--	(+/-)	-	(+/-)	(+/-)	--
Tzanetakos et al., 2017 [47]	Greece	+	-	(+/-)	+	+	+	--	--
Bansback et al., 2017 [48]	USA	+	+	--	-	-	+	--	--
Jansen et al., 2017 [49]	USA	+	+	+	+	+	+	+	--
Beresniak et al., 2011 [50]	Spain	+	-	--	(+/-)	(+/-)	-	--	--
Cimmimo et al., 2011 [51]	Italy	+	-	--	(+/-)	(+/-)	-	--	--
Claxton et al., 2018 [58]	USA	+	+	+	+	+	+	(+/-)	--
Chen et al., 2006 [59]	United Kingdom	++	-	(+/-)	+	-	++	-	--
Barton et al., 2004 [60]	United Kingdom	++	+	+	+	+	++	-	(+/-)
Jobanputra et al., 2002 [61]	United Kingdom	+	+	--	+	-	(+/-)	-	--
Malotki et al., 2011 [62]	United Kingdom	++	+	+	+	+	++	-	--

Bolded lines Studies having suitably addressed at least six issues of RA modelling (providing the rationale behind the choice of clinical criteria for describing disease activity, providing the rationale behind the clinical criteria for describing disease severity, conducting at least an adequate systematic review and meta-analysis, clear rational for sequences and structural assumptions, providing the rationale and technical details relevant to the estimation of outcomes and their data sources, and verifying whether the modelled treatments adhered to guidelines on RA management)

Scale: -- not considered, - unsatisfactory, (+/-) fair, + good, and ++ very good

AE: adverse event, *DMARDs* disease-modifying anti-rheumatic drugs, *ICER* Institute for Clinical and Economic Review, *OMERACT* Outcome Measures in Rheumatology, *RA* rheumatoid arthritis

simulation tracking RA patients with inadequate response or insufficient tolerance to csDMARDs and (2) combinations of csDMARDs considered as “standard” strategy to compare sequences of bDMARDs. This type of modelling was in line with RA management in the UK (e.g. the economic evaluation of bDMARDs commissioned by the NICE [7]). Similarly, the US studies [8, 49] provided details about treatment sequences with lines of treatments combining biological and targeted drugs. Second, prediction equations used to map utilities during the period 2000–2009 have been improved since 2013. For example, to address uncertainty regarding the linearity of the relationship between HAQ and utility frequently used in RA modelling, the Sheffield RA model [7] considered a non-linear econometric approach [62]. This model used patient characteristics, including HAQ, extracted from a large US sample of 100,000 observations.

The 24 remaining studies had major limitations. For example, they did not sufficiently include either the progression of activity or the severity of disease in the model. Furthermore, among these studies, two-thirds ($n = 16$ of 24, 67%) were not based on SLRs.

Although there were attempts to include costs and quality-of-life losses associated with acute events (e.g. serious infections) in all 31 studies, few (cf. Table 1) considered specific AEs, and when they were included, there was a lack of documentation about the occurrence of AEs during the time horizon of the evaluation and clear differentiation between the consequences of acute AEs (serious infections) and chronic AEs (e.g. cancers) on health outcomes. The values of AE disutilities were mostly based on expert opinions. However, two studies [7, 22] conducted reviews to estimate utility weights for AEs.

Regardless of the period of analysis (2000–2009 or 2010–2018), the scarcity of direct comparisons of biological treatments in the second and third lines was a major concern of all the selected economic evaluations, even though some of them considered several deterministic scenarios. Last but not least, the very small number of studies analysing heterogeneity emphasized the paucity of economic analyses stratified on RA risk factors or comorbidities. This may be explained by the lack of clinical trials and registries [68] providing information on risk factors.

4 Discussion

4.1 Main Findings

For the analysis of studies (with or without treatment sequences), our SLR showed that it was difficult to compare the health outcomes because of the high heterogeneity of studies in terms of stage of disease, lines of treatments recommended in the RA guideline of the studied country, the

sources of inputs, the study perspective, and the methods used for the estimation of quality of life. Nevertheless, this analysis provided informative results about the drivers of cost-effectiveness. Not surprisingly, the most frequent drivers were the effectiveness outcomes, such as progression or severity of the disease as defined using HAQ and its long-term change; the acquisition price of biological treatments; and sources of utilities.

The assessment of the quality of reporting of studies including sequences using the CHEERS statement checklist showed that the reporting of specific items such as uncertainty analysis and utility weights could be further improved. Contrary to the first descriptive analysis, the use of the CHEERS instrument did not allow us to assess the reporting safety/tolerability data since it does not contain a specific item about this type of data.

The assessment of study quality was based on the key issues for a reference for economic evaluation of sequences of bDMARDs. This analysis identified improvements in RA modelling. In particular, from 2010 onward, the use of patient-level simulations allowed the patients' health trajectories to be described from their first treatment (e.g. first bDMARD to further lines in a sequence, enabling us to include patient characteristics that might affect costs and QALYs).

From 2013 onward, the use of non-linear regressions based on “mixture model approaches” for the estimation of utilities improved the efficiency of mapping because of the use of more appropriate statistical distributions [7, 62]. This SLR identified concerns related to the consideration of treatment sequences, scarcity of long-term data on disease activity and safety and estimation of health-related quality of life (HRQoL) outcomes. Furthermore, reporting methods for estimating utilities and loss of quality of life related to AEs is still lacking, and structural uncertainty about these issues was not systematically examined. None of the economic evaluations incorporated adherence or a clear rationale about the inclusion of disutility related to AEs.

4.2 Comparison with Previous Literature Reviews

Our SLR differed from most previous literature reviews [6, 7, 69, 70] in that it was not limited to a review of the literature on first-line biological treatment, but covered studies evaluating biological treatments in second and subsequent lines and included published studies on tsDMARDs. In addition, we analysed the methods used to estimate utilities. We noted that there was insufficient documentation of both the sources of safety data and the manner of including the consequences of AEs in economic modelling. Some results of our SLR agreed with the following previous findings: (1) those of Tosh et al. (2014)

[6], who showed that treatment sequences have not been fully modelled; (2) those of Sullivan et al. (2013) [70], who underlined that only a limited pattern of switching (within or outside TNF- α blocking agents) have been evaluated for cost-effectiveness; and (3) those of an SLR (Heather et al. 2014, [71]) studying only the inclusion of AE consequences in economic evaluations of anti-TNF- α drugs that identified the related weaknesses.

4.3 Strengths and Limitations

Our SLR was conducted according to a protocol of eligibility focusing on sequences of bDMARDs for patients with moderate to severe RA previously treated with MTX and considered the reporting and quality assessment of the studies. In order to strengthen the review of treatment sequences and to better identify their issues, the search method covered studies published in French and English dealing with RA treatments for patients previously treated with csDMARDs.

In contrast to the standard systematic review of clinical literature, there is no standard checklist that quantifies the risk of bias in economic evaluations of health technologies. To address this issue, we considered a simplified list combining criteria from OMERACT (the checklist recommended for economic evaluation in RA) and Drummond (checklist of criteria for economic evaluation, which overlaps with CHEERS). These criteria were validated by the HAS RA experts and are in line with those recently proposed in a conceptual framework for developing models in RA to evaluate the cost-effectiveness of therapies [72]. Compared to the Consensus on Health Economic Criteria (CHEC) checklist [73], our assessment of the quality of studies emphasized the structural assumptions used in the modelling of sequences and treatment adherence. Furthermore, our criteria assessing the quality of studies are roughly comparable to the Bias in Economic Evaluation (ECOBias) checklist [74], which proposed a list of items describing the risks of bias related to the choices of economic evaluation methods.

This SLR has several weaknesses. The general limitations of the literature search carried out in our SLR were that (1) some economic evaluations might never have been published and that (2) only economic evaluations published in English or French were considered.

The number of economic evaluations including the new targeted tsDMARDs and sarilumab was small. This scarcity was due to the recent market entry of these drugs and to their limited effectiveness and safety data in real-life settings compared to bDMARDs. NICE's opinions on the new tsDMARDs (e.g. tofacitinib, baricitinib) and the second drug belonging to the class of inhibitors of interleukin-6 receptor mediated signalling (sarilumab) were recently published

[75–77]. These studies summarized assessments of the manufacturer-estimated cost-effectiveness, but they did not provide enough information (e.g. model choices) to include them in our analysis. This SLR did not identify economic evaluations including biosimilars.

4.4 Challenges

Compared to economic analyses of first-line biological treatment, there have been few studies dealing with second and subsequent lines. Long-term data on the pattern of switching (e.g. within or outside a biological therapeutic class) and safety (e.g. chronic AEs) are needed to improve the extrapolation of health outcome measures beyond second-line treatment (after the failure of MTX) [5, 70].

Model validation (in particular, external validation) [78] and the probabilistic analysis of many treatment sequences are among the important challenges that should also be considered in future economic evaluations of RA. As with other therapeutic domains, validation of RA decision models is challenging. Despite the large number of CUAs and CEAs on RA treatments, these studies tend to be poorly validated. This makes it difficult to trust their findings. Elaboration of conceptual RA models [74] and availability of long-term data on both severity and disease activity should allow the validation of RA models. Regarding the probabilistic analysis of treatment sequences, the current framework, which focuses on pairwise comparisons, should be extended to situations where there are many treatment sequences to be compared [6, 70].

5 Conclusion

This SLR identified 51 unique economic evaluations of disease-modifying therapy for patients with moderate to severe RA previously treated with DMARDs. Three-quarters of these studies included sequences of bDMARDs.

Despite recent improvements in modelling utility mapping and simulation of patients' pathways, we showed a lack of high-quality economic evaluations assessing sequences of bDMARDs. There were, strictly speaking, few studies that adequately addressed treatment sequences starting with bDMARDs. In order to improve economic evaluations of RA, clear health technology guidance on RA health-related quality must be provided, and data including the patterns of switching and long-term disease progression must be available. In addition to the healthcare characteristics of French RA management, this SLR helped to specify an HAS RA model based on patient-level simulations that describes the course of RA patients from the first bDMARD through switches to further lines in many sequences and uses adequate RA activity and disability criteria and reliable HRQoL instruments.

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Data Availability Statement All valid data from the current review are presented in the electronic supplementary material.

Compliance with Ethical Standards

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