PHARMACOECONOMIC MODELS IN RHEUMATOLOGY

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Abstract. *Pharmacoeconomic models of chronic diseases explore the development of the disease, patients' pathways through it and calculate the cost-effectiveness of the therapy with different medicines. The goal of the current study is to identify the pharmacoeconomic models used in rheumatology, their historical development and utilization. Systematic search in PubMed was performed with key words „pharmacoeconomic, models, rheumatology, and cost-effectiveness". On total 58 manuscripts were identified, describing mainly the rheumatoid arthritis development. The first one in line is the ACCES model of rheumatoid arthritis which have been validated in Sweden, Norway, etc. This is one of the first Markov models in rheumatology. Biological medicines are in the primary area of interest for modelling their therapeutic results. During the latest year scientists are working for the development of the web based platform to forecast the biological therapy (model PREDIRA). In alliance with other therapeutic areas with the development of artificial intelligence the pharmacoeconomic models is expected to increase, especially those built with data from real world clinical practice.*

Key words: *pharmacoeconomics, modelling, rheumatology, cost-effectiveness*

Introduction

Pharmacoeconomic analyzes aim to support the choice between available therapeutic alternatives in the treatment of specific diseases [1]. In the process of conducting them, rules of good research practice are followed in order to ensure the most reliable information and support decision-makers in an objective and impartial manner [2]. The choice of alternatives to therapeutic behavior must ensure the best investment for society without compromising the quality of health care [3]. For this purpose, a connection is needed between clinicians, pharmacoeconomists and drug regulators in the development of the design of the analyzes and the selection of appropriate methods and indicators for the evaluation of the therapeutic results [4].

Pharmacoeconomic models are one of the most commonly used methodological tools for presenting the course of the disease, the therapeutic process and the behavior of patients during treatment [5]. They use a wide range of data – epidemiological, data from randomized clinical trials and real clinical practice, expense related data, the probabilities of occurrence of a therapeutic result etc. [6]. These data serve to build an analytical, computational tool that allows to describe the therapeutic process, to predict the future behavior of patients, to calculate the cost of treatment and the expected therapeutic results [7]. The ultimate goal is to calculate the cost-effectiveness ratio for different behavioral alternatives and to support decision making.

Chronic, progressive diseases, among which are a large part of rheumatic diseases, have a probabilistic course in certain groups of patients and allow the application of probabilistic models. [8]. Studies of the types of pharmacoeconomic models in the field of rheumatology are limited, which provokes our interest in this topic.

The aim of the present work is to identify the pharmacoeconomic models used in rheumatology and the directions of their construction and development.

Materials and methods

A systematic study of PubMed publications with the keywords "pharmacoeconomic, models, cost-effectiveness, rheumatology" was conducted. The PubMed database was chosen because it references scientific journals in the field of medicine. There are no restrictions on the year of publication and the language of publication. The identification of publications also covers those proposed by the system, as related to the topic of the search.

The search results are presented in the PRISMA diagram in Figure 1.

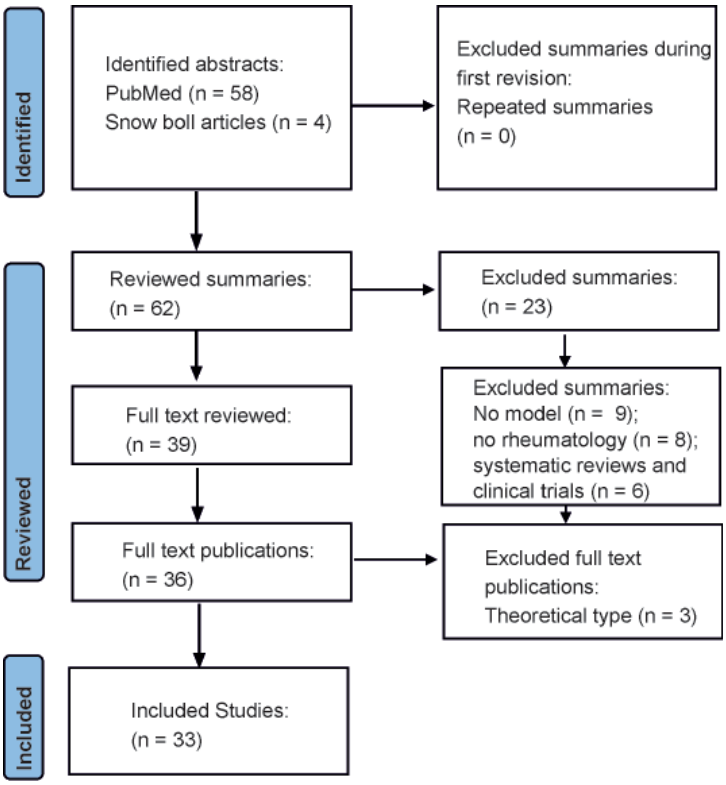

Fig. 1. PRISMA flow diagram for selection of studies [9]

Results

Table 1 summarizes the included publications on the main characteristics of the pharmacoeconomic studies described by Drummond et al [10]. The diagnoses for which models have been developed are rheumatoid arthritis (27 publications), gout (2 publications) and one publication each for psoriasis, psoriatic arthritis, ankylosing spondylitis and osteoarthritis. New biological molecules have been evaluated in 26 of the publications, JAK inhibitor tofacitinib in one, and coxibs in three publications. The majority of publications are conducted from the perspective of the paying institution and therefore direct medical costs are included, and only one includes indirect costs. Therapeutic outcome measures were either quality of life measures in 15 publications (QALY, quality-adjusted life year) or disease activity measures, among which low disease activity measured on the American College of Rheumatology and Health Assessment Questionnaire scales (HAQ).

Regarding the used pharmacoeconomic method, out of the 33 publications included one describes only the costs for treatment of rheumatoid arthritis, 23 aim to apply the cost-effectiveness method, 2 apply the cost-benefit method – 2; in one publication both cost-effectiveness and cost-utility are applied; in two cost-effectiveness and analysis of the budget impact are explained, in 3 publications an economic assessment was conducted and in one the benefits and risks were assessed.

In all pharmacoeconomic studies, except one, biological therapy was assessed as cost-effective, even for some health care systems as cost-saving.

The models used in the publications are Markov models (n = 15); patient-level simulation models (n = 5); modeling of discrete events (n = 3); population model (n = 2); decision tree (n = 2); linear regression model in cost analysis (n = 1); budget impact model (n = 2).

Since the object of this publication are the models used, in the subsequent analysis we will pay more attention to their structure and to the most frequently used ones.

One of the first publications presents the so-called ACCES model in the evaluation of celecoxib, which has been used in several countries. The model uses the decision tree technique to present results and consequences in the treatment of patients with celecoxib compared to other non-steroidal anti-inflammatory drugs (NSAIDs) (Figure 2).

Table. 1. Scenarios in a microsimulation model at the patient level (Navarro F., et al., 2020)

Scenario 1 DMARDs population	Tofacitinib 2xd + MTX	Rituximab + MTX	Tocilizumab sc + MTX	Etanercept + MTX	Certolizumab + MTX
	Adalimumab + MTX	Rituximab + MTX	Tocilizumab sc + MTX	Etanercept + MTX	Certolizumab + MTX
Scenario 2 DMARDs population	Tofacitinib 2xd + MTX	Adalimumab + MTX	Rituximab + MTX	Tocilizumab sc + MTX	Etanercept + MTX
	Baricitinib + MTX	Adalimumab + MTX	Rituximab + MTX	Tocilizumab sc + MTX	Etanercept + MTX
Scenario 3 TNFi population	Tofacitinib 2xd + MTX	Abatacept sc + MTX	Rituximab + MTX	Certolizumab + MTX	
	Tocilizumab sc + MTX	Abatacept sc + MTX	Rituximab + MTX	Certolizumab + MTX	
Scenario 4 TNFi population	Tofacitinib 2xd + MTX	Tocilizumab sc + MTX	Abatacept sc + MTX	Rituximab + MTX	
	Tocilizumab sc + MTX	Abatacept sc + MTX	Rituximab + MTX	Certolizumab + MTX	

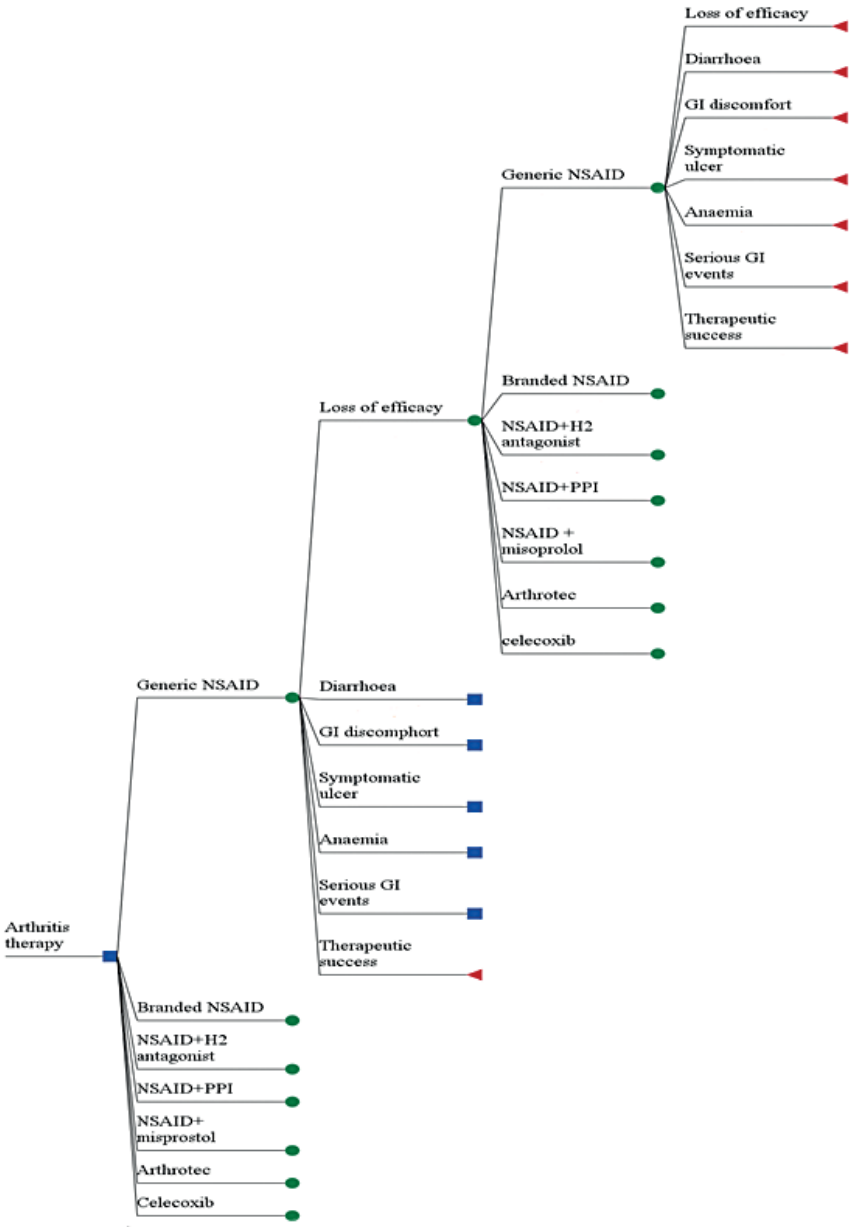

Fig. 2. Structure of the ACCES model (Svarvar P et al, 2000)

This model compares seven possible therapeutic behaviors in the treatment of arthritis, six of which are NSAIDs as monotherapy or in combination with other products. The branches of the decision tree represent therapeutic success, loss of efficacy, and the occurrence of adverse drug reactions (ADRs). Data from clinical practice and brief product characteristics were used for the incidence of ADRs. The treatment steps are repeated without specifying the treatment recurrence period, but it is stated that the time can vary between 0 and 365 days, so we assume that the treatment period is one year. The results are measured by years of life saved or the frequency of ADR, and the costs are those of the payer. A calculator in excel program for application of the model has been developed. The decision to choose a therapeutic alternative is made on the basis of the saved costs of prevented ADRs or the cost of a year of life saved. The advantages of this modeling technique are its flexibility in terms of therapy duration, compared alternatives, uncertainty calculations. It is possible for the input parameters to vary according

to the method of treatment and national characteristics.

The second model is a simulation-type decision tree for comparing two biological products after an inadequate response to previous treatment with a biological product in moderate to severe RA (Figure 3). The simulation model of the decision tree type allows to calculate variable distributions.

The publication presents 12 separate models developed to simulate 6 consecutive changes in therapy, consisting of 3 biological medicines. The results of the treatment were measured by 2 measures of therapeutic success – remission and low disease activity. The costs are direct medical costs. Data on the effectiveness of biologic therapy are taken from clinical trials published at the time of the model development in 2012.

A patient-level microsimulation model for health system purposes in Spain was developed to assess the sequence of tofacitinib treatment followed by biologic versus biologic therapy alone. Four scenarios for changing the treatment of patients have been developed (Figure 4).

Model parameters include demographic and clinical data [HAQ]. and response to long-term treatment. Efficacy was measured by changes in

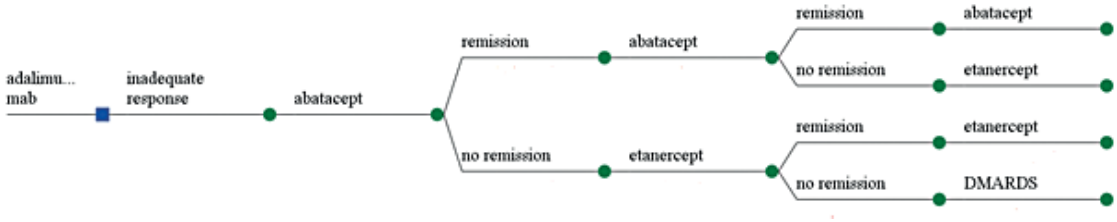

Fig. 3. Example of a simulation Model tree of solutions for second-line biological therapy (Puolakka K. et al., 2012)

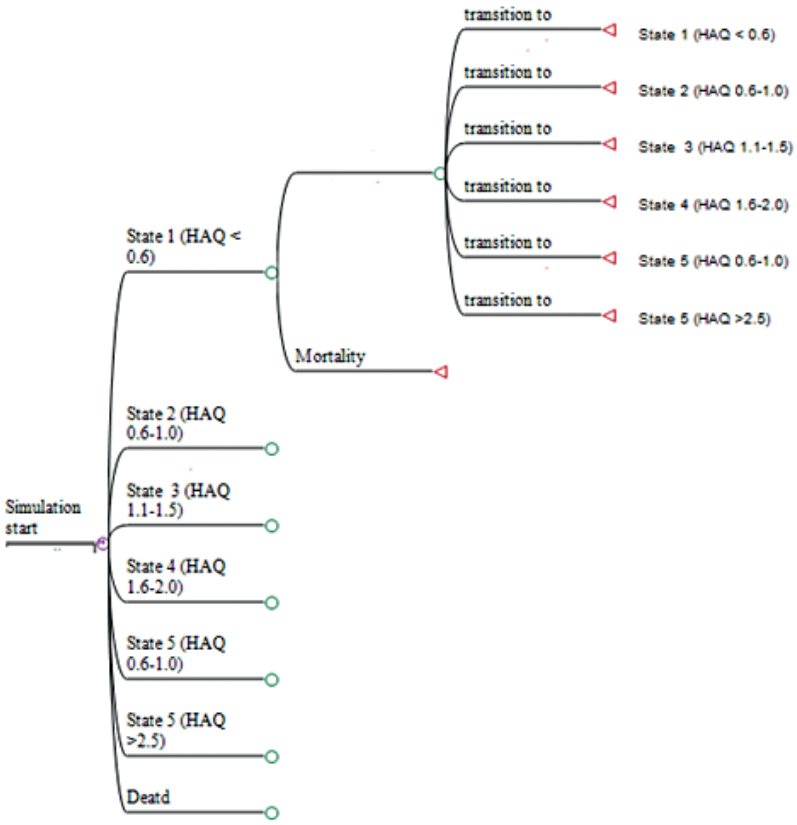

Fig. 4. Scheme of a Markov model for the treatment of RA (Kobelt G., 2003) [12]

HAQ values. Serious side effects are also included in the model. The costs are direct medical expenses and include expenses for medicines, parenteral administration, disease progression, treatment of serious ADRs.

One of Markov's first models was developed by Kobelt et al. to illustrate the progression of RA, which was subsequently used to assess the cost-effectiveness of infliximab in the treatment of RA – Figure 4. The model compares two treatment alternatives and non-treatment, with transitions from condition to condition being determined by changes in values of HAQ. Condition 1 has the lowest level of disability (HAQ < 0.6) and condition 6 has the highest degree of disability (HAQ02.6). After each one-year cycle, the model redistributes patients to each condition based on changes in HAQ values. Absorbing state is death. Data on the efficacy of infliximab as an alternative treatment in the second model were extrapolated from the ATTRACT clinical trial.

The model of Russell et al. examines transition states between low disease activity and remission when comparing abatacept and disease modifying antirheumatoid drugs (DMARDs). A similar transition is used by the model of Iannazzo et al. The model of Welsing et al. uses the DAS (disease activity score) as a measure of disease activity to describe patients' transition between health conditions when extrapolating short-term data from clinical trials.

Another Markov model initially described the sequence of the therapeutic process with the hitherto known medicinal products (Figure 5), and then, based on the therapeutic behavior and data from clinical trials, created a model with a transition from ACR exacerbation conditions (Figure 6).

Discussion

This publication complements previous developments in the field of therapeutic process modeling and the application of drugs in rheumatology. [14]. Undoubtedly, pharmacoeconomic models are increasingly used for mathematical description of treatment and prediction of its future development, as well as the cost-effectiveness of new molecules [15-49].

This work confirms that models for the treatment of rheumatoid arthritis predominate, and to a lesser extent for other rheumatological diagnoses.

With the introduction of new organic products, we can expect that the number of models will increase due to the requirements of regulatory institutions to prove the cost-effectiveness of new health and pharmaceutical technologies. However, these types of models are sometimes too schematic, as they target only a specific drug and use information about the therapeutic effect of clinical trials, which does not give a complete picture of all available alternatives on the market. More important are the models that describe the course of the disease in its treatment and compare more than two alternative behaviors [48, 49].

This study shows that the models in rheumatology are very limited in number compared to other therapeutic areas, such as endocrinology and diabetes. This is probably due to the individual course of the disease and the difficulty of including all possible treatment options. With the development of artificial intelligence and its wider application in the processing of data from real clinical practice, these problems will be overcome.

The current study has some limitations. In the first place, it includes publications only from PubMed. We have tried to overcome this limitation by including other studies recommended by the system, but there are probably models that are missing. Another limitation is that it does not include national surveys.

Conclusion

Pharmacoeconomic models in rheumatology are primarily for rheumatoid arthritis as the most common diagnosis. There is still no complete description of the development of the main rheumatological diagnoses. As in other therapeutic areas, with the development of artificial intelligence the importance of pharmacoeconomic models will increase, where these models are built with data from studies in real clinical practice.

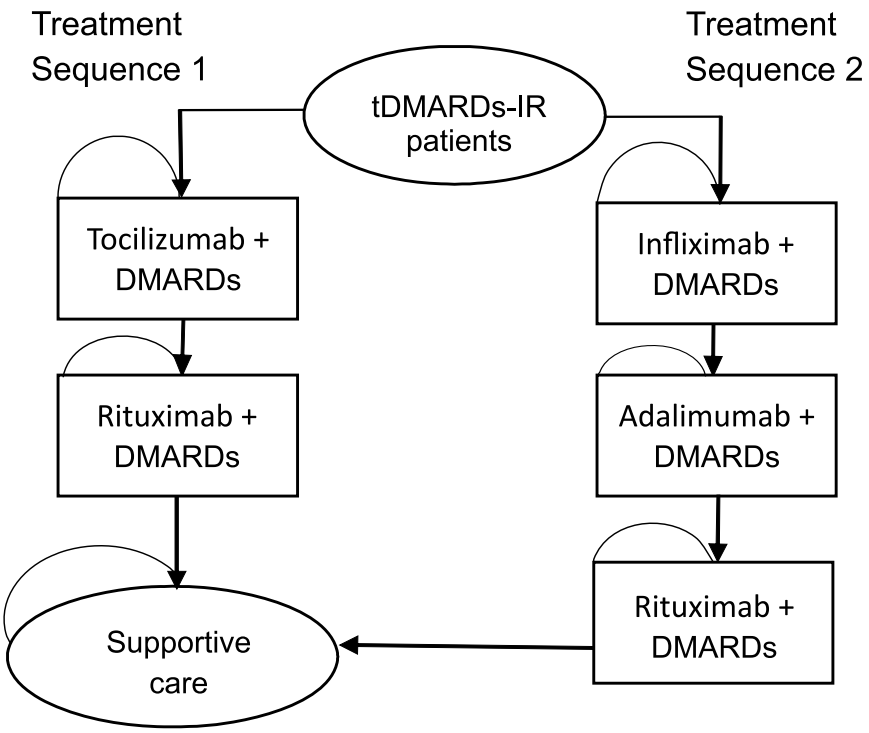

Fig. 5. Scheme of therapeutic process according to Hashemi-Meshkini A., 2016 [13]

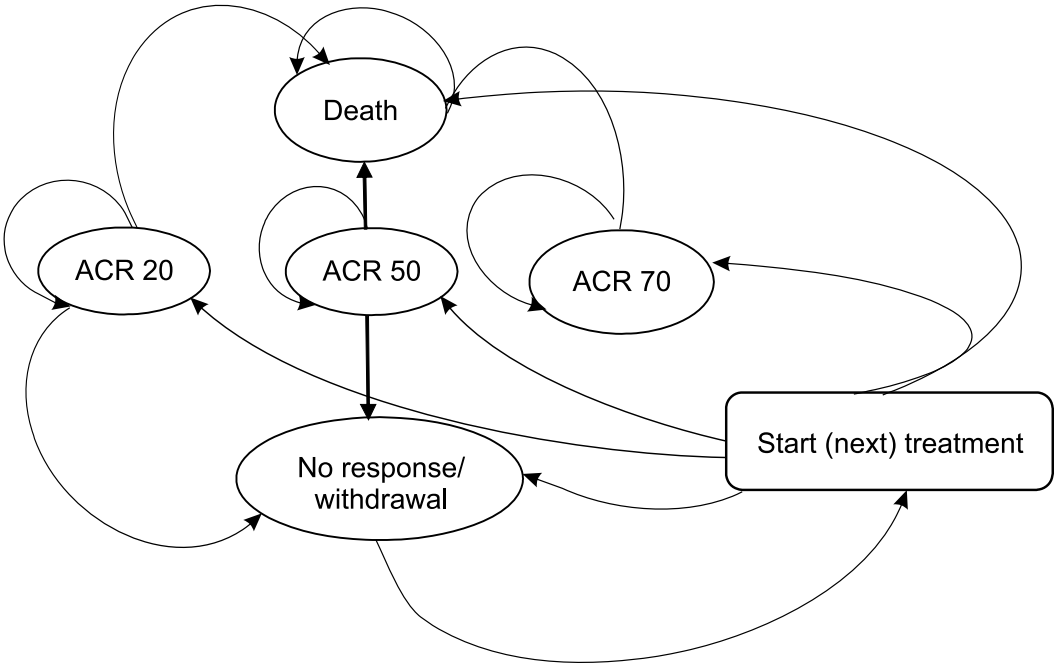

Fig. 6. Structure of transitions in RA according to Hashemi-Meshkini A., 2016

Table 2. Included studies

Authors	Aim	Type of model	Alternatives	Included costs	Measurement of results	Conclusion
Bessette L., et al. [1]	Cost-utility of celecoxib in three strategies for arthritis in Quebec, considering both upper gastrointestinal (GI) and cardiovascular (CV) events.	Markov model – 5 years	In first-line treatment, patients started on celecoxib; second-line – non-selective non-steroidal anti-inflammatory drug (NSAID) and switched to celecoxib; third-line- non-selective NSAID, added a proton pump inhibitor (PPI) and switched to celecoxib	Direct medical costs	Quality-adjusted life-years (QALY)	total cost is lower for second-line therapy (compared with the third one) the use of celecoxib before the combination of non-selective NSAIDs plus a proton pump inhibitor is cost-effective in the treatment of arthritis
Russell A., et al. [2]	Cost-effectiveness of abatacept compared to different biologic strategies for moderate to severe rheumatoid arthritis in Canada	Markov model	Abatacept, as first biologic agent after an inadequate response to DMARDs. Abatacept, as second biologic agent after an inadequate response to oneanti-TNF agent	Direct medical costs	low disease activity state“ (LGAS) and „remission“	Abatacept Is a cost-effective strategy in patients with an inadequate response to DMARDs or to one anti-TNF agent.
Puolakka K et al. [3]	Cost-effectiveness of therapeutic options in moderate or severe rheumatoid arthritis (RA) when a clinical response to a first TNF-blocker, either etanercept (ETA), adalimumab (ADA), or infliximab (INF), is insufficient.	Simulation modelling	first anti-TNF agent, ETA, ADA or INF, followed by abatacept (ABA) or rituximab (RTX) as a second therapeutic option, followed by another anti-TNF agent.	Direct medical costs	Effectiveness criteria: remission (RS), low disease activity (LDAS), and moderate to high disease activity (MHDAS).	The treatment sequences including ABA as the second option appear more cost-effective than those including RTX in a patients with moderate to severe RA.
Baser O., et al. [4]	Direct medical costs associated with rheumatoid arthritis (RA) in Turkey using nationwide real-world data.	Generalized linear models	No alternatives were compared	Total healthcare costs	No result measured	Significant portion of inpatient and outpatient costs were due to physician costs (31% for incident cases, 40% for prevalent cases). Total annual costs for RA are lower in Turkey than projected in Europe, with a significant part of them due to drug costs
Iannazzo S.et al. [5]	Health economic assessment in Italy.	PharmacoeconomicMarkov model with a 3-year time horizon	Switching to a different mechanism of action in rheumatoid arthritis (RA) patients after a first anti-TNF-α has proved to be effective.	Medicinal products costs	Effectiveness was measured as days gained in low disease activity (LDA; DAS28-ESR < 3.2) or in remission (DAS28-ESR < 2.6).	The switch to a different mechanism of action, namely tocilizumab, after the failure of a first anti-TNF-α agent seems a rational strategy
Purmonen Tet al. [6]	To assess the potential financial impact of secukinumab vs. adalimumab in the treatment of ankylosing spondylitis (AS) in Finland.	Budget impact analysis	In the base case analysis all adalimumab patients are assumed to switch to secukinumab. Patients not achieving response were switched to another biologic treatment.	Medicinal products costs	No result measured	Secukinumab is a cost-saving treatment option compared with adalimumab in the treatment of AS.
Svarvar P, et al. [7]	Economic and health impact of the introduction of celecoxib in Norway.	Arthritis Cost Consequence Evaluation System (ACCES) pharmacoeconomic model	Celecoxib and alternaties	Medicinal products costs, adverse drug reactions	No clinical result measured	Introduction and use of Celecoxib as a first-line agent, will provide societal benefits by improving healthcare at reduced cost in patients with OA and RA

Continued table 2.

Welsing P.M.J, et al. [8]	To extrapolate efficacy data from short-term clinical trials in rheumatoid arthritis to long term cost-effectiveness results	Markov model with health states defined by the disease activity score (DAS)	Newly diagnosed patients versus patients with expected development	Direct medical costs	QALY	The developed Markov model seems a valid model for use in economic evaluations in rheumatoid arthritis.
Oh K-T et al. [9]	Assessment of genotype-based dosing value by polymerase chain reaction (PCR) screening and cost-effectiveness for azathioprine treatment of rheumatoid arthritis and systemic lupus erythematosus patients in Korea.	Genotype-based dosing strategy with the conventional weight-based dosing strategy using a hypothetical cohort composed	Genotype-based dosing strategy with the conventional weight-based dosing strategy	Direct medical costs	The total expected cost and an incremental cost-effective ratio.	Genotype-based dosing strategy through PCR-based thiopurine methyl transferase (TPMT) polymorphism screening is less costly and more effective than the conventional weight-based dosing strategy.
Harrison M., et al. [10]	The value society places on aspects of RA treatment to inform policy making	A discrete choice experiment conditional logit regression model	No alternatives were compared	Costs are not included	The discrete choice experiment had seven attributes (route and frequency of administration, chance of benefit, chance of serious and minor side effects, confidence in evidence and life expectancy). A conditional logit regression model was used to estimate their significance	The evaluation of values the degree of confidence in the estimates of risks and benefits of RA treatments and the route of administration, as well as benefits and side effects. There is provided evidence to policy makers determining the cost-effectiveness of treatments in arthritis.
Jutkowitz E., et al. [11]	Additional studies to reduce the cost-effectiveness uncertainty of allopurinol and febuxostat for the treatment of gout.	Markov model	Allopurinol and febuxostat	Direct medical costs	QALY	Future studies are needed to evaluate the effectiveness of allopurinol and febuxostat dose escalation.
Salinas-Escudero G., et al. [12]	Cost-effectiveness analysis of etanercept compared with other biologic therapies in the treatment of moderate or severe rheumatoid arthritis in patients with previous unresponse reaction.	Pharmacoeconomicmodel based on decision analysis	Etanercept, infliximab, adalimumab or tocilizumab	Direct medical costs	With improve of 20 % or 70 % of the parameters established by the American College of Rheumatology (ACR 20 and ACR 70).	Treatment with etanercept is more effective and less expensive compared to the other drugs, considering incremental cost-effectiveness ratios for the treatment of rheumatoid arthritis.
Tanaka E., et al. [13]	Cost-effectiveness of biological disease modifying antirheumatic drugs (DMARDs) in patients with rheumatoid arthritis (RA) in a real-world setting in Japan	State-transition model	bDMARD group; adalimumab, etanercept, infliximab, and tocilizumab or methotrexate (control group)	Medicinal products costs	QALY	bDMARDs were cost-effective for RA patients based on a real-world setting in Japan. The best population for initiating bDMARD was RA patients less than 50 years old.
Hashemi-Meshkini A., et al. [14]	Cost-effectiveness of two common treatment strategies in Iran, comparing infliximab plus methotrexate with tocilizumab plus methotrexate in patients with rheumatoid arthritis with inadequate response to traditional disease-modifying antirheumatic drugs	A multistage Markov model	Infliximab plus methotrexate with tocilizumab plus methotrexate	Direct medical costs and direct nonmedical costs, from a payer perspective	QALY	Tocilizumab is not cost-effective as compared with an infliximab-containing regimen for patients with rheumatoid arthritis in Iran.

Continued table 2.

Incerti D., et al. [15]	Flexible open-source simulation model for patients with rheumatoid arthritis	Discrete-time individual patient simulation with 6-month cycles	Components: (i) modifiable R and C++ source code available in a GitHubrepository; (ii) an R package to run the model for custom analyses; (iii) detailed model documentation; (iv) a web-based user interface for full control over the model without the need to be well-versed in the programming languages; and (v) a general audience web-application	Costs are not included	Clinical results	In order for a decision model to remain relevant over time it needs to evolve along with its supporting body of clinical evidence and scientific in sight.
Tosh J., et al. [16]	Critical review of the evidence for the clinical and cost effectiveness based on submited in NICE data	a DMARD-experienced population model	Golimumab, comparator treatments	Healthcare costs	Clinically relevant range of outcomes	Golimumab should be recommended in combination with methotrexate as an option for patients with severe active RA who have failed on conventional DMARDs, TNF-α inhibitor and rituximab
Maetzel A., et al. [17]	The 5-year cost effectiveness of adding leflunomide (LEF) to a sequence of disease-modifying antirheumatic drugs (DMARDs) for rheumatoid arthritis (RA) management approach adopted by Canadian rheumatologists.	5-year simulation model where patients cycle through different treatment regimens	LEF, methotrexate, and placebo	Costs for adverse event management, monitoring costs. Wholesale prices of all drugs were adjusted by the allow able markup and prescription fees	Drug withdrawal rates, number and type of adverse events, choice of DMARD sequence, management of adverse events, and utilities	Adding LEF as a new option to a conventional sequence of DMARDs extends the time patients may benefit from DMARD therapy at a reasonable cost effectiveness and cost utility.
ClarkW, et al. [18]	Clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis (RA) in adults.	Systematic review of models	Anakinra compared to available alternatives to RA	Health costs	Benefit in monotherapy and when used in combination with methotrexate/QALY	Anakinra can be considered modestly effective in the treatment of RA based on ACR response, although no conclusion can currently be made on the effect of treatment on disease progression.
Alemao E., et al. [19]	Current approaches to economic modeling in rheumatoid arthritis (RA) and propose a new conceptual model for evaluation of the cost-effectiveness of RA interventions.	Conceptual model consists of three separate modules: 1) patient characteristic module, 2) treatment module, and 3) outcome module	No alternatives are included	Costs are not included	1) Using composite measures of disease activity to evaluate treatment response 2) conduct utility mapping based on disease activity measures; 3) subgroups based on recommended prognostic factors; 4) integrated realistic treatment patterns based on clinical practice/ registry datasets; 5) as simulate outcomes that are not joint related and assess mortality based on disease activity.	The proposed model framework as review with experts and could serve as a foundation for developing future cost-effectiveness models RA.

Continued table 2.

Ren S., et al. [20]	Clinical and cost effectiveness for the treatment of moderate to severe rheumatoid arthritis (RA) with baricitinib after the failure of DMARDs.	Discrete event simulation model	BARI in combination with MTX dominated all comparators except for certolizumab pegol (CTZ) in combination with MTX	Health costs	QALY	BARI in combination with MTX or a monotherapy is a cost-effective use of NHS resources in patients with severe RA, except in TNFi-IR patients who are RTX-eligible.
Uttley L.et al. [21]	Clinical and cost-effectiveness in the treatment of rheumatoid arthritis (RA) with tofacitinib (TOF; Xeljanz®) after the failure of conventional cDMARDs.	De novo model that assessed the cost-effectiveness	TOF plus methotrexate(MTX)	Direct medical costs	QALY	TOF plus methotrexate (MTX) dominates or extendedly dominates most comparators, while TOF monotherapy is slightly less effective and less expensive. For patients who are intolerant of MTX, or where MTX contraindicated, TOF monotherapy is recommended.
E. Wehler, et al. [22]	Budget impact of baricitinib addition into formulary and efficacy of baricitinib compares to other DMARDs with a similar indication in USA.	A budget impact model (BIM)	World without and with baricitinib	Medicines costs	Number needed to treat (NNT) and cost per additional responder	Baricitinib compared to other DMARDs, was a less expensive option with comparable efficacy in patients with inadequate response to TNFi. Adding baricitinib to formulary would likely be cost saving.
Bermejo I., et al. [23]	Clinical efficacy and cost-effectiveness of sarilumab (SAR; Kevzara®) in patients with previously treated moderate or severe rheumatoid arthritis (RA).	Markov model that assessed the cost-effectiveness of SAR from the perspective of the National Health Service (NHS)	SAR in combination with MTX or as monotherapy versus its comparators	Direct and indirect costs	QALY	SAR in combination with MTX or as monotherapy compared to alternatives leads to cost savings of £ 60,000 per lost QALY when SAR is less effective. Exceptions are patients with TNFi-IR therapy who meet RTX (when ICER meets SAR + MTX requirements compared to RTX + MTX is £ 130,691 per QALY gained) and in patients with moderate RA and DAS 28 of > 4.0 (where The ICER of SAR + MTX compared to MTX is £ 38,254 per QALY gained).
Schädlich P. K., et al. [24]	Incremental cost-effectiveness and cost-utility of the introduction of leflunomide as a follow-up therapy after DMARDs for patients with rheumatoid arthritis in Germany.	3-year simulation model	DMARD sequences including leflunomide were compared with those excluding leflunomide.	Costs comprised direct costs in cured by treatment and indirect costs incurred by loss of productivity	Response years gained (RYGs) according to the American College of Rheumatology (ACR) criteria for 20%, 50% and 70% improvement (ACR20/50/70RYGs) and QALYs gained (QALYGs).	leflunomide as an additional option in a DMARD treatment sequence extends the time patients benefit from DMARD therapy at reasonable additional direct costs. Adding leflunomide may even be cost saving when total (direct and indirect) costs are considered.
Nguyen C. M., et al. [25]	TNF-α inhibitor agent for the treatment of moderately to severely active RA from the US healthcare payers' perspective.	A Markov model	Five TNF-α inhibitors (in combination with methotrexate [+MTX].) versus MTX monotherapy	Cost-utility	QALY	Etanercept+MTX was a cost-effective treatment strategy in the base-case scenario; however, the model was sensitive to parameter uncertainties and American College of Rheumatology (ACR) response criteria.

Continued table 2.

Yang H., et al. [26]	Golimumab (Schering-Plough/ Centocor) to submit evidence for the clinical and cost effectiveness of this drug for the treatment of active and progressive psoriatic arthritis (PsA) in patients who have responded inadequately to previous DMARDs.	A Markov model	Golimumab versus etanercept, infliximab, adalimumab and golimumab	Medicines costs	Psoriatic Arthritis Response Criteria (PsARC) [RR 3.45, 95% CI 2.49, 4.87], and significantly improved response as measured by SeverityIndex	Etanercept, adalimumab and golimumab had almost equal costs and equal QALYs, and all had an ICER of about £15 000 per QALY versus palliative care, whilst infliximab, with a higher acquisition cost, was dominated by the other biologics.
NavarroF, et al. [27]	Cost-effectiveness of tofacitinib-containing treatment sequences versus standard biological therapies in patients with moderate-to-severe rheumatoid arthritis (RA) after the failure of conventional antirheumatic drugs and in patients previously treated with methotrexate (MTX) who shows an inadequate response to second-line therapy with any TNFi.	A patient-level microsimulation model	tofacitinib+MTX followed by sc Abatacept+MTX→ rituximab+MTX→ certolizumab+MTX versus sc Tocilizumab+MTX→ sc Abatacept+MTX→ rituximab+MTX→ certolizumab+MTX; and tofacitinib+MTX→ sc Tocilizumab+MTX→ sc Abatacept+MTX→ rituximab+MTX versus sc Tocilizumab+MTX→ sc Abatacept+MTX→ rituximab+MTX→ certolizumab+MTX	Health costs	QALY	Inclusion Of tofacitinib seems a dominant strategy in moderate-to-severe RA patients after csDMARDs failure.
Bermejo I., et al. [28]	Clinical and cost effectiveness of certolizumab pegol (CZP; Cimzia®) for the treatment of rheumatoid arthritis (RA) following inadequate response to -α TNFi	A Markov model	(1) a comparison against rituximab (RTX) in combination with methotrexate (MTX); (2) a comparison against DMARDs when MTX is contraindicated withdrawn	Total health costs	QALY	CZP plus MTX could not considered a cost-effective use of National Health Service resources when RTX plus MTX is a treatment option.
Smolen L. J., et al. [29]	To determine the cost-effectiveness of febuxostat vs allopurinol for the management of gout.	A stochastic microsimulation cost-effectiveness model	Febuxostat vs allopurinol, especially for patients with CKD stages 3 or 4.	Medicines costs	Serum uric acid (sUA), CKD incidence, progression, stages 3/4 progression, and stage 5 progression avoided incident T2DM, and death.	Febuxostat may be a cost-effective alternative to allopurinol, especially for patients with CKD stages 3 or 4.
FatemiB., et al. [30]	Cost-utility of Tofacitinib (TFC) in patients with severe rheumatoid arthritis (RA) who had not responded well to methotrexate for the Iranian payer's perspective.	microsimulation Markov model	Tofacitinib compared with adalimumab and etanercept	Direct medical costs	(ACR) response improvement criteria in 6 months; QALYs	TFC was found to be cost-effective in patients with severe RA who do not respond well to methotrexate compared to ADA, ETN in Iran.

Continued table 2.

Barbieri M., et al. [31]	Cost-effectiveness analysis and budget impact analysis on use of apremilast for the treatment of adult patients with moderate-to-severe plaque psoriasis	A Markov state-transition cohort model	with two alternative treatment sequences, with or without apremilast	Medicines costs	Quality of life	Apremilast would lead to savings to the Italian healthcare system with potential benefits in terms of patients' quality of life.
Tran-Duy A., et al. [32]	Long-term patient outcomes and cost effectiveness of treatment strategies with and without inclusion of BRMs following a clinical guideline for treatment decisions.	Discrete event simulation	The treatment strategy recommended by the Dutch Society for Rheumatology where both DMARDs and BRMs were available (Strategy 2) was compared with the treatment strategy without BRMs (Strategy 1).	Health costs	QALY	It is Possible to model the outcomes of complex treatment strategies based on a clinical guideline for the management of RA.
Tian L., et al. []	Cost-effectiveness of introducing to facitinib into the current treatment sequence in China for patients with moderate-to-severe rheumatoid arthritis who have csDMARDs-IR.	Markov model	The treatment sequence without tofacitinib included adalimumab, etanercept, recombinant human tumor necrosis factor receptor-Fc fusionprotein, infliximab, and tocilizumab.	Costs Were Derived From Publicly Available Sources	QALY	The introduction of tofacitinib into the current treatment sequence for moderate-to-severe RA patients with csDMARDs-IR in China was a cost saving option as first- and second-line treatment, and cost-effective as a third-line treatment option.

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