REVIEW ARTICLE

A Systematic Review of Models Used in Cost-Effectiveness of Treatments in Spondyloarthritis

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Conflict of Interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Abstract
This review was aimed to evaluate health economic models used in evaluations of different treatment strategies in spondyloarthritis (SpA). Model-based health economic evaluation studies are increasing and complex models with short-term and long-term horizon are applied to investigate the cost-effectiveness of SpA treatments. The objective of this study was to carry out a systematic review of the evolution of health economic models used in the treatment of SpA. Electronic searches within MEDLINE and EMBASE were carried out using a predefined search strategy. Inclusion and exclusion criteria were used to select relevant studies. Data on country, intervention, evaluation perspective, type of model, time horizon, types of costs and effectiveness measurement were extracted. Eighteen models were described in 22 publications, of which 81.8% were European. Study perspectives included the societal (n=6), healthcare system and payer (n=14), or patient and government (n=1). Time horizon ranged from 52 weeks to lifetime. Markov model was the most frequently used model, only one individual patient simulation models accounting for uncertainty in multiple parameters was reported. Most studies compared different biologics (including different TNFi/biosimilar and IL-17A antibody) with conventional care (NSAIDs) because of the high prize. Only half of studies took indirect costs into account. Modeling is of importance in health economic evaluations of SpA treatment. Long-term costs especially indirect costs should be considered when comparing different treatment alternatives in order to provide more information for policy makers and clinicians.

Key words: spondyloarthritis, cost-effectiveness, model

Introduction

Axial spondyloarthritis (SpA), including ankylosing spondylitis (AS) and nonradiographic axial SpA, is characteristic with chronic back pain with or without joint involvement and extra-joint manifestations. AS often causes severe disability and impaired quality of life[1]. The prevalence of AS is 0.1-0.5% worldwide[2] and a high prevalence of HLA-B27 is found. Although advance sacroiliac joint damage and spine ankylosing are present more in AS, the economic burden and utility damage are similar in nonradiographic axial SpA and AS patients[3,4]. The costs of AS consist of direct costs related to treatment and the indirect costs due to work disability[5]. More and more studies focused on the indirect costs due to work disability, absence from work or early retirement[6,7].

The aims of treatment in SpA are symptoms alleviation, function improvement, work-ability maintaining and quality of life improvement as much as possible. Nonsteroidal anti-inflammatory drugs (NSAIDs) was recommended as the first-line therapy by the Spondyloarthritis Research and Treatment Network, American College of Rheumatology, Spondylitis Association of America, Assessment of Spondyloarthritis International Society, and European League Against Rheumatism[8]. For patients without response or intolerance to NSAIDs, tumor necrosis factor inhibitors (TNFi) or an IL-17A antibody agent is considered. The introduction of biologics (TNFi and IL-17A antibody) to SpA has changed the treatment pattern, which were shown to be an effective treatment strategy, but overall direct costs associated with drugs increased substantially. However, the underlying improvement of function, work ability and quality of life may reduce the indirect costs in long-term. Therefore, economic evaluations are urgent needed for biologics in treatment of SpA.

The values of new health interventions are commonly assessed by modeling techniques. Studies evaluating cost-effectiveness of different treatment strategies by using modeling techniques have been conducted before[9-11]. The data provided by randomized controlled trials (RCTs) or observational studies is not long enough for economic evaluation. The model-based economic evaluation is of importance for health-care decision makers.

Several studies of the cost-effectiveness of AS treatments have been carried out in the last two decades. In 2012, a review of cost-effectiveness of therapeutic interventions in AS was conducted, which focus on the cost-effectiveness analysis[12] rather than modeling. Since that, new drugs and modeling techniques were introduced in the treatment of SpA. Therefore, the object of this study was to carry out a review of model-based studies to identify economic evaluation of AS treatments and to summarize the major structural characteristics of the published models.

Methods

This systematic review was performed by electronic searches of MEDLINE and EMBASE from 1974 to January 2021 followed the Preferred Reporting System for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[13]. Besides, references listed in relevant studies were hand searched to identify papers that were not identified in our electronic search.

Search strategy

We used MeSH headings and keywords to identify modeled analyses of SpA treatments. Details of the specific search strategies used for each database were listed in Appendix

1. Two reviewers independently screened the titles and abstracts of the identified citations according to the inclusion and exclusion criteria (Table 1). If disagreement between reviewers exists, both reviewers read and discussed the full text in order to

reach a consensus. Studies not based on model simulations were excluded as modeling techniques on treatment of SpA were focused rather than the cost-effectiveness or cost-utility ratios. The quality of included studies or the reliability of cost-effectiveness results generated by the models was not evaluated since this review focused on the illustrating and summarizing the evolution of key characteristics of models used in health economic evaluation of SpA.

Table 1. Inclusion and exclusion criteria.

Inclusion criteria (if all of the following met)	Exclusion criteria (if any of the following met)
1. Intervention was targeted at spondyloarthritis (including ankylosing spondylitis, non-radiographic axial spondyloarthritis and peripheral spondyloarthritis) in adults.	**1.** Studies not published in English.
2. Studies reporting models of health economic evaluation on SpA	**2.** Review, meta-analysis, commentaries/editorial, methodological paper
3. Studies included a cost-benefit analysis, cost-effectiveness analysis or cost-utility analysis on SpA.	**3.** No associated published full text.

Data extraction

Two reviewers extracted data on study characteristics, intervention characteristics, and economic evaluation information. Study country, time horizon, disease subtype of SpA, modeling techniques, types of cost and utility were extracted.

Result

Of 1089 articles identified from electronic search, 958 studies remained after duplication. After screening by title and abstract, 59 studies remained. A final total of 22 studies were included after screening for full-text. Included studies are detail in Table 2.

Eighteen models were used within 22 studies and some studies shared the same model structure in different countries. For example, Kobelt et al used same model for data analysis in UK[9] and Canada[14], Neilson et al[15] used the same model structure as Ara et al[16]. Eighteen (81.8%) of studies identified were based in a European setting, followed by Canada (9.1%), one from USA (4.5%) and one from Australia (4.5%). Only one study targeted in non-radiographic axial spondyloarthritis patients[17] while others focus on AS patients.

Table 2. Overview of studies included.

Reference	Country	Patient	Assessed intervention	Evaluation perspective	Type of model	Time horizon	Costs included		Effectiveness measurement	Discount rate	
							Direct	Indirect		cost	utility
Kobelt 2004	UK	AS	Infliximab vs. Placebo	Societal	Markov model	30ys	Y	Y	BASFI and BASDAI modelled onto utility	6%	1.5%
Boonen 2006	Netherlands	AS	Infliximab/etanercept vs. Usual care	Societal	Markov model	5ys	Y	Y	EQ-5D	4%	4%
Kobelt 2006	Canada	AS	infliximab vs. Placebo	Societal and healthcare payer perspectives	Markov model	30ys	Y	Y	EQ-5D	5%	5%
Ara 2007	UK	AS	Etanercept+NSAIDs vs NSAIDs	NHS perspective	Mathematical model	25ys	Y	N	BASFI and BASDAI modelled onto utility	3.5%	3.5%
Botteman 2007	UK	AS	Adalimumab vs. conventional therapy	Societal	Microsimulation model	30ys	Y	Y	BASFI and BASDAI modelled onto utility (HUI-3)	3.5%	3.5%
Jansen 2007	UK	AS	Etoricoxib vs non-selective NSAIDs	Societal	Decision-analytic model	52 weeks	Y	Y	BASFI and SF-36 modelled onto utility	NA	3.5%
Kobelt 2007	UK	AS	Infliximab vs. Placebo	Society and the NHS perspectives	Decision tree and Markov model	Life-time	Y	Y	EQ-5D	3.5%	3.5%
Kobelt 2008	Spain	AS	Infliximab vs. Placebo	Societal and healthcare payer perspectives	Decision tree and Markov model	40ys	Y	Y	BASFI and BASDAI modelled onto utility	3%	3%
Jansen 2010	UK	AS	Etoricoxib celecoxib diclofenac or naproxen	NHS perspective	Markov transition model	30ys	Y	N	BASFI and BASDAI modelled onto utility	3.5%	3.5%
Neilson 2010	Germary	AS	Etanercept+NSAIDs vs NSAIDs	Social health insurance and societal perspectives	Mathematical model	25ys	Y	Y	BASFI and BASDAI modelled onto utility (EQ-5D)	5%	5%
Jansen 2011	Norway	AS	Etoricoxib celecoxib diclofenac or naproxen	Health care perspective	Markov transition model	30ys	Y	N	BASFI and BASDAI modelled onto utility	4%	4%
Tran-Duy 2011	Netherlands	AS	Five available NSAIDs vs NSAIDs +two TNFi	Societal	Discrete event simulation model	70ys	Y	Y	EQ-5D	0.04 annual	0.015 annual
Tran-Duy 2015	Dutch	AS	NSAIDs vs NSAIDs + TNFi	Societal	Dynamic population model	20ys	Y	Y	BASFI and BASDAI modelled onto utility	4%	1.5%
Borse 2017	UK	AS	Golimumab vs conventional therapy and other TNFi	UK national health service perspective	Short-term decision tree and long-term Markov model	Life-time	Y	N	BASFI and BASDAI modelled onto utility	3.5%	3.5%
Borse 2018	Scotland	nr-axSpA	Golimumab vs conventional therapy and other TNFi	Scottish payer perspective	Short-term decision tree and long-term Markov model	Life-time	Y	N	EQ-5D	3.5%	3.5%
Colombo 2018	Italy	AS	Secukinumab	Italian national health service perspective	Cross-indication budget impact model	3ys	Y	N	NA	NA	NA
Emery 2018	UK	AS	Secukinumab vs TNFi or conventional care	UK national health service	Markov model	40ys	Y	N	BASFI and BASDAI	3.5%	3.5%

				perspective					modelled onto utility		
Schofield 2018	Australia	AS	Adalimumab vs. placebo	Patient and governmental perspectives	Microsimulation model	6ys	Y	Y	SF-36	NA	NA
Goeree 2019	Canada	AS	Secukinumab vs certolizumab pegol, adalimumab, Golimumab, etanercept and infliximab/biosimilar	Canadian healthcare system perspective	Decision-analytic model (semi-Markov)	60ys	Y	N	BASFI and BASDAI modelled onto utility	0.015 annual	0.015 annual
Purmonen 2019	Finland	AS	Secukinumab vs other biologics	Finnish health care system perspective	Decision-analytic model (semi-Markov)	Life-time	Y	N	BASFI and BASDAI modelled onto utility	3%	3%
Purmonen 2019	Finland	AS	Secukinumab vs adalimumab	Finnish health care system perspective	Spreadsheet model	5ys	Y	N	NA	NA	NA
Le 2020	US	AS	5 treatment strategies	US health care payer's perspective	economic patient-level simulation combining decision-tree and Markov models	10ys	Y	N	BASFI and BASDAI modelled onto utility	3%	3%

AS: ankylosing spondylitis, SpA: spondyloarthritis, NA: not applicable, Y yes, N no, NHS: National Health Service.

Interventions

Three studies[10,18,19] compared different NSAIDs in treatment of AS, while others included biologics (mainly TNFi and IL17A antibody). Of those studies including biologics, most of them compared TNFi/IL-17A antibody vs. placebo or NSAIDs. Three studies compared different biologics directly[20-22]. In other studies[23-25], sequential treatment strategies were assessed according to different treatment guidelines.

Interventions

Markov models (n=6), mathematical models (n=2), microsimulation models (n=2), decision-analytic models (n=3), decision tree and Markov models (n=4), discrete event simulation models (n=1), dynamic population models (n=1), cross-indication budget impact models (n=1), spreadsheet models (n=1) and economic patient-level simulation combining decision-tree and Markov models (n=1) were used.

Interventions

Fifteen studies stated that their analysis was performed from healthcare system and payer perspectives, six articles reported the societal perspective and one used patient and government perspective. All studies reported from societal perspective included indirect costs, while other eleven studies from healthcare system perspective considered direct costs only.

Discount rates

All articles discounted both costs and benefits, and one article discounted utility only[10]. Fifteen articles used same discounted rates (range from 3% to 5%) in costs and benefits, while two analysis[9,24] used different rates for costs and benefits. Only two articles justified the dependence of particular rates including "Dutch guideline"[26] and "UK guideline"[16] respectively.

Time horizon

All analyses were modeled based on data from RCTs or meta-analysis of previous studies, the time horizon ranged from 54 weeks to 10 years (n=6), 20-30 years (n=8), 40-70 years (n=4), life-time (n=4).

Reporting of costs

Half of studies reported both direct and indirect costs while others included direct costs only. Questionnaires assessing economic resource were used in same studies[11,27] while others gained information from local or country database. Direct costs such as drug acquisition costs, adverse events, general practitioner visits and inpatient costs were included. Indirect costs included sick leave, early retirement and working time reduction. Human capital approach[9-11,24] was used to assess indirect costs, both human capital approach and friction cost method were used in other two studies[15,26].

Reporting of utility

Several methods were used to measure health utility and expressed as quality adjust life year. In some studies, utility value is calculated by BASDAI, BASFI, gender and age[20,21,25,28,29]. Other measurements such as EQ-5D[11,15,23,24,26,30], Health Utilities Index 3[27] and SF-36 scores[10,31] were used. By using Health Utilities Index 3 and SF-36 scores, special models were constructed to estimate long-term utility through BASDAI and BASFI.

Reporting of cost-effectiveness

Most of studies reported TNFi[9,11,14-16,20,27,30] is cost-effective vs conventional therapy below willing to pay threshold or in the acceptable range. For NSAIDs, etoricoxib was found to be cost-effective compared to non-selective NSAIDs[10]. One study[15] indicated the cost-effectiveness of etanercept are different depending on a social health insurance (direct costs only) or a societal (direct plus indirect costs). Reporting of sensitivity analyses

One-way sensitivity analyses were performed to assess the robustness of their findings[15,16,20,26,28,30,32]. Probabilistic sensitivity analysis, which uncertainties were deal with sampling from distributions, was performed in two studies[17,25]. Both methods are used in another two studies[21,29].

Discussion

With the introduction of biologics such as TNFi and IL-17A antibody to SpA, the cost-effective of new interventions have been realized due to health-care budget constraint. Modeling has been used in the assessment of cost-effectiveness of SpA as an important decision analysis tool. This review provides an outline in terms of the development of modeling in SpA treatment.

Modeling techniques are increasingly used in the evaluation of cost-effectiveness of new interventions. Decision tree and Markov models are the most frequently used methods in health economic evaluation[33]. The decision tree has the simplest structure with associated probabilities and outcome measures. The Markov model is a health-state transition model in discrete time where patients moving through health states in predetermined time cycles. Markov models is usually used in chronic diseases such as osteoporotic fractures[34] and chronic kidney disease[35]. In this review, about half of included studies involved with Markov model. In Markov model, several states are identified and independent from each other, which is known as "memoryless"[36]. Discrete-event simulation and individual level model can account for the effect of individual patient history on future events that addressed the memoryless limitation of decision tree and Markov models[25,37]. Dynamic population model would consider new incident case as well as patients leaving the population over time because of death, it also takes treatment history and patient characteristics into consideration. There is one study used discrete-event simulation and one used individual level model in this review.

The recommended first-line treatment of active AS is continuous NSAIDs[8], while no preferred NSAID was recommended. Non-selective NSAID have been associated with an increased risk of gastrointestinal side effects because their inhibition of the gastroprotective COX-1 isoform. COX-2 selective inhibitors such as etoricoxib or celecoxib were developed to reduce gastrointestinal adverse effects when compared with nonselective NSAIDs. Three studies compared the cost-effectiveness of selective NSAIDs with non-selective NSAIDs, only one study[10] included indirect costs related to sickness absence rather than work disability or early retirement. All three studies indicated that etoricoxib was a cost-effective therapy compared with non-selective NSAIDs in AS patients. Previous models of cost-effectiveness studies in AS focused the comparisons between TNFi with conventional care or placebo. With the increasing types and frequently use of biologics, newly published studies also compared cost-effectiveness in different kinds of biologics. In addition, Tran-Duy[23] et al used sequential drugs such as different NSAIDs and TNFi to avoid unrealistic comparators such as a single TNFi against a single placebo or NSAIDs. Le at el[25] investigated the cost-effectiveness of different treatment strategies such as the sequential use of 2 TNFi and a TNFi followed by an IL-17A antibody agent, which is closer to real-world use of biologic and treatment guidelines. The use of memory models such as discrete-event simulation can also make it closer to realistic data.

Utility data is often retrieved form clinical trials or observational study and is expressed as QALY, which incorporates survival time and changes in quality of life expressed in utilities. Both direct measurement and indirect calculation method are used to assess QALY value. Visual analogue scale (VAS), standard gamble and time trade-off techniques are belonging to direct methods. Indirect methods include the health utilities index, the quality of well-being scale and the EQ-5D. EQ-5D is a widely applied[38] and a preferred instrument to calculate QALY by the health technology assessment guidelines in the majority of Central and Eastern Europe countries[39]. For AS patients, several tools including EQ-5D, SF-6D and the well-being rating scale were compared, and no special recommendation was made[40]. Utility are correlated with both disease activity and functional impairment in AS so that BASDAI/BASFI scores were used to calculate utility values in some studies. The chronic development course of AS make it hard to assess the change of functional impairment (BASFI) and some studies assumed the change of BASFI annually. Lack of real-world long-term data about quality of life of AS patients in natural course and after treatment is a limitation.

The data of studies included was retrieved from clinical trials or meta-analysis of RCT, which focused on active AS patients. There are lot of difference considering patient selection, difference in co-medications and co-morbidities and treatment adherence between RCT and clinical practice. RCT usually excludes patients with HBV or TB infections so that related medical costs may be underestimated in real world. It is important that studies also examine the cost-effectiveness within a real-world setting. Both short-term disease activity and long-term disease progression are related to cost-effectiveness in AS. Health economic benefit of TNFi for AS patients may be result to the improvement of BASDAI and BASFI from baseline and may be less dependent on changes in these scores over time. For this reason, the extrapolation of long-term results from a relatively short-term clinical trial may be limited. Some of studies used observational data and included response and

discontinuation rates in the model[9,11,14]. When non-responders stopped using high-cost interventions, the long-term cost of TNFi decreased during the subsequent years. It is inefficient to continue expensive treatments without an adequate response both from patients' and economic' view. It is reported that less than half of AS patients remain on their first TNFi after 5 years[41]. Reasons result in discontinuation include adverse event, high drug costs, efficacy decreased due to anti-drug antibody[42-44]. Discontinuation of biologic cannot be ignored because of the long-term course of cost-effectiveness analysis and major impact on costs. Besides, the management in stable stage of AS should be taken into consideration. Disease activity may be reduced quickly and stabilized after biologic treatment, the subsequent drug switch (switch to NSAIDs) or dose reduction may be considered in developing countries for reducing societal and personal burden.

AS mainly affects patients of working age and previous studies indicated indirect costs dominate total costs[45]. Indirect costs such as loss of wages, loss of productivity, early retirement should be taken into account when evaluating the cost-effectives of novel interventions. A societal perspective would incorporate direct costs, indirect costs and costs on added life years, and is recommended in some economic guidelines[46,47]. Categories of costs in the model should be in line with the evaluation perspective[34]. For some models without including indirect costs, the result of cost-effectiveness should be interpreted more carefully.

Conclusion

Modeling is of importance in health economic evaluations of SpA treatment. Model with individual level and allows new incident, can overcome the memorylessness so that is preferred. Long-term costs especially indirect costs should be considered when comparing different treatment alternatives in order to provide more information for policy makers and clinicians.

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