Pharmacoeconomics:Open Access
ISSN: 2472-1042

Tolley et al., Pharmacoeconomics 2018, 3:2
DOI: 10.4172/2472-1042.1000118

Review Article Open Access

A Systematic Literature Review and Critical Appraisal of Economic Modelling Approaches of Pharmacologic Interventions for Systemic Lupus Erythematosus (SLE)

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Abstract

Background: Systemic lupus erythematosus (SLE) is a complex, autoimmune disorder with long-term health consequences. Economic evaluation is used by health technology assessment (HTA) bodies to guide drug pricing and reimbursement decisions.

Objective: To conduct a systematic review to identify published economic analyses of pharmacologic treatments for SLE and summaries and critically appraise the modelling techniques used.

Methods: Electronic database searches were performed from January–February 2017. Supplementary searches of conference proceedings and HTA websites were conducted. Reference lists of included papers were examined for relevant studies.

Result: Fifteen relevant economic analyses were identified; all compared belimumab plus standard of care (SOC) with SOC. Most were full economic evaluations (n=13), with two considering a budget impact analysis alone. Eleven used a simulation structure to model interdependencies between multiple dimensions of SLE; one original model and ten country-level adaptations of the same model. Key assumptions were associated with duration of treatment effect for belimumab plus SOC and extrapolated treatment duration.

Conclusion: Limited economic evaluations of pharmacological treatments for SLE were identified. Future economic models in SLE should meet dual aims of transparency and robustness. Key recommendations include that a lifetime model is essential for handling short and long-term complications of SLE, including organ damage and flares, and whilst the simulation model has been shown to be acceptable, for transparency and ease of interpretation the Markov model could be an acceptable and robust modelling approach.

Keywords: Economic evaluations; Systemic lupus erythematosus; Appraise modelling techniques

Introduction

Systemic lupus erythematosus (SLE) is a complex, multi-organ, autoimmune disorder characterized by the production of pathogenic autoantibodies and tissue deposition of immune complexes that result in widespread tissue damage. SLE primarily affects women of childbearing age (the female to male ratio is approximately 9:1) [1]. A recent study reviewing the worldwide incidence and prevalence of SLE found that the greatest estimates of incidence and prevalence were in North America (23.2/100,000 person-years [95% confidence interval {CI} 23.4–24.0] and 241/100,000 people [95% CI 130–352], respectively), the lowest incidences of SLE were reported in Africa and Ukraine (0.3/100,000 person-years), and the lowest prevalence was in Northern Australia (0 cases in a sample of 847 people) [2]. The long-term health consequences of SLE include the impact on multiple organs such as the brain, blood and kidney, among others. The mechanism of organ damage is complex and may be caused by genetic, environment, hormonal, epigenetic and immunoregulatory factors [1]. In addition, the affected organ may be further damaged by local factors. Steroids have been the first and most frequently used immunosuppressant agents in SLE. Long-term steroid therapy is often associated with adverse effects, such as infections, diabetes, cataracts, osteoporosis, potential organ damage, and accelerated cardiovascular disease [3,4]. SLE impairs a patient's health-related quality of life (HRQOL) and imposes a significant economic burden on the health services that provide care for them, the patients themselves and society — as suggested by a systematic review of evidence on the humanistic and economic burden of SLE [5]. Treatments that can alleviate this burden are therefore likely to be highly valued by patients.

In 2007, the European League Against Rheumatism released recommendations for the treatment of SLE [6]. Their recommendations included that in patients with SLE without major organ manifestations, glucocorticoids and antimalarial agents may be beneficial, and that nonsteroidal anti-inflammatory drugs may be used for short periods in patients at low risk for complications from these drugs. They recommended that immunosuppressive agents (e.g. azathioprine, mycophenolate mofetil, methotrexate) can be considered in refractory cases or when steroid doses cannot be reduced to levels for long-term use. Biologic agents considered for SLE comprise monoclonal antibodies (chimeric, humanized or fully human), fusion molecules or antibody

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Received August 18, 2018; **Accepted** September 14, 2018; **Published** September 21, 2018

Citation: Tolley K, Cranmer H, Desta B, Tummala R, Tafesse E (2018) A Systematic Literature Review and Critical Appraisal of Economic Modelling Approaches of Pharmacologic Interventions for Systemic Lupus Erythematosus (SLE). Pharmacoeconomics 3: 118. doi:10.4172/2472-1042.1000118

fragments mostly consisting of B cell-targeted therapies beside anti-cytokines as well as T-cell-targeted therapies. The evidence on biologics is mostly provided by case series or uncontrolled studies. Larger randomized controlled clinical trials have frequently missed their primary endpoints with the exception of the BLISS clinical trials (BLISS-52 and BLISS-76) and a Phase IIb clinical trial for anifrolumab [7].

There is uncertainty as to which treatment provides the most cost-effective option and many health technology assessment (HTA) bodies, such as the National institute for Health and Care Excellence (NICE) in the UK, and the Institute for Clinical and Economic Review in the US, use the results of economic evaluations to provide information to healthcare payers, and to aid pricing and reimbursement decisions. Within an economic model, the long-term and multiple organ involvement nature of SLE leads to complex methodological approaches and assumptions required to extrapolate long-term outcomes. Varying these assumptions can potentially have a significant impact on the valuation of treatments. However, a comprehensive review of the methodologies used in published studies considering the economic evaluation of pharmacologic treatments for SLE is lacking. Therefore, we sought to systematically review and collate the current economic evaluation evidence associated with pharmaceutical interventions for SLE and to identify modelling methodologies that have been used previously in SLE, with a focus on how the complexities of long-term disease outcomes have previously been modelled. This review aims to assist researchers and decision makers in the development and interpretation of future health economic models in this complex area.

Methods

Literature search

We performed a systematic search to identify studies reporting on economic evaluations in SLE. The following databases were searched: Ovid MEDLINE, MEDLINE In-Process, Ovid EMBASE, EconLit, Database of Abstracts and Review of Effects and the Cochrane Library. Additionally, key international HTA websites were searched: NICE, Scottish Medicines Consortium, Canadian Agency for Drugs and Technologies in Health, Institute for Quality and Efficiency in Healthcare. Searches for grey literature were undertaken to capture evidence presented at relevant conferences that had not yet been published as full-text journal articles. Only conference abstracts published within the last four years were considered for inclusion. Searches were conducted between January and February 2017 and were in line with HTA requirements for systematic reviews. The full search strategy is presented in Appendix A.

Study selection

Two reviewers independently screened the titles and abstracts of the unique citations to determine their relevance based on pre-defined inclusion and exclusion criteria (primary screening). Any disagreements were resolved by discussion and consensus. The two reviewers then retrieved the full text of the citations included from primary screening and applied the criteria (secondary screening). The following inclusion criteria were applied: (1) adults (≥ 18 years) with SLE including specific manifestations of organ damage in SLE, (2) pharmacologic interventions for SLE, (3) economic outcomes: cost per quality-adjusted life-year (QALY), cost per life year, cost per clinical outcome or budget impact, (4) economic evaluations: cost-consequence, cost-minimisation, cost-effectiveness, cost-utility, cost-benefit, cost of illness and budget impact models, (5) publication types: journal articles, reports and summaries, (6) English studies and (7) full-text papers published from 2006 (inclusive) to 2017 and conference abstracts published within the last four years.

Papers considering pregnant patients with SLE were excluded. Furthermore, papers considering healthy volunteers, animals or patients with lupus nephritis were excluded. Systematic literature reviews were excluded after the reference list had been checked for any relevant studies not captured by the search criteria. Letters, newsletters, bulletins, editorials, commentaries and fact sheets were excluded.

Data extraction and analysis

We developed a data extraction table in Microsoft Excel to record the characteristics and results of each included study. The extracted data included: study characteristics (including: location, perspective, objective, study design and treatments), model design (including: model structure, time horizon, cycle length, description of health states, main outcomes and key assumptions), efficacy data (including: source of data, measurement of response, after trial benefit of treatment, extrapolation of long-term outcomes, treatment discontinuation rules and organ damage considered), baseline patient characteristics, costs, resource use, HRQOL and key results (including base case results, scenario analyses and sensitivity analyses). Where available, descriptive statistics, such as means and percentages, populated the data extraction table. Data were extracted from all the included full text articles by one reviewer. All extracted data were then quality checked against the original source article by a second researcher. The extraction table provided a basis to obtain a general overview of the studies and their methodology.

Quality appraisal

Included papers were appraised using the quality appraisal checklist for economic evaluations presented in the Methods for the Development of NICE Public Health Guidance (third addition) [8]. This particular checklist was selected as it aligns with key HTA requirements, specifically NICE. The main aim of the checklist is to determine whether a study provides evidence that is useful to inform the decision-making of the public health advisory committees. The checklist considers two themes: (1) the applicability of the paper to the review questions and (2) the study limitations in terms of the level of methodological quality. The checklist comprises three different sections: applicability, limitations and overall assessment; each section contains several subsections. Overall, 20 criteria were assessed shown in Table 1. The checklist allowed for categorical responses: "yes", "partly", "no", "unclear" and "NA" for 19 criteria. The final criteria allowed for a summary of the overall assessment.

Results

Studies identified

A total of 4831 papers were identified from the electronic searches. After removal of duplicates, 3695 papers remained. After title and abstract screening, 3655 papers were removed as these were not of relevance to the research question. A total of 41 articles were assessed in full for further evaluation. Of these, 30 were excluded based on publication type (n=17), outcome (n=9), study type (n=3) and date (n=1). This left a total of 11 papers for data extraction. Manual searches for key international HTA websites and disease-specific conference websites identified four additional papers and resulting in 15 papers for data extraction. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram depicting the flow of the economic evaluation review is presented in Figure 1. Of these

Categories to complete with "yes", "partly", "no", "unclear" and "NA" responses
Author
Year
Study title
Applicability
1.1 Is the study population appropriate for the topic being evaluated?
1.2 Are the interventions appropriate for the topic being evaluated?
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?
1.4 Was/were the perspective(s) clearly stated and what were they?
1.5 Are all direct health effects on individuals included, and are all other effects included where they are material?
1.6 Are all future costs and outcomes discounted appropriately?
1.7 Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)?
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?
Study limitations
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?
2.3 Are all important and relevant outcomes included?
2.4 Are the estimates of baseline outcomes from the best available source?
2.5 Are the estimates of relative 'treatment' effects from the best available source?
2.6 Are all important and relevant costs included?
2.7 Are the estimates of resource use from the best available source?
2.8 Are the unit costs of resources from the best available source?
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?
2.11 Is there any potential conflict of interest?
2.12 **Overall assessment:** minor limitations/potentially serious limitations/very serious limitations. Comments here. Comment on the applicability to HTA modelling within the countries specific to lupus

Table 1: Checklist used in the critical appraisal of identified studies.

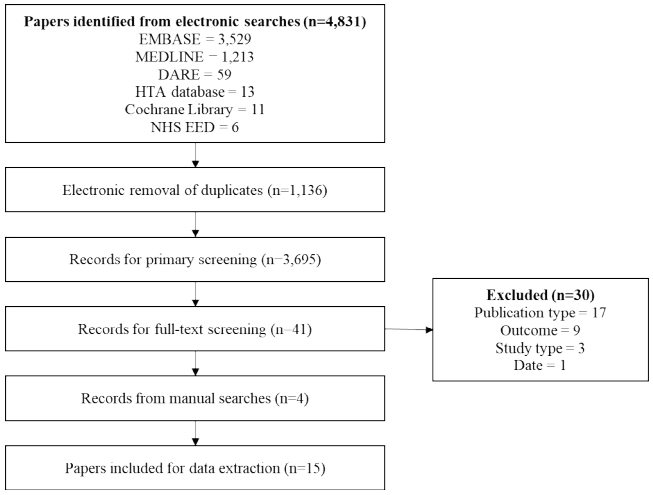

Figure 1: PRISMA diagram of the systematic literature search. EED Economic Evaluation Database, HTA health technologist assessment, n number, NHS National Health Service, PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses, SLE systemic lupus erythematosus.

47% (7/15) could be considered to be fully peer reviewed articles - three selected studies were from peer reviewed journals, and four were HTA submissions, so had also been through a rigorous process of peer review by academic bodies as part of the HTA process.

Study characteristics

Table 2 provides an overview of the study characteristics of the 15 papers identified by the systematic review. Among the identified studies, seven were presented in an abstract format limiting the amount of information available from these publications, four were HTA submissions, three were journal articles and one study was described in both an abstract and a poster. Ten studies were conducted in Europe (including the UK), one in Canada, one in Hong Kong, one in Russia and two papers did not report a setting. All identified papers reporting an intervention and comparator related to one therapy belimumab plus standard of care, compared with standard of care (n=13).

Table 3 presents the methods and assumptions of the 15 papers identified by the systematic review and Table 4 presents the results associated with these studies. Belimumab is indicated as an adjunctive therapy in adult patients with active SLE, autoantibody-positive, with a high degree of disease activity (e.g. anti-double-stranded DNA [dsDNA] positive and low complement) [9]. Ten studies reported on this population, five of which did not provide sufficient detail as to the specific population covered. Of the ten belimumab studies that reported on the high disease activity subgroup, four specifically consider patients with a Safety of Estrogens in Lupus Erythematosus National Assessment SLE disease activity index (SELENA-SLEDAI) score ≥ 10 and one study presented results for SELENA-SLEDAI score ≥ 10 and SELENA-SLEDAI score ≥ 6. Nine studies reported from a payers' perspective, two studies considered a societal perspective and one study considered a social insurance perspective. Three studies did not specify a perspective. The two studies that reported on a societal perspective included indirect costs in Spanish and Portuguese setting with one study specifying use of the human capital method in capturing these costs.

The time horizon was typically stated and justified based on the nature of the disease or the duration required to capture all costs

Type of publication	Number of studies (%)
Abstract	7 (46.67%)
HTA submission	4 (26.67%)
Full publication	3 (20%)
Abstract and poster	1 (6.67%)
Setting	
Europe	10 (66.67%)
Canada	1 (6.67%)
Hong-Kong	1 (6.67%)
Russia	1 (6.67%)
Not reported	2 (13.33%)
Treatments	
Belimumab plus standard of care	13 (86.67%)
standard of care	13 (86.67%)
Not reported	2 (13.33%)
Model structure	
Simulation model	11 (73.33%)
Budget impact model	2 (13.33%)
Multistate Markov model	1 (6.67%)
Simulation and deterministic model	1 (6.67%)
Main outcomes	
ICER	11 (73.33%)
Budget impact	2 (13.33%)
Not reported	2 (13.33%)

Table 2: Overview of identified study characteristics (HTA: Health Technology Assessment; ICER: Incremental Cost-Effectiveness Ratio).

relevant to the decision problem. Twelve studies presented results over a lifetime horizon, the two budget impact models for belimumab considered a 4-year and 5-year time horizon and one study did not report a time horizon. Discount rates applied were shown to vary by jurisdiction. A discount rate of 3.5% was the most widely applied (n=5) with discount rates of 3.0% and 5.0% applied in three studies each. The belimumab model submitted to NICE considered a discount rate applied to the QALYs accrued in the model of 1.5% in a scenario analysis. The rationale was that the appraisal met the criteria for differential discounting of health benefits which can be applied in submissions to NICE when treatment effects are both substantial in restoring health and sustained over a very long period. However, this rationale was rejected by the NICE Committee as the treatment effect associated with belimumab beyond 52 weeks is uncertain.

Model structure

Most identified evaluations were full economic evaluations (n=13), two of which considered a budget impact analysis alone. All evaluations were designed as a computer model (typically in Microsoft Excel®). The simulation model was the most frequent structure (n=11) adopted with incremental cost-effectiveness ratio (ICER) as the main outcome. The micro-simulation model submitted by GlaxoSmithKline (GSK) to NICE in 2011, henceforth termed the NICE UK model, was the earliest economic evaluation identified for the treatment of SLE and formed the basis of ten country-level adaptations reported across 11 studies. The model was adapted for both Canadian and Scottish submissions (and a re-submission) but was also locally adapted to the following countries: Poland (n=1), Hong Kong (n=1), Portugal (n=1), Spain (n=1), Greece (n=1) and Italy (n=2). The Italian adaptation was reported in two publications describing the same model. The remaining identified studies used a Markov model, a microsimulation/alternative deterministic model and two budget impact models.

The economic model submitted to NICE (NICE UK model) was a simulation model capturing interdependencies between patient characteristics, disease activity (based on SELENA-SLEDAI), organ damage, mortality and steroid treatment [10-15]. Organ damage and complications was considered across 12 disease domains obtained from the Systemic Lupus International Collaborative Clinics score and included cardiovascular, diabetes, gastrointestinal, malignancy, musculoskeletal, neuropsychiatric, ocular, peripheral vascular, premature gonadal failure, pulmonary, renal and skin disorders. The model used an integrated set of regression equations to predict the long-term outcomes (organ damage and mortality) from the short-term observed trial outcomes (SELENA-SLEDAI). The model simulated patients' baseline characteristics and then each year the patients' situation was re-established [16-21]. The economic analysis considered the results of 50,000 simulated patients, with the incremental results averaged across all simulated patients. The NICE UK model, though capturing most of the outcomes relevant to SLE, did not capture outcomes associated with flares. This model structure did not appear to vary across any of the model adaptations.

One study [22,23] presented a multistate Markov model based on health states defined on long quiescence (or remission), chronic activity and relapsing-remitting (or flare). SLE disease activity patterns were defined using Physician Global Assessment (PGA) and SLEDAI: long quiescent, SLEDAI/PGA=0 for all visits; relapsing-remitting, periods of disease activity (SLEDAI/PGA>0) interspersed with periods of disease inactivity (SLEDAI/PGA=0); chronic active, SLEDAI/PGA scores>0 for all visits. Multistate Markov models were used to provide estimates of relative transition rates and identified predictors of change in disease activity patterns.

One study [24] compared the NICE UK model with an alternative deterministic model. The authors aimed to overcome the disadvantages associated with microsimulation models (increased simulation time and advanced programming) by rebuilding the NICE UK model in an alternative deterministic framework. The alternative structure assumed that organ damage health states were not mutually exclusive, and this reduced the number of required health states from 4,096 to 15. Results associated with SELENA-SLEDAI, average mean SELENA-SLEDAI and musculoskeletal damage over time were similar between the two models, with relatively small differences in total costs and QALYs estimated with the two modelling approaches. Total costs estimated with the microsimulation model in the standard of care arm were £102,000 compared to £97,000 per patient with the deterministic model, and QALYs estimated were similar at 9.27 and 9.52 per patient with the simulation and deterministic models respectively. Differences in costs and QALYs in the belimumab arm did also not exceed 7%. Hence, these results are supportive of the use of a simpler deterministic modelling approach.

Two studies [21,22] reported on a budget impact model; one that estimated the budget impact from the introduction of belimumab and one that estimated both the budget impact and the impact on exacerbations (flares) – outcomes associated with organ damage were not considered.

Efficacy data

Only three data sources were reported across all identified studies: two pivotal Phase III clinical trials (BLISS-52 and BLISS-76) and registry data recording data on a large population of patients with SLE from Baltimore, Maryland (John Hopkins Registry). The NICE UK model utilised all three data sources to establish links between

Reference	Type of publication	Perspective	Population	Model structure	Time horizon	Discount rate	Key assumptions
GlaxoSmithKline 2011 [10]	NICE submission	UK NHS and PSS	High degree of disease activity (e.g. anti-dsDNA positive and low complement) and SELENA-SLEDAI score ≥ 10	Simulation model	Lifetime	3.50%	Constant treatment effect after 52 weeks
							Maximum 6-year treatment duration
							Annual discontinuation rate of 13%
							Only patients achieving an improvement in SELENA-SLEDAI score of ≥ 4 at week 26 continue treatment
GlaxoSmithKline 2012 [11]	CADTH submission	Canadian payers	High degree of disease activity (e.g. anti-dsDNA positive and low complement) and SELENA-SLEDAI score ≥ 10	Simulation model	Lifetime (~25-years)	NR	Maximum 6-year treatment duration
							Only patients achieving an improvement in SELENA-SLEDAI score of ≥ 4 at week 26 continue treatment
GlaxoSmithKline 2012 [12]	SMC submission	Scottish payers	High degree of disease activity (e.g. anti-dsDNA positive and low complement) and SELENA-SLEDAI score ≥ 10	Simulation model	Lifetime	3.50%	Maximum 6-year treatment duration
							Annual discontinuation rate of 8%
							Only patients achieving an improvement in SELENA-SLEDAI score of ≥ 4 at week 26 continue treatment
GlaxoSmithKline 2017 [13]	SMC re-submission	Scottish payers	High degree of disease activity (e.g. anti-dsDNA positive and low complement) and SELENA-SLEDAI score ≥ 10	Simulation model	Lifetime	3.50%	Maximum 6-year treatment duration
							Annual discontinuation rate of 8% in year one then 11.7% in subsequent years
							Only patients achieving an improvement in SELENA-SLEDAI score of ≥ 4 at week 26 continue treatment
Walczak et al. 2013 [14]	Abstract	Polish public payer		Simulation model	Lifetime	NR	NR
Lee et al. 2013 [15]	Abstract	Hong-Kong healthcare		Simulation model	Lifetime	5%	NR
Gouveia et al. 2013 [16]	Abstract	Portuguese societal		Simulation model	Lifetime	5%	Maximum 3-year treatment duration
Vallejo-Aparicio et al. 2014 [17]	Abstract	Spanish societal		Simulation model	Lifetime	3.00%	Maximum 2-year treatment duration
Athansakis et al. 2014 [18]	Abstract and poster	Greek social insurance		Simulation model	Lifetime	3.50%	NR
Pierotti et al. 2015 [19]	Full publication	Italian NHS		Simulation model	Lifetime	3.00%	Maximum 6-year treatment duration
							Treatment effect assumed from 52 weeks to 6-years.
Specchia et al. 2014 [20]	Full publication	Italian NHS		Simulation model	Lifetime	3.00%	Maximum 10-year treatment duration
Kulikov et al. 2014 [21]	Abstract	Russian		Budget impact model	5-year	5.00%	NR
Fu et al. 2016 [22]	Abstract	NR		Multistate Markov model	NR	NR	NR
Pierotti et al. 2017 [23]	Full publication	Italian National Health System		Budget impact model	4-year	Not applied	Market share assumed to be 10%, 33.50% and 49.30% for belimumab in years 1-3.
							Frequency of flares at week 52 was assumed constant in the subsequent years
							Discontinuation at 6 months based on the BLISS trials
							Drug wastage included
Van Oostrum et al. 2016 [24]	Abstract	UK NHS and PSS		Microsimulation and alternative deterministic model	Lifetime	3.50%	NR

Table 3: Overview of methodology of published economic evaluations of pharmacological interventions for SLE.

Reference	Incremental cost-effectiveness ratio (cost per QALY)[a]	Budget impact results
GlaxoSmithKline 2011 - NICE submission [10]	£59,946 (without PAS)	
GlaxoSmithKline 2012 - CADTH submission [11]	$CaD112,883	
GlaxoSmithKline 2012 - SMC submission [12]	£44,516	
GlaxoSmithKline 2017 - SMC re-submission [13]	£26,756 (with PAS)	
Walczak et al. 2013 [14]	113,986 PLN	
Lee et al. 2013 [15]	$US79,407	
Gouveia et al. 2013 [16]	€ 25,917	
Vallejo-Aparicio et al. 2014 [17]	€ 23,158	
Athansakis et al. 2014 [18]	€ 27,254	
Pierotti et al. 2015 [19]	€ 32,859	
Specchia et al. 2014 [20]	€ 32,859	
Kulikov et al. 2014 [21]		The use of belimumab led to a reduced difference in the required budget funds from 2,118,449 RUB/ €45,581 to 1,876,965 RUB/ €40,385 and the reduction ran as high as 241,484 RUB/ €5,196 for 5 years.
Fu et al. 2016 [22]	NR	
Pierotti et al. 2017 [23]		Incremental budget impact: €4,436,492, €14,611,342 and €20,387,228.
Van Oostrum et al. 2016 [24]	NR	

Table 4: Overview of results of published economic evaluations of pharmacological interventions for SLE (all relate to belimumab). CaD: Canada; CADTH Canadian Agency for Drugs and Technologies in Health; ICER: Incremental Cost-Effectiveness Ratio; NICE: National Institute for Health and Care Excellence; NR: Not Reported; PAS: Patient Access Scheme; PLN: Polish Zloty, QALY: Quality Adjusted Life Year, RUB: Russian Ruble, SLE: Systemic Lupus Erythematosus; SMC: Scottish Medicines Consortium; SoC: Standard of Care; US: United States, [a]Total costs and QALYs were not reported across studies. Additionally, the ICER presented for the NICE submission represents the final ICER that was used for decision making.

short term outcomes (SELENA-SLEDAI) and long-term outcomes (organ damage and mortality) that are integrated into the model using 13 regression equations. The short-term disease activity (SELENA-SLEDAI) data were obtained from the BLISS-52 and BLISS-76 clinical trials. Data associated with SLEDAI and long-term organ damage was obtained from the John Hopkins registry. To provide a link between the two data sources it was assumed that the small difference in classifications between SELENA-SLEDAI and the original SLEDAI would not influence model results. Disease activity models were fit to these data such that the adjusted mean SLEDAI (AMS) score could be predicted for patients based on treatment and response. From this, organ damage and mortality was predicted as a function of AMS score. The model used AMS score rather than SELENA-SLEDAI score to reflect disease activity over time, as the SELENA-SLEDAI score only reflects disease activity during the preceding 10 days. AMS was calculated as the area under the curve of disease activity measurements between two time-points and divided by time of follow-up. Adverse events were not included in the model as no significant difference was observed in this outcome in the clinical trials. In a review of the NICE UK model, the review group concluded that the methods were necessary (given lack of alternative data) and appropriate. However, there were concerns associated with the differences in population characteristics between the BLISS clinical trials and the John Hopkins registry. These methods appeared to be used in all the model adaptations of the NICE UK model. One study also updated the epidemiological data based on country specific Hong-Kong inputs, where available.

The multistate Markov model used data only from the John Hopkins registry. Patients with SLE were followed up quarterly in the Hopkins Lupus cohort for 1–28 years. Medication, disease activity (PGA and SLEDAI), complement levels (C3 and C4), anti-dsDNA, antiphospholipid antibodies and urine protein/creatinine ratio were recorded at each visit. For each patient, visits were divided into 1-year blocks. Any 1-year block with only one visit or patients followed for only 1-year were excluded in the analysis. Multistate Markov models were then used to provide estimates of relative transition rates and identified predictors of change in disease activity patterns.

Pierotti et al. [23] required inputs associated with discontinuation and prevalence of flares within their budget impact model. The probability of discontinuation (19.5%) at 6-months and the total number of severe and non-severe flares were obtained from the pooled analysis of the BLISS-52 and BLISS-76 clinical trials. Two studies did not report efficacy source.

Cost data

Costs were obtained from country specific sources. The NICE UK model included costs associated with treatment and administration, management of SLE, disease activity and long-term organ damage. Belimumab is an intravenous biologic drug, available as a 120-mg vial and a 400-mg vial, and the dose depends on the weight of the patient (10 mg/kg). Therefore, in some cases wastage is expected for patients whose weight requires them to receive only a part of a vial. The NICE UK model considers the optimal vial combination and accounts for costs associated with wastage. These assumptions are consistent with those reported in Pierotti et al. and Pierotti et al. 2016 [23,19]. None of the other identified studies specified assumptions associated with wastage.

In the NICE UK model, costs associated with management of SLE included surgeries or procedures, accident and emergency attendances, nursing home or rehabilitation centres, overnight hospitalisations, hospital stay, healthcare professionals, tests and diagnostic procedures. A regression equation estimated 6-month direct costs as a function of disease activity (SELENA-SLEDAI), predicting: £515.06 for no disease activity, £664.16 for mild disease activity (score 1–4), £813.26 for moderate disease activity (score 5–12) and £962.36 for severe disease activity (score>12). A literature search was conducted to identify costs associated with each of the 12 organ systems included in the model. Costs were differentiated based on first, second and subsequent years after development of organ damage. For country adaptations of the NICE UK model, local cost sources were used. Where country specific costs were unavailable, UK costs were converted into the local currency using exchange rates (reported in two studies and implied in a further two studies). The first budget impact model included drug costs, administration, diagnostic laboratory and instrumental procedures, inpatient and outpatient visits, SLE complications and adverse event costs in the total direct costs. The later budget impact model included drug costs, administration, clinical monitoring (tests, exams and visit costs) and cost of flares. Two studies did not report any detail on costs.

HRQOL data

SLE can have a substantial impact on HRQOL. With the cumulative effect of oral corticosteroid use and the natural progression of organ damage, HRQOL is likely to decrease over time. HRQOL impact was captured in 12 of the 15 papers identified in this review.

The only reported source of HRQOL data associated with SLE in the identified studies was from the two Phase III clinical trials. The EQ-5D, a generic HRQOL instrument, was collected during BLISS-52 and BLISS-76. The submission to NICE describes in detail how these data were applied in the economic model. Pooled EQ-5D data from the BLISS trials were converted into utility values using a UK-specific algorithm [25]. A linear mixed model was fit to these data and included baseline variables (baseline characteristics, organ damage and organ involvement). Variables with a p-value ≤ 0.05 were selected for the final model. Based on this selection criterion the following variables were maintained: age, black ethnicity, SELENA-SLEDAI score and damage in ocular, neuropsychiatric, musculoskeletal and diabetes organs. No statistically significant relationships between other organ damage items and HRQOL were found. However, this was not considered to imply that there was no HRQOL impairment associated with these manifestations. Rather, this finding was a result of limitations with the data; only 41% of patients in the trials had organ damage and only 18% had an SDI score ≥ 1. Therefore, there were insufficient data to establish relationships between HRQOL impairments and types of organ damage. To account for this, the final utility equation did not include any types of organ damage and disutilities associated with each manifestation were then applied to this utility if a patient developed the specific organ damage in the model. The final utility equation was:

$$Utility = 1.275 - 0.140 \times \log(AGE) - 0.036 \times BLACK - 0.009 \times SELENASLEDAI$$

It was noted that patients can experience disease flares at any time and not necessarily at the time point at which the EQ-5D was completed in the clinical trials. Therefore, the EQ-5D data from the BLISS clinical trials may underestimate the impact on HRQOL.

Assumptions

All economic models incorporate a set of assumptions; key assumptions were associated with the duration of treatment effect for belimumab plus standard of care and extrapolated treatment duration. These assumptions are shown to vary across the publications (Table 3). Of the simulation models, maximum treatment with belimumab plus standard of care was assumed to be 6-years (n=5), 10-years (n=1), 2-years (n=1), 3-years (n=1) and one study did not report on this assumption. Only three papers reported on annual discontinuation rates: 13% (n=1), 8% (n=1) and 8% in year one followed by 11.7% in subsequent years (n=1). Four studies also reported on the stopping rule whereby only patients who achieved an improvement in SELENA-SLEDAI score of ≥ 4 at week 26 continued treatment. As part of the NICE submission for belimumab plus standard of care, NICE commissioned the Decision Support Unit (a UK-based academic unit that supports NICE in addressing methodological challenges that arise in company submissions) to conduct additional work into the discontinuation rates associated with treatment. However, the results from three clinical experts showed large variability which could not be used robustly in economic analyses. None of the other identified studies presented rationale or evidence to support assumptions associated with treatment duration. Another critical assumption was around the extrapolation of the treatment effect for belimumab plus standard of care beyond the trial data. Because of a lack of data, it was assumed that the treatment effect was maintained from week 52 to the point of discontinuation of belimumab treatment – this was reported in two of the identified studies.

Results and sensitivity analyses

Across the identified cost-effectiveness analyses, the ICER for belimumab plus standard of care vs. standard of care alone varied greatly. However, comparisons between papers are difficult due to the different settings reported, different currencies and the lack of detail provided on model inputs.

Five studies reported the main drivers of the model results via a one-way deterministic sensitivity analysis and/or scenario analyses; four relating to the simulation models and one budget impact model. One-way analyses were conducted by varying each parameter within the model, in turn, between their lower and upper bounds. Scenario analyses involved varying selected parameters of interest. These drivers were either presented in a tornado diagram, in a table or both. In the simulation models, the most prominent model drivers were the treatment effect associated with belimumab after 52 weeks and the discontinuation rate from belimumab assumed (i.e. the duration of treatment). The main outcome in these studies was the ICER (Table 4): the smaller the treatment effect associated with belimumab relative to standard of care was, the lower the incremental QALYs and the greater the estimated ICERs. Treatment duration with belimumab impacts both incremental QALYs and costs and thereby the ICER. In some analyses, the terms comprising the utility equation were also shown to have a significant impact on results. Scenario analyses assuming no vial wastage in the administration of belimumab and inclusion of indirect costs (e.g. economic productivity outcomes) produced improved cost-effectiveness results for belimumab. However, one-way sensitivity analyses and scenario analyses do not account for the correlation between variables and so these results should be interpreted with caution and alongside the results of the probabilistic sensitivity analyses. The budget impact model reporting a deterministic sensitivity analysis found that the prevalence of patients diagnosed with SLE, active disease and mean body weight were the biggest drivers in the model. Scenarios based on treatments per year (instead of patients per year) and use of rituximab independent of the availability of belimumab also had an impact on the budget impact estimates.

Six studies reported results associated with a probabilistic sensitivity analysis; five simulation models and one budget impact model. In the NICE submission, the probability of belimumab being cost-effective was unavailable because the manufacturer's price discount applied to belimumab was confidential. However, without the price discount, belimumab was associated with a 0% chance of being cost-effective at a threshold of £30,000. Four studies considered the probability of belimumab being cost-effective compared with standard of care based on a threshold of €30,000, and these probabilities varied from 29.1% to 68%. The probabilistic sensitivity analysis conducted as part of the budget impact analysis found that the uncertainty interval for the overall budget impact ranged from €26,057,629 to €56,186,750.

Quality of studies

We assessed the quality of the identified studies using the checklist presented in Table 1. Nineteen criteria were assessed based on categorical responses, which were collated and presented for each study in Figure 2. It is shown that the NICE submission for belimumab was considered the most robust source of economic evidence with ~90% of the criteria considered. The checklist found that the majority of studies

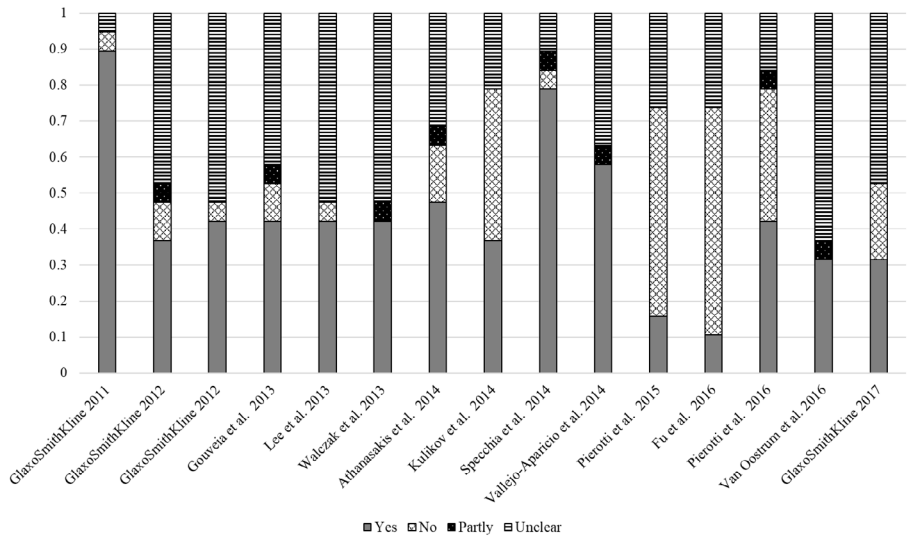

Figure 2: Overview of the results of the quality appraisal checklist assessment of the economic studies.

were lacking sufficient detail and as such it was unclear whether the criteria had been considered – this is in line with what we would expect, as the review identified multiple abstracts. The four identified studies that did not use a simulation model were shown to be of low quality with the majority of responses as "no" or "unclear", highlighting the lack of informed alternatives to the simulation model for economic evidence.

Discussion

This systematic review aimed to assess the methods used in published studies considering the economic evaluation and budget impact of treatments for SLE. The quality of information reported in the identified studies varied; several publications provided a detailed description of model structure and inputs. However, most of the identified studies were abstracts only, with insufficient information from which to draw conclusions on the robustness of the models.

Our review highlighted the limited economic modelling of SLE that has been published. Of the 15 studies identified, only one therapy has been evaluated – belimumab. As only one therapy has been covered, it is not surprising that the same model structure has been adopted in almost all of the full economic evaluations (i.e. the simulation model), with adaptations for country specific and HTA settings. This model has undergone validation and review through the HTA processes in the UK and Canada, and via peer review in the Italian context (see Table 2). These countries have robust HTA review processes designed to aid pricing and reimbursement decisions, hence providing some degree of confidence in the validity and robustness of the model for decision making purposes. However, its applicability to countries outside of these settings has not been formally assessed. For real-world decisions making the characteristics observed in the BLISS clinical trials provide some indication as to the generalizability of the model results. However, further research into real-world data for SLE is required to quantify the potential bias. Only two studies presented alternative structures — a multistate Markov model and an alternative deterministic model, the methodology of which was difficult to assess as findings had been reported in abstract form only. Eleven papers discussed the same simulation model, which was written up in detail as part of the NICE submission [TA397], with country-specific adaptations such as costs and discount rates relevant to the specific jurisdiction. Furthermore, each country adaptation used different assumptions associated with the duration of treatment with belimumab.

This systematic review has several strengths: six major electronic databases were searched, and the electronic searches were supplemented with a search of grey literature, a PRISMA diagram is presented depicting the iterative process through which studies were included in the review and consistency and transparency are reflected at each stage of the review. Owing to differences across studies and insufficient detail provided in some studies, a robust conclusion with regards to the cost-effectiveness of belimumab plus standard of care was not possible to draw. This review provides an overview of the economic evaluations considering treatment of SLE and collates the methodologies and results into a tabular form that can quickly provide information to decision makers or economists exploring this area. In SLE to date the simulation model has been the structure predominantly used to estimate the cost-effectiveness of belimumab for SLE. The simulation model is described in detail in the literature, with key areas of uncertainty highlighted across the different country-level adaptations. The main strength of this modelling approach is that it can handle better variation in patient characteristics and the complexity associated with the range of possible long term health consequences associated specifically with SLE, compared to simpler modelling structures. The main limitation is the additional complexity and data needs for such a model, and the ability for an HTA decision making committee to understand the methods and results from such an economic analysis. This review has emphasised the data gaps within the literature, particularly with regards to: long-term treatment duration, and indicates where there would be value in collecting more data. Unfortunately, the identified studies themselves do not provide much information related to alternative modelling approaches, validation nor generalizability.

There are several limitations associated with the review: (1) only studies in English were included. Although this included most of the articles published, this may be considered a possible source of bias in the review and it is possible that economic evaluations for SLE other than those evaluating belimumab exist. However, we think this

is unlikely. (2) We used the quality appraisal checklist for economic evaluations presented in the Methods for the Development of NICE Public Health Guidance (third addition) to systematically assess the quality of the included studies. This checklist is based on subjective ratings which ask whether the study includes a certain feature and not how it is performed. The quality assessment of the 15 studies indicated that there is variability in quality, but this is related to the quality of reporting across studies, as most of the studies used a common economic model structure. Therefore, results do not reflect the quality of the methodology and should be interpreted with caution. This is also a common limitation of other quality-assessment tools, such as the Consolidated Health Economic Evaluation Reporting Standards tool. (3) We only included studies published within the last ten years and abstracts published within the last three. Although studies published prior to this are likely to be outdated and good quality abstracts are likely to have been published in full, this may also be considered as a possible source of bias in the review.

The cost-effectiveness and budget impact of belimumab has been explored across several countries and country-specific HTA bodies. Apart from the budget impact assessments, all studies have been cost-utility analyses, reflecting the preference of HTA bodies that evaluate cost-effectiveness as part of the value assessment. As shown from this review the results are variable, and the question of value is heavily country-specific and dependent on the specific value framework adopted, and the willingness to pay thresholds adopted. Belimumab has been evaluated across a wide range of country and HTA jurisdictions (UK, other European countries US, Canada, Russia) that adopt different criteria for assessing value (e.g. in the UK an upper limit of £30,000 per QALY gained is typically applied, whereas in the US it has been suggested that different public and private insurance programs could use different thresholds, reflecting variability in their budgets) [26]. The US has not typically adopted cost-effectiveness criteria directly for decision making regarding the funding of pharmaceuticals, although the Institute for Clinical and Economic Review in the US has adopted methodology very similar to that of NICE in producing reports assessing the cost-effectiveness of new therapies and is starting to be influential on payers and health care policy makers in the US. To date, the Institute for Clinical and Economic Review have not evaluated SLE therapies but that could change in the future if new 'high-cost' SLE therapies reach the market. As well as different assessments of value, decision makers may differ in their need for or preference for type of modelling approach. For example: in the UK, NICE and SMC require robust modelling methods which can include simulation, Markov type models or a range of other model structures in order to provide the most reliable estimates of cost-effectiveness of new therapies. A large number of other HTA bodies across countries are in line with the UK requirements, including Netherlands, Sweden, and in the US the Institute for Clinical and Economic Review). However, in some countries such as Spain and Italy budget impact has been more dominant in decision making, and economic modelling is less directly impactful. As a cautionary note, even those countries with more sophisticated HTA systems that require full economic evaluations, may not be inclined to consider novel or different approaches to modelling which limit comparability with previous drug appraisals.

With the lack of variety in economic modelling approaches across a range of SLE therapies, it was difficult to be fully conclusive from the review of the existing published economic evaluations regarding learnings for future economic models in SLE. The modelling approach used for the one SLE therapy to have been subject to a full economic evaluation, belimumab, has been the simulation model. This has been generally accepted as an appropriate approach by the HTA bodies in the UK and Canada that have rigorously appraised the economic models submitted – in that, in principle, modelling based on individual patient characteristics can better capture the complex and heterogeneous pathways of disease progression over the long-time horizon of SLE than a Markov model. However, one study that explored the use of a simpler deterministic model for the cost-effectiveness of belimumab produced similar results to those from a simulation model. Nonetheless, because of the many pathways of SLE disease progression, a standard Markov model could become unwieldy and complex in terms of the number of health states and the complexity of the interactions. More evidence of the use of Markov models would have enabled a more thorough discussion of the pros and cons of each modelling approach, but the only Markov study found was of limited value due to the lack of detail presented [22]. The criticism often levelled at simulation models by HTA bodies is a lack of transparency (i.e. fear of being a 'black box'), so it is advisable that any future developments of SLE models based on the simulation approach be fully transparent and easy to understand.

Based on this review, there are a number of recommendations that can be made that researchers should consider in the development and presentation of future health economic models of drug therapies in SLE for HTA purposes:

- Any economic model for SLE therapies should adopt a lifetime horizon, as the consequences of SLE are both short and long term and impact on both HRQOL and mortality risk, and so to provide an adequate reflection of cost-effectiveness for HTA decision making lifetime modelling is necessary.

- De-novo economic models should be clearly described in terms of structure and methodology. Any future economic model should consider all aspects of SLE, including organ damage and flares. These chronic adverse effects have a prolonged impact on costs and HRQOL and so should be included. A simulation model approach in principle appears an optimal structure to deal with the complexities and variability in short and long-term complications and has been accepted by NICE as appropriate for the belimumab modelling. However, there is a lack of experience with the use of a Markov modelling approach for long term extrapolation, hence further work is needed to explore the use of this modelling structure for new SLE therapies, as it is generally viewed as more transparent and less complex by HTA bodies. However, for HTA submissions the rationale for any departure from the simulation model approach previously used should be clearly stated.

- The John Hopkins registry dataset represents a valuable real-world dataset with which to estimate the impact of SLE on organ damage and can be used to extrapolate long term outcomes based on short term outcome measures captured within SLE therapy clinical trials (e.g. SELENA-SLEDAI score).

- Generic utility measures such as the EQ-5D may not be adequate in capturing the impact of flares on HRQOL in patients with SLE. Use of utility estimates elicited from disease specific measures (e.g. via mapping to EQ-5D) in sensitivity analysis represents an alternative option. Furthermore, the utility values derived from a UK tariff may not reflect the specific setting in which these values are applied, hence country specific values need to be applied to models submitted to HTA bodies in different countries.

- High uncertainty is likely to remain in extrapolation of long term treatment duration and effects, due to limited follow-up time in SLE drug clinical trials. Feedback from clinical experts can help

to inform the robustness of long-term extrapolations associated with the treatment effect and treatment duration. Due to the variability in clinical practice, we recommended seeking feedback from at least 3 clinical experts per country to arrive at a meaningful consensus that can be used in economic evaluations.

- Extensive deterministic and probabilistic sensitivity analysis should be employed to explore the robustness of results given the uncertainty encompassed within the inputs. Scenario analyses should test the assumptions within the model and vary assumptions associated with treatment effect and treatment duration.

Adaptations to the existing disease activity model embedded within the cost-effectiveness model should be clearly specified so it is clear where differences in results arise from. Alternative economic model inputs (e.g. costs, treatment pathway differences, comparators used in clinical practice) are likely to be required for submission to HTA bodies across different countries.

Conclusion

Limited economic analyses of SLE pharmacologic treatments have been performed and have primarily used a simulation approach to handle the complexities of long term outcome modelling. The available evidence suggests that the only relevant pharmacologic treatment for SLE is belimumab as an adjunct to standard of care. Belimumab plus standard of care is compared with standard of care alone in three unique cost-effectiveness models (two of which are not described in detail) and two unique budget impact models. It is difficult to draw any robust conclusions about cost-effectiveness and value from these evaluations because of the lack of distinct separation in the modelling approach, with only one therapy evaluated, but also because of differences in methods employed and settings across the economic studies. The main source of evidence was the submission to NICE for belimumab and there is limited evidence available on alternatives to this model structure and methodology. The key drivers of cost-effectiveness were the assumed treatment effect of belimumab relative to standard of care and the treatment duration with belimumab. For HTA purposes, future economic models in SLE should meet dual aims of transparency and robustness. Key recommendations in future economic modelling of new SLE therapies for HTA purposes include that a lifetime model is essential for handling short and long-term complications of SLE, and whilst the simulation model has been shown to be acceptable, for transparency and ease of interpretation the Markov model could be an acceptable and robust modelling approach, but more work is needed to explore this. There is clearly a need for more work around validation and peer review of alternative economic model structures in SLE across countries.

Compliance with Ethical Standards

Funding

This study was supported by AstraZeneca Pharmaceuticals LP. The authors received no financial support or compensation for publication of this manuscript.

Conflict of interest

H. Cranmer and K. Tolley received financial support for the research that supported this manuscript, B. Desta, R. Tummala and E Tafesse are employees of AstraZeneca who sponsored the original research.

Author's contributions

H. Cranmer conducted the literature review and was lead writer of the manuscript; K. Tolley contributed to the literature review and assisted with writing all sections of the manuscript; B. Desta, R. Tummala and E Tafesse, interpreted the evidence from the literature review and contributed to all sections of the manuscript writing and review.

Acknowledgement

Emma Boulton, Tolley Health Economics for preparation and proof reading of the manuscript. Kathleen Jenks-Grobben, AstraZeneca, for formatting of the manuscript in preparation for journal submission.

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