Cost-Effectiveness of Golimumab in Ankylosing Spondylitis from the UK Payer Perspective

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ABSTRACT

Introduction: Golimumab is a tumor necrosis factor-α (TNF-α) inhibitor for treatment of patients with severe, active ankylosing spondylitis. This study evaluated the cost-effectiveness of golimumab compared with conventional care and other TNF-α inhibitors in treatment of AS from the UK National Health Service perspective.

Methods: A long-term Markov model (with initial decision tree) was developed to simulate the progression of a hypothetical cohort of patients with active AS over a lifetime. The effectiveness outcome was quality-adjusted life-years (QALYs). Utilities were estimated by mapping Bath Ankylosing Spondylitis Functional Index scores, and the primary response measure was ≥50% improvement on the Bath Ankylosing Spondylitis Disease Activity Index at 12 weeks. Direct, medication, and AS management costs were included. Costs and outcomes were discounted at 3.5%.

Results: All TNF-α inhibitors were comparable to each other and superior to conventional care. The incremental cost-effectiveness ratios (ICERs) for TNF-α inhibitors were £19,070–42,532 per QALY gained compared with conventional care. Analyses of the ICERs for each TNF-α inhibitor compared with conventional care demonstrated that golimumab was the most cost-effective treatment, and that adalimumab and etanercept were dominated by golimumab. Sensitivity analyses confirmed the robustness of these analyses.

Conclusions: Golimumab may be considered a cost-effective treatment alternative for patients with active AS. With comparable costs and efficacy among TNF-α inhibitors, the choice of TNF-α inhibitor to treat AS is likely to be driven by patient and physician choice.

Funding: Merck & Co., Inc.

Keywords: Ankylosing spondylitis; Cost-effectiveness; Golimumab; TNF-α inhibitor; UK

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic, systemic rheumatic disease with major
consequences for patient health and well-being. It is the most common form of spondyloarthritis, and is characterized by progressive inflammation in the spine and sacroiliac joints that may be accompanied by extra-articular or peripheral joint manifestations affecting the eyes, skin, gut, or cardiovascular system [1]. The predominant symptom of AS is inflammatory back pain; as the disease progresses, a considerable proportion of patients may experience progressive limitation of spinal mobility [2]. In Europe, the prevalence of AS is estimated to be ~23.6 cases per 10,000, with variation between countries in prevalence and the criteria used to classify AS [3]. Men are ~2–3 times more likely to have AS than women [4]. The National Institute for Health and Clinical Excellence (NICE) has suggested that the prevalence of “clinically significant” AS is ~0.15% in the UK, and that there are ~2300 new cases each year in England and Wales [5].

AS has cost implications for healthcare services as well as wider society. In the UK, annual direct medical costs associated with AS per patient were estimated at £15,973 [6]. Elsewhere, mean annual direct costs associated with AS were reported to be €4578 in Canada, €4675 in Spain, and $17,728 in the USA [7–9]. Direct healthcare costs for AS have been found to be strongly correlated with both disease activity and functional disability [6, 10]. Functional disability is the most important predictor of total costs attributed to AS, indicating that interventions that preserve or increase patient functional ability might have the greatest potential to reduce costs associated with AS [10].

The short- and long-term goals of AS treatment are to relieve symptoms, reserve function, and maintain quality of life (QoL) [11]. Current standard care includes non-steroidal anti-inflammatory drugs (NSAIDs) for symptom relief; the use of disease-modifying anti-rheumatic drugs (DMARDs) has decreased due to evidence of lack of benefit [11]. Biologic therapies such as tumor necrosis factor-α (TNF-α) inhibitors have been shown to have efficacy in slowing disease activity. NICE has recommended the use of TNF-α inhibitors etanercept, adalimumab, certolizumab pegol, and golimumab in adults with active AS, to slow disease progression beyond reducing symptoms and potentially prevent structural damage [5, 12].

Key evidence for the clinical efficacy of golimumab in AS has come from the GO-RAISE trial, a phase 3, multi-center, randomized, double-blind, placebo-controlled study through week 104, and an open-label extension up to 5 years. In this trial, significantly more patients receiving golimumab (50 or 100 mg) achieved ≥20% reduction in Assessment in AS international Society (ASAS20) criteria compared with patients on placebo [13, 14]. Clinical improvement of the primary endpoint, ASAS20 at week 14, was sustained through week 256. Patients treated with golimumab also experienced significant improvement in physical function as early as week 14, which was maintained up to 5 years [13, 14].

While TNF-α inhibitors have been shown to be effective in reducing disease activity and improving function, they are relatively costly, and questions have been raised regarding their cost-effectiveness [15]. Accordingly, the aim of this study was to assess the cost-effectiveness of golimumab compared with conventional care and alternative TNF-α inhibitors for treatment of AS.

**METHODS**

**Study Design**

This study was a cost-utility analysis of golimumab using a decision-analytic model. The model comprised an initial decision tree for the induction phase and a Markov model for the maintenance phase. An initial short-term decision tree was used to represent patient pathways at the initiation of TNF-α inhibitor treatment in the GO-RAISE trial. The long-term Markov model simulated chronic progress in AS; its use in economic evaluations for AS was supported by existing studies [15–18]. Since AS has an impact on both morbidity (and thereby QoL) and mortality (i.e., overall survival), the utility of quality-adjusted life-years (QALYs) was employed. The analysis was undertaken from the perspective of the UK National Health Service (NHS) and personal and social services.
Model Structure

Figure 1a, b present the conceptual structure of the analytic model. Patients enter the initial decision tree on conventional care (Fig. 1a) or TNF-α inhibitor therapy if they have responded inadequately to conventional care. Patients who receive conventional care initially remain in the conventional care arm for the remainder of the time horizon (e.g., lifetime in base-case). Response to treatment is evaluated at 12 weeks and defined as an improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥50% from baseline (BASDAI50) [13, 19]. Patients responding to a TNF-α inhibitor continue on the initial treatment; other patients are switched to conventional care.

After the short-term decision tree, patients enter the Markov model (Fig. 1b) with a model cycle of 12 weeks to reflect the recommended response assessment at 12 weeks after initiation of treatment [5]. If patients have been on TNF-α inhibitors, they either stay on therapy (‘On treatment’), or discontinue due to lack of efficacy or adverse events (AEs) and switch to

Fig. 1 Model structure: a short-term model structure; b long-term Markov model structure. AS ankylosing spondylitis, TNF tumour necrosis factor
conventional care (‘Not on anti-TNFs’). It is assumed that patients stay on treatment with one TNF-α inhibitor and do not switch to a second TNF-α inhibitor, in line with the absence of available clinical evidence for sequential use. To account for gradual loss of treatment benefit in terms of Bath Ankylosing Spondylitis Functional Index (BASFI) scores after discontinuation [20], the model includes two 12-week tunnel states (‘Just discontinued’ and ‘Discontinued’) with a BASFI score halfway between that of conventional care and that of TNF-α inhibitors. Individuals who have been on conventional care are assumed to continue on this treatment. Patients can die at any point in the model. For the base-case analysis, a lifetime time horizon is employed that is consistent with the scope of this appraisal. Patients are followed up until 99 years of age, at which point 0.2% of patients are expected to be alive.

**Patient Characteristics**

This evaluation focused on patients eligible for the GO-RAISE trial (i.e., active AS according to the modified New York criteria) [21], aged ≥18 years with no previous history of active or latent tuberculosis. Active AS is defined as a BASDAI (scale: 0–10) score ≥4, and a spinal-pain visual analogue scale (VAS) (scale: 0–10) score ≥4, recorded on two separate occasions ≥12 weeks apart without any change of treatment (as defined by NICE) [5]. This population was similar to those studied in clinical trials of other TNF-α inhibitors in AS [22–26]. The baseline data for patients entering the analysis are based on the GO-RAISE trial, considering patients had a mean age of 39.3 years; had mean BASFI and BASDAI of 5.04 and 6.54, respectively; and 71.6% were male [13].

**Clinical Strategies**

In line with the scope for this study, other comparators for golimumab are biologic treatments licensed for use in the treatment of AS that have robust evidence for efficacy at the appropriate stage of the treatment pathway. In the model, the following TNF-α inhibitors were considered:

- **Golimumab:** 50 mg once monthly
- **Adalimumab:** 40 mg once every 2 weeks
- **Certolizumab pegol:** 400 mg at weeks 0, 2, and 4, then 400 mg every 4 weeks
- **Etanercept:** 50 mg once a week
- **Infliximab:** 5 mg/kg at weeks 0, 2, and 6, then every 6–8 weeks (mid-point of 7 weeks is assumed in the model)

Conventional care is defined as a combination of NSAIDs, COX-2 inhibitors, DMARDs, and physiotherapy.

**Model Inputs**

**Comparative Efficacy**

The key short-term comparative efficacy between clinical strategies was derived from clinical trials of TNF-α inhibitors identified through a systematic literature review and assessed using mixed treatment comparison, because of the absence of head-to-head clinical trials. To identify data to inform the network meta-analysis (NMA), two reviewers working independently, and in duplicate conducted a systematic literature search. MEDLINE, Embase, and the Cochrane Library were searched (from inception to February 2014). A search of health technology assessment (HTA) documents produced by NICE was also undertaken to identify any additional evidence. NMA was conducted within a Bayesian framework [27]. BASDAI50 at 12 weeks in relation to baseline from the NMA was used as short-term clinical outcome and response criterion, as recommended by AS guidelines [5, 15, 19]. NMA was also used for discontinuation and serious AEs (SAEs). The absolute treatment effect was used to calculate relative risk (RR) from odds ratios (ORs), for use in the economic model.

For long-term efficacy, long-term disease progression was captured by BASFI and BASDAI scores. Data from GO-RAISE were used to develop predictive equations of mean change from baseline in BASDAI and BASFI scores up to 24 weeks (the double-blind period), and between 24 and 104 weeks (the open-label extension):
• BASFI score (up to 24 weeks) = baseline BASFI – (0.1008 – 0.0284*age + 0.1780*baseline BASFI + 1.8096*treatment + 0.04156*male + 5.2226*week^(-2) – 14.6396*treatment*week^(-2))
• BASDAI score (up to 24 weeks) = baseline BASDAI – (0.4685 – 0.03999*age + 0.2212*baseline BASDAI + 2.0620*treatment + 0.2652*male – 3.4664*week^(-2) – 7.1029*treatment*week^(-2))
• BASFI score (24–104 weeks) = baseline BASFI – (0.4933 – 0.03915*age + 0.5706*baseline BASFI + 0.6523*male + 0.09524*log(week))
• BASDAI score (24–104 weeks) = baseline BASDAI – (0.6277 – 0.03531*age + 0.5762*baseline BASDAI + 0.2196*male + 0.2196*log(week))

The equations developed for golimumab were also used for other clinical strategies, assuming they produced the same improvement as golimumab.

After the trial period (104 weeks), BASFI score was assumed to deteriorate at a rate of 0.07 units/year for patients on conventional care. For patients on TNF-α inhibitors, it is assumed to level off for a further 2 years, then deteriorate at a rate of 0.035 units/year (i.e., 50% of the deterioration rate of conventional care), based on data in the literature [15, 28–31]. BASDAI scores were assumed to remain constant after the trial period.

It is assumed that patients discontinued treatment either due to a lack of efficacy or to SAEs. To week 12, response rate for each TNF-α inhibitor (assessed through BASDAI50) is therefore the key driver of difference in discontinuation rate between TNF-α inhibitors (i.e., if patients do not respond, they discontinue). In the absence of long-term discontinuation data for TNF-α inhibitors, the all-cause, annual rate of discontinuation for patients on golimumab was retrieved from the GO-RAISE 5-year follow-up [14] and applied to all TNF-α inhibitors in the model. The annual discontinuation rate of 6.1% is applied for the entire time horizon after week 12 in the base-case analysis (lower than the long-term, annual discontinuation rate of 15.0% stated in the previous review [15]). Patients who discontinued treatment are assumed not to switch to another TNF-α inhibitor. Patients on conventional care are assumed not to discontinue treatment due to lack of alternatives.

There is no published evidence on the impact of TNF-α inhibitors on mortality [15]. However, in view of evidence that AS reduces life expectancy [32–34], a standardized mortality ratio (SMR) of 1.47 was applied for all AS patients to mortality rates from the general population [33, 34] to estimate adjusted mortality rates for patients with AS.

AEs were included in the model to reflect the tolerability and safety profiles of comparator treatments. They were considered an event, not a separate health state, and their associated costs and disutilities were taken into account in the calculations. The NMA found no statistically significant difference between the rates of SAEs for different TNF-α inhibitors, so equivalence was assumed between these drugs. The rates of AEs for TNF-α inhibitors were calculated by multiplying the rates for conventional care obtained from the GO-RAISE trial with the OR of AEs for each TNF-α inhibitor obtained from the NMA. Only those AEs (16 events, including infections requiring/not requiring hospitalization and/or intravenous antibiotics; tuberculosis; nausea; abdominal pain; heart failure; hypersensitivity reaction; fever; headache; depression; lupus erythematosus-like syndrome; pruritus; injection-site reaction; blood disorder; skin cancer; and lymphoma) considered to have cost or QoL implications were included in the analysis.

Utility Estimates
Utilities were estimated with the help of a published linear regression based on cross-sectional postal-survey data on 1413 AS patients in the UK [1, 18]. In this regression, utility is a function of BASDAI, BASFI, gender, and age:

\[
\text{Utility value} = 0.8772129 - 0.0384087 \times \text{BASDAI} - 0.0322519 \times \text{BASFI} - 0.0278913 \times \text{Male} + 0.0016809 \times \text{Age}
\]

Disutilities for AEs were assumed to be 0.01.

Cost
According to the UK guidelines by NICE [35], NHS and Personal and Social Services perspective was used for this study, including only direct medical costs. Costs included those
directly related to managing AS and the AEs of treatments, such as medication, medical staff visits, hospitalizations, and personal and social services. In the absence of published data, short-term (12-week) resource use was elicited via a physician survey. Long-term costs were estimated using an exponential regression equation based on BASFI: [15]

- Costs = 1585.30*exp (0.1832*BASFI)

  Unit costs were obtained from publicly available sources [36]. Drug costs (online supplementary Table S1) were extracted from the British National Formulary [36]. Based on a physician survey reflecting UK clinical practice, cost of conventional care was estimated at £382.28 per cycle. To calculate the cost of physiotherapy in the UK, average costs of different hospital and community physiotherapist visits were applied. Where required, estimated costs were inflated to 2013 prices (when this analysis was conducted for a NICE submission) using an appropriate inflator index [36]. The weighted-average treatment costs for an AE while on TNF-\(\alpha\) inhibitors and conventional care were £218.42 and £401.75 (inflated), respectively. The higher AE cost for conventional care was because the highest cost AE (skin cancer) was observed more with conventional care, although there were more AEs with TNF-\(\alpha\) inhibitors.

Model Analyses

The values used in the base-case analysis are outlined in Table 1. In accordance with the NICE Reference Case, an annual discount rate of 3.5% was used for both costs and benefits in the base-case analysis [35].

The model was designed to produce both deterministic (which provides point estimates for model outcomes) and probabilistic (which quantifies parameter uncertainty, and provides distribution of outcome) sensitivity analysis to generate a cost-effectiveness acceptability curve.

For the deterministic analysis, one-way sensitivity analyses were provided for all major model variables in order to identify model drivers and examine key areas of uncertainty within the model. Where available, 95% CIs were used and in the absence of any published ranges, mean ±30% were considered reasonable upper and lower bounds. In addition, numerous scenario analyses were run to investigate the effect of changing the base-case assumptions.

For the probabilistic analysis, distributions for parameters were based on recommendations [37] and were detailed in Table 1. A lognormal distribution was applied to the relative risks for outcomes, including BASDAI50, AEs, and the SMR for AS. A gamma distribution was applied to the costs [37]. A normal, truncated distribution was applied to baseline age, to avoid inclusion of patients aged <18 years. A normal, truncated distribution was applied to the baseline BASFI and BASDAI scores to ensure that the range was limited to between 0 and 10. A gamma distribution was applied to disutilities and a beta distribution was applied to the discontinuation rate. A normal, truncated distribution was applied to the annual rates of progression of the BASFI score for conventional therapy [38]. Since parameters estimated by regression analysis (e.g., for disease progression from the GO-RAISE trial) were not independent, a Cholesky decomposition of the covariance matrix was employed where variance–covariance matrices were available (e.g., progression of the BASFI and BASDAI scores) [37]. Since variance–covariance matrices were not available for the long-term cost and utility regression, their parameters were assumed to be distributed normally. The probabilistic analysis was undertaken with 10,000 simulations.

Compliance with Ethics Guidelines

This article is a modeling study using data derived from previously conducted studies, and does not contain any new studies with human or animal subjects performed by any of the authors.

RESULTS

Comparative Efficacy and Safety in the NMA

The screening process of the systematic review yielded 25 studies for final data extraction [13, 14, 23, 25, 26, 39–49]. The full network of
Table 1  Summary of variables considered in base-case analysis

| Variable                                      | Value  | Variability | Distribution       |
|-----------------------------------------------|--------|-------------|--------------------|
| Time horizon                                  | Lifetime | –    | –                  |
| Cycle length                                  | 12 weeks | –    | –                  |
| Discount rate, %                              | 3.5     | –    | –                  |
| Starting age in the model, years              | 39.3    | SE 0.82    | Normal, truncated  |
| Gender, % males                               | 71.6    | ±30       | –                  |
| Baseline BASDAI score                         | 6.54    | SE 0.11    | Normal, truncated  |
| Baseline BASFI score                          | 5.04    | SE 0.16    | Normal, truncated  |
| SMR for AS                                    | Male: 1.63 | SE 0.11 | Lognormal |
|                                               | Female: 1.38 | SE 0.32 | Lognormal |
| RR for response with ADA (BASDAI50)           | 3.23    | SE 3.14    | Lognormal |
| RR for response with CZP (BASDAI50)           | 3.64    | SE 9.74    | Lognormal |
| RR for response with ETN (BASDAI50)           | 3.31    | SE 4.52    | Lognormal |
| RR for response with GLM (BASDAI50)           | 3.34    | SE 3.58    | Lognormal |
| RR for response with IFX (BASDAI50)           | 5.45    | SE 51.32   | Lognormal |
| Response rate with conventional care, absolute treatment effect (BASDAI50) | 0.15 | SE 0.05 | Beta |
| RR for ≥1AE rate for ADA                      | 1.26    | SE 3.24    | Lognormal |
| RR for ≥AE rate for CZP                       | 1.14    | SE 0.00    | Lognormal |
| RR for ≥AE rate for ETN                       | 1.01    | SE 1.34    | Lognormal |
| RR for ≥AE rate for GLM                       | 1.12    | SE 2.31    | Lognormal |
| RR for ≥AE rate for IFX                       | 1.24    | SE 0.00    | Lognormal |
| ≥AE rate for conventional care, absolute treatment effect | 0.56 | SE 0.26 | Beta |
| RR for SAE rate for ADA                       | 0.89    | SE 1.64    | Lognormal |
| RR for SAE rate for CZP                       | 1.74    | SE 0.00    | Lognormal |
| RR for SAE rate for ETN                       | 2.66    | SE 41.87   | Lognormal |
| RR for SAE rate for GLM                       | 0.71    | SE 1.90    | Lognormal |
| RR for SAE rate for IFX                       | 2.78    | SE 6.88    | Lognormal |
| RR for SAE rate for conventional care, absolute treatment effect | 0.04 | SE 0.10 | Beta |
| RR for ISR rate with ADA                      | 1.90    | SE 0.00    | Lognormal |
| RR for ISR rate with CZP                      | 1.90    | SE 0.00    | Lognormal |
Table 1 continued

| Variable                                              | Value   | Variability | Distribution |
|-------------------------------------------------------|---------|-------------|--------------|
| RR for ISR rate with ETN                             | 2.60    | SE 4.13     | Lognormal    |
| RR for ISR rate with GLM                             | 2.52    | SE 6.99     | Lognormal    |
| RR for ISR rate with IFX                             | 1.20    | SE 1.85     | Lognormal    |
| ISR rate with conventional care, absolute treatment effect | 0.10    | SE 0.12     | Beta         |
| Annual discontinuation rate with TNF-α inhibitors, %  | 6.1     | SE 2.00     | Beta         |
| Annual discontinuation rate with conventional care (absolute treatment effect), % | 0.0     | –           | –            |
| Rebound assumption                                    | Rebound to baseline | –           | –            |
| 12-week cost of ADA, £                               | 2112.84 | SE 634.00   | Gamma        |
| 12-week cost of CZP, first cycle, £                   | 0.00    | SE 0.00     | Gamma        |
| 12-week cost of CZP, second and subsequent cycles, £  | 2145.00 | SE 644.00   | Gamma        |
| 12-week cost of ETN, £                                | 2145.00 | SE 644.00   | Gamma        |
| 12-week cost of GLM, £                                | 2112.82 | SE 634.00   | Gamma        |
| 12-week cost of IFX, first cycle, £                   | 6256.18 | SE 187.00   | Gamma        |
| 12-week cost of IFX, second and subsequent cycles, £  | 3128.09 | SE 938.00   | Gamma        |
| 12-week cost of conventional care, £                  | 382.28  | SE 115.00   | Gamma        |
| Short-term treatment cost (TNF-α inhibitors), £       | 1198.66 | –           | Gamma        |
| Short-term treatment cost (conventional care), £      | 1646.45 | –           | Gamma        |
| Weighted average AE cost (TNF-α inhibitors), £        | 218.42  | SE 65.53    | Gamma        |
| Weighted average AE cost (conventional care), £       | 401.75  | SE 120.52   | Gamma        |
| Cost of ISRs, £                                       | 94.18   | SE 28.25    | Gamma        |
| Coefficient for BASFI score (long-term cost regression) | 0.18    | SE 0.05     | Normal       |
| Intercept (long-term cost regression), £              | 1585.30 | SE 476.00   | Normal       |
| Disutilities due to AEs                               | 0.01    | SE 0.00     | Gamma        |
| Annual disease progression according to BASFI (conventional care) | 0.07    | 0.03–0.09   | Normal, truncated |

ADA adalimumab, AE adverse event, AS ankylosing spondylitis, BASDAI50 improvement ≥50% in bath ankylosing spondylitis disease activity index, BASFI bath ankylosing spondylitis functional index, CZP certolizumab pegol, ETN etanercept, GLM golimumab, IFX infliximab, ISR injection (infusion)-site reaction, RR relative risk, SAE serious adverse event, SMR standardized mortality ratio, TNF tumor necrosis factor

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evidence is shown in Fig. 2. Dark blue lines denote comparisons against active treatments, whilst orange lines denote comparisons against placebo. For the efficacy outcomes, each TNF-α inhibitor had significantly greater efficacy compared to placebo assessed through BASDAI50, with the greatest treatment effect noted for infliximab. There were no statistically significant differences between TNF-α inhibitors supporting the conclusion that all TNF-α inhibitors are similarly effective for the treatment of AS (this conclusion is considered in the economic modeling, as BASDAI50 is the key driver of response considered in the model). For safety outcomes, there were no significant differences in AEs or SAEs between both TNF-α inhibitors and placebo, and between the different TNF-α inhibitors when compared with each other.

Cost-Effectiveness

Treatment with TNF-α inhibitors resulted in increased QALYs compared with conventional care, ranging from 1.033 for etanercept to 1.143 for certolizumab pegol (Table 2a), with increased cost (from £20,590 when golimumab is administered to £48,019 for infliximab). The cost-effectiveness analysis of TNF-α inhibitors vs. conventional care demonstrated that although the ICERs were close to each other, golimumab had the best cost-effectiveness (ICER: £19,070). The comparative analysis suggested that adalimumab, etanercept, and infliximab were dominated by golimumab and/or certolizumab pegol (Table 2b).

Uncertainty in the Model

A tornado diagram illustrates the results of the deterministic one-way sensitivity analysis by showing the input parameters to which the results are most sensitive. The most influential parameters in descending order were: the long-term cost regression; 12-week cost of golimumab; BASFI scores in AS based on regression; and annual disease progression according to BASFI on conventional care (Fig. 3).

Several scenarios were investigated with regard to model characteristics, efficacy, and cost assumptions by changing each assumption, all other things being equal (Table 3). Based on the key assumptions shown, TNF-α inhibitors

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**Fig. 2 NMA network.** ADA adalimumab, CZP certolizumab pegol, eow every other week, ETN etanercept, GLM golimumab, IFX infliximab
are more cost-effective as the time horizon increases, a more cost-effective treatment for younger patients (e.g., aged 30 years), cost-effective regardless of gender (except infliximab), and cost-effective regardless of discontinuation rate.

At a willingness-to-pay (WTP) threshold of £20,000, there is a 20% probability that treatment with golimumab or adalimumab is likely the most cost-effective treatment for AS and a 30% probability that certolizumab pegol is likely the most cost-effective treatment option. However, cost-effectiveness acceptability curves and the cost-effectiveness frontier highlight the considerable uncertainty in differentiating the cost-effectiveness of golimumab, adalimumab, certolizumab pegol, and etanercept (Fig. 4).

**DISCUSSION**

The advent of TNF-α inhibitors in recent years has markedly changed the clinical outlook for people with AS. In the UK, patients with this chronic debilitating disease are no longer limited to receiving conventional care (including NSAIDs and DMARDs). However, the broadening of standard therapy to include additional therapeutic options has raised questions about optimal treatment selection. The aim of this study is to assess the cost-effectiveness of golimumab for treatment of patients with active AS compared with conventional care and with other TNF-α inhibitors, from the perspective of the UK NHS and personal and social services. Its approach was to develop a decision-analytic

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**Table 2** Cost-effectiveness analysis of TNF-α inhibitors

| Treatment                        | Total costs, £ | Total QALYs | Incremental costs, £ | Incremental QALYs | Incremental cost per QALY, £ |
|----------------------------------|----------------|-------------|---------------------|-------------------|-----------------------------|
| **(A) TNF-α inhibitors vs. conventional care** |                 |             |                     |                   |                            |
| Conventional care (reference)    | 160,837        | 10.553      | –                   | –                 | –                          |
| Golimumab                        | 181,427        | 11.633      | 20,590              | 1.080             | 19,070                      |
| Adalimumab                       | 181,589        | 11.630      | 20,752              | 1.077             | 19,275                      |
| Certolizumab pegol               | 183,017        | 11.696      | 22,180              | 1.143             | 19,401                      |
| Etanercept                       | 183,540        | 11.586      | 22,703              | 1.033             | 21,972                      |
| Infliximab                       | 208,856        | 11.682      | 50,019              | 0.969             | 26,000                      |
| **(B) Between different TNF-α inhibitors** |                 |             |                     |                   |                            |
| Conventional care (reference)    | 160,837        | 10.553      | –                   | –                 | –                          |
| Golimumab                        | 181,427        | 11.633      | 162                 | –0.003            | Dominated by GLM            |
| Adalimumab                       | 181,589        | 11.630      | 1428                | 0.067             | Dominated by both GLM and CZP |
| Certolizumab pegol               | 183,017        | 11.696      | 523                 | –0.110            | Dominated by CZP            |
| Etanercept                       | 183,540        | 11.586      | 25,316              | 0.096             | Dominated by CZP            |

TNF tumor necrosis factor, QALY quality-adjusted life-year, CZP certolizumab pegol, GLM golimumab, QALY quality-adjusted life-year, TNF tumor necrosis factor.
model comprising a decision tree for the initial 12 weeks and a long-term Markov model.

Our overall findings indicate that golimumab improves health outcomes compared with conventional care, and results in QALYs marginally higher than or similar to other TNF-α inhibitors. As expected, costs are higher with golimumab than with conventional care. However, they are comparable to those for adalimumab, certolizumab pegol, and etanercept. This is supported by the fact that, compared with conventional care, golimumab, adalimumab, certolizumab pegol, and etanercept all produce similar ICERS. The results were driven mainly by drug costs, the long-term disease management costs, and BASFI scores. This later influenced the ICER directly as the score at treatment initiation and a measure describing disease progression, but also indirectly through increased costs and lower utilities with worse BASFI scores. The cost of conventional care and the use of physiotherapy were also influential.

Previous modeling studies have compared the cost-effectiveness between different TNF-α inhibitors and conventional care. Four studies [28, 50–52] were submitted as part of NICE HTA guidance of adalimumab, etanercept, and infliximab for AS [53] and were further described in a systematic review [15]. The results from those studies showed that the ICERS of etanercept and adalimumab were roughly similar, falling below an assumed willingness-to-pay threshold of £30,000, while the ICER for infliximab was in the range of £40,000–50,000 per QALY. However, none of the models make direct or indirect comparisons between three TNF-α inhibitors. Three other studies [54–56] reported cost-effectiveness of golimumab as part of NICE HTA guidance of golimumab for AS [12], using the same model structure as in our analysis. The model comprised a decision tree followed by a Markov component to compare golimumab with conventional care, adalimumab, and etanercept from a NHS perspective. The results of those analysis showed that all TNF-α inhibitors were similarly cost-effective compared to conventional care. However, those studies still did not compare all of the current approved treatment interventions for AS. Thus, applying the same model structure from the NICE golimumab appraisal, our analysis

Fig. 3 Tornado diagram of results of one-way sensitivity analysis. *BASDAI*regression *Bath Ankylosing Spondylitis Disease Activity Index* (BASDAI) scores in AS based on regression, *BASDAIregression24* BASDAI scores in AS based on regression in the first 24 weeks, *BaselineBASFI* baseline BASFI score, *BASFIregression* BASFI scores in ankylosing spondylitis (AS) based on regression, *cCoefBASFI* coefficient for Bath Ankylosing Spondylitis Functional Index (BASFI) score in the long-term cost regression, *cConv* 12-week cost of conventional care, *cGLM* 12-week cost of golimumab, *cIntercept* intercept in the long-term cost regression, *ICER* incremental cost-effectiveness ratio, *progConv* annual disease progression according to BASFI on conventional care, *QALY* quality-adjusted life-year, *u_coefBASFI* coefficient for BASFI score in the long-term utility regression.
Table 3  Effect of key variables and scenario analyses on the ICER for each TNF-α inhibitor vs. conventional care

| Variable                        | Parameter for base case | Alternative parameter | Golimumab | Adalimumab | Certolizumab pegol | Etanercept | Infliximab |
|---------------------------------|-------------------------|-----------------------|-----------|------------|-------------------|------------|------------|
| Base case                       | –                       | –                     | £21,311   | £21,291    | £19,153          | £22,177    | £44,872    |
| Time horizon                    | Lifetime                | 5 years               | £30,855   | £30,868    | £23,600          | £31,911    | £63,281    |
| Age at baseline, years          | 39.3                    | 30                    | £17,975   | £17,954    | £16,043          | £18,775    | £39,884    |
|                                 |                         | 60                    | £32,147   | £32,131    | £28,757          | £33,237    | £61,684    |
| Gender, % males                 | 71.6                    | 0                     | £23,190   | £23,168    | £20,983          | £24,102    | £47,894    |
|                                 |                         | 100                   | £20,590   | £20,570    | £18,452          | £21,438    | £43,706    |
| Response measure                | BASDAI50                | ASAS20                | £21,231   | £21,137    | £19,227          | £20,463    | £45,037    |
| Long-term discontinuation rate  | 6.1                     | 15.0                  | £19,612   | £19,609    | £15,325          | £19,892    | £46,951    |
| (annual), %                     |                         | 23.7                  | £19,033   | £19,045    | £12,692          | £19,892    | £46,951    |
| Rebound assumption              | Rebound to baseline     | Rebound to conventional | £26,817   | £26,799    | £24,458          | £27,772    | £52,327    |
| SAE disutility<sup>a</sup>      |                         |                       |           |            |                   |            |            |
| TNF-α inhibitors                | 0.01                    | 0.1                   | £21,432   | £21,443    | £19,423          | £22,659    | £45,891    |
| Conventional care               | 0.01                    | 0.1                   | £21,144   | £21,124    | £19,003          | £22,003    | £44,519    |
| Annual BASFI progression        |                         |                       |           |            |                   |            |            |
| Conventional care               | 0.07                    | 0.03                  | £28,150   | £28,128    | £25,744          | £29,132    | £54,545    |
|                                 |                         | 0.09                  | £18,050   | £18,030    | £16,000          | £18,867    | £40,435    |

All values were calculated using deterministic analyses. <sup>a</sup> Varied for TNF-α inhibitor, kept same for conventional care, and vice versa. *ASAS20* ≥20% reduction in assessment in ankylosing spondylitis international society criteria, *BASDAI50* ≥50% improvement in BASFI, *BASFI* bath ankylosing spondylitis functional index, *ICER* incremental cost-effectiveness ratio, *SAE* serious adverse event, *TNF* tumour necrosis factor
provided an overall evaluation between all different TNF-α inhibitors.

One strength of this study is its use of NMA to generate comparative efficacy between TNF-α inhibitors. The ISPOR-AMCP-NPC Good Practice Task Force published guidelines on NMA [57]. For this study, the network comparing TNF-α inhibitors was well informed, containing data from numerous well-conducted studies, with data reported for appropriate outcomes and at appropriate time points. Application of a random-effects model managed the limited heterogeneity of the studies.

The economic analysis can be considered robust for a number of reasons. First, it is based on an approach that was developed for a NICE appraisal. Secondly, key elements of the model have been informed by evidence from RCT and its open label follow-up in the appropriate patient population (from the GO-RAISE 5-year study [14]). The availability of long-term data from the GO-RAISE 5-year follow-up enhanced the robustness of the analysis by informing rates of long-term disease progression and discontinuation of treatment. Finally, the comparative efficacy of each TNF-α inhibitor was informed by an indirect comparison using the most recently published data. It is important to note that the data produced by this NMA did not demonstrate any statistically significant differences in efficacy and safety between TNF-α inhibitors.

The analysis has limitations, due to the nature of decision-analytic models and a lack of relevant data. Firstly, the model excludes the possibility of sequential treatments with TNF-α inhibitors. This is potentially significant, given evidence suggesting a continued response after treatment-switching. However, information on this effect is limited to changes in specific response criteria in the short term, and does not distinguish between different potential sequences [58]. Secondly, in our analysis, patients with a waning response to TNF-α inhibitors were assumed to return to a BASFI score equal to that in patients experiencing natural disease progression on palliative care, rather than their baseline BASFI score. This assumes that patients not only lose their treatment benefit but also progress very quickly following loss of response. These assumptions are conservative and may underestimate the true benefit of TNF-α inhibitor treatment. Thirdly, our analysis did not capture the extended benefits

Fig. 4 Cost-effectiveness acceptability curves. WTP willingness-to-pay
of patients taking golimumab due to the selected perspective. For example, golimumab (the only once-a-month TNF-α inhibitor) may reduce productivity loss in patients with AS. The patient support program alongside golimumab treatment may also reduce societal cost by saving hospital pharmacy resources. In reality, these productivity and societal costs can create a significant economic burden for AS, and their inclusion could substantially reduce the ICERs compared with conventional care.

CONCLUSIONS

This study showed that treatment with the TNF-α inhibitor golimumab can be a cost-effective treatment alternative compared with conventional care for patients with active AS. In addition, with its comparable costs and efficacy to other TNF-α inhibitors, the golimumab position in the AS treatment pathway is likely to be driven by patient and healthcare professional choice.

ACKNOWLEDGEMENTS

This study was funded by Merck & Co., Inc., Kenilworth, NJ, USA. Article processing charges were funded by Merck & Co., Inc. The sponsor was involved in the design of the study and writing of this manuscript but had no involvement in the data management, data analysis, or interpretation of the results. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. The authors are grateful to James Farrell, a previous employee from the MSD UK office, for the initial programming in this study. The authors received writing/editorial support in the preparation of this manuscript from Yunyu Huang, PhD, of Excerpta Medica, funded by Merck & Co., Inc., Kenilworth, NJ, USA. Rebekah H. Borse, Noemi Muszbek, and Mohammad Ashraf Chaudhary contributed to the study design. Rebekah H. Borse, Sumesh Kachroo and Chloe Brown contributed to data analysis. All authors contributed to data interpretation, and planning and critical review of the manuscript content. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

Disclosures. Rebekah H. Borse is employee of Merck & Co., Inc., Kenilworth, NJ USA. Chloe Brown is employee of MSD Ltd, Hoddesdon, UK. Mohammad Ashraf Chaudhary was employee of Merck & Co., Inc., Kenilworth, NJ USA at the time of the study. Noemi Muszbek is employee of Evidera, London, UK and Evidera were paid consultants to Merck & Co., Inc., Kenilworth, NJ USA. Sumesh Kachroo is employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA, and holds stock and options.

Compliance with Ethics Guidelines. This article is a modelling study using data derived from previously conducted studies, and does not contain any new studies with human or animal subjects performed by any of the authors.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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