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Original article

Cost-effectiveness of etanercept in patients with severe ankylosing spondylitis in Germany

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Abstract

Objectives. To estimate the cost-effectiveness of etanercept (ETN) plus usual care (including NSAIDs) compared with usual care alone (including NSAIDs) in patients with severe AS in Germany.

Methods. A mathematical model previously applied to the UK was adapted using resource use and cost data (for 2007) from the national database of the German Collaborative Arthritis Centres. Social health insurance (SHI) and societal perspectives were analysed. Assumptions on initial response and changes in health-related quality of life were based on Phase III randomized controlled trials. Initial treatment response according to British Society for Rheumatology guidelines were assumed as a conservative estimate in the German context. Long-term disease progression was based on the available literature. Incremental cost–effectiveness ratios (ICERs) were expressed as euros/quality-adjusted life year (QALY), for a cohort of 1000 patients over 25 years. Sensitivity analyses explored uncertainty in results.

Results. In the base case, ETN plus usual care (including NSAIDs) yielded 1475 more QALYs at an additional cost of €80 827 668 (SHI) or €32 657 590 (societal) leading to an ICER of €54 815/QALY and €22 147/QALY, respectively. Over a shorter time horizon of 10 years, the ICERs were €59 006 and €29 815 for SHI and societal viewpoints, respectively. Assumptions having the largest impact on results included withdrawal rates from ETN, quality of life, disease costs and initial response.

Conclusions. Cost-effectiveness for ETN in patients with severe AS in Germany differs according to the cost perspective. Study estimates were higher than in the UK but comparable with reported cost-effectiveness of anti-TNF treatments in patients with RA in Germany.

Key words: Tumour necrosis factor, Quality of life, Cost-effectiveness, Cost–utility, Economic evaluation, Ankylosing spondylitis.

CLINICAL SCIENCE

Introduction

For patients with AS failing drug treatment with NSAIDs, TNF-α inhibitors are currently the most promising treatment option and the only alternative for patients with active progressive disease. Recommendations on the use of anti-TNF treatment in patients with AS proposed by the international assessment in AS in 2005 [1] define patients eligible for treatment with active disease for $\geqslant$4 weeks in terms of BASDAI $\geqslant$ 4 (a scale of 0–10, where 10 = worst). In the UK, a further criterion for eligibility to be met is a spinal visual analogue scale (VAS) $\geqslant$ 4 U [2]. Response to treatment is defined as a 50% relative change in BASDAI or absolute change of 20 mm (on a scale between 0 and 100) and expert opinion in favour of continuation. In the UK additionally, a reduction of the spinal VAS $\geqslant$ 2 U is applied.

The use of biologic agents in the treatment of AS has emphasized the need for information about the current burden of disease to estimate and answer more fully the questions on the cost-effectiveness of these drugs [1, 3]. Furthermore, to support rational decision making on the financing of TNF-α inhibitors in patients with severe AS, economic model-based evaluations are a useful tool that extrapolates what is relatively short-term data to long-term outcomes [4]. Studies conducted for several countries have reported on the cost-effectiveness of etanercept (ETN): UK [5], The Netherlands [6]; of adalimumab:

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UK [7]; and of infliximab: UK [8, 9], The Netherlands [6], Spain [10] and Canada [11]. However, transferability from one country to another is usually restricted [12, 13]. Thus, country-specific evaluations are required that take into account country-specific features such as treatment policies, epidemiology of AS, service patterns and unit costs.

The aim of the present study was to adapt an existing economic model, previously applied to the UK setting [5], to the German health care system and to treatment patterns typical of rheumatological care in Germany. The adapted model was used to estimate the cost-effectiveness of ETN treatment in combination with usual care (including NSAIDs) for patients with severe AS in Germany over the long term, with both international and German-specific treatment regimens in comparison with usual care (including NSAIDs) alone. Analyses from both the German social health insurance (SHI) and societal perspectives were performed.

Methods

Overview

As in the earlier UK analysis [5], the model uses both the BASDAI and the BASFI to represent response and efficacy of treatment [14, 15]. These measurements are validated and established measurements in AS and have been shown to have strong associations with both disease costs and utilities [9, 11]. The current study has been constructed around these relationships and utilizes changes in BASDAI and BASFI measurements to predict changes in health-related quality of life (HRQoL) and German-specific disease costs.

The model was developed in Microsoft Excel and was used in the current study to compare ETN plus usual care (including NSAIDs) with usual care (including NSAIDs) alone. British Society for Rheumatology (BSR) guidelines for ETN [2] for defining treatment response were applied [16]. The cost perspective in the UK study involved direct health care costs only according to the National Institute for Health and Clinical Excellence (NICE) reference case for conducting economic evaluations. The current study for Germany included assessments of both direct costs only (SHI perspective) and direct and indirect costs (societal perspective). Patient-level data from Phase III randomized controlled trials (RCTs) informed clinical effectiveness and changes in HRQoL [16–19]. Long-term disease progression is based on published evidence, and the costs and benefits extrapolated for a time horizon of 25 years. Cost-effectiveness estimates defined as the incremental costs per quality-adjusted life years (QALYs) are calculated for both shorter and long-term time horizons. Future costs and benefits are discounted at 5% in accordance with current German recommendations [20, 21].

Data

The pivotal evidence used in the model is derived from a European multicentre, randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of ETN 50 mg once weekly compared with 25 mg twice weekly in subjects with AS or placebo for 12 weeks [16]. As there was no significant difference in outcomes, data from the two ETN arms were pooled. This outcomes evidence is supported by data from a predominantly US-based RCT, where patients were randomized to receive ETN 25 mg twice weekly or placebo for 24 weeks supplemented by 4-year evidence from an open-label extension [18, 22].

HRQoL data collected during the European study are used to model changes in utilities. As >88% of patients in the placebo arm of the RCTs received NSAIDs, these data were used to inform the comparator arm. Table 1 shows the patient demographics from the clinical studies. German-specific AS disease costs are derived from a retrospective (12-month) analysis examining the direct and indirect costs of AS patients ($n = 433$ with BASDAI scores and $n = 220$ with BASFI scores) attending 24 rheumatology outpatient centres in Germany [23, 24]. Comparison of the German data set used to estimate disease costs with the data set used in the UK economic evaluation is presented in Table 1.

Clinical pathway

The current model follows the BSR guidelines as they offer explicit criteria for a treatment algorithm, as is needed for health economic modelling. Therefore, the model assumes that all patients have tried and failed to respond to at least two consecutive NSAIDs and have a BASDAI measurement $\geqslant 40$ before entering the model. To continue on treatment with ETN, patients must respond to treatment where response is defined as: reduction of BASDAI to 50% of the pre-treatment value or a fall of $\geqslant 2$ U (scale 0–10) and a reduction in the spinal pain VAS of $\geqslant 2$ U. Based on RCT evidence [16, 17], and using a similar approach to that reported in Ara *et al*. [5], 67% respond to ETN at Week 12 [16] and 55% continue to respond to ETN at Week 24 [16, 17]. In the comparator arm, the corresponding response rates are 24 and 16% [16] at Weeks 12 and 24 [16, 17], respectively. It is assumed that 10% withdraw from ETN each year [25, 26]. On withdrawal of treatment it is assumed that patients continue to receive NSAIDs.

Estimating benefit

The magnitudes of initial efficacy were derived from patient-level data using patients with a baseline BASDAI of $\geqslant 40$ [16, 17]. The mean BASDAI and BASFI measurements at Weeks 12 and 24 for responders and non-responders to treatment (as defined by the BSR criteria) and reported in the UK cost-utility analysis [5] were used as a conservative approach to reflect the German setting.

For responders to treatment, open-label data suggest that initial response to ETN is sustained over a further 4 years [19]. We therefore assumed in the model that response at Week 24 would be maintained up to 4 years.

TABLE 1 Patient characteristics from AS314 and Davis RCTs, OLE study and German NCCRD AS data

Setting (source) Region	RCT (AS314, Van der Heijde *et al*. [16]) Multicentre European			RCT (Davis *et al*. [17]) Multicentre mostly USA		NCCRD AS data[a] Germany [24]		UK [5]
Treatment arm	Placebo ($n = 51$)	ETN 1 × 50 mg ($n = 155$)	ETN 2 × 25 mg ($n = 150$)	Placebo ($n = 139$)	ETN 2 × 25 mg ($n = 138$)	BASDAI values ($n = 433$)	BASFI values ($n = 220$)	$n = 147$
Male, %	76	69	76	76	76	59	63	87
Age, mean, years	39.5	41.7	39.7	42	42	50.8	48.0	50.7
Disease duration, mean, years	8.5	9.0	10.0	10.5	10.1	17.3	16.3	17.9
Mean BASFI, range 0–100	60	60.6	57.7	56.3	51.7		35	44
Mean BASDAI, range 0–100	61.1	62.4	59.4	59.6	58.1	40		43
Concomitant treatment								
DMARDs, %	33	41	37	31	32	37	29	34
NSAIDs, %	78	80	85	92	91	61	51	85
Coxibs, %	–	–	–	–	–	17	17	–

[a]Based on an assessment of German AS patients not treated with biologics in 2007.

Beyond this point, patients are subject to possible long-term treatment withdrawal and to changes in BASFI measurements. For patients who continue responding to treatment, it is assumed that their BASDAI and BASFI measurements remain constant at the levels observed at Week 24 in the RCTs. For patients who withdraw from treatment, it is conservatively assumed that BASDAI and BASFI measurements revert back to baseline values immediately on withdrawal. Alternative assumptions are considered in sensitivity analyses.

While patients with AS will suffer from a natural progression of disability, there is a lack of evidence on possible changes in BASDAI and BASFI measurements in Germany. Ara *et al*. [5] used evidence for natural progression of the disease derived from a cross-sectional survey of >100 UK AS patients, which reported a mean absolute change in BASFI of 0.7 (scale 0–100) per annum [9]. Similar rates have been reported from a 5-year longitudinal study in 74 UK patients in which BASFI increased 1.26 (95% CI 0.13, 2.29) U per annum [27]. With mortality risk equal in both arms, German age- and sex-specific life tables were adjusted using a standardized mortality ratio of 1.5 [28, 29].

Quality of life

The current model has been developed based on projecting patients' long-term movements in BASDAI and BASFI measurements. These clinical outcomes have been mapped onto a generic indirect utility instrument, the EuroQol (EQ)-5D. Choosing not to adjust for BASDAI/BASFI may not be discriminative or responsive in differences between different levels of disease severity and preference-based assessments for these health states. As in the UK analysis [4], life years were transformed into QALYs using a relationship derived from the BASDAI, BASFI and EQ-5D data collected during the European RCT [utility = 0.923 − (0.004 × BASFI) − (0.004 × BASDAI); $R^2 = 0.52$].

Estimating resource use

Drug and monitoring costs

The sick fund cost per 50 mg vial of ETN in Germany is €418.20 (2007 values) and the dose is 50 mg once weekly [30]. In the UK, analysis used a price of £89.38 per 25 mg vial given twice weekly (i.e. £178.76 for 50 mg). The price differences for ETN can partly be explained by currency exchange rates. In the UK study [5], the price year is not explicitly stated but resource use from December 2003 to June 2004 is described, and the article refers to 'Annual disease costs (2006)'. Assuming a price year for the UK cost calculations of 2006, the German price of ETN for the same year is ~€286.19 (2006 year average exchange rate of €1 = GBP 0.68434 [31]), or looked at another way the UK price of £178.76 is approximately equivalent to €261.22. Further, it needs to be considered that in Germany value-added tax (VAT) of 19% is fully applied

Table 2 Summary of key model parameter assumptions and the values used

Model parameter	Value	Parameter 1	Parameter 2	Distribution	Source
ETN responders					
At Week 12	0.666	203	305	β	Van der Heijde *et al*. [16]
At Week 24	0.554	169	305	β	Van der Heijde *et al*. [16], Davis *et al*. [17]
Annual withdrawal rate from ETN	0.10	13.2	132	β	Tahir *et al*. [25], Kristensen *et al*. [26]
Sustained response period with ETN	4 years				Davis *et al*. [19]
Quality-of-life: utility (EQ-5D)				Multivariate normal	Van der Heijde *et al*. [16], Ara *et al*. [5]
BASFI	−0.0043	0.0007			
BASDAI	−0.0040	0.0008			
Constant	0.9235	0.0170			
Standardized mortality rates (assumed equal in both arms)	1.50	17	26.08	β	Lehtinen [28]
Total treatment costs[a]	€5466			Fixed	Rote Liste Service GmbH [30], KBV: EBM; V.7.0; www.kbv.de [32]
First 3 months					
Subsequent 3 months	€5444			Fixed	
Annual AS disease costs: direct (log transformed)				Univariate normal	The national database of the German Collaborative Arthritis Centres [23, 24]
Direct costs only (SHI perspective)					
BASFI	0.0052 (95% CI 0.0004, 0.0109)				
Constant	8.1508 (95% CI 7.8590, 8.4426)				
Direct and indirect costs (societal perspective)					
BASFI	0.022				
Constant	8.1524 (95% CI 7.4564, 8.8483)				
Discount rate per annum					
Costs, %	5				IQWIG [20], Hannover Consensus [21]
Benefits, %	5				
Long-term disease progression measured using annual changes in BASFI (scale 0–100), per annum					
Usual care	0.7				Ara *et al*. [5], Kobelt *et al*. [9]
ETN non-responders	0.7				
ETN responders	0.7				Ara *et al*. [5], Van der Heijde *et al*. [16], Davis *et al*. [17]

[a]Administration and monitoring resource use with ETN assumed to include radiology (chest X-ray), full blood count, ESR and biochemical profile. Resource use valuation in the first 3 months assumes: 1/4/4/1 U. Resource use valuation in subsequent 3 months assumes: 0/1/1/1 U.

to drugs that are being distributed by pharmacists, whereas VAT in the UK is 0%. Costs of ETN are larger in the first 3 months due to the additional set-up and monitoring costs (Table 2). The monitoring and administration assumptions (quantities) come from BSR guidelines [2] and are valued using German prices [32].

Disease costs

We used data from the national database of the German Collaborative Arthritis Centres previously described in detail [23], provided to us by the German Rheumatism Research Centre as an update of 2007. In brief, rheumatologists in 24 arthritis centres have recorded the clinical data of all outpatients with inflammatory rheumatic diseases once a year since 1993 and patients have answered a comprehensive questionnaire. The rheumatologists are supposed to register each outpatient with an inflammatory disease, except those who refuse to participate. The database comprises newly referred and prevalent cases. Patients seen on a regular basis are registered once a year. Thereby data on resource utilization have also been routinely collected [33].

Assessment of annual resource use was based on these data for 2007 [24]. Data of adult outpatients with AS, who were enrolled in the national database of the German Collaborative Arthritis Centres in 2007, were analysed. The total numbers of patients for the analyses with BASDAI/BASFI measurements available and who had not received treatment with biologics were: $n = 433$ (BASDAI) and $n = 220$ (BASFI). Data on health care consumption, out-of-pocket expenses (including transportation costs) and productivity losses were derived from doctors and patients. For example, of the 433 BASDAI-grouped AS patients, 392 (90.5%) answered the annual patient

questionnaire about general health- and disease-related questions and resource utilization, so that questions concerned the cost calculations. In the remainder of patients [41 (9.5%)], calculations were based on physician documentation only. Productivity losses were assessed by both the human capital approach (HCA) and the friction cost approach [23]. The friction period was applied only to patients on permanent retirement for health reasons and not to those on sick leave. The sick leave days are the cumulated numbers of absence days due to the respective disease. Productivity losses were then appraised by assuming that a day of lost productivity costs society as much as the average daily German wage estimated by population data.

We based disease costs on the resource utilization from a German AS patient sample to establish the total annual direct and indirect costs attributable to AS patients in Germany. Resource consumption quantities over 1 year were initially valued using prices for the year 2002 and then inflated to their 2007 values according to the German health care-specific price inflation index [34].

Direct costs included physician visits, drugs (e.g. DMARDs, NSAIDs and Coxibs), non-drug treatments (e.g. physical therapy, endoprosthetic surgery), diagnostic and monitoring procedures (e.g. imaging), but excluding laboratory tests, inpatient treatment (in acute hospitals and in rehabilitation clinics) and out-of-pocket expenses. Drug and hospital costs were taken from various sources [23]. Indirect costs (productivity losses) included sick leave and permanent work disability and were calculated using the HCA.

The current analysis is based on data for 2007 of all outpatients with confirmed diagnoses of AS, and had been in rheumatological care for at least 1 month and had not received biologic treatment. Costs were calculated for each patient for the 12 months preceding the day of documentation. Huscher *et al*. [23] collected BASDAI and BASFI since 2005. Patients were grouped according to BASDAI/BASFI in steps of 10 score units.

A unique relationship between BASDAI and BASFI measurements and German annual costs was established and used to estimate the costs offset by improvements in disability (Table 2). Costs associated with NSAIDs were assumed to be included in the annual disease costs as 61% of patients in the National database of the Collaborative Centres for Rheumatic Diseases (NCCRD) cohort (with BASDAI scores and 51% with BASFI scores) received NSAIDs. Annual disease costs also included other drugs such as DMARDs. We used a German sick fund price of €418.20 per 50 mg ETN injection in the base case analysis. The assumed annual cost of ETN administration and monitoring was €21 777, with an additional intensive monitoring cost of €22 in the first 3 months.

Analysis and model development

A similar methodology to that employed in the UK economic model of ETN in severe AS [5] was used to simulate the health care costs and benefits of 1000 hypothetical patients (each treated with ETN plus usual care or usual care alone), over a 25-year time horizon for the German health care setting. A further adaptation of the model to Germany was the evaluation of both direct health care costs and indirect costs.

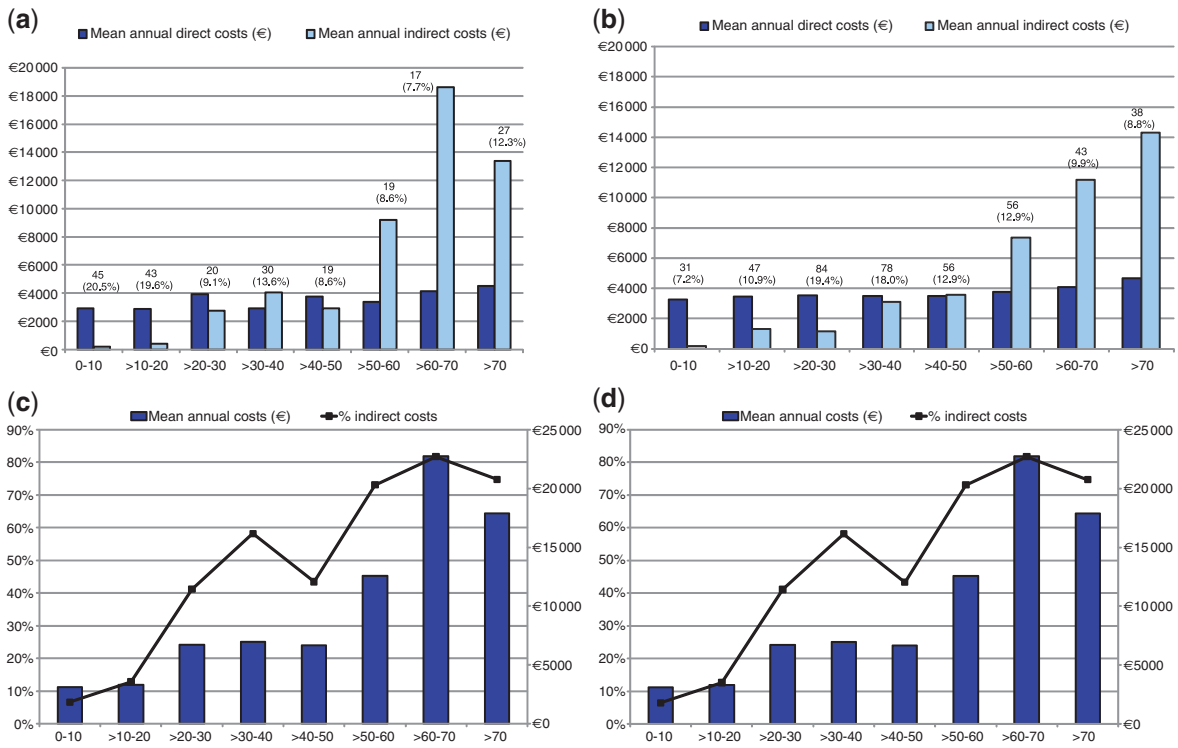
The baseline patient characteristics were sampled from the demographics of the European study RCT, ankylosing spondylitis etanercept study 314 (AS314) (Table 1). The general structure of the model involves an individual sampling procedure to attribute a response in terms of BASFI and BASDAI to a proportion of patients on treatment.

Model parameters, base case values and probability distributions used to generate each simulation for the German setting are presented in Table 2. Health effects and costs were estimated using the resource use and cost data from the national database of the German Collaborative Arthritis Centres described above for the year 2007 (based on total sample, $n = 433$ cases). A SHI perspective (direct costs only) and a societal perspective (direct and indirect costs) were analysed. Clinical assumptions used in the original model were based on individual patient data from Phase III RCTs to inform the proportion and magnitude of initial response and changes in HRQoL. Definition of initial treatment response according to BSR guidelines were assumed to be a conservative estimate of initial response in the German context because of the inclusion of the spinal VAS criterion, which is generally not used in Germany. Assumptions on long-term disease progression were derived from published literature. Incremental cost–effectiveness ratios (ICERs) are calculated in euros/QALY gained for an extrapolated 25-year time horizon. To test for uncertainty in the model results, all key assumptions used in the base case were varied in one-way sensitivity analyses.

Results of the AS costing evaluation

The mean annual total costs per patient estimated using BASDAI groups was €8401 comprising direct costs of €3679 (44%) and indirect costs of €4721 (56%). Using BASFI groups resulted in a total cost per patient of €8457 with €3403 (40%) direct and €5054 (60%) indirect costs, respectively. Proportionally speaking, costs relating to treatment with DMARDs represented 5.4% (BASDAI data) to 4.5% (BASFI data) of total costs. Costs relating to treatment with NSAIDs as part of Other Drugs e.g. including Coxibs, represented 8.0% (BASDAI data) to 12.4% (BASFI) of total mean costs. The numbers and percentages of patients in each of these bands together with mean annual costs are shown in Fig. 1. Both types of cost accelerate steeply with worsening disease. Figure 1a and b suggest that annual mean direct costs do not vary markedly across the lower level BASDAI/BASFI bands. However, for patients with BASDAI/BASFI measurements >50, indirect costs have a much greater impact and are substantially higher than for those with BASDAI/BASFI measurements <50. Consequently, total annual costs increase sharply for patients with BASDAI/BASFI measurements of $\geqslant 50$ as shown in Fig. 1c and d. On average, indirect costs represent 76% of total annual costs in

FIG. 1 Mean annual costs with (**a**) BASFI ($n = 220$) and (**b**) BASDAI group ($n = 433$) and percentage of indirect cost with (**c**) BASFI ($n = 220$) and (**d**) BASDAI ($n = 433$).



patients with BASFI measurement >50 compared with 27% on average for those with measurements ⩽50. Corresponding values for BASDAI are 71 and 34%, respectively.

Individual patient-level data were not available for Germany, but as in the original UK analysis it was assumed that the data on costs were skewed [35]. Linear regressions on the log-transformed costs were performed. A relationship was established between BASDAI/BASFI measurements and mean overall annual costs: (BASDAI $R^2 = 0.951$; BASFI $R^2 = 0.822$) and both were significant predictors ($P < 0.000$) of the log-transformed costs. We chose to use the BASFI regression model to predict annual AS disease costs (Table 2) in the base case as we wanted to explore later, alternative assumptions concerning (BASFI) disease progression. However, we also conducted a scenario replacing the BASFI regression with the BASDAI regression to explore the impact on costs and effectiveness. We also conducted two further scenarios analysing the impact of delaying BASFI progression by a period of some months and a final scenario using alternative assumptions on initial response to treatment. Several studies have reported on the time to relapse after discontinuation. Brandt *et al*. [36] reported on the cumulative prevalence of relapse after discontinuation of ETN as part of a 54-week open observational study. In the study, 26 AS patients received 25 mg s.c. ETN twice weekly after several months of discontinuation following a 6-month RCT with the same agent. The authors reported that the data indicated that more than two-thirds of the patients already had a relapse after 12 weeks and almost all patients had a relapse after 24 weeks. In a previous study the same authors reported that, after discontinuation of ETN, 75% of patients showed a relapse after a mean of 6 weeks within a follow-up period of 3 months [37].

Results

Cost-effectiveness

Table 3 shows the resulting changes in total mean direct and indirect costs, and the total QALYs gained by a cohort of 1000 patients in the ETN and comparator arms over the 25-year period. Over the long term, the total incremental discounted QALYs gained by a cohort of 1000 patients was 1475 (UK 1585) at an additional cost of €80 828K (SHI) or €32 658K (societal) giving an incremental cost per QALY of €54 815 (SHI) or €22 147(societal).

Sensitivity analysis

As has been described earlier, a number of one-way sensitivity analyses were performed to test for uncertainty. The results are presented in Table 4 and illustrated as tornado diagrams (Fig. 2). Three variables appear to

TABLE 3 Breakdown of costs and time horizons incurred for a cohort of 1000 patients over four time periods[a]

Time horizon, years	2	5	10	15	25
Total discounted QALYs					
ETN	1203	2651	4391	5567	6882
Comparator	881	1925	3272	4246	5408
Incremental QALYs	321	726	1119	1321	1475
Total discounted costs					
SHI perspective, €					
ETN	33 722 705	67 593 710	104 118 798	126 065 590	148 142 209
Comparator	9 076 304	21 416 471	38 065 931	50 808 175	67 314 541
Incremental costs	24 646 401	46 177 239	66 052 866	75 257 415	80 827 668
Societal perspective, €					
ETN	44 642 335	98 381 356	168 052 770	220 668 395	291 300 065
Comparator	28 977 505	72 554 479	134 676 669	185 668 742	258 642 475
Incremental costs	15 664 830	25 826 877	33 376 100	34 999 652	32 657 590
Incremental cost per QALY, €					
SHI perspective	76 757	63 584	59 006	56 963	54 815
Societal perspective	48 786	35 563	29 815	26 492	22 147

[a]For 1000 patients in each treatment arm.

have a large impact on the 25-year results from both cost perspectives. First, lowering the annual withdrawal rate from ETN treatment from 10 to 5% resulted in ICERs ranging from €6.7K (societal) to €36.6K (SHI) per QALY. On the other hand, increasing the rate of withdrawal to 20% resulted in ICERs ranging from €55.7K (societal) to €81.4K (SHI). Secondly, when using the 95% CIs for disease costs, ICERs range from €47.2K to €57.9K per QALY (SHI) and from cost saving to €53.4K per QALY (societal). Thirdly, when using the 95% CIs to represent benefits associated with HRQoL, the ICERs range from €40.7K to €83.9K (SHI) and from €16.2K to €33.9K (societal) per QALY. The discount rate and BASFI progression rate had less influence on direct costs, but comparatively somewhat greater importance for indirect costs.

Using alternative assumptions regarding initial response by using the upper CI from the AS314 and Davis trials essentially includes values closer to a situation where initial response was defined without the spinal VAS (Table 4). The ICERs decrease to €38.0K (SHI) and €4.9K (societal). In a second scenario, we replaced the BASFI regression to predict annual disease costs with the BASDAI regression. The ICERs increased only by 1.5% for the SHI perspective but increased by 57.6% for the societal perspective (Table 4). As mentioned earlier, patients in the ETN arm comprise a proportion of patients who continue responding to treatment and a proportion who withdraw. The former incur high treatment costs but comparatively low disease costs, while the latter incur low treatment costs but the costs associated with increased disease severity. The average costs are an aggregate of all the patients in the ETN treatment arm. Likewise, patients in the comparator arm incur higher disease costs relative to the ETN treatment arm. In a final scenario, the results were robust to delaying BASFI progression by 3 months after withdrawal of ETN treatment.

Discussion

When calculated from a societal perspective the results of this study demonstrated that ETN treatment in AS patients is comparable to reported estimates using anti-TNF agents in patients with other active rheumatic diseases in Germany such as RA. In a recent study, Schulze-Koops *et al*. [38, 39] estimated the cost-effectiveness of ETN in combination with MTX compared with MTX monotherapy in patients with RA in Germany from the societal perspective. For a time horizon of 10 years, ETN in combination with MTX resulted in an additional 1.09 QALYs at an additional €42 662 per patient giving an ICER of €38 682 per QALY. In our study, ETN in combination with usual care (including NSAIDs) generated comparable QALYs of 1.12 (per patient) by 10 years, at an increased additional cost of €33 376 yielding an ICER of €29 815 per QALY. In a second study, Rubbert *et al*. [40] reported on the cost-effectiveness of using rituximab as second line after anti-TNF therapy option in patients with RA with a value of €21 970 per QALY from the societal perspective (lifetime). Applying the same 3.5% discount rate used by Rubbert *et al*. [40], we estimate a cost per QALY for ETN in patients with severe AS in Germany of €20 626.

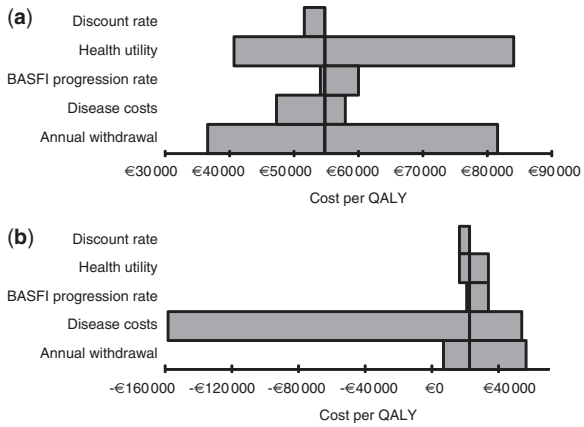
When calculated from the SHI perspective (direct costs only), the ICERs for Germany are higher than in the UK case where an identical method was used [5] and in comparison with published cost per QALY estimates of TNF-α in AS patients in several other countries [5–11]. These discrepancies can in part be explained by the difference in the price of ETN between countries. For example, when re-estimating our base case for the same price used in the

Table 4 Results of one-way sensitivity analyses for 1000 patients using a 25-year time horizon for Germany (Euro 2007)[a]

Cost (perspective)	Incremental costs		Incremental QALYs		ICER		Percentage change from base case	
	SHI	Societal	SHI	Societal	SHI	Societal	SHI, %	Societal, %
Base case (BASFI regression for AS disease costs)	80 827 668	32 657 590	1475	1475	54 815	22 147		
Replacing with BASDAI regression for AS disease costs	82 042 964	51 473 443	1475	1475	55 639	34 908	1.5	+57.6
(i) Initial response rates using UCI from AS314 and Davis [16,17][b]	79 038 197	10 443 558	2079	2096	38 025	4983	−30.6	−77.5
(ii) Discount rate								
0% costs and benefits	107 486 841	34 403 419	2083	2083	51 590	16 153	−5.9	−27.1
3% costs and benefits	89 650 118	33 598 550	1673	1673	53 599	20 088	−2.2	−27.1
(iii) Health utility								
UCI	80 827 668	32 657 590	963	963	83 945	33 917	53.1	53.1
LCI	80 827 668	32 637 590	1986	1986	40 694	16 442	−25.5	−25.6
(iv) Disease progression								
No progression for any patients	81 521 607	45 399 304	1359	1359	59 998	33 413	9.5	50.9
BASFI at 0.35 for responders to ETN and 0.7 for comparator and non-responders	80 966 355	33 615 897	1445	1445	56 046	23 269	2.2	5.1
BASFI at 0.7 for all patients	81 107 718	34 669 096	1415	1415	57 331	24 506	4.6	10.7
Delay in BASFI progression of 3 months following ETN withdrawal	80 717 740	31 275 495	1495	1495	53 985	20 918	−1.5	−5.5
(v) Disease costs								
UCI	69 631 669	−232 241 909	1475	1475	47 222	−157 500	−13.9	Cost saving
LCI	85 374 645	78 695 330	1475	1475	57 899	53 369	5.5	14.1
(vi) Long-term annual withdrawal rate for ETN								
Annual withdrawal of 5%	78 856 546	13 495 749	2153	2023	36 635	6672	−33.2	−69.9
Annual withdrawal of 15%	81 821 823	42 832 527	1132	1184	72 258	36 174	31.8	63.3
Annual withdrawal of 20%	82 184 196	51 749 092	1009	928	81 455	55 748	48.6	151.7

SHI includes only an assessment of direct costs. Societal includes direct and indirect cost assessments. [a]For 1000 patients in each treatment arm. [b]For changes in these parameters within the current model—we have to regenerate response and withdrawal results and hence a re-sampling process is taking place when we run a simulation for direct costs only perspective and then next running a simulation using a societal perspective. One would expect the number of QALYs to be the same for both cost perspectives—however, the model requires to be re-run for each simulation and for each iteration of the model randomly generates the number for QALYs for each treatment group. UCI: upper confidence interval; LCI: lower confidence interval.

FIG. 2 Tornado plot of one-way sensitivity analyses for the 25-year horizon. (**a**) SHI cost perspective. (**b**) Societal cost perspective.



UK study (€202 for 50 mg) this yields an ICER of €21 803 (SHI) by 25 years or equivalent to ~£19 284 per QALY. Ara *et al*. [5] estimated an ICER of £22 704 per QALY for the UK.

Variables in the German analysis, as with the UK economic evaluation [5], were found to have the largest impact on results included health utility values and long-term withdrawal rates for ETN. Ara *et al*. [5] additionally found that using the 95% CIs for annual AS disease costs had a large impact on results (based on UK Stoke data set regression, $n = 147$ cases) with ICERs ranging from 9.3 to −57.2% compared with the base case. Our results for Germany do not vary to such a degree with ICERs ranging from 5.5 to −13.9%. Our cost regressions are also based on a larger sample size and therefore might be expected to be subject to less variability/uncertainty.

In terms of assessment of costs, this study has addressed direct as well as indirect, an important addition to the current literature on the cost-effectiveness of TNF-α treatment in patients with AS [5]. The disease costs used in this study are representative of those accrued by patients with AS attending outpatient centres in Germany. In the UK study using BASDAI/BASFI measurements of 20, 50 and 80, the annual diseases costs (assumed 2006 prices—without inflation) were estimated to be €0.7K, €1.6K and €2.9K, respectively (2006 year average of 1€ = GBP 0.68434). We estimate the approximate corresponding average annual disease costs in Germany (e.g. BASDAI groups) to be €3.5K, €3.8K and €4.6K, respectively. Therefore, annual disease costs are in general much higher in Germany's AS populations compared with those in the UK.

With regard to definition of treatment response used in the present study, it may be argued that using the BSR guidelines may be too restrictive for defining response within the Germany setting and that actually trial criteria for defining response are more appropriate. In the current model, regression equations are used to predict treatment response at Weeks 12 and 24 according to BSR criteria. These regression equations might be interpreted as generating initial response rates somewhat lower than would be the case if the criteria for treatment response used excluded the spinal VAS. For example, in the key trials, response rates were 66.7 *vs* 72.8% and 55.4 *vs* 69.2% at Weeks 12 and 24 respectively, for ETN. Presumably patients' BASDAI and BASFI measurements would also be different due to the difference in definition of treatment response (i.e. including or excluding the spinal VAS). Running the model with the current set of BSR criteria assigned mean values to represent treatment response. Assuming BSR criteria in this situation may be considered an essentially conservative approach for the estimation of costs and benefits for reflecting the German setting. Assuming higher treatment (%) response rates, may better reflect a situation in which less rigid criteria were used. To explore the impact of this assumption, we performed a sensitivity analysis using these upper confidence limits for initial response estimated from individual patient-level trial data [16]. This assumption involved assigning more subjects to the status treatment responder at Weeks 12 and 24, i.e. for ETN treatment, moving from 67 to 83% and from 56 to 77%, respectively. The resulting ICER improved (decreased) by 30.6 and 77.5% for SHI and societal perspectives, respectively [(Table 4(i)]. Alternative assumptions on the initial response rate were not reported in the Ara *et al*.'s publication [5] to enable comparisons with our findings for Germany. The study has several limitations. First, for a number of model parameters, German-specific data were not available. For example, clinical data on long-term disease progression either while responding to treatment or long-term natural progression were not based on a uniquely German-treated AS patient population. That being said, even in the UK model, some assumptions were not derived from solely UK-treated AS patient populations or studies, but rather international trials and available publications [18, 22]. AS-related utilities in the UK model were based on data collected during the European trial (AS314) and therefore were neither strictly UK nor German specific. Some other parameters are generally unknown for the time being in ETN-treated AS populations such as duration of protection/response [although up to 4 years has been reported in open label extension (OLE)]. Assumptions on treatment effectiveness over the long term had to be made, which were, however, varied in sensitivity analysis wherever possible. It was shown for instance that the influence of disease progression assumptions on the cost-effectiveness results was considerably lower than the effect from varying withdrawal rate or health utilities.

On the matter of estimating health utilities (which have a large impact on our study results), QALY values are produced from both direct measurements using patients' preferences and an indirect calculation method using general population preferences, and due to differences in the health states they describe and their different approaches to deriving utility values they may give different costs per QALY. Direct methods include the VAS, standard gamble and time trade-off techniques. Indirect instruments

include the Health Utilities Index, the Quality of Well-Being scale and the EQ-5D. There is some disagreement in literature on the best approach and choice of instrument, but the EQ-5D is the most widely evaluated and applied [41]. The latter is part of NICE's reference case for conducting cost–effectiveness analysis and stipulates that the measurement of changes in HRQoL should be reported directly from patients, and the value of changes in patients' HRQoL (that is, utilities) should be based on public preferences using a choice-based method, preferably using the EQ-5D [42]. However, given that there is currently no preferred method of calculating QALY, it is recommended that different approaches are compared [41, 43]. When adopting a broader societal perspective, it has been argued that economic evaluations should include all potential health benefits as well as all potential costs [44]. Decision makers need to be able estimate the impact of ETN in the treatment of severe AS on long-term effectiveness, costs and cost-effectiveness in order to decide which therapies are of greatest clinical as well as economic value. Interpretation of the economic modelling results for Germany is limited as no explicit cost-effectiveness acceptability threshold exists in Germany to determine whether a health care intervention is cost-effective, and good use of resources, *vs* one that is regarded as representing poor value for money. There is no definite consensus on an acceptable threshold of cost–effectiveness ratio and how much society is willing to pay for health improvements. However, in the USA, $50 000 per QALY is a threshold commonly used to delineate cost-effectiveness. Cost-effectiveness thresholds for interventions in England and Wales National Health Service, by NICE are estimated to be ~£30 000 per additional QALY [45] for what is acceptable to society. An ICER <€50 000 per QALY has been cited in the recent rheumatology literature in relation to biologic therapy for RA [46–48], and recently a theoretical cost-effectiveness threshold of €60 000/QALY has been suggested in the literature for Germany to represent a cost-effective treatment [49]. Taking €50 000 QALY as a hypothetical ceiling threshold, most of our analyses (e.g. Table 4) are higher than this value (from the SHI perspective) and well below this value (from the societal perspective). Moreover, it is notable that Nord *et al*. [50] recently raised the question as to whether one single method of valuation (e.g. direct or societal) is indeed sufficient to inform priority setting in different contexts when valuing and comparing interventions and treatment programmes for people with different degrees of severity of illness and different potentials for health. Nord suggests as an alternative approach '. . . fair deliberative processes could be used to determine a range of cost-per-QALY thresholds according to context (rather than modifying the QALY itself). Such an approach could consist in establishing a set of ''priority classes'' to which treatments are assigned according to other criteria than cost-effectiveness (for instance, the severity of the condition, the lack of better treatment alternatives, or special end-of-life considerations) . . . '.

In the current study, estimates of treatment effectiveness are based on patients with severe AS treated within an RCT setting. It is therefore important that studies also examine the cost-effectiveness within a real world setting. The use of observational data (e.g. on response and discontinuation rates) would enable an assessment of the current study's external validity to be more precisely determined. In addition, the place of ETN in the treatment of patients with severe AS against the broader spectrum of treatment of patients is mentioned in the revised versions of our manuscript. For example, examination of the entire NCCRD cohort (real practice data for German AS patients for 2007) according to International Statistical Classification of Diseases and Related Health Problems 10th Revision codes with valid data for BASDAI and BASFI revealed that almost half of these patients received biologics (587/1035). The other patients received other drugs such as NSAIDs.

For AS patients not receiving biologics, 193/433 had BASDAI scores of >4.0 and 83/220 had BASFI scores of >4.0. The mean BASDAI score for AS NCCRD cohort patients receiving biologic therapy is 3.6 (S.D. 2.2). Thus, NCCRD data suggest that the use of biologic therapies in AS patients only with e.g. BASDAI scores of $\geqslant 4$ is not necessarily the situation with regard to treating the broader spectrum of AS patients in real life, i.e. the practice of using biologics appears to be somewhat less restrictive/stringent in real clinical German practice. In contrast, a Spanish study of AS patients commencing biologic therapy had a reported mean BASDAI score of 4.5 [51]. On the other hand, a population-based cohort of patients with AS commencing biologic therapy extracted from a national biologic registry in Australia, found that in comparison with participants in RCTs of biologic therapy [16, 17], Australian Rheumatology Association Database AS participants were older (mean age 45.1 *vs* 41.9 years), had a longer disease duration (mean 18.5 *vs* 12.6 years) and had higher baseline BASDAI scores (mean 7.6) already having significant comorbidities.

Oldroyd *et al*. [52] also make the point that 'comparable efficacy between RCTs and clinical practice is hardly ever achieved due in part to patient selection, differences in co-medications and co-morbidites and treatment adherence'. Therefore, the participants in RCTs of biologic therapies for AS may not be entirely representative of German patients with AS commencing biologic therapies in routine care. For example, being older, having longer disease duration and more active disease, a history of verified malignancy, all these points highlight the importance of systematically collecting post-marketing longitudinal outcome data for biologic therapy in routine care. For example, it has been emphasized that registries and observational data sets should examine reasons and rates of withdrawal and mortality and follow the sequence of treatments given to patients, as well as incorporating economic end points (HRQoL and costs) [53, 54].

Apart from cost-effectiveness, it is of equal relevance how much resources will be required to finance a biologic therapy programme including ETN for several decades,

thus addressing the question of whether long-term ETN treatment is affordable (i.e. the net budget impact). This objective was beyond the scope of the current study.

A broad societal perspective on value, i.e. costs and benefits, facilitates informed discussion and decisions about access and use of new medical technologies. Non-medical costs and production losses dominate costs in AS (further demonstrated in this study) and it has been argued that economic evaluation should therefore adopt a societal perspective [9]. The purpose of economic evaluations conducted on behalf of many national Health Technology Assessment agencies, including NICE (UK), Canadian Agency for Drugs and Technologies in Health (Canada) and Institute for Quality and Efficiency in Health Care in the German context, do not currently recommend a broad societal (cost) perspective on value in HTA studies aimed at informing decisions (advising payers) about allocation of resources. If productivity losses are substantially affected by a new health technology, consideration could be given to including them as a health benefit side, although this is controversial. Whatever estimation method is used to calculate indirect costs, these costs should be reported separately with full accounting of the cost content and method employed. The current study followed this overall approach.

Conclusion

Cost-effectiveness results for ETN in patients with severe AS in Germany are considerably different depending on whether a SHI (direct costs only) or a societal (direct plus indirect costs) viewpoint is considered. In Germany as well as in other European countries, AS patients are often affected at a relatively young age which makes the disease's impact on work productivity (and hence indirect costs) a substantial burden on German society. The treatment of severe AS with ETN compares favourably with anti-TNF treatments in other rheumatic diseases in Germany.

Rheumatology key messages

- Treatment of severe AS with ETN has comparable cost-effectiveness to anti-TNF treatment of other rheumatic diseases in Germany.
- Results demonstrate substantial economic benefits when taking a societal cost perspective.

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