The cost-effectiveness of infliximab in the treatment of ankylosing spondylitis in Spain. Comparison of clinical trial and clinical practice data

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Objective: To estimate the cost-effectiveness of treating ankylosing spondylitis (AS) with infliximab (Remicade®) in Spain for up to 40 years.

Methods: A previously published disease model was adapted to the Spanish setting using resource consumption from a cross-sectional burden of an illness study in 601 patients in Spain. Cost-effectiveness estimates were based on a placebo-controlled clinical trial as well as an open clinical study in Spain. In the model, patients with insufficient response to treatment at 12 weeks [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) <4 or $\geqslant 50\%$ reduction] discontinue treatment. The results are presented in 2005 euros, from societal and health-care payer perspectives.

Results: In the societal perspective, infliximab treatment dominates standard treatment in both analyses. In the perspective of the health-care system, with the assumption that, over the long term, functional ability of patients on treatment would decline at half the natural rate, the cost per quality-adjusted life year (QALY) gained was estimated at EUR 22 519 (double-blind trial) and EUR 8866 (open study). Assuming that patients' function on treatment remains stable, the cost-effectiveness ratios are EUR 15 157 and EUR 5307, respectively. Under the most conservative assumption (no effect of treatment on progression), the ratios are EUR 31 721 and EUR 13 659, respectively. In addition, the results are sensitive to the time horizon and discontinuation rates.

Conclusions: Our results indicate that infliximab therapy for patients with active AS should be cost-effective both in the societal perspective (dominating) and in the perspective of the health-care system (ranges from EUR 5300 to EUR 32 000 per QALY) in Spain.

The gradual physical impairment and inflammatory activity associated with ankylosing spondylitis (AS) have a detrimental effect on health-care costs and work capacity as well as on patients' quality of life (QoL) (1–7).

Functional capacity has been identified as the main cost-driver in all studies (1) (4–7). In an earlier study in the UK, mean annual costs increased from EUR 3500 for patients with no functional impairment [Bath Ankylosing Spondylitis Functional Index (BASFI) of 1] (8) to EUR 57 000 for the most impaired patients with a BASFI of 7 or more (4). Similar results were found in a Canadian study but with overall lower costs (5). The steepest increase was found in Spain, with costs ranging from EUR 5000 to EUR 75 000, predominantly due to intensive use of informal care by patients with functional impairment (6, 7).

In all three studies, utility (a QoL score on a scale between 0=death and 1=full health) was equally correlated with function and disease activity [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)] (9) and decreased in a similar fashion from scores of around 0.80 for patients at BASFI/BASDAI below 3 to around 0.4 for patients at BASFI/BASDAI of 7 and above. Patients in Spain rated the very severe disease states lower than in the UK and Canada (0.25), and this may be due to cultural differences. A comparison of population scores obtained with the EuroQoL visual analogue scale indicates values in Spain that are overall lower than in the UK and Canada, and a steeper decline with age (10).

Thus, with costs increasing and QoL decreasing as the disease worsens, controlling disease activity and preventing functional decline should have a positive

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socioeconomic effect in the long run (11–13). This has been shown using cost-effectiveness models in the UK and Canada (4, 14, 15) based on controlled and open clinical trials with infliximab (16–21). In these trials, infliximab (5 mg/kg every 6 weeks) was shown to be efficacious in the treatment of AS, but its cost is substantially higher than standard treatment. Although cost offsets were shown in the models, these did not fully compensate for the cost of infliximab, and the results were highly sensitive to the treatment regimen adopted.

Cost-effectiveness estimates depend on the effectiveness of a treatment but also on the underlying cost-structure, that is the quantity of resources consumed and their unit price (13). While effectiveness is generally comparable across countries, costs are not. Cost-effectiveness results cannot therefore be transferred directly between settings. The purpose of this analysis was to adapt the earlier cost-effectiveness models based on a double-blind trial (16, 18, 19) to Spain, using local cost and utility data from a recent observational study (7). The results were then compared to those obtained using an open multicentre study in clinical practice in Spain that had used a different treatment regimen than the double-blind trials (22, 23).

Methods

Data

The AS model is based on three data sets that all include BASFI and BASDAI measurements: data on the effectiveness of treatment, data on disease progression, and data on costs and utilities at different levels of disease severity (4, 14, 15).

Effectiveness data. For the main analysis, we used effectiveness data for infliximab (5 mg/kg every 6 weeks) from an international double-blind placebo-controlled 12-week clinical trial with open extension in 70 patients with confirmed AS and active disease (BASDAI$\geq$4) (16–19). Seventy-one per cent of the patients completed the first year of treatment and, of these, 94% completed the second year. Efficacy assessments were comparable at 54 and 102 weeks (18).

The second analysis was based on data from an open multicentre clinical trial in Spain in 42 patients with refractory spondylarthropathies, using a different treatment regimen for infliximab (5 mg/kg every 8 weeks) (22, 23). After 30 weeks, the remaining 39 patients were assessed for response [BASDAI <4 or erythrocyte sedimentation rate (ESR) <30 mm/h and C-reactive protein (CRP) <5 mg/L]. Responders continued at the same dose up to 62 weeks, while non-responders were offered treatment every 6 weeks. At this time 11 responders decided to discontinue, considering their disease to be under control (mean BASDAI 1.7, SD 1.3). For the cost-effectiveness analysis (comparison to no treatment), we adapted the placebo group from the double-blind trial to represent a hypothetical untreated cohort of patients with the same demographic and disease characteristics as patients in the open Spanish trial.

In the models, only responders, defined as patients achieving an improvement in BASDAI of $>50\%$ or >2 points, were allowed to continue treatment. These criteria for treatment cessation are similar to those suggested by the British Society for Rheumatology (24). Although these stringent criteria result in small samples that continue into the long-term extension for both trials (18 and 15, respectively), they represent better use of scarce resources in clinical practice. Non-responders continued on standard treatment.

Disease progression. Disease progression in the model was expressed by changes in BASFI, as disease activity outside flares remains essentially stable over time. Average absolute progression per year was estimated at 0.07 BASFI, using data for 1110 patients who had answered two postal surveys at the University of Bath (UK), 10 years apart (1992 and 2002) (4, 9). Patients in this survey were slightly older than patients in the double-blind trial ($\sim$7 years) but had the same age as patients in the Spanish study. Because of the limited number of data points available, and in the absence of more detailed data, the same rate of progression was used for all patients regardless of age or level of disability. Sensitivity analysis for a different rate of natural progression is, however, presented.

Costs and utility. Costs and utilities were available from a cross-sectional retrospective survey in 601 randomly selected AS patients in Spain, as described elsewhere (6, 7). The survey was carried out in 51 geographically distributed specialized clinical centres and achieved a response rate of 86%. The mean age in the sample was 48 years, 80% were male and 91% were less than 65 years old. Functional disability was relatively mild, with a mean BASFI of 3.4 (SD 2.85) and 46% of patients at a BASFI below 3. One-third of patients also had a BASDAI below 3 (mean BASDAI in the sample 4.3, SD 2.45). However, all levels of disease severity were represented and as many as 17% had BASDAI/BASFI scores of 7 and above.

Costs were assessed from the societal perspective, including all health-care consumption as well as patient-borne costs and productivity losses. Resource use was collected retrospectively from patients using the questionnaire developed previously in the UK and Canada (4, 5), translated and adapted to the Spanish setting and pretested with 30 patients. Health-care utilization was valued with unit costs obtained from public sources. Informal care was valued using the replacement method, where it is

assumed that, if family help is not available, services would have to be performed by health-care professionals. They were therefore considered a direct but non-health-care cost. Indirect costs (sick leave, early retirement and reductions in working time due to the disease) were estimated with the human capital method, which considers that the cost of employment (gross salary plus employers' contributions) is representative of an individual's productivity.

Mean annual costs in the sample were EUR 20 328 (SD EUR 39 639), of which 33.7% were productivity losses, 34% informal care costs (family help), 9.5% devices and investments and only 22.8% health-care costs. Costs increased more than tenfold for patients with very severe disease (BASFI/BASDAI >7) compared to patients with a BASFI/BASDAI <3 (EUR 5000) (Figure 1).

Utility was estimated with the EQ-5D (25), using the original health status system (26) to compare results to the UK and Canadian studies. Mean utility in the sample was 0.59 (SD 0.3), decreasing from 0.80 for patients with BASFI/BASDAI <3 to 0.25 for patients with BASFI/BASDAI >7.

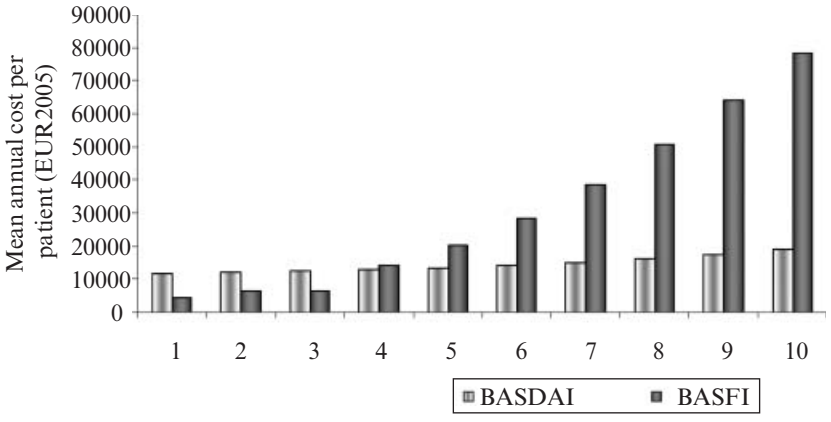
The model

Structure of the model. The model is illustrated in Figure 2. It combines a decision tree representing the clinical trial period with a Markov model representing the open extension periods and beyond. Markov states are defined according to treatment state but include functional capacity and disease activity, as well as age and gender, to estimate costs and utilities. The model uses annual cycles and runs for up to 40 years. Results are expressed as cost per quality-adjusted life year (QALY) in 2005 EUR. Data input and assumptions are summarized in Table 1.

Effectiveness of treatment. At each measurement point in the trials, patients who had a reduction in their BASDAI of less than 50% or 2 points discontinued treatment and reverted to their baseline scores. Similarly, patients on placebo returned to their baseline scores at the end of the trial. Patients then entered the Markov model either 'on treatment' (responders only) or 'off treatment' and were assigned the mean BASDAI and BASFI scores of the new groups. The disease then progressed according to the mean absolute annual change in BASFI scores (4), while BASDAI scores were assumed to remain constant outside special events such as treatment discontinuation or adverse events. Thus, small fluctuations due to minor flares were ignored during the cycle. The model incorporates normal mortality, but sensitivity analysis is presented for a standardized mortality risk of 1.5 (27).

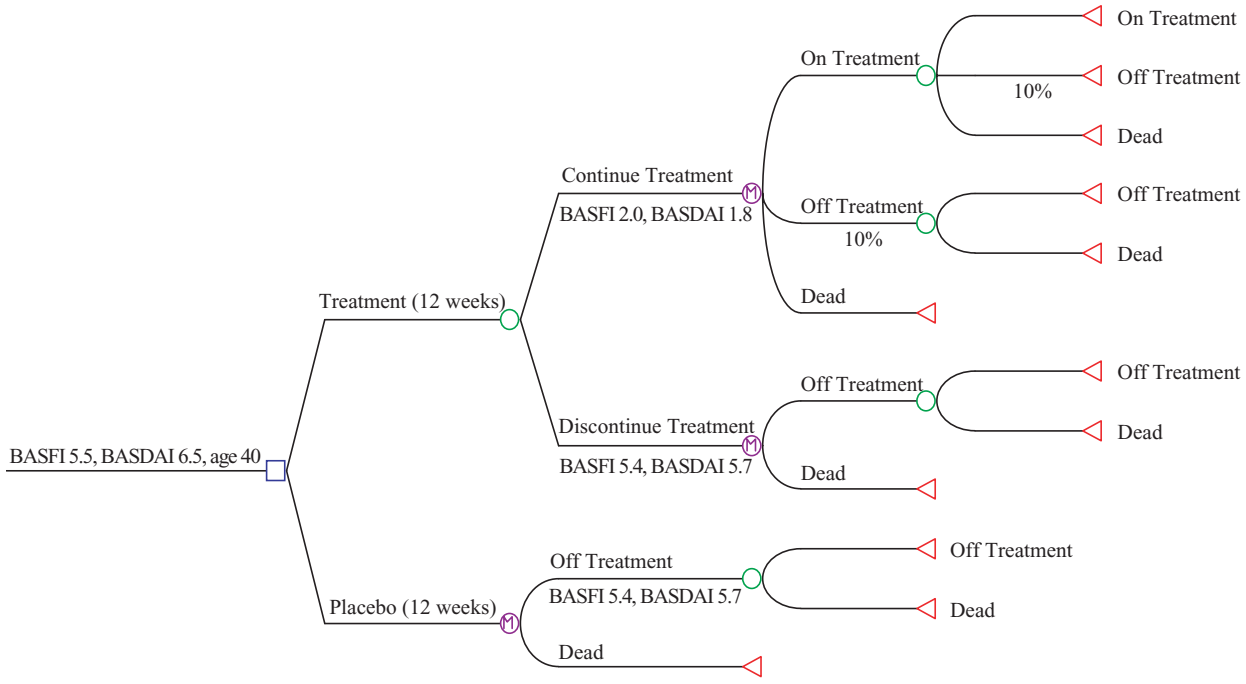
Assigning costs and utilities. Costs were assigned to individual patients during the initial trial periods or to the group of patients in the Markov model according to their BASFI and BASDAI scores as well as age. Indeed, BASDAI and BASFI correlate significantly ($r^2=0.77$) and there is a co-linearity between functional disability and age (4–6). Costs were therefore estimated with a two-stage regression analysis, where first the probability that a patient used a given resource (conditional upon BASDAI, BASFI and age) and then the expected cost of the resource were estimated.

Around one-quarter of patients in the Spanish survey were using infliximab, the only tumour necrosis factor (TNF)-inhibitor licensed for AS in Spain at the time of the study. When excluding the cost of infliximab and controlling for BASFI and BASDAI, costs for these patients did not differ



BASDAI = Bath ankylosing spondylitis disease activity score [9]
BASFI = Bath ankylosing spondylitis functional index [11]

Figure 1. Mean annual cost per patient as a function of either functional impairment (BASFI) or disease severity (BASDAI). Both measures are significantly correlated with costs, as well as with each other ($r^2=0.7$).



BASDAI = Bath ankylosing spondylitis disease activity score [9]

BASFI = Bath ankylosing spondylitis functional index [11]

Figure 2. During the first 12 weeks, patients' individual BASFI and BASDAI scores measured at weeks 0, 6 and 12 in the double-blind period of the clinical trial are used and costs and utilities assigned based on their profile. In the extension, mean scores are used and patients' functional disability progresses according to natural history in the no-treatment group, and according to different assumptions for patients with treatments: 50% of the natural progression of the no-treatment group, no progression while on treatment or natural progression (i.e. no effect of treatment on progression). Only patients responding to treatment (>50% or 2 points reduction in BASDAI) enter the treatment arm, while placebo patients will revert to their baseline scores during the first year in the extension.

significantly from patients not on infliximab (7). We therefore used cost information (excluding infliximab) for all patients in the model.

Utilities were grouped in a 5×5 matrix based on 2-point intervals of BASFI and BASDAI corresponding to one of the effectiveness criteria used in the model, and scores for the specific patient profiles calculated by linear interpolation within this matrix. Unfortunately, the Spanish sample was not large enough to populate all cells in the matrix with sufficient numbers, and some cells either contained very few patients or were empty. We therefore used the utility scores from the larger cohort in the earlier UK study (n=1413) (4). Scores in Spain were similar, with the exception, however, of the most severe health states (Figure 3), which were rated worse by Spanish patients.

Cost-effectiveness estimates

Simulations are presented including either all costs (societal perspective) or health-care costs only, over a period of 40 years, and costs and utilities are discounted with 3%. In view of the short clinical trials used in the analysis, a number of assumptions had to be made. The most important relate to the disease progression while on treatment, the discontinuation rate and the effectiveness of infliximab when using a different dose.

In the absence of conclusive data on the progression of functional impairment when disease activity is controlled continuously, we present results based on three hypotheses: no worsening of BASFI while on treatment, no effect of treatment on BASFI (i.e. natural disease progression), and half the natural rate of progression. In the open extension of the double-blind trial, no functional decline was seen (19). For the responders included in our model, mean BASFI scores were stable at 2.0 over time, while mean BASDAI scores improved from 1.8 at 12 weeks to 1.5 after 2 years. This latter effect is not included in the model, where BASDAI is assumed to remain stable while on treatment. It is, however possible that treatment effect is reduced over the longer term even when treatment is persistent.

The long-term annual discontinuation rate for both analyses was calculated from the 2-year open extension of the double-blind trial (19) as an average of 10%. This is lower than the withdrawal rate observed during the first year of the trial (29%).

Table 1. Summary of data inputs and assumptions in the model.

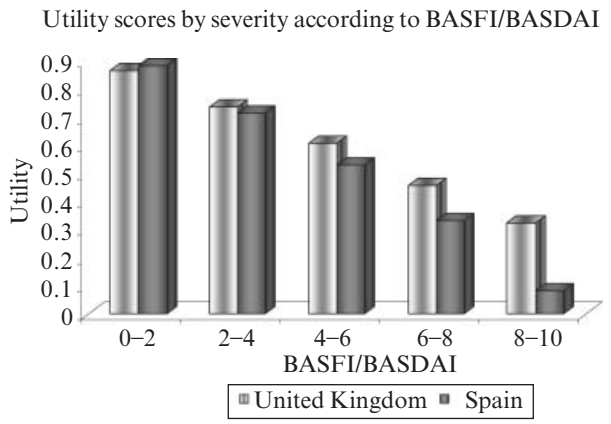
Decision trees (treatment arms)	
Double-blind trial	
Start	BASFI 5.5, BASDAI 6.5, mean age 40 (30 patients)
12 weeks	Patients withdrawing during the trial (n=3) and non-responders (BASDAI >4 or less than 50% improvement) discontinue treatment, and 18 responders enter the long-term extension
Spanish trial	
Start	BASFI 6.8, BASDAI 7.1, mean age 40 (42 patients)
12 weeks	Patients withdrawing during the first period (n=3) and non-responders (BASDAI >4 or less than 50% improvement) discontinue treatment, and 15 responders enter the long-term extension
Markov model	
Markov states	'On treatment', 'off-treatment', 'death'
Cycle length	One year
Time horizon	Base case 40 (10, 20, 30) years
Discount rate	3% (0%, 5%)
Transitions	To 'off-treatment': treatment withdrawal 10% (5%, 15%) To 'death': normal population mortality (SMR 1.5)
Disease progression	Based on BASFI, annual progression 0.07 points
Disease activity	BASDAI assumed to be stable while on treatment
Costs	Assigned with two-step multiple regression based on the mean BASFI/BASDAI scores and age of the group at each cycle
Utility	Assigned with linear interpolation from a 5×5 matrix (BASFI/BASDAI), based on the mean BASFI/BASDAI scores and age of the group at each cycle
Simulations	
Starting state	
Double-blind trial	'Off treatment': BASFI 5.4, BASDAI 5.7 (reverting to baseline, BASFI 5.5, BASDAI 6.3, during the first cycle), utility 0.51 'On treatment': BASFI 2.0, BASDAI 1.8 (responders), utility 0.79
Spanish trial	'Off treatment': BASFI 6.8, BASDAI 7.3, utility 0.49 'On treatment': BASFI 3.9, BASDAI 3.1 (responders), utility 0.74
Disease progression	'Off treatment': BASFI +0.07 per year (0.05) 'On treatment': BASFI 50% of off-treatment (0%, 100%)
Proportion on treatment	0.8% after 40 years (11.3% after 20, 34.0% after 10)
Proportion of deaths	38.5% after 40 years (6.6% after 20, 2.1% after 10)

However, first-year discontinuation is de facto included in the model, as patients who do not meet the efficacy criteria at the end of the 12-week double-blind period discontinue treatment, and only 69% enter long-term treatment. In the Spanish trial, substantially more patients withdrew from the trial (45%) after the formal study period of 30 weeks because of the 11 patients who considered themselves in remission. In the extension period to 62 weeks, three out of 28 continuing patients withdrew, and the 10% long-term withdrawal rate was therefore also used in the analysis of the Spanish trial.

The list price for infliximab in Spain is EUR 547.22 for a 100 mg vial, resulting in an annual treatment cost of EUR 18 540 for an average patient, using the dosing regimen in the clinical trial. With the dosing regimen from the Spanish trial, where 54% of patients were effectively treated with infusions every 8 rather than every 6 weeks, annual costs are estimated at EUR 13 390. The cost of adverse events possibly related to treatment was estimated by assessing the treatment requirements in routine care, as indicated by clinical specialists, for all events observed in the first year of the double-blind clinical trial. The total cost in Spain for all events was estimated and a mean cost per patient of EUR 67 assigned to all patients who started treatment for the first year in the model, regardless of whether they experienced an adverse event or not. The reason for this was to keep adverse event costs within the treatment arm in the model, even when discontinuing patients integrated into the no-treatment arm. In subsequent years of the trial, adverse events were extremely rare and mild, and only one in five patients withdrawing from treatment did so because of adverse events. We therefore conservatively assigned the first-year cost for adverse events to 20% of patients withdrawing from treatment in the model. No utility loss for adverse events was incorporated, as no data were available.

Results

Results are presented for both trials with the three assumptions regarding the effect on disease progression, from the societal and health-care payer perspectives (Table 2). For illustrative purposes, we present the flow of patients between the three states (Figure 4) and the cumulative QALY gain over the



Utility = Score between 0=death and 1=full health
BASDAI = Bath ankylosing spondylitis disease activity score[9]
BASFI = Bath ankylosing spondylitis functional index[11]

Figure 3. Comparison of utility scores in Spain (N=601) and the UK (N=1413). Utilities were grouped into a 5×5 matrix with 2 points difference in BASFI and BASDAI, and the figure illustrates the mid-values (i.e. patients with both values below 2, or between 2 and 4, etc.). With the exception of the most severe level, utilities were not significantly different.

40-year time horizon (Figure 5), using the double-blind trial. As the Spanish trial did not include a placebo group, sensitivity analyses are performed using the double-blind trial.

In the societal perspective, infliximab treatment dominates no treatments in all simulations, that this treatment is more effective and less costly. In the perspective of the health-care system and assuming 50% BASFI progression while on treatment, the incremental cost per QALY gained is estimated at EUR 22 520 with the double-blind trial. Using the Spanish data, the ratio is estimated at EUR 8866, essentially because of the less intensive dosing schedule. Assuming that patients' function does not decline while on treatment reduces the cost per QALY to EUR 15 152 and EUR 5307, respectively. If treatment is assumed not to affect progression of functional disability, the ratios are EUR 31 721 and EUR 13 695, respectively.

Varying the discontinuation rate between 5% and 15%, increasing the cost of adverse events by 100% or adding a disutility of 0.08 for them, using discount rates between 0% and 5%, incorporating disease-specific mortality or reducing the time horizon to 10 years did not change results in the societal perspective and treatment remained dominant. When the time horizon is reduced to 2 years, the cost per QALY is slightly above EUR 30 000. In the health-care perspective, results are most sensitive to the treatment regimen and the time horizon, but also to treatment discontinuation (Table 3).

Discussion

Estimating the cost-effectiveness of treatments in AS requires modelling, for a number of reasons. Functional capacity is the major driver of costs, but it may take many years to progress to severe impairment. Biological treatments have been shown to reduce disease activity, and thereby also improve function in the short term, but their effect on permanent functional impairment is not yet known. Effectiveness data are limited in terms of both the duration and the sample size in clinical trials. Functional impairment and disease activity are highly correlated but they affect costs and utility at different times in the disease course. In early disease, costs are driven by inflammation, while in more advanced disease physical impairment causes costs to increase exponentially (Figure 1) (7). Thus, both BASFI and BASDAI need to be taken into account at every time point for calculation of costs and utility of each individual patient. In addition, disease progression is correlated with age (or disease duration). This makes it necessary to adopt a long-term

Table 2. Cost per QALY gained over 40 years.

	Double-blind trial			Spanish trial		
	Incremental cost	Incremental effect	Incremental cost per QALY	Incremental cost	Incremental effect	Incremental cost per QALY
50% of natural disease progression while on treatment						
All costs included (societal perspective)	−198 637	2.255	Dominant	−634 731	2.705	Dominant
Health-care costs only	50 780	2.255	22 520	23 982	2.705	8866
No progression while on treatment						
All costs included	−248 092	2.959	Dominant	−710 659	3.077	Dominant
Health-care costs only	44 836	2.959	15 152	16 331	3.077	5307
No effect of treatment on progression						
All costs included	−137 142	1.824	Dominant	−541 979	2.429	Dominant
Health-care costs only	57 859	1.824	31 721	33 177	2.429	13 659

Cost and effects discounted with 3%.

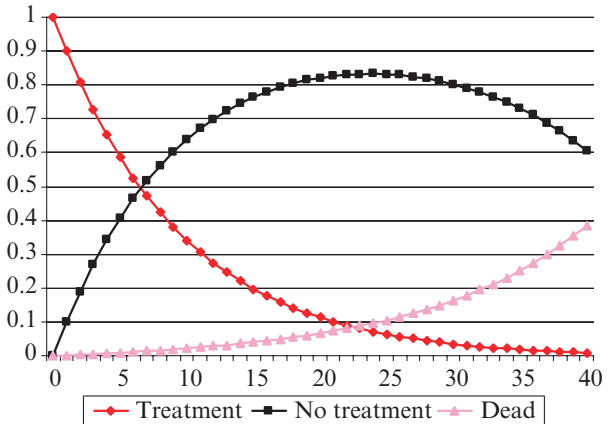


Figure 4. The transition of patients at a mean age of 40 who are initially on treatment (i.e. 100% of patients on treatment). Over time, patients withdraw from treatment and a certain proportion dies (normal mortality).

perspective using disease models that, by definition, imply a number of assumptions.

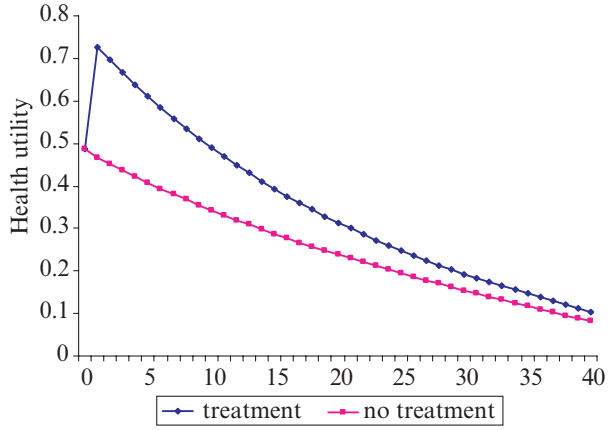
The first trial to establish the effectiveness of infliximab in AS was a relatively small 3-month trial (16). Although a larger study has now been published (21), its duration is still limited to 6 months. Currently, more than 3 years of follow-up data are available for the first study, making it the only data that provide a basis for assumptions regarding longer-term treatment in modelling studies. As the model is based on patient-level data during the first period, it was not possible to use a meta-analysis of the two trials. Instead, it would have been necessary to merge the trials, which in view of differences in the protocols appeared inappropriate.

Previous economic analyses have shown that cost-effectiveness is sensitive to the treatment cost, and a number of small trials have tested less intensive dosing regimens with infliximab (20, 22, 23, 28). The Canadian trial showed that by adapting dosing regimens to each individual patient over time, the overall effectiveness was comparable to the double-blind trials (20). Similarly, the Spanish study showed comparable effectiveness at 30 weeks with 8-week instead of 6-week dosing (22), and using this dosing regimen reduced the cost per QALY gained by 60%.

Shortening the dosing interval to 6 weeks in non-responders in the Spanish study did not improve the outcome in this group substantially after 62 weeks (23). This argues for discontinuing treatment in patients with an inadequate response, as is currently recommended in a number of countries. Discontinuation for non-responders has been included in previous modelling studies (4, 14), and is again included in this current model, although no formal guidelines exist in Spain for discontinuing treatment in Spain. Economic models are meant to support decision making in the absence of final data, and as such they may speculate on the most efficient way to use scarce resources. From an economic viewpoint it is clearly inefficient to continue expensive treatments in patients without an adequate response, supporting our modelling approach. The limitation of using very stringent criteria for response is, however, that the extension period in our models is based on a very small number of patients.

Thus, for both trials used in the analysis, patients with inadequate response discontinue treatment at the end of the trial periods (12 and 30 weeks, respectively), and revert to their baseline BASFI and BASDAI scores over the next year. As a consequence, responders in the double-blind trial continue with considerably lower mean BASFI and BASDAI scores than the published end-of-trial scores (ITT analyses).

The opposite is true for the Spanish trial, where some of the best responders at 30 weeks withdrew from the trial. This is most probably a good representation of what happens in clinical practice, where a patient will temporarily stop treatment and restart when the disease flares again. The issue for our current model was that no data on restart were available, and we therefore included only patients who continued beyond 30 weeks in the extension rather than make assumptions about retreatment and its effectiveness. This highlights the importance of follow-up in clinical practice (e.g. in registries) to fully evaluate the effectiveness of treatment. In our model, the consequence is that patients enter the long-term extension at higher BASFI/BASDAI



Note: The treatment group represents only patients initially responding to treatment.

Figure 5. In the model, both groups start at the same baseline (trial baseline). During the trial and the first year of the extension, disease severity of patients off treatment worsens, based on progression of functional disability. Patients on treatment and responding experience a large improvement, and their disease progresses at half the speed of untreated patients. Low utility values after 40 years are explained by the large proportion of patients who have died (~40%, utility 0, see Figure 4), as well as the effect of discounting by 3% to net present value

scores than in the double-blind trial. Nevertheless, the QALY gains are similar in the simulations of the two trials because baseline scores in the Spanish study were also higher, and the difference between the no-treatment and responder groups therefore similar.

As in previous models, the long-term annual discontinuation rate was set at 10%, based on the extension studies in the double-blind trial. This is further confirmed by the discontinuation rate in the second part of the Spanish trial, where three out of 28 patients discontinued treatment. It is difficult to assess whether this rate is at the higher or lower end, as published data were never based on a situation where non-responders systematically discontinued treatment. Continuation rates with infliximab in rheumatoid arthritis (RA) in Sweden in patients exceeding 1 year of treatment (66%) have been estimated at 77% in the second year, and in those patients continuing beyond 2 years at 88% (29). This would support a slightly higher rate. However, persistence rates in patients with AS have been reported to be higher than in RA over a period of 3 years (hazard ratio for discontinuation 0.66) (30).

Currently, data on the effect of anti-TNF drugs on disease progression are still scarce. We have therefore used three scenarios: (i) BASFI is stable as long as patients remain on treatment, (ii) BASFI progresses at half the natural progression rate (base case) and (iii) treatment has no effect on progression. Clinical data over 2 to 3 years argue for the first scenario (19, 31) and clearly against the third. However, in view of the limited information available, we have chosen the second scenario as our base case.

Information is also rare regarding mortality of patients with AS, and even more so, of a possible effect of anti-TNF treatment. We have therefore only included standardized population mortality in our base case, and present a sensitivity analysis for inclusion of an increased mortality risk in both groups (27). This analysis, however, still assumes no treatment effect on mortality. To include such an effect, mortality would need to be linked to disease progression. Such detailed data are currently not available.

In the societal perspective, infliximab is less expensive and more effective than no treatment in all scenarios and does not change when the time horizon is shortened to 10 years. Over 5 or 2 years, infliximab is no longer dominant but the cost per QALY remains well below the threshold generally considered acceptable in Europe (EUR 50 000). When looking only at costs occurring in the health-care system, the cost per QALY gained remains below this threshold for time horizons of 10 years and more.

Results for Spain indicate a lower cost per QALY than in our similar study in Canada, although the overall findings remain the same. With treatment as in the double-blind trial, the cost per QALY in Canada over 30 years was EUR 36 500 in the perspective of the health-care payer, compared to EUR 27 200 in Spain (50% progression on treatment). While it is difficult to compare these results directly, the major reason for the difference lies in the underlying costs, as in both cases the utility matrix from the UK (4) has been used. The cost increase with worsening disease in Spain is much steeper than in Canada. Markov models are driven by the differences in costs and utilities between the health states, not by their absolute levels. Consequently, there are more opportunities for cost off-sets by keeping patients in more benign disease states in Spain. The analyses using the reduced dosing schemes present a similar difference, despite different dosing schedules and hence different intervention costs (20, 22).

Another cost-effectiveness analysis was conducted recently in the Netherlands (32), where Boonen et al compared infliximab and etanercept over a time frame of 5 years and found very high cost-effectiveness ratios. The large differences compared to our results can be attributed to differences in the underlying data and the modelling approach used in the Dutch study. First, within a 5-year time horizon, the potential benefit of treatment is much more limited.

Table 3. Sensitivity analyses.

		Cost per QALY gained	
	QALY gain	Societal perspective	Health-care perspective
Base case*	2.26	Dominant	22 520
Effectiveness reduced by 20%	2.15	Dominant	24 216
Progression 0.05/year	2.05	Dominant	26 209
Mortality SMR 1.5	2.20	Dominant	23 460
Drop-out rates			
5%	2.57	Dominant	36 050
15%	2.11	Dominant	14 173
Adverse event			
Double cost of AE	2.26	Dominant	22 536
Disutility of 0.08	2.21	Dominant	22 945
Discount rates			
0%	3.43	Dominant	12 733
5%	1.80	Dominant	28 249
Time horizon			
2 years	0.26	30 876	94 639
5 years	0.59	7657	70 223
10 years	1.13	Dominant	48 735
20 years	1.74	Dominant	34 748
30 years	2.07	Dominant	27 181

*Double-blind trial, time horizon 40 years, BASFI progression off treatment 0.07/year, 50% progression on treatment, annual drop-out rate 10%, costs and effects discounted 10%.

Ratios in our model more than double when the time horizon is reduced to 10 years and exceed the generally accepted threshold for periods shorter than 10 years. Second, possibly due to the short time-frame, the Dutch model does not incorporate changes in BASFI, the major cost-driver in our study. Third, the researchers used only two levels of costs, above and below BASDAI 4, which makes the model less sensitive to small changes. Fourth, they use the friction cost method to calculate indirect costs (33). This method ignores long-term production losses and thereby limits potential cost-offsets.

Other cost-effectiveness analyses have been conducted or evaluated recently by health technology assessment groups. Differences compared to our analysis appear to be similar to those mentioned above for the Dutch study and relate to assumptions: time horizons, the effect of treatment on function, more limited cost and utility data. In addition, there are obviously differences due to the country where the study is performed.

In conclusion, in this study we investigated the cost-effectiveness of infliximab in Spain, using real-world cost and utility data and patient-level data from two clinical trials. In addition to extrapolating the effect of treatment seen in a double-blind trial, a second analysis was conducted using patient-level data from an open Spanish study investigating a different dosing regimen. The paucity of data in the areas of treatment continuation and progression of functional disability while on treatment was addressed by offering several scenarios for analysing cost-effectiveness. It was observed that irrespective of the scenario chosen, and for the patient population included in the studies, cost-effectiveness ratios fall within the acceptable range.

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