The Cost-Effectiveness of Infliximab (Remicade®) in the Treatment of Ankylosing Spondylitis in Canada

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ABSTRACT. ***Objective***. To estimate the cost-effectiveness of the treatment of ankylosing spondylitis (AS) with infliximab (Remicade®) in Canada over the long term, with both international and Canadian treatment regimens.

Methods. A previously published disease model based on functional capacity and disease activity was adapted to the Canadian setting. Current resource consumption from a cross-sectional bottom-up burden-of-illness study in 545 patients at different levels of severity of AS in 4 Canadian provinces was incorporated into the model. Cost-effectiveness estimates were based on a 3-month placebo-controlled clinical trial with 2-year open extension as well as a 4-year followup study of clinical practice in Canada. In the cost-effectiveness model, patients with insufficient response to treatment at 12 weeks (≥ 50% reduction in Bath Ankylosing Spondylitis Disease Activity Index) discontinue treatment. In view of the long disease duration, simulations over a 30-year timeframe were performed, incorporating disease progression from cohort studies and assumptions about treatment continuation beyond the clinical trial from the trial extension period. Results are presented in Canadian dollars, from the societal and healthcare payer perspectives, with both costs and effects discounted at 5%.

Results. Over a 30-year timeframe, with the assumption that patients' disease would remain stable while on treatment, the cost per quality-adjusted life-year (QALY) gained in the societal perspective is $37,491, using the treatment regimen in the clinical trial (5 mg/kg every 6 weeks). Using the dosing regimen of the Canadian study (75% at 3 mg/kg every 8 weeks, 15% at 3 mg/kg every 6 weeks, and 10% at 5 mg/kg every 8 weeks) the cost per QALY is $10,264. Assuming that patients on treatment progress at half the rate of untreated patients, the cost-effectiveness ratios are $45,121 and $13,883, respectively, while the most conservative assumption that progression is the same in both arms, the ratios are $54,137 and $18,712, respectively. The results are sensitive to the dosing regimen adopted, the discontinuation rate, and assumptions concerning disease progression while on treatment.

Conclusion. Our results indicate that infliximab therapy for patients with active AS would be cost-effective (ranges $10,264–$54,137 per QALY) in a Canadian setting. (J Rheumatol 2006;33:732–40)

Key Indexing Terms:
COST EFFECTIVENESS
INFLIXIMAB
QUALITY-ADJUSTED LIFE-YEAR
ANKYLOSING SPONDYLITIS

The impact of ankylosing spondylitis (AS), in particular of the gradual physical impairment, on healthcare costs and work capacity has been shown in a number of studies in Europe and in North America[1-4]. Functional capacity has been identified as the main cost driver in all studies. In a recent study in Canada mean annual costs, in Canadian dollars, ranged from $3,850 for patients with mild functional disability, defined as a score less than 3 on the Bath Ankylosing Spondylitis Functional Index (BASFI)[5], to $23,330 for patients with a BASFI score of 7 or above[6]. For patients with both very severe functional disability and very high disease activity, costs could be as high as $40,000 per patient and year.

Similarly, the effect on patients' quality of life is considerable[4,7,8], and utility has been shown to decrease with increasing functional impairment and more active disease[4]. In the study in the United Kingdom, mean utility ranged from 0.80 for a BASFI < 3 to 0.47 for BASFI ≥ 7. Using the disease activity score (Bath Ankylosing Spondylitis Disease Activity Index, BASDAI[9]), the scores ranged from 0.80 for BASDAI < 3 to 0.39 for BASDAI ≥ 7[4]. The Canadian study showed very similar scores, with utility ranging from 0.78 to 0.40[6].

With costs increasing and quality of life decreasing as the disease worsens, a treatment that prevents or slows disease progression and controls disease activity will avoid or delay the high healthcare costs and productivity losses combined with low quality of life associated with severe disease. This has been shown using 2 cost-effective models in the UK, one representing a within-trial analysis of the short term double-blind clinical trial comparing infliximab to placebo[10], and one

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representing a longterm analysis where trial data are extrapolated based on the open extension in the trial[4,11]. In the clinical trials, infliximab was shown to be very efficacious in the treatment of AS, but its cost is substantially higher than current treatments. Thus, although substantial cost offsets were shown in both models, these did not compensate for the increased treatment cost with infliximab.

As a consequence, direct costs of AS will increase in the short term, and the additional cost will have to be weighed against the health gains obtained with treatment. More important, however, the average annual cost of treatment is highly dependent on the dosage regimen used. In Canada, it can range from around $14,000 per annum for a dosage of 3 mg/kg every 8 weeks as used in a Canadian study[12], to $31,500 per annum using the regimen of the double-blind clinical trial (5 mg/kg every 6 weeks).

We examined the earlier cost-effectiveness model in a Canadian setting and investigated cost-effectiveness using a treatment regimen tested in a followup study of 34 patients in clinical practice in Canada[12].

MATERIALS AND METHODS

Data. Cost-effectiveness analysis in chronic progressive disease generally requires modeling, as all the required data are seldom available from a single data set over the relevant timeframe. The AS model is based on 3 different data sets, which all include BASFI and BASDAI measurements: data on effectiveness of treatment, disease progression, and on costs and utilities at different levels of disease severity.

Effectiveness data. The effectiveness of infliximab was taken from a double-blind placebo-controlled 12-week clinical trial with open extension in 70 patients with confirmed AS and active disease (BASDAI $\geq$ 4)[10,11,13]. Patients were randomized to 5 mg/kg infliximab every 6 weeks, with a loading dose at 2 weeks, or to placebo. After the double-blind phase, all patients were offered treatment with infliximab. Seventy-one percent of patients completed the first year of treatment and of these, 94% completed the second year. Mean BASFI scores improved from 5.5 at baseline to 3.2 at 12 weeks and 2.8 after 54 weeks in the treatment group. BASDAI scores improved from 6.5 to 3.4 and 2.8. Efficacy assessments were comparable at 54 and 102 weeks, and the side effect profile during the second year was similar to the first year.

Disease progression. Disease progression in the model is expressed with changes in BASFI. Average progression per year was estimated from 2 data sets. BASFI and BASDAI scores were available at 2 data points for 1,110 patients who answered 2 mail surveys at the University of Bath (UK) 10 years apart (1992 and 2002)[4,14] and a cohort of 495 patients followed at the Bath Royal National Hospital for Rheumatic Diseases (UK) for a period of 9 years[15]. In both datasets the mean absolute annual change in BASFI was +0.07, while BASDAI did not show any progression over time. Due to the limited data points available, the same rate of progression was used for all patients regardless of age or level of disability.

Resource utilization and cost data. Resource utilization was measured in a cross-sectional retrospective survey where information was collected directly from patients. Using a specially developed questionnaire, patients were asked about their consumption of healthcare and community services related to AS during the past 3 months, out-of-pocket expenses such as over-the-counter medication and investments, informal care needs, and work capacity (changes in work situation, short and longterm sick leave, and early retirement). All community and academic rheumatologists in the city of Edmonton who cared for patients in Northern Alberta, the Ontario Spondylitis Association, and The Arthritis Society (British Columbia Division) participated in the study, and a total of 545 completed questionnaires were included[6].

Unit costs (basis 2004) for the healthcare resources were taken from publicly available sources such as the *Compendium of Pharmaceuticals and Specialties*, the *Liste de médicaments du Quebec*, the PPS Pharma publication manual, the Ontario Hospital Insurance Plan Schedule of Benefits, and the case-cost database of the London Health Sciences Centre (London, Canada). Patients' out-of-pocket costs were based on indications by patients. Informal care was considered a direct cost and was estimated using the replacement method (i.e., the cost of community care). Loss of work capacity included sick leave, reductions in working hours due to AS with a reduction in earnings, and early retirement; this was estimated using the average gender-specific hourly wage (http://www.statcan.ca/english/Pgdb/labr69a.htm, August 2004). For more details on costing, see Kobelt, *et al*[6].

Utility data. Utility was assessed using the EuroQol 5-dimensional health status classification (EQ-5D) from the UK[16,17] to ensure comparability to the earlier study. Although a tariff for North America has recently been published, it was not available for general use at the time of our analysis[18].

The model

Structure of the model. The model combines patient-level data from the 12-week double-blind period of the clinical trial by Braun, *et al* and a Markov model with annual cycles using group data from the open extension of the trial in order to form assumptions regarding treatment continuation (Figure 1). The basic data inputs and assumptions are described below and summarized in Table 1.

During the double-blind period, BASDAI and BASFI scores for each period between the measurements in the trial (baseline, 6 and 12 weeks) are assigned to patients continuing treatment using linear interpolation between the data points. Patients withdrawing from treatment during the 12-week trial period revert to their baseline scores at the next data point, and costs and utilities are assigned in the same way.

It was necessary to adjust the placebo arm from the trial, because the 2 groups differed in terms of their baseline BASDAI and BASFI (6.5/5.5 for the intervention group vs 6.3/5.1 for the placebo group). Although the difference was not statistically significant, it had a considerable influence on the calculation of costs and utilities when these are assigned taking BASDAI, BASFI, and age into account. This would have led to artificially lower costs and higher utilities in the placebo group from the start and throughout the model, and to a considerable bias in view of the 30-year timeframe. To adjust for this, both groups started with the baseline values of the treatment group, and patients in the placebo group were then assigned mean changes of BASDAI and BASFI measured over 12 weeks in the placebo group.

At the end of the double-blind period, patients who do not respond adequately to treatment according to the efficacy criteria in the trial, i.e., reduction in BASDAI score of at least 50%, discontinue treatment and revert to their baseline scores. A total of 9 patients thus discontinued treatment at or before 12 weeks (3 during the first 6 weeks of the trial), and 9 patients were withdrawn from treatment at 12 weeks due to lack of efficacy according to the efficacy criteria used in the model.

For the extension period, patients are entered in the Markov model, in one of 3 states: "on treatment," "off treatment," and "dead." The Markov model is parametric and uses mean BASDAI and BASFI scores for the group of patients concerned. Thus, at the start of this extension period, patients are assigned the mean BASDAI and BASFI scores of the new groups, calculated as 5.7/5.4 for the no-treatment group and 2.0/1.8 for the reduced treatment group. (If all patients completing the 12-week period were to continue treatment, the mean BASDAI and BASFI scores would be 3.3/3.3 and would result in higher costs and lower utilities in the "on treatment" arm at the start of the simulation and consequently a reduced benefit compared to the no-treatment group.) The disease then progresses according to the mean absolute annual change in BASFI scores, while BASDAI scores are assumed to remain constant. Changes in disease status and resulting costs and utilities are calculated within the Markov states by tracking time. The discontinuation rate during the extension period is estimated using the dropout rate from the open followup in the clinical trial (10%). Patients withdrawing from treatment during the extension revert to the mean scores of the no-treatment group over a period of 12 weeks.

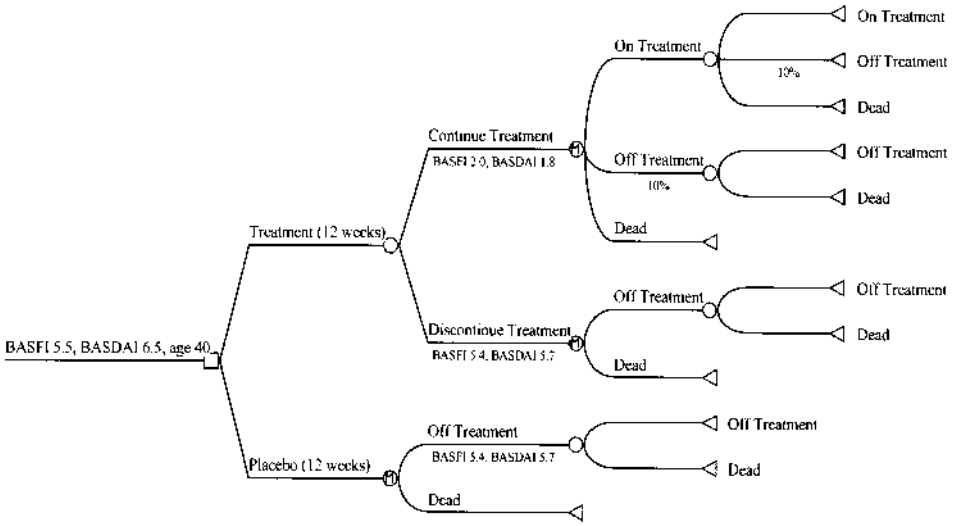

Figure 1. Structure of the model. During the first 12 weeks, patients' individual BASFI and BASDAI scores measured at weeks 0, 6, and 12 in the double-blind period of the clinical trial are used, and costs and utilities are assigned based on their profile. In the extension, mean scores are used and patients' functional disability progresses according to natural history in the no-treatment group, and according to different assumptions for patients with treatments: same as, or 50% of, the progression of the no-treatment group, or no progression while on treatment.

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

	Data Inputs and Assumptions
Basic model	
Markov states	On treatment, off treatment, death
Cycle length	1 year
Time horizon	Base case 30 years (10, 20 yrs)
Discount rate	5% (0%, 3%)
Transitions	10% (5%, 15%) of patients withdraw from treatment every year and move to off-treatment Transition to death based on life tables (normal mortality)
Disease progression	Based on BASFI only, annual progression 0.07 (0.05) points
Disease activity	BASDAI assumed to be stable
Costs	Assigned with 2-step multiple regression based on the mean BASFI/BASDAI score of the group at each cycle
Utility	Assigned with linear interpolation from a 5 × 5 matrix (BASFI/BASDAI), based on the mean BASFI/BASDAI score of the group at each cycle
Simulations	
Starting state	Off treatment: BASFI 5.4, BASDAI 5.7, utility 0.63, cost/1st year CDN$ 13,508. On treatment: BASFI 2.0, BASDAI 1.8, utility 0.89, cost/1st year CDN$ 28,928.
Disease progression	Off treatment: + 0.07 BASFI per year On treatment: Same as off-treatment, 50% of off-treatment, no progression while on treatment
Proportion on treatment	3.2% after 30 years (11.1% after 20, 34.0% after 10)
Proportion death	22.0% after 30 years (8.0% after 20, 2.3% after 10)

BASFI: Bath AS Functional Index; BASDAI: Bath AS Disease Activity Index.

The model incorporates only normal mortality, as no data on disease-specific mortality are available.

Assigning costs. The resource utilization survey included measurement of functional disability (BASFI) and disease activity (BASDAI). Both measures of disease severity showed a high correlation with costs[4,6], as shown in Figure 2. They were not normally distributed and were therefore estimated with stepwise regression analysis to relate them to specific patient profiles including BASFI, BASDAI, and age. (Gender and disease duration were not significant in the regressions.) First, the probability that a patient used a given resource was estimated using a logit model. Second, the expected cost of the resource

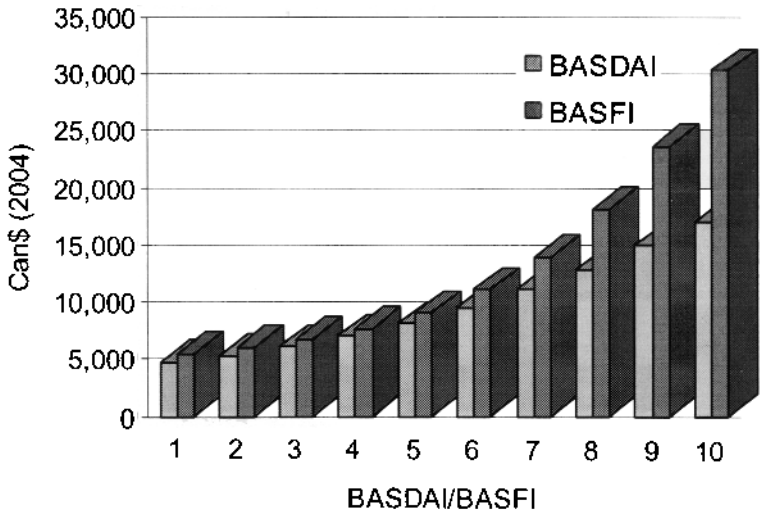

Figure 2. Total costs by disease severity according to BASDAI and BASFI. Mean total annual cost per patient as a function of either functional impairment (BASFI) or disease severity (BASDAI). Both measures are significantly correlated with costs, as well as with each other ($r^2 = 0.7$), but function is a stronger driver of costs, particularly in late disease.

(quantity × unit cost) was estimated, followed by the multiplication of the 2 terms. In the model, these costs from the survey are then assigned to patients with their specific disease profile and age for each 6-week period between the measurement points during the trial period, and to the mean BASDAI/BASFI scores of the groups during each cycle during the longterm extrapolation.

Assigning utilities. Utilities correlated with both BASFI and BASDAI, but as for costs, they were highly skewed, making it difficult to apply a linear regression model. Consequently, in the earlier model in the UK, utility scores were grouped in a 5 × 5 matrix based on BASFI and BASDAI (i.e., 25 cells), and scores for the specific patient profiles were calculated by linear interpolation within this matrix. Unfortunately, the Canadian sample contained a large number of patients with mild disease, and a number of cells in the more advanced states in this matrix had either very few patients or were empty. However, overall utility scores and scores in cells of the matrix containing at least 10 patients were very similar to the results of the earlier study in the UK, as shown in Figure 3. Therefore, rather than impute missing values, the utility matrix from the larger sample in the UK (n = 1,413) was applied (Figure 4).

Cost-effectiveness estimates. Simulations are presented for the societal and healthcare payer perspectives, over a period of 30 years, and costs and utilities are discounted at 5%. The first 3 months in the model are based directly on BASFI and BASDAI measurements in the clinical trial, but for the extension period a number of assumptions had to be made. The most important assumptions relate to the disease progression in the treatment group, the discontinuation rate, and the dosing regimen of infliximab. Results are sensitive to all these criteria, and are presented when these criteria are varied.

1. The placebo group progresses by 0.07 BASFI points every year. For patients on treatment, the most conservative analysis assumes that patients on treatment progress at the same speed as untreated patients (but start from an

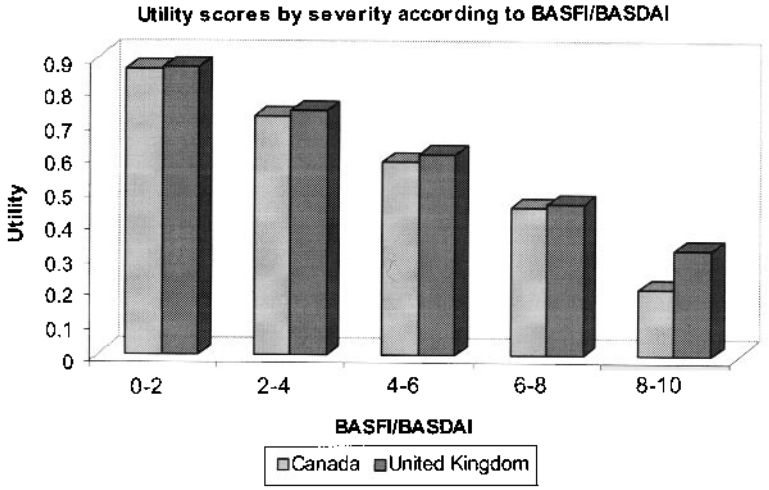

Figure 3. Comparison of utility scores in Canada and the United Kingdom. Comparability of utility scores is illustrated using a subgroup of patients from both studies, representing the diagonal axis of a 5 × 5 matrix with 2 points difference in BASFI and BASDAI (see also Figure 4). The illustration includes patients who had both scores at a similar level (i.e., between 0 and 2, 2 and 4, etc.). Note that the Canadian group at the most severe level (BASDAI > 8 and BASFI > 8) contains only 9 patients and no conclusions can therefore be drawn.

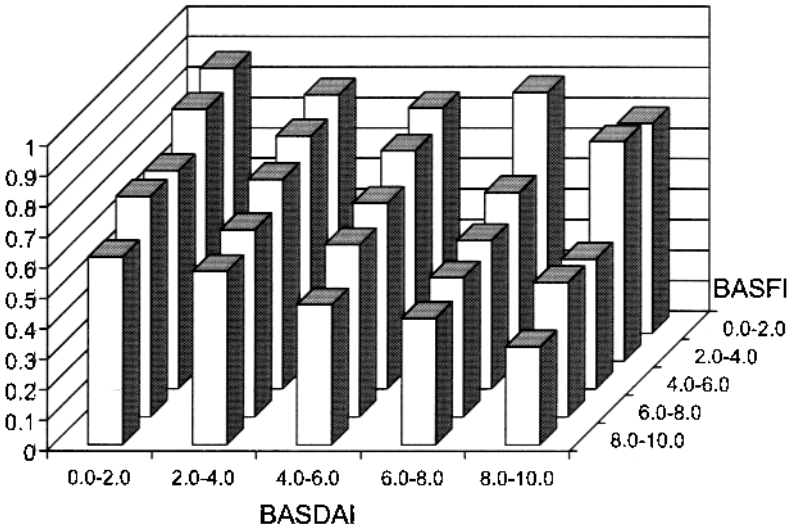

Figure 4. Patients were grouped into 25 states according to their BASDAI/BASFI scores. Utilities for patients with a given profile are calculated from this matrix using linear interpolation between the values. Although the Canadian study (n = 545) did not populate all cells with enough patients to allow conclusions, results overall were similar to the UK study, and the UK matrix shown here (n = 1413) was used in the Canadian analysis.

improved level at the end of the trial). A second and probably more realistic analysis assumes that patients on treatment progress at half the rate of untreated patients. The third and most optimistic analysis, but supported by data from the 3-year extension of the trial, assumes that patients will not progress while on treatment. Indeed, for patients with an adequate efficacy at 12 weeks according to our criteria and hence continuing on treatment in our model, the mean BASFI was stable at 2.0 over time, while the mean BASDAI scores decreased from 1.8 at 12 weeks to 1.6 and 1.5 after 1 and 2 years, respectively.

2. After 12 weeks, patients with an inadequate response are assumed to discontinue treatment. During the extension, 10% of patients will withdraw from treatment every year, as was seen in the second and third years of the clinical trial. A similar rate was also seen in the Canadian 4-year followup of 34 patients: over 4 years, 14/34 patients withdrew, i.e., an overall withdrawal rate of 41%[12].

3. The list price for infliximab in Canada is $940 for a 100 mg vial. The model uses 2 different cost scenarios for the intervention: the treatment regimen used in the clinical trial by Braun, *et al* (5 mg/kg body weight every 6 wks) and the more flexible individualized schedule used in the 4-year study in Canada[12]. In this trial, 34 patients were started with a dose of 3 mg/kg every 8 weeks. After 4 years of followup, 20 patients were still receiving treatment, 15 at the initial low dose, 3 at a dose of 3 mg/kg every 6 weeks, and 2 at a dose of 5 mg/kg every 8 weeks. In the first scenario, the total drug cost for the first year, in Canadian dollars, is $34,700 with a treatment regimen as in the clinical trial and $31,500 from the second year onwards. In the second scenario, the average treatment cost for a maintenance year (year 2 onwards) is estimated at $16,200. For each infusion, the cost of an outpatient visit to the hospital was added.

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 clinical trial by Braun, *et al*. The total cost for all events was estimated and a mean cost per patient of $45.40 assigned to all patients who started treatment for the first year in the model. In subsequent years of the trial, adverse events were extremely rare and mild, and only one in 5 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

We first present the flow of patients between the 3 states over the 30-year time horizon (Figure 5). Table 2 presents the analysis using the treatment regimen from the double-blind trial. The base case assumes that BASFI scores of patients do not progress while on treatment. In the societal perspective, where all costs are included, the cost per QALY gained is estimated, in Canadian dollars, at $37,491. When only healthcare costs are included, the cost per QALY gained increases slightly to $45,767. Assuming that patients on treatment progress at half the rate of untreated patients leads to $45,121 and $53,733 per QALY gained, in the societal and healthcare payer perspectives, respectively. The number of QALY gained is estimated at 2.96, 2.27, and 2.58 in the 3 scenarios.

In addition, we present the cost per QALY for treatment as in the clinical trial, with patients entering the longterm extension regardless of whether they reached the efficacy criterion of 50% improvement in BASDAI or not. In these most conservative calculations, patients progress at the same rate, regardless of whether they are on treatment or not, and the cost per QALY gained is estimated at $84,642.

The effectiveness of individualized treatment as studied in the Canadian trial appears to be similar to the double-blind trial, and we therefore apply the treatment cost resulting from this regimen (Table 3). In this scenario, the cost per QALY gained, assuming no progression while on treatment, is reduced to $10,264 and $18,540 in the societal and healthcare payer perspectives, respectively. With half the progression of untreated patients, the cost per QALY is estimated at $13,883 and $22,496, and with the same progression in both groups at $18,712 and $27,360. Assuming that the effectiveness with the Canadian regimen is reduced by 20% compared to the

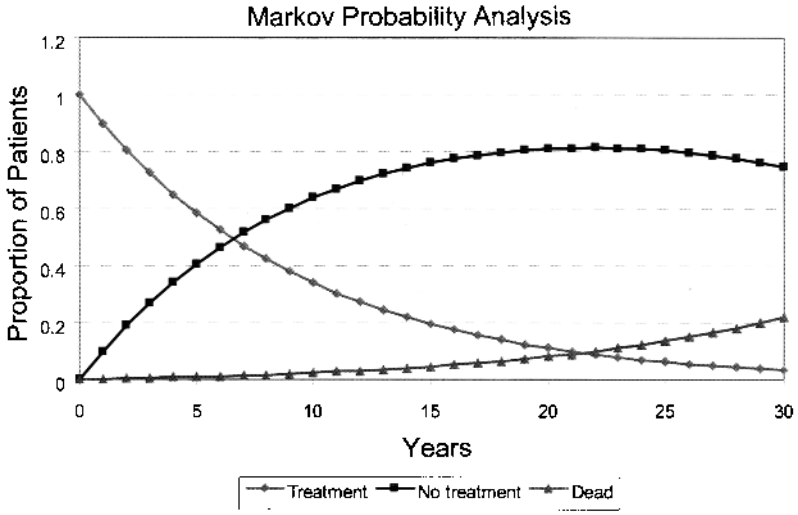

Figure 5. Movement of the treated cohort between the Markov states over 30 years. The transition of patients at a mean age of 40 years who are initially on treatment (i.e., 100% of patients on treatment). Over time, patients withdraw from treatment and a certain proportion dies (normal mortality).

Table 2. Cost per quality-adjusted life-year (QALY) gained over 30 years, using the treatment regimen of the double-blind trial[10] (5 mg/kg every 6 weeks). Values are Canadian dollars.

	Incremental Cost[a], $	QALY Gain[a]	ICER ($/QALY)[a]
No progression while on treatment			
All costs included	110,822	2.96	37,491
All direct costs[b]	119,416	2.96	40,399
Healthcare costs only	135,283	2.96	45,767
50% progression while on treatment			
All costs included	116,250	2.58	45,121
All direct costs[b]	123,599	2.58	47,973
Healthcare costs only	138,441	2.58	53,733
Same progression in both groups			
All costs included	122,993	2.27	54,137
All direct costs[b]	128,882	2.27	56,729
Healthcare costs only	142,641	2.27	62,785
Treatment of all patients beyond 12 weeks[†]			
All costs included	164,786	1.95[c]	84,642
All direct costs [b]	169,819	1.95[c]	87,228
Healthcare costs only	187,374	1.95	96,245

[a] Cost and effects discounted with 5%. [b] Direct medical and nonmedical costs, investments, and informal care. [c] When all patients continue treatment, the mean BASDAI/BASFI scores are higher as patients with a lesser treatment effect are incorporated, reducing the difference between the 2 arms compared to the base case. [†] Patients continue as in the trial (regardless of effect, same progression in both groups).

double-blind trial, the cost per QALY gained (no progression while on treatment) is estimated at $15,031 and $24,397, respectively.

Sensitivity analyses are further presented for a slower BASFI progression, i.e., different discontinuation rules (< 30% improvement), different continuation rates, different discount rates, and different timeframes, using as the base case the cost of the Canadian treatment regimen and assuming that patients do not progress while on treatment (Table 4). Results are most sensitive to the number of patients withdrawing from treatment every year.

DISCUSSION

Estimating the cost-effectiveness of treatments in ankylosing spondylitis is challenging in several respects. First, although functional capacity is the major driver of costs, the progres-

Table 3. Cost per quality-adjusted life-year (QALY) gained over 30 years, using the treatment regimen of the Canadian trial[12] (75% at 3 mg/kg every 8 weeks, 15% at 3 mg/kg every 6 weeks, 10% at 5 mg/kg every 8 weeks). Values are Canadian dollars.

	Incremental Cost[a], $	QALY Gain[a]	ICER ($/QALY)[a]
No progression while on treatment			
All costs included	30,341	2.96	10,264
All direct costs[b]	38,935	2.96	13,172
Healthcare costs only	54,802	2.96	18,540
50% progression while on treatment			
All costs included	35,769	2.58	13,883
All direct costs[b]	43,118	2.58	16,735
Healthcare costs only	57,960	2.58	22,496
Same progression in both groups			
All costs included	42,512	2.27	18,712
All direct costs[b]	48,401	2.27	21,304
Healthcare costs only	62,160	2.27	27,360

[a] Cost and effects discounted with 5%. [b] Direct medical and nonmedical costs, investments, and informal care. ICER: incremental cost-effectiveness ratio.

Table 4. Sensitivity analyses (using the cost of the treatment regimen of the Canadian trial[12]). Values are Canadian dollars.

	Incremental Cost[a], $	Qaly Gain[a]	ICER (CDN$/QALY)[a]
Base cases[b]			
All costs included	30,341	2.96	10,264
Healthcare costs only	54,802	2.96	18,540
Effectiveness reduced by 20%			
All costs included	34,985	1.89	15,031
Healthcare costs only	56,784	2.33	24,397
Patients with < 30% effect discontinue			
All costs included	39,639	3.66	10,832
Healthcare costs only	68,469	3.66	18,710
Progression 0.05/year			
All costs included	34,490	2.43	16,866
Healthcare costs only	59,626	2.43	24,578
Dropout rates			
5% (all costs)	63,629	3.33	19,093
5% (healthcare costs)	89,646	3.33	26,901
15% (all costs)	11,626	2.75	4,236
15% (healthcare costs)	35,256	2.75	12,845
Discount rates			
0% (all costs)	5,017	5.21	963
0% (direct healthcare costs)	49,344	5.21	9,470
3% (all costs)	23,234	3.62	6,690
3% (healthcare costs)	54,567	3.62	15,063
Timeframe			
10 yr (all costs)	46,043	1.72	26,719
10 yr (healthcare costs)	60,419	1.72	37,596
20 yr (all costs)	40,480	2.53	16,007
20 yr (healthcare costs)	61,252	2.53	24,221
40 yr (all costs)	23,303	3.17	7,360
40 yr (healthcare costs)	49,017	3.17	15,481

[a] Cost and effect discounted with 5% except when otherwise stated. [b] Time horizon 30 years, BASFI progression off treatment 0.07/year, no progression while on treatment, annual dropout rate 10%. ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year.

sion to severe impairment is slow. This makes it necessary to adopt a longterm perspective using disease models that, by definition, imply a number of assumptions. Second, functional impairment and disease activity are highly correlated (r^2 = 0.7), but these affect costs and utility at different times. Thus, to estimate costs and utility for patients with a given disease profile, both measures (BASFI and BASDAI), as well as age, need to be taken into account. Third, data on treatment are limited as far as duration of the trials and the size of the samples in clinical trials are concerned, requiring modeling. Last, current treatment and patient management is not very costly, but the social cost of the disease is substantial, due to a high loss of work capacity and need for informal care. As a consequence, economic evaluation should be performed from the societal perspective to cover all consequences of treatment.

Our earlier study in the UK took all these factors into account, using different models, and the current study for Canada is based on this earlier work. However, a number of issues, in particular the specific assumptions made in this analysis, require discussion.

Our results are most sensitive to the treatment cost and thus the dosing scenario that is adopted. In the clinical trial by Braun, *et al*, patients received 5 mg/kg every 6 weeks, but other regimens have been successfully tested, particularly in Canada[12]. The study showed that effective treatment can be provided with individualized dosing schedules ranging between 3 and 5 mg/kg every 6–8 weeks. Although the model is based on patient-level data from the double-blind trial, in part of our analysis, we have assumed that effectiveness for the 2 regimens was similar. Almost 60% of patients in the Canadian observational cohort demonstrated a reduction of 50% in the BASDAI by week 14. Further, all 15 (45%) patients in this cohort that continued infliximab (median followup 1209 days) maintained a ≥ 50% decrease in BASDAI during followup. However, it is impossible to compare the trials directly, and we present a sensitivity analysis for a reduced effectiveness with the lower dose.

In our base case analysis, patients with inadequate response are taken off treatment after 3 months. This cannot be currently verified in clinical practice in Canada. However, as an example and following recommendations of the ASsessments in Ankylosing Spondylitis (ASAS) Working Group guidelines[20], the UK Society for Rheumatology treatment guidelines stipulate that patients with less than 50% or 2 points improvement in BASDAI should not continue to receive treatment. Thus, it is possible that a similar treatment guideline will be established in other countries.

We present 3 different scenarios for disease progression beyond the clinical trial. The no-treatment group progresses according to the rate estimated from cohort studies, while patients on treatment either remain stable or progress at half the average rate, or at the same rate, as no-treatment patients. The first and most optimistic scenario is supported by the data from the 2-year trial extension, where the mean BASFI score of patients included in the treatment group in the model remains stable. The most conservative assumption, i.e., that patients' function declines at the same rate over time whether on treatment or not on treatment, implies an effect only on disease activity and not on progression of functional disability. This appears overly conservative, as it is generally accepted that inflammation leads to functional decline. However, in the case where all patients in the trial continue treatment, regardless of whether they achieve the efficacy endpoint or not, one might argue that the longterm effectiveness of treatment could be lower than when only responders are treated. For these reasons, we present a "middle of the road" scenario, where patients who achieve the efficacy endpoint continue at half the annual rate. However, this assumption is not supported with empirical data. Nevertheless, considering the 2 extremes of unchanged progression or no progression, this scenario appears acceptable. Also, all of these scenarios may be underestimating the effect in the first year, as the BASFI/BASDAI scores from 12 weeks onwards are held stable, while the BASDAI scores actually improve.

Results are also sensitive to the withdrawal rate in the extension period. In the clinical trial, around 10% of patients discontinued treatment every year, and the low-dose trial in Canada showed similar rates, with 14 of 34 patients withdrawing over 4 years. We have therefore assumed an annual dropout rate of 10% in the model. However, this rate may be somewhat high, considering that patients with inadequate response are not entering the longterm extension in the model. Patients will thus only withdraw due to adverse events or other reasons. Adverse events were rare, both in the double-blind and in the Canadian trials, and one might expect the rate to be lower than in the trials. In such a case, the cost-effectiveness ratios would increase somewhat. However, there is no data to support a lower withdrawal rate, and it is therefore more adequate to use the rate from the 2 trials.

We have used the EQ-5D to measure utilities in the cross-sectional survey, despite availability of a more specifically Canadian instrument, the Health Utility Index (HUI)[21]. The choice of the EQ-5D allowed comparison with the UK[4] and other European studies[2]. Utilities in Canada were similar to those in the UK, which allowed using the scores from the larger UK sample in the current study for Canada. The sample in Canada did not provide scores for all combinations of BASFI/BASDAI, and rather than impute values, or use scores from very small groups of patients, we decided to apply the UK matrix. It might appear (Figure 3) that Canadian scores are overall slightly lower. However, cost-effectiveness models are based on the differences between scores at given levels of disease severity rather than absolute values, and results would thus not be affected. The only exception to this would be the most severe state, with BASDAI/BASFI above 8, but this score is based on less than 10 patients in Canada. It is therefore preferable to use the UK values, bearing in mind that

cost-effectiveness ratios would be reduced slightly, if this low value was confirmed.

We have investigated the cost-effectiveness of infliximab, using "real-world" cost and utility data that was collected from a large cohort of Canadian patients living with AS. The first Canadian study of its kind, it offers insights into the cost-effectiveness of infliximab treatments under different assumptions. 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 analyzing cost-effectiveness. It was observed that irrespective of the scenario chosen, and for the patient population included in the study, cost-effectiveness ratios fall within the acceptable range.

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