Cost-Effectiveness of Abatacept in Patients with Moderately to Severely Active Rheumatoid Arthritis and Inadequate Response to Tumor Necrosis Factor-α Antagonists

MONTSERRAT VERA-LLONCH, ELENA MASSAROTTI, FREDERICK WOLFE, NANCY SHADICK, RENE WESTHOVENS, OLEG SOFRYGIN, ROSS MACLEAN, TRACY LI, and GERRY OSTER

ABSTRACT. ***Objective.*** To assess cost-effectiveness of abatacept in patients with rheumatoid arthritis (RA) with inadequate response to tumor necrosis factor-α antagonists (anti-TNF).

Methods. We developed a simulation model to depict progression of disability [in terms of Health Assessment Questionnaire Disability Index (HAQ-DI)] in women aged 55–64 years with moderately to severely active RA and inadequate response to anti-TNF. At model entry, patients were assumed to receive either oral disease modifying antirheumatic drugs (DMARD) only or oral DMARD plus abatacept. Patients were then tracked from model entry until death. Future health-state utilities and medical-care costs (except study therapy) were estimated based on predicted values of the HAQ-DI. The model was estimated using data from a Phase III clinical trial of abatacept plus secondary sources. Cost-effectiveness was expressed in terms of incremental cost (2006 US$) per quality-adjusted life-year (QALY) gained alternatively over 10 years and a lifetime. Future costs and health effects were discounted at 3% annually.

Results. Over 10 years, abatacept would yield 1.0 additional QALY (undiscounted) per patient (4.0 vs 3.0 for oral DMARD) at an incremental (discounted) cost of $45,497 ($100,648 vs $55,151) respectively; over a lifetime, corresponding figures were 1.6 QALY (5.8 vs 4.2) and $64,978 ($140,714 vs $82,489). Cost-effectiveness was [mean (95% CI)] $50,576 ($47,056, $54,944) per QALY gained over 10 years, and $45,979 ($42,678, $49,932) per QALY gained over a lifetime. Findings were robust in sensitivity analyses.

Conclusion. Abatacept is cost-effective by current standards of medical practice in patients with moderately to severely active RA and inadequate response to an anti-TNF. (First Release July 15 2008; J Rheumatol 2008;35:1745–53)

Key Indexing Terms:
ABATACEPT TUMOR NECROSIS FACTOR-α RHEUMATOID ARTHRITIS
OUTCOMES COST-EFFECTIVENESS

Tumor necrosis factor-α antagonists (anti-TNF) represent a significant advance in the management of rheumatoid arthritis (RA). Their clinical effects are related to inhibition of TNF-α, a key cytokine in the pathophysiology of rheumatoid synovitis[1]. Three such agents are currently available: infliximab, etanercept, and adalimumab. Their efficacy has been reported to be similar[2,3].

Acquired drug resistance[4] or gradual drug failure[5] increasingly have been reported among RA patients receiving anti-TNF; problems of tolerability and safety also have been noted. In retrospective cohort studies, only about one-half to two-thirds of patients who initiate therapy with an anti-TNF have been reported to still be receiving the same agent 12 months subsequently[6-16]; at 24 and 36 months, even lower rates of persistency have been reported (50% and 40%, respectively)[6]. While findings from a number of small studies support the clinical value of switching to a second anti-TNF following failure with the first such agent[14-21], interest in new therapeutic alternatives for patients who experience inadequate response to an anti-TNF remains keen.

Abatacept is a selective costimulation modulator that binds to T cell surface receptors CD80 and CD86, thereby

From Policy Analysis Inc. (PAI), Brookline; Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts; National Data Bank for Rheumatic Diseases, Wichita, Kansas, USA; University Hospital, Katholieke Universiteit Leuven, Leuven, Belgium; and Bristol-Myers Squibb, Princeton, New Jersey, USA.

M. Vera-Llonch, MD, PAI; E. Massarotti, MD, Harvard Medical School, Brigham and Women's Hospital; F. Wolfe, MD, National Data Bank for Rheumatic Diseases; N. Shadick, MD, Harvard Medical School, Brigham and Women's Hospital; R. Westhovens, MD, University Hospital, Katholieke Universiteit Leuven; O. Sofrygin, MD, PAI; R. Maclean, MD; T. Li, MD, Bristol-Myers Squibb; G. Oster, PAI.

Address reprint requests to G. Oster, Policy Analysis Inc., Brookline, MA 02445. E-mail: goster@pai2.com

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blocking interaction with CD28[22,23]. This interaction provides a costimulatory signal necessary for full activation of T lymphocytes (T cells), which has been implicated in the pathogenesis of RA. The efficacy and safety of abatacept were recently evaluated in adult patients with active RA [according to American College of Rheumatology (ACR) criteria][24] in 5 randomized, double-blind, placebo-controlled clinical trials. In one such trial, the Abatacept Trial in Treatment of Anti-TNF Inadequate Responders (ATTAIN)[25], 258 RA patients with inadequate response to anti-TNF therapy (about two-thirds had received infliximab, and the remainder, principally etanercept) were randomized to receive abatacept or placebo for 6 months in addition to their stable doses of oral disease modifying antirheumatic drugs (DMARD).

At 6 months, ACR 20, ACR 50, and ACR 70 responses (which reflect improvement in tender and swollen joint counts and in 3 of the following 5 measures — physician global assessment, patient global assessment, pain, disability/function, and inflammatory biomarkers) were significantly higher for patients randomized to receive abatacept, as was the percentage of patients achieving a "major clinical response" (defined as ACR 70 response for 6 consecutive months). Patients receiving abatacept also were reported to have significantly greater improvements in physical function as measured by the Health Assessment Questionnaire Disability Index (HAQ-DI)[26].

Much like other biologic response modifiers, however, the cost of abatacept therapy is substantially higher than that of nonbiologic DMARD. While formal economic evaluations have been undertaken for infliximab, etanercept, adalimumab, and anakinra[27-32], the cost-effectiveness of abatacept has not yet been reported. We examined the cost-effectiveness of abatacept in patients with moderately to severely active RA and inadequate response to anti-TNF.

MATERIALS AND METHODS

Model description. We developed a simulation model[33-36] to depict progression of functional disability over time in women, aged 55–64 years, with moderately to severely active RA and inadequate response to anti-TNF. Functional disability was expressed in terms of the HAQ-DI, which ranges from 0 (no limitation in activities of daily living) to 3 (complete inability to perform these activities). The HAQ-DI was estimated on a quarterly basis (model periodicity), and was assumed to increase over time as a result of disease progression.

At model entry, patients were assumed to receive either their stable doses of oral DMARD ("oral DMARD"), or oral DMARD plus abatacept ("abatacept"). [Abatacept was the first agent approved for the treatment of RA in patients who had failed therapy with an anti-TNF. While other therapies now have a similar indication (e.g., rituximab), at the time our study was conducted, efficacy data in this patient population were available for abatacept only. We therefore assumed that, following therapy failure with an anti-TNF, the only alternative to abatacept would be treatment with an oral DMARD.] Patients receiving abatacept were assumed to initiate treatment [500–1000 mg (based on body weight) intravenous infusion over 30 min] on day 1, and to receive additional infusions on day 14, day 29, and every 4 weeks thereafter. Consistent with data from the ATTAIN trial[25], abatacept therapy was assumed to result in improvement in the HAQ-DI in comparison with oral DMARD alone. Patients with HAQ-DI improvements of –0.50 or greater at 6 months were assumed to continue to receive abatacept; those failing to achieve this level of clinical benefit were assumed to discontinue treatment. Patients also were assumed to possibly discontinue abatacept for other reasons, including side effects, intercurrent illness, and surgery. All patients discontinuing abatacept (irrespective of reason) were assumed to continue to receive stable doses of oral DMARD. We did not consider switching from abatacept to another biologic DMARD (e.g., etanercept, rituximab), as there are no data on the efficacy of the latter agents given prior failure with abatacept.

Improvement in the HAQ-DI during the first 6 months of therapy was estimated based on data from the ATTAIN clinical trial[25]. For patients continuing to receive abatacept beyond 6 months, the improvement at 6 months was assumed to persist over time. For patients discontinuing abatacept, the HAQ-DI was assumed to return to a value equal to what it would have been in the absence of such treatment (i.e., assuming treatment with oral DMARD only). Side effects of abatacept were not considered, except as they might result in therapy discontinuation, as there are no data on their influence on health-state utilities, and the associated cost of treatment is probably negligible in comparison with other medical care costs of patients with RA; a similar approach has been employed in other evaluations[27,30,31].

Outcomes and costs were simulated alternatively over 10 years and a lifetime for a hypothetical cohort of 1000 women between the ages of 55 and 64 years (this group is representative of many patients with RA[37], and is consistent with the characteristics of study subjects in the ATTAIN trial, on which our estimates of abatacept efficacy were based). Each patient in the cohort was entered into the model, one at a time, and then tracked on a quarterly basis from model entry until death. At model entry, each patient in the cohort was randomly assigned an initial value of the HAQ-DI by sampling from an assumed initial probability distribution for this measure. Future values of the HAQ-DI were estimated based on the assumed initial value, the expected rate of disease progression, and the expected effect of treatment (abatacept plus oral DMARD or oral DMARD alone). A schematic of our model is provided in Figure 1.

Mortality risk was estimated based on age and the expected value of the HAQ-DI. Health-state utilities and medical-care costs (other than study therapy and associated monitoring) were similarly estimated based on expected future values of the HAQ-DI. Costs were estimated from a third-party payer perspective and included medical treatment only; neither direct nonmedical costs (e.g., hired help, assistive devices, home modifications) nor lost productivity due to RA-related disability were considered.

Summation of outcomes and costs across all 1000 patients in the model cohort yielded expected values for the measures of interest; means and 95% confidence intervals (95% CI) were generated using second-order, Monte Carlo simulation. The cost-effectiveness of abatacept was expressed in terms of the incremental cost per quality-adjusted life-year (QALY) gained versus oral DMARD alone. Costs and health effects were discounted at an annual rate of 3% (health effects are also reported on an undiscounted basis to aid in interpretation of findings), consistent with recommendations of the US Public Health Service Panel on the Cost-Effectiveness of Health and Medicine[38].

Model estimation. Model inputs are reported in Table 1. Unit costs of medication and other direct medical-care services are reported in Table 2.

Pretreatment HAQ-DI. At model entry, each patient in the model cohort was randomly assigned an initial value for the HAQ-DI by sampling (with replacement) from the actual distribution of HAQ-DI values at study entry in the ATTAIN trial [data on file, Bristol-Myers Squibb (BMS)]. HAQ-DI scores at therapy initiation therefore were allowed to vary from patient to patient.

Disease progression with oral DMARD. For patients receiving oral DMARD only, the HAQ-DI was assumed to increase by 0.065 annually to reflect disease progression. This estimate was based on the reported mean annual increase in the HAQ-DI during periods of nonresponse to treatment

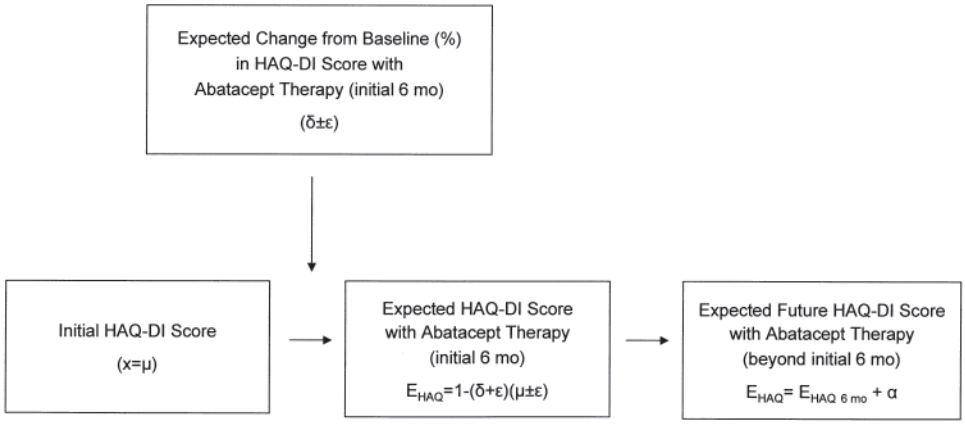

Figure 1. The simulation model. α: Change in HAQ-DI reflecting disease progression.

Table 1. Clinical parameters used in abatacept cost-effectiveness model.

Pretreatment HAQ-DI (% of patients, by HAQ-DI interval)	
0.00– < 0.25	1.0
0.25– < 0.50	0.5
0.50– < 0.75	1.8
0.75– < 1.00	4.4
1.00– < 1.25	6.9
1.25– < 1.50	8.2
1.50– < 1.75	14.7
1.75– < 2.00	14.7
2.00– < 2.25	17.0
2.25– < 2.50	15.4
2.50– < 2.75	4.6
2.75–3.00	10.8
HAQ-DI change (vs pretreatment) with abatacept (mean ± SD) (%)	
3 months	–21.0 ± 27.9
6 months	–25.5 ± 33.7
Annual HAQ-DI progression	
Abatacept	0.015
Oral DMARD	0.065
Threshold for clinically meaningful improvement in HAQ-DI at 6 mo	–0.5
Annual discontinuation for reasons other than lack of efficacy (%), year 1	8.10
Annual discontinuation for all reasons (%), subsequent years	8.10
Mortality, odds ratio	1.80
Health-state utility (mean ± SD), by HAQ-DI interval	
0.00– < 0.25	0.86 ± 0.16
0.25– < 0.50	0.80 ± 0.13
0.50– < 0.75	0.76 ± 0.14
0.75– < 1.00	0.71 ± 0.15
1.00– < 1.25	0.66 ± 0.15
1.25– < 1.50	0.59 ± 0.18
1.50– < 1.75	0.51 ± 0.19
1.75– < 2.00	0.43 ± 0.21
2.00– < 2.25	0.33 ± 0.24
2.25– < 2.50	0.23 ± 0.25
2.50– < 2.75	0.12 ± 0.27
2.75–3.00	0.03 ± 0.33

among patients participating in the Early Rheumatoid Arthritis Study who previously had failed treatment with 2 DMARD[27]. To our knowledge, estimates specific to patients who have failed prior anti-TNF therapy are not available at this time.

Table 2. Unit-cost estimates used in abatacept cost-effectiveness model (2006 US$).

Medication	
Abatacept (1 mg/kg) per month	
First year	19,387
Subsequent years	16,802
Administration (per infusion)	129
Oral DMARD (methotrexate, 15 mg weekly)	600
Monitoring	
First year	
Oral DMARD	181
Oral DMARD + abatacept	190
Subsequent yrs	
Both treatment groups	181
All other direct medical care services (mean ± SD), by HAQ interval	
0.00– < 0.125	1,839 ± 6,100
0.25– < 0.375	2,367 ± 6,124
0.50– < 0.625	2,658 ± 6,751
0.75– < 0.875	2,876 ± 6,513
1.00– < 1.125	3,263 ± 7,225
1.25– < 1.375	3,794 ± 8,019
1.50– < 1.625	4,545 ± 9,293
1.75– < 1.875	5,308 ± 10,975
2.00– < 2.125	6,061 ± 12,103
2.25– < 2.375	7,260 ± 14,470
2.50– < 2.625	8,214 ± 15,762
2.75– < 3.00	8,779 ± 15,231

Disease progression with abatacept. For patients initiating treatment with abatacept, the expected percentage change in the HAQ-DI 3 and 6 months following therapy initiation was obtained by sampling (with replacement) from the actual distribution of this measure at these points in time among subjects in ATTAIN randomized to receive abatacept (data on file, BMS). The estimated mean (± SD) percentage HAQ-DI change 3 months after therapy initiation in ATTAIN was 21.0% (± 27.9%); at 6 months, it was 25.5% (± 33.7%). The distribution of the HAQ-DI change with therapy was assumed to be truncated normal, based on visual inspection of data.

Among patients continuing to receive abatacept, the percentage reduction in the HAQ-DI (i.e., clinical benefit) was assumed to remain constant at the level prevailing at 6 months, based on the observation that maximal effects of other biologic response modifiers are attained by 6 months and sustained over time[39-41]. To reflect disease progression, however, the HAQ-DI value against which this percentage reduction was applied was increased by 0.015 annually, based on estimates reported by Brennan, *et al* for patients receiving biologic therapies[27]. For patients discontinuing abatacept

therapy (irrespective of reason), the HAQ-DI was conservatively assumed to revert immediately to the level prevailing among those receiving oral DMARD only (i.e., benefits were assumed not to persist).

Discontinuation of abatacept therapy. Patients failing to attain a clinically meaningful improvement with abatacept were assumed to discontinue treatment. The threshold for clinically meaningful benefit was assumed to be a 0.50 reduction in the HAQ-DI at 6 months, or approximately the mean change in the HAQ-DI in ATTAIN among patients with an ACR 20 response (data on file, BMS). Alternative values for this parameter (0.25, 0.75) were examined in sensitivity analyses. Discontinuation due to lack of efficacy was assumed to occur in the first year only.

Patients also were assumed to possibly discontinue treatment for reasons other than lack of efficacy, including side effects, intercurrent infection, surgery, and various other considerations. In the ATTAIN study, 8.1% of patients randomized to abatacept discontinued treatment during the first 6 months for reasons other than lack of efficacy (data on file, BMS). We assumed that this rate would apply to the first year and all subsequent years.

Mortality. Mortality risk was assumed to be a function of gender, age, and HAQ-DI; the latter was based on evidence from observational studies of a positive relationship between the HAQ-DI and mortality[42-45]. Abatacept therapy therefore was assumed to confer a mortality benefit. Mortality risk for patients with a HAQ-DI value of 0 was assumed to be the same as that of their gender- and age-matched peers in the general population[46]. For patients with HAQ-DI values > 0, mortality risk was calculated by multiplying gender- and age-specific mortality by an odds ratio (OR) of 1.8 (HAQ-DI) (i.e., each 1-point increase in the HAQ-DI was assumed to result in a 1.8-fold increase in mortality risk). This estimate was based on analyses of data from the National Data Bank for Rheumatic Diseases (NDB), a research organization with longitudinal data on patients with various rheumatic disorders recruited from US rheumatology practices. In sensitivity analyses, we examined the robustness of our findings with respect to this assumption.

Health-state utilities. Health-state utility values were assumed to depend on the value of the HAQ-DI; this relationship was estimated using data on the EurQol (EQ-5D) Weighted Health Index (WHI)[47] and the HAQ-DI for about 19,000 persons with RA in the NDB (Table 1). Within each of the model-defined HAQ-DI intervals, the conditional distribution of the EQ-5D WHI was assumed to be truncated normal, based on visual inspection of the data.

Costs. Following an initial infusion, abatacept was assumed to be administered on days 14 and 29, and every 4 weeks thereafter, for a total of 15 infusions during the first year and 13 infusions every year thereafter (Table 2)[48]. Patients weighing < 60 kg were assumed to receive 2 vials (500 mg) per infusion; 60–100 kg, 3 vials (750 mg); and > 100 kg, 4 vials (1 g). The distribution of RA patients by body weight (< 60 kg, 23.5%; 60–100 kg, 65.7%; > 100 kg, 10.8%) was estimated using data from the US Third National Health and Nutrition Examination Survey (NHANES III)[49]. The cost of abatacept was assumed to be $450 per 250 mg vial[50]. The cost of each 30 min infusion was assumed to be $129 (data on file, BMS). Oral DMARD therapy was assumed to consist of MTX, as this was the therapy that the vast majority (~80%) of patients in the ATTAIN clinical trial were receiving at trial entry[25]. The annual cost of treatment with MTX was assumed to be $600 (or about $12 per week), based on an assumed dose of 15 mg weekly[50].

Estimates of the cost of baseline and routine monitoring for patients receiving abatacept were based on product labeling[48], published guidelines[51], and Medicare payment rates for selected Common Procedural Terminology – 4th edition (CPT-4) codes[52]. Patients initiating abatacept were assumed to require a tuberculin skin test [CPT-4 86580 (tuberculosis, intradermal) and 86585 (tuberculosis, tine test)] at a cost of $9. Patients receiving oral DMARD (alone or with abatacept) were assumed to require a complete blood count, an alanine aminotransferase test, and an albumin test every 6 weeks[51], with the annual cost of such monitoring estimated to be $181, based on prevailing reimbursement rates for CPT-4 codes 85027, 82040, and 84460, and a conversion factor of $36.20. Pretreatment evaluations (e.g., chest radiographs, hepatitis serology) were not added to the cost of oral DMARD, as all patients were assumed to be receiving stable doses of such therapy prior to model entry.

Estimates of the cost of all other direct medical-care services included all inpatient and outpatient services, irrespective of reason, as it is difficult to disentangle RA-related from non-RA-related care. Direct nonmedical care costs (e.g., hired help, assistive devices for the home, transportation services) were not considered, nor was the value of lost productivity associated with RA-related disability. The cost of all other direct medical-care services was assumed to vary with the HAQ-DI; this relationship was estimated using patient-level data from the NDB (Table 2). The conditional distribution of direct medical-care costs given the HAQ-DI was assumed to be log-normal, based on visual inspection of the data. Reimbursed amounts (i.e., payments) from the NDB were used in the analyses as a proxy for costs. All costs are reported as US dollars and were adjusted to 2006 average price levels, as necessary, using the Consumer Price Index for Medical Care Services[53].

Analyses. Monte Carlo simulation techniques[33-36] were employed to estimate the effect of abatacept on HAQ-DI values over time. First-order simulations (also sometimes referred to as "microsimulation" or "random walk")[54] were performed by running each patient in the hypothetical cohort through the model, one at a time. Outcomes for the cohort as a whole were obtained by summing the measures of interest across all patients. Time horizons of 10 years and a lifetime were alternatively employed. The cost-effectiveness of abatacept was expressed in terms of the incremental cost per QALY gained in comparison with oral DMARD alone. Costs and health effects were discounted at an annual rate of 3%.

Second-order simulations (to account for parameter uncertainty) were performed by running the model for 100 samples of 1000 patients each. Three key model parameters — percentage change in the HAQ-DI at 6 months with abatacept therapy, health-state utility value by HAQ-DI interval, and total cost of all other direct medical-care services by HAQ-DI interval — were allowed to vary stochastically in these simulations, based on assumed (normal) probability distributions of the mean values.

Tallying results across all simulations, an expected value was obtained for each measure of interest; a 95% CI also was obtained for the cost-effectiveness ratio. The probability that abatacept would be cost-effective at various willingness-to-pay thresholds (i.e., maximal costs per QALY) also was calculated.

Deterministic sensitivity analyses were undertaken varying selected assumptions and parameter estimates for which probability distributions were not available, including: (1) discontinuation of abatacept therapy for lack of efficacy or other reasons; (2) timing of therapy discontinuation due to lack of efficacy (i.e., 3 vs 6 months); (3) OR for mortality associated with each 1-point increase in the HAQ-DI; (4) assumption of mortality benefit with abatacept; (5) expected rate of disease progression (i.e., increase in HAQ-DI over time); and (6) threshold for clinically meaningful improvement in the HAQ-DI (i.e., –0.25 and –0.75 vs –0.50). We also examined cost-effectiveness for women of ages other than 55–64 years, and for men.

RESULTS

Outcomes. The estimated mean value of the HAQ-DI at model entry was 1.8; at 10 years, it was 2.4 for patients receiving oral DMARD only, and 2.1 for those assumed also to receive abatacept. Estimated mean HAQ-DI values over a lifetime horizon are shown in Figure 2. The estimated mean value of the EQ-5D at baseline was 0.39. Abatacept was estimated to yield an average gain of 1.0 QALY (undiscounted) per patient over 10 years in comparison with oral DMARD alone (4.0 QALY vs 3.0 QALY, respectively; Table 3). Over a lifetime, the corresponding figure was 1.6 QALY (5.8 QALY vs 4.2 QALY).

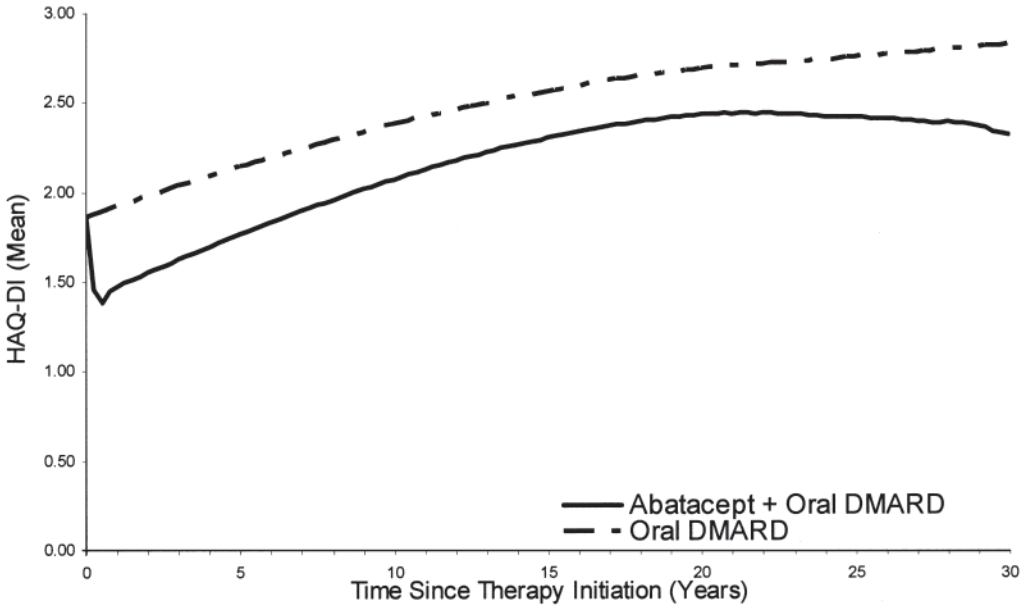

Figure 2. Expected mean HAQ-DI score over time, by treatment.

Table 3. Estimated mean life-years, quality-adjusted life-years (QALY), and total per-patient medical-care costs over 10 years and a lifetime for patients receiving abatacept versus oral DMARD.

	Outcomes				Costs (2006 US$)			
	Life-Years		Quality-Adjusted Life-Years		Medical Care*			
Time Horizon and Treatment	Undiscounted	Discounted*	Undiscounted	Discounted*	Study Medication	Administration & Monitoring	All Other Medical Care	Total
Timeframe: 10 years								
Oral DMARD	8.6	7.5	3.0	2.7	4,495	1,349	49,308	55,151
Abatacept	8.8	7.7	4.0	3.6	51,855	6,502	42,290	100,648
Timeframe: Lifetime								
Oral DMARD	13.4	10.6	4.2	3.4	6,368	1,910	74,211	82,489
Abatacept	14.4	11.2	5.8	4.7	64,929	8,328	67,457	140,714

* Discounted at 3% annually.

Medical-care costs. Over 10 years, total costs of therapy (discounted at 3%), including administration and monitoring, were estimated to average $58,357 for patients receiving abatacept plus oral DMARD, and $5,844 for those receiving oral DMARD alone (Table 3). Corresponding estimates of all other direct medical-care costs (discounted) were $42,290 and $49,308, respectively; the lower value for abatacept reflects estimated cost savings resulting from slower disease progression. Over 10 years, mean total medical-care costs (discounted) were estimated to be $45,497 higher for patients receiving abatacept ($100,648 vs $55,151 for oral DMARD only).

Over a lifetime, total costs of therapy (discounted), including administration and monitoring, were estimated to average $73,257 for patients receiving abatacept plus oral DMARD, and $8,278 for those receiving oral DMARD alone. All other direct medical-care costs (discounted) were estimated to average $67,457 and $74,211, respectively. Mean total lifetime medical-care costs (discounted) therefore were estimated to be $58,225 higher for patients receiving abatacept ($140,714 vs $82,489 for oral DMARD only).

Cost-effectiveness. Over a 10-year time horizon, the cost-effectiveness of abatacept was estimated to be [mean (95% CI)] $50,576 ($47,056, $54,944) per QALY gained (3% discount rate used for both costs and effectiveness). On a lifetime basis, cost-effectiveness was $45,979 ($42,678, $49,932) per QALY gained. Cost-effectiveness acceptability curves depicting the probability that abatacept would be cost-effective at various willingness-to-pay thresholds are presented in Figure 3. At a threshold of $100,000 per QALY, the probability that abatacept would be cost-effective was 1 (over both 10-year and lifetime horizons). Conversely, at a threshold of $20,000 per QALY, abatacept would be unlikely to be cost-effective (probability = 0). The probability that

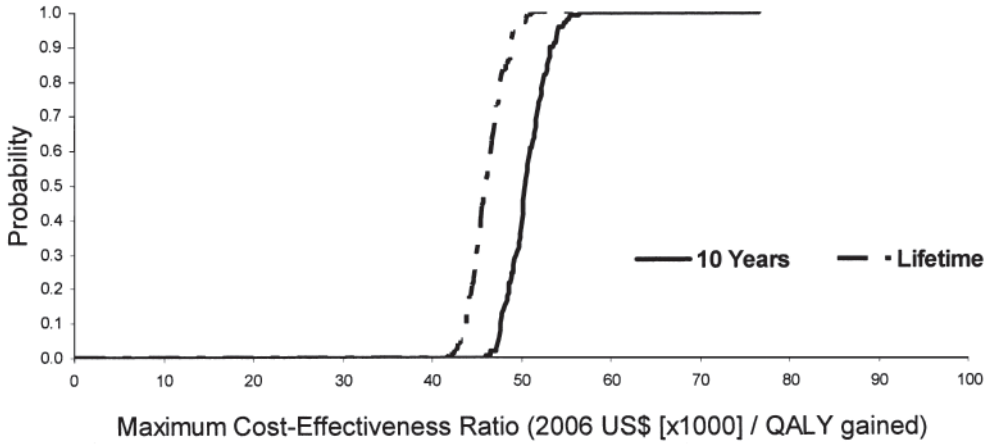

Figure 3. Cost-effectiveness acceptability curves for abatacept as add-on therapy to oral DMARD in patients with inadequate response to anti-TNF, by modeling horizon.

abatacept would be cost-effective at a threshold of $50,000 per QALY was 0.39 over a 10-year time horizon, and 1 when a lifetime perspective was employed.

Sensitivity analyses. Findings from sensitivity analyses are reported in Table 4. Over a 10-year time horizon, the mean incremental cost per QALY gained for abatacept ranged from $43,443 to $80,673; when a lifetime perspective was employed, it ranged from $40,836 to $70,419 per QALY gained. Cost-effectiveness was worse (i.e., ratio was higher) when patients not experiencing an improvement of at least –0.50 in the HAQ-DI at 6 months nonetheless were assumed to continue therapy, and when it was assumed that abatacept patients who did not achieve this level of improvement by 3 months would discontinue therapy. The ratio also was higher when the assumed difference in the rate of disease progression between the 2 treatment groups was smaller, and when abatacept was assumed not to confer a mortality benefit. Cost-effectiveness was better (i.e., the ratio was lower) when a higher threshold (–0.75) was used to define a clinically meaningful improvement in the HAQ-DI at 6 months; it was worse when a lower threshold (–0.25) was employed. The ratio was relatively insensitive to variation in the assumed OR for RA-related mortality associated with each 1-point increase in the HAQ-DI. Estimates of cost-effectiveness were insensitive with respect to patient age and gender.

DISCUSSION

Abatacept, a selective costimulation modulator, was recently approved in the US for the treatment of moderately to severely active RA in patients with inadequate response to MTX or anti-TNF. An earlier study reported that its cost-effectiveness in patients with inadequate response to MTX was $47,910 per QALY gained over a 10-year time horizon, and $43,041 per QALY gained on a lifetime basis[55]. Our study suggests that the cost-effectiveness of abatacept in patients with inadequate response to anti-TNF is similar — $50,576 per QALY gained over 10 years, and $45,979 per QALY gained over a lifetime.

To our knowledge, there are no comparable published estimates of the cost-effectiveness of any of the anti-TNF agents following treatment failure with another anti-TNF. A recent technology appraisal of rituximab, a genetically engineered, chimeric murine/human monoclonal antibody, that was undertaken by the UK National Institute for Clinical Excellence (NICE) reported that the cost-effectiveness of rituximab as add-on therapy to MTX in patients with inadequate response to one or more anti-TNF was about $40,000 per QALY gained (£18,823)[56]. In patients with inadequate response to MTX and no history of treatment with a biologic response modifier, the cost-effectiveness of anti-TNF has been reported to range from $43,006 to $67,683 per QALY gained[27,31,32] [after adjustment of published estimates to 2006 US price levels (US Bureau of Labor Statistics 2006) and/or conversion of foreign currencies to US dollars].

It is important to note that comparison of our cost-effectiveness ratio for abatacept with those reported for anti-TNF may be confounded by significant variation in modeling assumptions and methods across studies. Some prior evaluations have used different discount rates for costs and health effects (6% and 1.5%, respectively)[27,29,30], and in one instance included economic benefits (i.e., cost savings) resulting from improvements in productivity[30]. Use of different time horizons, and different assumptions regarding the duration, nature, and magnitude of therapeutic benefit, also may preclude comparisons across studies. For example, some have assumed that treatment confers a mortality benefit, while others have not. Dropping this assumption, our cost-effectiveness ratios increase by about 4% to 6% (or at most a few thousand US$ per QALY gained). Overall, we believe that our estimates of the cost-effectiveness of abatacept are probably conservative, as we used the same discount rate (i.e., 3%) for costs and health effects (use of a

Table 4. Results of sensitivity analyses on key model assumptions and parameter estimates.

Scenario	Change in Assumption or Parameter Estimate	Δ Cost (2006 US$)/Δ QALY, mean (95% CI) 10-year	Lifetime
Base case	No changes	50,576 (47,056, 54,944)	45,979 (42,678, 49,932)
1	No therapy discontinuation for lack of efficacy or other reasons	78,962 (70,297, 88,211)	59,875 (54,811, 65,309)
2	Therapy discontinuation for lack of efficacy occurs at 3 mo (rather than 6 mo)	80,673 (68,583, 99,601)	70,419 (60,183, 87,068)
	Mortality odds ratio for each 1-point increase in HAQ-DI		
3	1.5	50,531 (46,688, 54,402)	45,748 (42,416, 48,661)
4	2.0	50,111 (46,107, 54,926)	45,948 (43,344, 49,571)
5	No mortality benefit with abatacept therapy	52,526 (48,039, 58,490)	48,743 (45,019, 54,047)
	Annual increase in HAQ-DI for MTX		
6	0.031	52,669 (49,149, 57,980)	49,708 (45,236, 55,084)
	Annual increase in HAQ-DI for MTX		
7	0.031	55,965 (51,230, 61,456)	51,860 (45,233, 58,179)
8	0.130	43,443 (41,128, 46,668)	40,836 (38,093, 44,074)
	Annual increase in HAQ-DI for both treatment groups		
9	0.031	58,957 (53,471, 64,620)	56,068 (50,131, 63,268)
	Threshold for clinically meaningful improvement in HAQ-DI at 6 months		
10	–0.25	56,577 (51,987, 61,784)	51,686 (48,250, 56,044)
11	–0.75	46,675 (41,863, 52,470)	42,460 (38,760, 47,033)
	Patient gender and age, yrs		
	Women		
12	18–34	49,851 (46,137, 53,541)	44,181 (41,243, 47,816)
13	35–44	50,036 (46,855, 54, 604)	44,364 (41,015, 47,569)
14	45–54	50,349 (46,283, 53,348)	45,460 (42,216, 49,112)
15	55–64	50,576 (47,056, 54,944)	45,979 (42,678, 49,932)
16	65–74	50,420 (46,095, 55,610)	47,236 (43,308, 51,946)
17	75–84	51,602 (46,911, 60,547)	49,485 (45,494, 54,938)
18	> 85	57,780 (51,059, 64,562)	57,780 (51,059, 64,562)
	Men		
19	18–34	50,485 (45,768, 54,918)	44,258 (40,765, 47,500)
20	35–44	50,308 (46,577, 55,134)	44,888 (41,897, 48,378)
21	45–54	49,932 (46,379, 53,986)	45,444 (41,861, 48,537)
23	55–64	50,635 (46,611, 54,943)	46,654 (43,249, 51,578)
24	65–74	50,922 (47,426 56,539)	47,473 (43,058, 51,947)
25	75–84	51,926 (47,514, 57,797)	50,504 (45,512, 56,956)
26	> 85	57,231 (50,466, 66,569)	57,231 (50,466, 66,569)

higher rate for costs than health effects yields lower ratios), included a relatively short time horizon (i.e., 10 years) in our analysis, and excluded potential cost savings arising from reductions in direct nonmedical-care expenses and improvements in productivity.

Several aspects of our study merit discussion. For one, we compared abatacept to oral DMARD, as the latter was the comparator of interest in the ATTAIN study[25]; at the time our study was conducted, abatacept also was the only drug approved for use in patients with inadequate response to an anti-TNF. We similarly assumed that patients failing abatacept therapy due to lack of efficacy or other reasons would revert to treatment with oral DMARD only. Given limited data on the efficacy of a second anti-TNF following failure with 2 biologic response modifiers (i.e., an anti-TNF, followed by abatacept), we believe this assumption is reasonable. We also thought that we could not establish a reasonable treatment algorithm for such patients over a 10-year timeframe or, moreover, a lifetime; similar concerns have been expressed by others[31,57].

We employed both 10-year and lifetime horizons in our analyses. We believe the former is reasonable and conservative; it also has been employed in prior modeling evaluations of anti-TNF[30,31]. Use of a lifetime horizon, while prevalent in many cost-effectiveness studies, entails highly artificial assumptions, as it must be grounded on an assumed future stream of care spanning decades, and thereby ignores the influence of therapeutic innovation and likely changes in clinical practice. Nonetheless, the estimated cost-effectiveness ratios for the 2 time horizons were relatively close, and our reporting of a lifetime cost-effectiveness ratio should facilitate comparisons with ratios reported for other biologic therapies in patients with active RA.

We assumed that the benefit of abatacept among patients remaining on therapy beyond 6 months would be sustained. In fact, the duration of clinical response to abatacept in

patients with prior anti-TNF failure has not been established. In patients beginning anti-TNF therapy, clinical response at one year has been reported to be maintained at 2 to 4 years[39-41].

Estimates of disease progression employed in our model (0.065 annual increase in HAQ-DI for patients receiving oral DMARD only; 0.015 increase for those receiving abatacept) similarly were not derived from studies of patients with prior anti-TNF failure, as such information has not been reported. Our findings, however, are not especially sensitive to these rates. When we used alternative published estimates in our sensitivity analysis, the cost-effectiveness ratio for abatacept varied by no more than 15% to 20%.

Data were limited with which to estimate health-state utilities and the costs of direct medical-care services (excluding medication) in relation to the value of the HAQ-DI. While our estimates were based on data from the NDB for patients receiving synthetic and/or biologic DMARD, they nonetheless may not be generalizable to other settings of interest.

While we focused attention in our analyses on women 55–64 years of age (a group that is certainly representative of patients with moderately to severely active RA), our cost-effectiveness estimates did not differ notably when analyses were undertaken for women of different ages or men of any age (data not shown).

Finally, as is typical in modeling studies, our estimates of treatment efficacy were based on data from a randomized controlled trial (i.e., ATTAIN). Outcomes of treatment in clinical practice, however, may differ from those observed in experimental settings[22,58]. Should the efficacy of abatacept in clinical practice differ substantially from that reported in the ATTAIN trial, cost-effectiveness would accordingly differ.

In summary, our findings indicate that abatacept therapy is cost-effective by current standards of medical practice in patients with moderately to severely active RA and inadequate response to anti-TNF. Our study therefore highlights the potential value of abatacept therapy in patients for whom existing treatment options may be limited.

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