Cost–effectiveness of abatacept in patients with moderately to severely active rheumatoid arthritis and inadequate response to methotrexate

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Objective. To assess cost–effectiveness of abatacept in patients with moderately to severely active RA and inadequate response to MTX.

Methods. We developed a simulation model to depict progression of disability [in terms of the HAQ Disability Index (HAQ-DI)] in women aged 55–64 yrs with moderately to severely active RA and inadequate response to MTX. At model entry, patients were assumed to receive either only MTX or MTX 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 various secondary sources. Cost–effectiveness was expressed in terms of incremental cost (2006 US$) per quality-adjusted life-year (QALY) gained over alternatively 10 yrs and a lifetime. Costs and health effects were both discounted at 3% annually.

Results. Over 10 yrs, abatacept would yield 1.2 additional QALYs (undiscounted) per patient (4.6 vs 3.4 for MTX) at an incremental (discounted) cost of $51 426 ($103 601 vs $52 175, respectively); over a lifetime, corresponding figures were 2.0 QALYS (6.8 vs 4.8) and $67 757 ($147 853 vs $80 096). Cost-effectiveness was [mean (95% CI)] $47 910 ($44 641, $52 136) per QALY gained over 10 yrs and $43 041 ($39 070, $46 725) 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 MTX.

Key words: Abatacept, Methotrexate, Rheumatoid arthritis, Outcomes, Cost–effectiveness.

Introduction

RA is a chronic and usually progressive inflammatory joint disease that may involve extra-articular structures. Management of RA is intended to prevent or control joint damage, to prevent loss of function, to diminish pain and to maintain or improve quality of life [1]. MTX has been shown to slow the progression of RA and has been the standard against which new drugs are evaluated [2]. However, many RA patients either fail to respond to MTX therapy or cannot tolerate it. Active disease despite MTX therapy is a common inclusion criterion in clinical trials of new agents for the treatment of RA [3].

In recent years, several biology DMARDs have been approved for the treatment of RA, alone or often in combination with MTX or other non-biologic DMARDs. Three such agents—infliximab, etanercept and adalimumab— inhibit the actions of TNF-α, which is a critical mediator of inflammation in RA and an important therapeutic target in this disease. The efficacy of these agents appears to be similar [4]. While TNF-α blockers represent a significant advance in the management of RA, intensification of concomitant therapy, progressive dose escalation and treatment discontinuation are nonetheless often reported, suggesting that clinical management may remain suboptimal for many patients with active RA who receive these agents. The need for new treatments therefore remains pressing [5].

Abatacept is a selective co-stimulation modulator that binds to T cell surface receptors CD80 and CD86, thereby blocking interaction with CD28. This interaction provides a co-stimulatory 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 ACR criteria) [6] in five randomized, double-blind, placebo-controlled clinical trials. In one such trial [Abatacept in Inadequate Responders to Methotrexate (AIM)], 638 patients with inadequate response to MTX were randomized to receive abatacept or placebo for 1 yr in addition to their stable weekly doses of MTX [7]. At 6 months, ACR 20, ACR 50 and ACR 70 responses (which reflect improvement in tender and swollen joint counts and in three of the following five measures—physician global assessment, patient global assessment, pain, disability/function and inflammatory biomarkers) were significantly higher for patients receiving abatacept, as was the percentage of patients achieving a ‘major clinical response’ (defined as ACR 70 response for six consecutive months). Patients randomized to receive abatacept also had significantly greater improvements in physical function, as measured by the HAQ Disability Index (HAQ-DI) [8], and in all eight domains of the Medical Outcomes Study (MOS) 36-Item Short-Form Health Survey (SF-36) [9].

Much like other biologic response modifiers, however, the cost of abatacept therapy is substantially higher than that of MTX or other non-biologic DMARDS. While formal economic evaluations of infliximab, etanercept and adalimumab have been undertaken [10–15], the cost–effectiveness of abatacept has not yet been reported. In this study, we examine the cost–effectiveness of abatacept in patients with moderately to severely active RA and inadequate response to MTX.

Methods

Model description

We developed a simulation model [16–19] to depict progression of functional disability over time in women, aged 55–64 yrs, with moderately to severely active RA and inadequate response to MTX. A similar modelling approach was employed in a recent...
evaluation of etanercept [11]. 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) [8]. 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 MTX (15 mg once weekly) (‘MTX’) or MTX plus abatacept (on days 1, 14 and 29, and every 4 weeks thereafter) (‘abatacept’). Patients receiving abatacept were assumed to initiate treatment [500–1000 mg (based on body weight) i.v. infusion over 30 min] on day 1, and to receive additional infusions on days 14 and 29, and every 4 weeks thereafter; they were also assumed to continue to receive MTX. Consistent with data from the AIM trial, abatacept therapy was assumed to result in improvement in the HAQ-DI in comparison with MTX 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 MTX. 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 AIM clinical trial. 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 MTX only). Side-effects of abatacept were not considered, except as they might result in therapy discontinuation, as there are no data on their impact 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 [11, 12].

Outcomes and costs were simulated alternatively over 10 yrs and a lifetime for a hypothetical cohort of 1000 women between the ages of 55 and 64 yrs (this group is representative of many patients with RA [20], and is consistent with the characteristics of study subjects in the AIM trial, on which our estimates of abatacept efficacy were based); we also conducted sensitivity analyses in which we estimated cost-effectiveness for patients of other characteristics. 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 MTX or MTX alone).

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 non-medical 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% CIs 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 vs MTX 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).

**Model estimation**

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

**Pre-treatment 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 AIM trial (Table 1) [data on file, Bristol-Myers Squibb (BMS)]. HAQ-DI scores at therapy initiation were therefore allowed to vary from patient to patient.

**Disease progression with MTX.** For patients receiving MTX only (all with inadequate response, by definition), 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 non-response to treatment among patients participating in the Early Rheumatoid Arthritis Study (ERAS) who previously had failed treatment with two DMARDs [11].
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 estimated using data from two randomized trials [31], which were combined to estimate a lower bound for the percentage change in HAQ-DI. The estimated mean (± s.d.) percentage HAQ-DI change at 3 months following therapy initiation in ACRE was −30.2% (±36.1%); at 6 months, it was −35.2% (±37.6%). 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 [22]. 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. [11] for patients receiving biologic therapies. For patients discontinuing abatacept therapy (irrespective of reason), the HAQ-DI was conservatively assumed to revert immediately to the level prevailing among those receiving MTX 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 ACRE 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 were also assumed to possibly discontinue treatment for reasons other than lack of efficacy, including side-effects, intercurrent infection, surgery and various other considerations. Consistent with data from the ACRE clinical trial, 8.1% of patients receiving abatacept were assumed to discontinue treatment during the first year for all other reasons (data on file, BMS). In the second and all subsequent years, this rate was assumed to be 11.1%, once again based on data from ACRE (data on file, BMS).

Mortality. Mortality risk was assumed to be a function of gender, age and the HAQ-DI; the latter was based on evidence from observational studies of a positive relationship between the HAQ-DI and mortality [23–26]. 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 [27]. 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 one-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 EQ-5D Weighted Health Index (WHI) [28] and the HAQ-DI for ~19 000 persons with RA in the NDB (Table 1). The conditional distribution of the EQ-5D WHI given the HAQ-DI 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) [29]. Patients weighing <60 kg were assumed to receive two vials (500 mg) per infusion; 60–100 kg, three vials (750 mg); and >100 kg, four 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) [30]. The cost of abatacept was assumed to be $450/250 mg vial [31]. The cost of each 30-min infusion was assumed to be $129 (data on file, BMS). The annual cost of MTX therapy (15 mg weekly) was assumed to be $600 (or about $12/week) [31].

Estimates of the cost of baseline and routine monitoring for patients receiving abatacept were based on product labelling [29], published guidelines [1] and Medicare payment rates for selected Common Procedural Terminology—4th (CPT-4) Edition codes [32]. Patients initiating abatacept were assumed to require a tuberculin skin test (CPT-4 86580 (tuberculosis, intradermal) and 86585 (tuberculosis, skin test)) at a cost of $9. Patients receiving MTX (alone or with abatacept) were assumed to require a complete blood count (CBC), an alanine aminotransferase (ALT) test and an albumin test every 6 weeks [1]; the annual cost of such monitoring was estimated to be $181, based on prevailing reimbursement rates for CPT-4 codes 85027, 82040 and 84460, and a conversion factor of $36.20. Pre-treatment evaluations (e.g. chest X-rays, hepatitis serology) were not added to the cost of MTX, as all patients were assumed to have initiated MTX 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 non-medical 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. All costs are reported as US dollars and

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Table 2. Cost estimates used in abatacept cost–effectiveness evaluation (2006 US$)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept (1 mg/kg) per month</td>
<td>[31]</td>
</tr>
<tr>
<td>First year</td>
<td>19387</td>
</tr>
<tr>
<td>Subsequent years</td>
<td>16802</td>
</tr>
<tr>
<td>Administration of abatacept (per infusion)</td>
<td>(BMS, data on file)</td>
</tr>
<tr>
<td>Methotrexate (15 mg weekly)</td>
<td>600</td>
</tr>
<tr>
<td>All other direct medical-care services</td>
<td>(NDB)*</td>
</tr>
<tr>
<td>(mean ± s.d.), by HAQ interval</td>
<td></td>
</tr>
<tr>
<td>0.00–0.125</td>
<td>1839 ± 6100</td>
</tr>
<tr>
<td>0.25–0.375</td>
<td>2367 ± 6124</td>
</tr>
<tr>
<td>0.50–0.625</td>
<td>2658 ± 6751</td>
</tr>
<tr>
<td>0.75–0.875</td>
<td>2876 ± 6513</td>
</tr>
<tr>
<td>1.00–1.125</td>
<td>3263 ± 7225</td>
</tr>
<tr>
<td>1.25–1.375</td>
<td>3794 ± 8019</td>
</tr>
<tr>
<td>1.50–1.625</td>
<td>4545 ± 9293</td>
</tr>
<tr>
<td>1.75–1.875</td>
<td>5308 ± 10975</td>
</tr>
<tr>
<td>2.00–2.125</td>
<td>6061 ± 12103</td>
</tr>
<tr>
<td>2.25–2.375</td>
<td>7260 ± 14470</td>
</tr>
<tr>
<td>2.50–2.625</td>
<td>8214 ± 15762</td>
</tr>
<tr>
<td>2.75–3.00</td>
<td>8779 ± 15231</td>
</tr>
</tbody>
</table>

*National Data Bank for Rheumatic Diseases (unpublished data).
were adjusted to 2006 average price levels, as necessary, using the Consumer Price Index for Medical Care Services [33].

Analyses. Monte Carlo simulation techniques [16–19] were employed to estimate the impact of abatacept on HAQ-DI values over time. First-order simulations (also sometimes referred to as ‘microsimulation’ or ‘random walk’) [34] 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 yrs 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 MTX alone. Costs and health effects were discounted at an annual rate of 3%, consistent with recommendations of the US Public Health Service Panel on the Cost-Effectiveness of Health and Medicine [35].

Second-order simulations (to account for parameter uncertainty) were performed by running the model for 100 samples of 1000 patients each (our choice of a cohort of 1000 patients was based on the observation that a sample of this size yielded mean values that were comparatively stable across different runs of the model). Three key model parameters—the percentage change in the HAQ-DI at 6 months with abatacept therapy, the health-state utility value by HAQ-DI interval and the 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 by varying selected assumptions and parameter estimates for which probability distributions were not available, including: (i) discontinuation of abatacept therapy for lack of efficacy or other reasons; (ii) timing of therapy discontinuation due to lack of efficacy (i.e. 3 vs 6 months); (iii) OR for mortality associated with each one-point increase in the HAQ-DI; (iv) assumption of mortality benefit with abatacept; (v) expected rate of disease progression (i.e. increase in the HAQ-DI); and (vi) 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 yrs and for men.

Results

Outcomes

The estimated mean value of the HAQ-DI at model entry was 1.7; at 10 yrs, it was 2.2 for MTX patients and 1.9 for those assumed to receive abatacept plus MTX. Abatacept was estimated to yield an average gain of 1.2 QALYs (undiscounted) per patient over 10 yrs in comparison with MTX alone (4.6 QALYs vs 3.4 QALYs, respectively) (Table 3). Over a lifetime, the corresponding figure was 2.0 QALYs (6.8 QALYs vs 4.8 QALYs).

Medical-care costs

Over 10 yrs, total costs of therapy (discounted at 3%), including administration and monitoring, were estimated to average $65 620 for patients receiving abatacept plus MTX and $59 16 for those receiving MTX alone (Table 3). Corresponding estimates of all other direct medical-care costs (discounted) were $37 981 and $46 259, respectively; the lower value for abatacept reflects estimated cost savings resulting from slower disease progression. Over 10 yrs, mean total medical-care costs (discounted) were estimated to be $51 426 higher for patients receiving abatacept ($103 601 vs $52 175 for MTX only).

Over a lifetime, total costs of therapy (discounted), including administration and monitoring, were estimated to average $84 322 for patients receiving abatacept plus MTX, and $85 17 for those receiving MTX alone. All other direct medical-care costs (discounted) were estimated to average $63 531 and $71 579, respectively. Mean total lifetime medical-care costs (discounted) therefore were estimated to be $67 757 higher for patients receiving abatacept ($147 853 vs $80 096 for MTX only).

Cost-effectiveness

Over a 10 yr time horizon, the cost-effectiveness of abatacept was estimated to be [mean (95% CI)] $47 910 ($44 641, $52 136) per QALY gained (3% discount rate used for both costs and effectiveness). On a lifetime basis, cost-effectiveness was $43 041 ($39 070, $46 725) 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 Fig. 1. At a threshold of $100 000 per QALY, the probability that abatacept would be cost-effective was 1 (over both 10 yr 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 abatacept would be cost-effective at a threshold of $50 000 per QALY was 0.80 over a 10 yr time horizon, and 0.99 when a lifetime perspective was employed.

Sensitivity analyses

Findings from sensitivity analyses are reported in Table 4. Over a 10 yr time horizon, the mean incremental cost per QALY gained for abatacept ranged from $40 190 to $70 209; when a lifetime perspective was employed, it ranged from $37 551 to $60 106 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

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Life-years</th>
<th>QALYs</th>
<th>Costs (2006 US$)</th>
<th>Medical carea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time horizon and treatment</td>
<td>Undiscounted</td>
<td>Discounted</td>
<td>Undiscounted</td>
<td>Discounted</td>
</tr>
<tr>
<td>Time frame: 10 yrs</td>
<td>MTX</td>
<td>8.7</td>
<td>7.6</td>
<td>3.4</td>
</tr>
<tr>
<td>Abatacept + MTX</td>
<td>8.9</td>
<td>7.8</td>
<td>4.6</td>
<td>4.1</td>
</tr>
<tr>
<td>Time frame: lifetime</td>
<td>MTX</td>
<td>13.9</td>
<td>10.9</td>
<td>4.8</td>
</tr>
<tr>
<td>Abatacept + MTX</td>
<td>15.0</td>
<td>11.6</td>
<td>6.8</td>
<td>5.5</td>
</tr>
</tbody>
</table>

*Discounted at 3% annually.*
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 two 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 six 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 one-point increase in the HAQ-DI. Cost-effectiveness for all practical purposes was invariant with respect to patient age and gender.

Discussion

Abatacept, a selective co-stimulation modulator, was recently approved in the USA for the treatment of moderately to severely active RA in patients with inadequate response to MTX (or TNF-α antagonists). Our study suggests that its cost-effectiveness is $47 910 per QALY gained over a 10 yr time frame, and $43 041 per QALY gained over a lifetime. This ratio is consistent with cost-effectiveness ratios that have been reported for other biologic DMARDs in similar patient populations (e.g. $43 006–$66 895 per QALY gained for etanercept [10, 11], and $43 946–$67 683 per QALY gained for infliximab [12, 14], after adjustment of published estimates to 2006 US price levels and/or conversion of foreign currencies to US dollars). (While ratios in excess of $200 000 per QALY gained have been reported for etanercept and infliximab in another study [15], both therapies were assumed to be used as the third agent in a sequence of DMARDs in this particular evaluation).

It nonetheless should be noted that comparison of cost-effectiveness ratios for abatacept with those reported for other biologic DMARDs is confounded by significant variation in assumptions and methods across studies. Evaluations of other biologic DMARDs have sometimes used different discount rates for costs and health effects (6 and 1.5%, respectively) [11–13, 15], and—in one instance—included benefits resulting from improvements in productivity [12]. Use of different time horizons, and different assumptions regarding the duration, nature and

![Figure 1](image_url)

Cost–effectiveness acceptability curves for abatacept as add-on therapy to MTX in patients with moderately to severely active RA and inadequate response to MTX, by modelling horizon.

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

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Change in assumption or parameter estimate</th>
<th>10-yr</th>
<th>Lifetime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>No changes</td>
<td>47 910 (44 641, 52 136)</td>
<td>43 041 (39 070, 46 725)</td>
</tr>
<tr>
<td>1</td>
<td>No therapy discontinuation for lack of efficacy or other reasons</td>
<td>70 209 (63 330, 79 390)</td>
<td>52 740 (48 100, 57 915)</td>
</tr>
<tr>
<td>2</td>
<td>Therapy discontinuation for lack of efficacy occurs at 3 months (rather than 6 months)</td>
<td>68 641 (58 373, 83 283)</td>
<td>60 106 (52 620, 71 488)</td>
</tr>
<tr>
<td>3</td>
<td>Mortality OR for each one-point increase in HAQ-DI 1.5</td>
<td>47 962 (44 755, 51 949)</td>
<td>43 032 (39 718, 46 708)</td>
</tr>
<tr>
<td>4</td>
<td>Mortality OR for each one-point increase in HAQ-DI 2.0</td>
<td>47 336 (44 129, 51 018)</td>
<td>42 905 (39 985, 45 836)</td>
</tr>
<tr>
<td>5</td>
<td>No mortality benefit with abatacept therapy</td>
<td>49 919 (45 866, 54 093)</td>
<td>46 071 (41 518, 51 474)</td>
</tr>
<tr>
<td>6</td>
<td>Annual increase in HAQ-DI for abatacept 0.031</td>
<td>49 841 (45 369, 54 120)</td>
<td>46 065 (42 863, 49 719)</td>
</tr>
<tr>
<td>7</td>
<td>Annual increase in HAQ-DI for MTX 0.130</td>
<td>53 367 (49 161, 57 714)</td>
<td>48 727 (44 715, 54 030)</td>
</tr>
<tr>
<td>8</td>
<td>Annual increase in HAQ-DI for both treatment groups 0.031</td>
<td>40 190 (38 063, 43 284)</td>
<td>37 551 (35 211, 40 297)</td>
</tr>
<tr>
<td>9</td>
<td>Threshold for clinically meaningful improvement in HAQ-DI at 6 months −0.25</td>
<td>56 584 (51 192, 62 861)</td>
<td>52 474 (47 012, 58 758)</td>
</tr>
<tr>
<td>10</td>
<td>Threshold for clinically meaningful improvement in HAQ-DI at 6 months −0.75</td>
<td>53 579 (49 633, 57 641)</td>
<td>47 856 (44 568, 51 318)</td>
</tr>
<tr>
<td>11</td>
<td>Gender and age (in yrs) Female 18–34</td>
<td>43 640 (40 310, 47 898)</td>
<td>39 724 (37 327, 42 541)</td>
</tr>
<tr>
<td></td>
<td>Gender and age (in yrs) Female 35–44</td>
<td>47 837 (44 872, 51 451)</td>
<td>41 108 (38 141, 44 731)</td>
</tr>
<tr>
<td></td>
<td>Gender and age (in yrs) Female 45–54</td>
<td>47 570 (44 633, 51 293)</td>
<td>41 730 (39 334, 44 306)</td>
</tr>
<tr>
<td></td>
<td>Gender and age (in yrs) Female 65–74</td>
<td>47 619 (44 310, 50 936)</td>
<td>42 271 (39 051, 46 019)</td>
</tr>
<tr>
<td></td>
<td>Gender and age (in yrs) Female 75–84</td>
<td>47 165 (42 650, 51 785)</td>
<td>43 888 (41 203, 47 231)</td>
</tr>
<tr>
<td></td>
<td>Gender and age (in yrs) Male 75–84</td>
<td>47 092 (43 359, 51 280)</td>
<td>45 534 (42 307, 50 019)</td>
</tr>
<tr>
<td></td>
<td>Gender and age (in yrs) Male &gt;85</td>
<td>52 559 (48 001, 58 885)</td>
<td>52 559 (48 001, 58 885)</td>
</tr>
</tbody>
</table>

![Diagram](image_url)

Cost–effectiveness acceptability curves for abatacept as add-on therapy to MTX in patients with moderately to severely active RA and inadequate response to MTX, by modelling horizon.
magnitude of therapeutic benefit, also can complicate comparisons across studies. Nevertheless, 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 higher rate for costs than health effects yields lower ratios), included a relatively short time horizon (i.e. 10 yrs) in our analyses, and excluded potential cost savings arising from reductions in direct non-medical-care expenses and improvements in productivity. For example, had we used a 6% discount rate for costs and only a 1.5% discount rate for effects, our cost–effectiveness ratios would have improved (i.e. declined) by about 15–25%.

Several aspects of our study merit discussion. For one, we compared abatacept with MTX, as this was the comparator of interest in the AIM study. In this respect, our approach is similar to that of published economic evaluations of other biologic response modifiers, in which conventional DMARDs—principally MTX—were the comparators of interest [10, 14]. This approach also obviated the need to specify ‘downstream’ treatment strategies for patients assumed to discontinue abatacept therapy due to lack of efficacy or other reasons. We thought that we could neither establish a reasonable treatment algorithm for such patients over a 10 yr timeframe—or moreover a lifetime—nor accurately estimate the expected change in the HAQ-DI with follow-on therapy conditional upon success or failure of prior therapy. Prior models that have specified ‘downstream’ treatment strategies have implicitly assumed independence of treatment effects given failure of prior therapies, due to lack of data [11, 15]. As has been noted [36], we are doubtful that this assumption is realistic. For these reasons, we assumed that patients who discontinue abatacept would continue to be treated with MTX alone. While this assumption is certainly unrealistic, it nonetheless provides a framework for interpretation of the benefits of abatacept that is not confounded by assumptions regarding the sequence of subsequent therapies and their efficacy in this context.

In contrast to some other evaluations, we employed both 10 yr and lifetime horizons in our analyses. We believe the former is reasonable and conservative; it has also been employed in prior analyses [10, 12]. 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 impact of therapeutic innovation and likely changes in clinical practice. Nonetheless, estimated cost–effectiveness ratios for the two time horizons were relatively close, and our reporting of a lifetime cost–effectiveness ratio should facilitate comparisons with ratios reported for other therapies.

We assumed that the benefit of abatacept among patients remaining on therapy beyond 6 months would be sustained. This is consistent with the findings from prior research in which the observed clinical response for DMARDs and biologic therapies during the first year was maintained over 2–4 yrs [18, 19]. While we incorporated disease progression into our model (0.065 annual increase in HAQ-DI for patients receiving MTX, 0.015 for patients receiving abatacept), we acknowledge the limited data with which these parameters were estimated, as progression rates observed in clinical trials have not been confirmed in clinical practice. Our results, however, are not especially sensitive to these rates. When we used alternative published estimates in a sensitivity analysis, the cost–effectiveness ratio for abatacept varied by no more than 15–20%.

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

While we limited our attention to women aged 55–64 yrs of age—a group that is representative of many patients with moderately to severely active RA—our cost–effectiveness estimates did not differ appreciably when analyses were undertaken for women of different ages or for men. On a related note, while abatacept is also indicated for use in patients with inadequate response to TNF-α antagonists, we did not examine its cost–effectiveness in this context.

Finally, as is typical in modelling studies, our estimates of treatment efficacy were based on data from a randomized controlled trial (i.e. AIM). Outcomes of treatment in clinical practice, however, may differ from those observed in experimental settings [37]. Should the efficacy of abatacept in clinical practice differ substantially from that reported in the AIM trial, cost–effectiveness would accordingly change.

In summary, our findings indicate that abatacept is cost-effective by current standards of medical practice in patients with moderately to severely active RA and inadequate response to MTX. Cost–effectiveness ratios for abatacept are comparable with those of other biologic DMARDs. Our study therefore highlights the potential value of abatacept therapy in this patient population.

**Rheumatology key message**

- In patients with moderately to severely active RA and inadequate response to MTX, abatacept therapy is cost-effective by current standards of medical practice.

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Cost–effectiveness of abatacept in RA


