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Cost-Effectiveness Analysis of Abatacept Compared with Adalimumab on Background Methotrexate in Biologic-Naive Adult Patients with Rheumatoid Arthritis and Poor Prognosis

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ABSTRACT

Objectives: To assess cost effectiveness of abatacept versus adalimumab, each administered with methotrexate, in treating patients with rheumatoid arthritis (RA) stratified according to baseline anticitrullinated protein antibody (ACPA) levels (marker of poor prognosis in RA). **Methods:** A payer-perspective cost-effectiveness model simulated disease progression in patients with RA who had previously failed conventional disease-modifying antirheumatic drugs and were starting biologic therapy. Patients commenced treatment with abatacept or adalimumab plus methotrexate and were evaluated after 6 months. Therapy continuation was based on the European League Against Rheumatism treatment response; disease progression was based on the Health Assessment Questionnaire Disability Index score. These score changes were used to estimate health state utilities and direct medical costs. Quality-adjusted life-years (QALYs) and incremental cost per QALY gained were calculated by baseline ACPA groups (Q1, 28–234 AU/ml; Q2, 235–609 AU/ml; Q3, 613–1045 AU/ml; and Q4, 1060–4894 AU/ml). Scenario analysis and one-way and probabilistic sensitivity analyses were used to evaluate robustness of model assumptions. **Results:** Abatacept resulted in QALY gain versus adalimumab in ACPA Q1, Q3, and Q4; between-treatment difference (difference: Q1, −0.115 Q2, −0.009 Q3, 0.045; and Q4, 0.279). Total lifetime discounted cost was higher for abatacept versus adalimumab in most quartiles (Q2, £77,612 vs. £77,546; Q3, £74,441 vs. £73,263; and Q4, £78,428 vs. £76,696) because of longer time on treatment. Incremental cost per QALY for abatacept (vs. adalimumab) was the lowest in the high ACPA titer group (Q4, £6200/QALY), followed by the next lowest titer group (Q3, £26,272/QALY). **Conclusions:** Abatacept is a cost effective alternative to adalimumab in patients with RA with high ACPA levels.

Keywords: abatacept, ACPA, adalimumab, cost effectiveness, economic model, ICER, QALY, rheumatoid arthritis, treatment costs.

Introduction

Rheumatoid arthritis (RA) imposes substantial economic burden on patients, their carers, and the health care system. In 2009, the economic burden of RA was estimated to be up to £4.75 billion per year in the United Kingdom [1], with other sources estimating the overall cost to the UK economy of productivity losses at almost £8 billion per year [2]. About 30% of patients give up work within 1 year of diagnosis, whereas 60% do so within 6 years [2].

RA is characterized by progressive disability, systemic complications, and early mortality [3]. Autoantibody production, including rheumatoid factor (RF) and anticitrullinated protein antibody (ACPA), is believed to play a role in RA disease pathogenesis, and both RF and ACPA assays may be used to detect RA [4]. Although the sensitivities of ACPA and RF appear to be similar, ACPA has demonstrated a higher specificity than RF in detecting early RA [4], resulting in the incorporation of ACPA testing into RA diagnostic criteria in 2010 [5].

In ACPA-positive patients, ACPA is associated with the human leukocyte antigen - antigen D related, which is associated with severe RA through the involvement of $CD4^+$ T cells [3,6]. Thus, patients with RA who are ACPA-positive have a less favorable prognosis and develop a more aggressive disease than those who are ACPA-negative [7,8], suggesting that this distinction may be of clinical value [3]. ACPA is relatively stable over time for an individual patient [9] and, as a biomarker, has been shown to improve the identification of those at risk of developing clinical RA [10,11]. In addition, it appears that ACPA positivity may be important in assessing the mortality risk in patients presenting with early RA [12].

Although clinical practice data demonstrate that the presence of ACPA in people with RA is a strong predictor of structural damage (joint erosions) and radiographic progression, its predictive value for treatment outcomes is not well understood [4,13].

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Recent studies have shown that outcomes of biologic treatment can vary by ACPA status, and certain biologic disease-modifying antirheumatic drugs (DMARDs) such as abatacept (Orencia®, Bristol-Myers Squibb, New York, NY, USA) have demonstrated a better clinical response in ACPA-positive patients compared with ACPA-negative patients [14].

In the phase IIIB, multinational, prospective, randomized Abatacept versus adaliMumab comParison in bioLogic-naivE (AMPLE) study of subjects with RA with background methotrexate (MTX), abatacept was compared directly with adalimumab (Humira®, AbbVie Inc, North Chicago, IL, USA) in biologic-naive patients with RA who had inadequate response to MTX [15,16]. In subgroup analysis by baseline ACPA levels, each treatment was more effective in ACPA-positive patients than in ACPA-negative patients, according to various measures. Greater improvements were observed for patients who received abatacept compared with those who received adalimumab in the highest ACPA quartiles with regard to the Disease Activity Score 28 (DAS28) and the Health Assessment Questionnaire Disability Index (HAQ-DI) score [17]. Notably, the mean improvements in DAS28 and HAQ-DI scores with abatacept were significantly greater for the highest ACPA concentration quartile than for the lower three quartiles combined, whereas for adalimumab the improvements were similar across all quartiles for both measures [17]. The effects observed for patients with higher ACPA titers may be driven in part by abatacept's mechanism of action [18]. Abatacept is a selective modulator of T-cell activation [6]. Abatacept is thought to block CD28 costimulatory signals required for T-cell activation, thereby limiting the activation of T cells [19].

Given the observed clinical benefits of abatacept in ACPA-positive patients, the objective of this analysis was to assess the benefits and costs of abatacept compared with those of adalimumab, each administered with MTX, in treating patients with RA who had inadequate response to MTX and stratified by their baseline ACPA levels. The choice of adalimumab as a comparator was driven by data availability, and the AMPLE study was the only published study to provide a direct comparison with another agent and presented data by patient ACPA level. Anti–tumor necrosis factors (TNFs), and in particular adalimumab, are currently the standard of care in patients who fail MTX; thus, the choice of the comparator is appropriate from a payer perspective. Given the mechanism of action of the anti-TNFs, one could assume that the results of this analysis could be similar to nonadalimumab anti-TNFs.

Methods

Overall Model Structure

A cost-effectiveness simulation model was developed on the basis of an individual patient simulation (IPS) approach. The model concept is similar to that of the "Birmingham rheumatoid arthritis model" [20] with certain elements incorporated from the "Sheffield rheumatoid arthritis health economic model" [21], and it was programmed in Microsoft Excel. The model (Fig. 1) adopted a payer perspective and tracked a large number of individual patients with different baseline characteristics (age, sex, and HAQ-DI score) over a lifetime, with the follow-up time being divided into 6-month cycles. Model simulation began after a patient had failed conventional DMARDs and was eligible for a biologic DMARD and assumed that each patient received a given treatment until switching to an alternative treatment. All eligible patients were prescribed a biologic DMARD in the model. Patients were generated by sampling from baseline distributions of sex, age, and HAQ-DI score on the basis of the AMPLE study population.

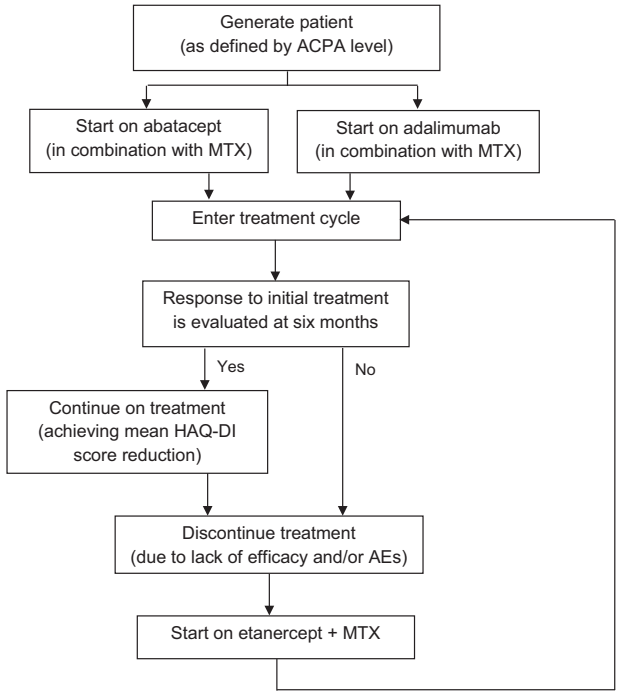

Fig. 1 – Overview of the patient-level simulation model. ACPA, anticitrullinated protein antibodies; HAQ-DI, Health Assessment Questionnaire Disability Index; MTX, methotrexate.

Each generated patient commenced treatment with either abatacept or adalimumab in combination with MTX and was evaluated on that treatment after a fixed time period (i.e., 6 months), after which the patient either remained on treatment, if the therapy was effective and there were no adverse effects, or switched to another biologic DMARD, that is, anti-TNF drug etanercept. Patients failing on etanercept were switched to palliative care.

Treatment responses for adalimumab and abatacept were based on the European League Against Rheumatism (EULAR) criteria at 6 months as measured in the AMPLE study. The EULAR response criteria classify patients as good responders, moderate responders, or nonresponders, on the basis of the DAS28-C-reactive protein (CRP) value at baseline and the change in DAS28-CRP from baseline to 6 months, using the method of Fransen and van Riel [22]. Patients who achieved EULAR good or moderate response were retained on therapy. Apart from lack of response, switching could also be due to a patient experiencing adverse effects. For patients who continued on therapy, the length of time on each treatment was estimated from data presented in a health technology assessment of RA treatments [23]. Similar to current modeling approaches in RA, we do not discriminate between primary treatment failure and secondary treatment. The first treatment switch was treated as a single event, that is, a composite of lack of efficacy and/or adverse events [24].

Change in the HAQ-DI score (a measure of physical functioning) over a lifetime was used to simulate disease progression for each patient (including mortality). The HAQ-DI score ranged from 0 (best) to 3 (worst) in multiples of 0.125 [25]. If a patient responded to therapy, then the therapy was assigned with an initial drop in the HAQ-DI score (i.e., improvement). This HAQ-DI score change was subtracted from the baseline HAQ-DI score to simulate the

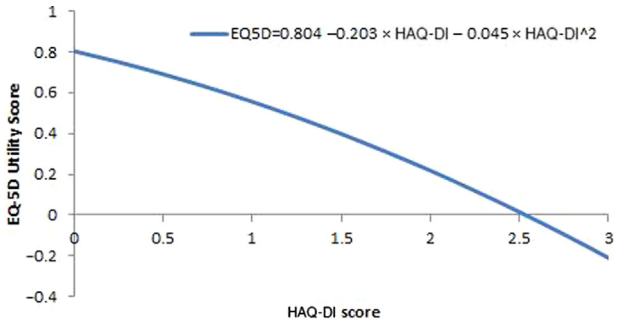

Fig. 2 – Correlation of the HAQ-DI score to EQ-5D utility [23]. EQ-5D, EuroQol five-dimensional questionnaire; HAQ-DI, Health Assessment Questionnaire Disability Index.

impact of treatment on disease progression. Any improvement in the HAQ-DI score was lost on quitting the treatment over the 6-month cycle. At the point of treatment failure, the patient experienced a further increase in the HAQ-DI score (rebound effect) before commencing the next predefined treatment within the sequence, at which point the process started again. The baseline HAQ-DI score and the treatment-specific HAQ-DI score change were derived from the AMPLE study. The HAQ-DI score change was used to estimate health state utility (quality of life) and direct medical costs (disease-related hospitalization and joint replacement costs); change in the HAQ-DI score was therefore the prime driver of both benefits and costs in the model. It was assumed that a patient's HAQ-DI score remained constant over time while receiving treatment with biologic DMARDs, which was tested in a sensitivity analysis. Patients experienced disease progression after their initial response to therapy if they discontinued biologic DMARD and moved to palliative care, in which case the HAQ-DI score increased at the rate of 0.06/y [23]. HAQ-DI progression was separated into initial response (i.e., the first 6 months) and subsequent response on the basis of treatment and long-term disease progression.

Death was able to occur at any time within the model (at 6-month intervals) and was RA- and HAQ-DI–dependent. The probability of mortality was a function of age, sex, and having RA, using age and sex-specific mortality rates for the general population and estimates of increased mortality risk by the HAQ-DI score. Mortality rates were related to the HAQ-DI score over a given period [26]. A relative risk of 1.33 per unit HAQ-DI was applied to the general population mortality probabilities [26].

Quality-adjusted life-years (QALYs) were calculated on the basis of the National Institute for Health and Care Excellence (NICE) reference case [27]. An inverse relationship between the HAQ-DI score (disease progression) and quality of life was applied using the EuroQol five-dimensional questionnaire (EQ-5D) utility score based on UK tariffs [23]. The regression equation used in the model to link the HAQ-DI score to EQ-5D scores was a quadratic equation, of the form EQ-5D utility = $0.804 - 0.203 \times \text{HAQ-DI} - 0.045 \times \text{HAQ-DI}^2$ (see Fig. 2) [23]. This equation estimates utilities less than 0 for the highest values of the HAQ-DI score. Other linear mapping equations were tested in a sensitivity analysis. We chose the nonlinear mapping algorithm for the base case because it provided a better overall model fit compared with a linear regression model. It was assumed that events (transitions) occurred about halfway through a cycle and hence a half-cycle correction was applied by taking the average of the HAQ-DI score at the beginning and the end of a cycle. Parameter uncertainty from the mapping algorithm regression equations was taken into account in the probabilistic sensitivity analysis (PSA).

Model Inputs

Patient Baseline Characteristics

The initial run of the model simulated 15,000 patients with baseline characteristics taken from the AMPLE study [15,16]. Of the 646 patients randomized and treated in the AMPLE study, 86.2% (274 of 318) of the abatacept-treated patients and 82% (269 of 328) of the adalimumab-treated patients completed the study. The overall AMPLE study population is described elsewhere [15,16]. Patients had baseline ACPA levels in the range of 28 to 4894 AU/ml. In line with the AMPLE study [15,16], patients were divided into four ACPA groups based on quartiles: Q1 (28–234 AU/ml), Q2 (235–609 AU/ml), Q3 (613–1045 AU/ml), and Q4 (1060–4894 AU/ml). The use of ACPA level quartiles rather than ACPA level as a continuous measure enabled the analysis of subgroups on the basis of ACPA level while overcoming the limitation of skewed patient distribution across the ACPA level range. The baseline patient characteristics of patients in the AMPLE study according to baseline ACPA groups are presented in Table 1. The model was run for each ACPA group separately, with efficacy data (Tables 2 and 3) for the individual quartile groups being derived from the AMPLE study in each case.

Disease Progression and Treatment Sequence

Clinical inputs applied to determine treatment switching and simulate disease progression comprised EULAR responses for

Table 1 – Key baseline characteristics of patients modeled in the economic model.

Characteristic	Quartile by ACPA (anti-CCP2 concentration, AU/ml)							
	Q1: 28–234		Q2: 235–609		Q3: 613–1045		Q4: 1060–4894	
	ABA (n = 42)	ADA (n = 55)	ABA (n = 51)	ADA (n = 46)	ABA (n = 46)	ADA (n = 51)	ABA (n = 46)	ADA (n = 51)
Age (y)	52.0 (24.0, 80.0)	58.0 (21.0, 83.0)	50.0 (22.0, 70.0)	50.0 (19.0, 78.0)	52.0 (21.0, 78.0)	49.0 (22.0, 73.0)	47.5 (25.0, 73.0)	52.0 (26.0, 78.0)
Female (%)	84.8	85.2	88.1	83.6	80.4	87.0	82.6	80.4
HAQ-DI score	1.3 (0.0, 2.9)	1.4 (0.0, 2.6)	1.4 (0.0, 2.5)	1.3 (0.0, 2.5)	1.7 (0.0, 2.8)	1.6 (0.0, 2.9)	1.4 (0.0, 2.8)	1.6 (0.0, 3.0)
CRP (mg/dl)	0.8 (0.1, 8.4)	0.6 (0.0, 4.8)	0.9 (0.0, 9.4)	1.3 (0.1, 5.8)	0.9 (0.1, 11.3)	1.0 (0.0, 9.0)	0.9 (0.0, 13.9)	0.7 (0.0, 11.8)
DAS28-CRP	5.0 (3.1, 7.6)	5.5 (3.1, 7.3)	5.6 (3.5, 7.6)	6.0 (2.8, 7.4)	5.5 (2.8, 8.1)	5.7 (3.7, 7.9)	6.0 (2.7, 7.8)	5.3 (1.7, 7.8)

Note. Data are expressed as median (minimum, maximum), unless otherwise stated.
ABA, abatacept; ACPA, anticitrullinated protein antibodies; ADA, adalimumab; CCP2, cyclic citrullinated peptide-2; CRP, C-reactive protein; DAS28, Disease Activity Score 28; HAQ-DI, Health Assessment Questionnaire Disability Index; Q, quartile.

Table 2 – EULAR response probabilities at 6 mo.

Treatment	EULAR response at 6 mo (% probability)							
	Q1		Q2		Q3		Q4	
	Good	Moderate	Good	Moderate	Good	Moderate	Good	Moderate
ABT + MTX	55.00	22.50	47.92	39.58	40.00	46.67	62.22	33.33
ADA + MTX	56.00	34.00	52.27	36.36	51.02	30.61	52.08	35.42
ETN + MTX	49.67	31.74	46.36	33.95	45.25	28.58	46.19	33.06

ABT, abatacept; ADA, adalimumab; ETN, etanercept; EULAR, European League Against Rheumatism; MTX, methotrexate; Q, quartile.

abatacept and adalimumab at 6 months, on the basis of the AMPLE study. Patients in the AMPLE study were categorized by the type of response they achieved at 6 months. No data were available for etanercept by quartile; its EULAR response by quartile was derived by estimating the relative rate of response between each quartile and the overall population for adalimumab in the AMPLE arm and applying these relative rates to the EULAR response rate for etanercept in an overall population obtained from a previous mixed treatment comparison [28] (Table 2). Patients who did not achieve a good or moderate EULAR response 6 months after switching to etanercept were switched to palliative care for the remaining duration of the time horizon.

Treatment Duration

Patients who attained a good or moderate response continued on therapy, with the length of treatment based on a time on treatment survival curve derived from the British Society for Rheumatology Biologics Registry data using a Weibull model [23]. Following the approach used previously, the time on treatment was sampled from this distribution [23]. A curve was generated for each treatment and a random sample estimate was drawn from this distribution to determine a time on each treatment for each simulated patient (mean 4.06 years for abatacept plus MTX and for adalimumab plus MTX) [23]. In the base case, mean time on treatment was assumed to be the same for abatacept and adalimumab in patients with an initial moderate or good response. In a sensitivity analysis, the mean time on treatment was allowed to differ between abatacept and adalimumab. A lifetime time horizon was applied in the base case, aligning with NICE guidance [27]. Further time horizons were analyzed in sensitivity analyses. Age-specific yearly mortality probabilities were sourced for the UK population and converted to 6-monthly rates by applying the methodology of Briggs et al. [29].

Treatment Costs and Outcomes

Costs comprised drug costs and monitoring costs and were calculated in 2015 pound sterling. The model included an annual drug cost for each treatment, including any initial loading cost reflecting higher dosage and additional monitoring early in treatment. Drug costs were applied within the model on the basis of the recommended dosage over each of the model's 6-month cycles. Drug cost data inputs for the United Kingdom and annual administration and drug monitoring costs are presented in Table 4. Unit costs for adalimumab and etanercept were drawn from the British National Formulary [30]. Given that a patient access scheme for abatacept is in place in the United Kingdom, the cost of abatacept was estimated to be the average cost of a number of biologic DMARDs approved in the United Kingdom (£9244), to fairly reflect actual treatment costs for abatacept in the country. Additional sensitivity analyses were conducted on the abatacept cost using average cost across five major markets as well as using the British National Formulary list price. To reflect clinical practice, no additional loading dose cost was assumed in the first year; this assumption was also tested in a sensitivity analysis. Monitoring resource use and costs (biochemical profile, chest x-ray, full blood cell count, and erythrocyte sedimentation rate) for MTX were calculated to be £137.13 for the first 6 months and £59.63 after 6 months. It

Table 3 – Estimated mean HAQ-DI score change from baseline for each therapy by quartile [15].

Treatment	HAQ-DI score change from baseline (SE) at 6 mo			
	Q1	Q2	Q3	Q4
ABT + MTX	−0.58 (0.09)	−0.62 (0.08)	−0.67 (0.09)	−0.95 (0.09)
ADA + MTX	−0.64 (0.08)	−0.59 (0.09)	−0.63 (0.09)	−0.75 (0.09)
ETN + MTX	−0.59	−0.54	−0.58	−0.69

ABT, abatacept; ADA, adalimumab; ETN, etanercept; HAQ-DI, Health Assessment Questionnaire Disability Index; MTX, methotrexate; Q, quartile; SE, standard error.

Table 4 – Drug treatment costs, treatment monitoring costs, and acquisition costs.

Treatment	Drug cost (steady-state annual cost) (£)
ABT	9244
ADA	9156
ETN	9295
MTX	31.20

Treatment	Monitoring cost (in first 6 mo only) (£)	Monitoring cost (subsequent 6-mo cycles) (£)
ABT + MTX	904.53	164.88
ADA + MTX	904.53	164.88
ETN + MTX	904.53	164.88

ABT, abatacept; ADA, adalimumab; ETN, etanercept; MTX, methotrexate.

Table 5 – Annual cost of hospitalization by the HAQ-DI score.

HAQ-DI score range	Annual cost (£)
0 < 0.5	173.69
0.5 < 1.0	106.39
1 < 1.5	378.36
1.5 < 2.0	543.33
2.0 < 2.5	1293.02
2.5 < 3.0	2788.83

HAQ-DI, Health Assessment Questionnaire Disability Index.

was assumed that monitoring for biologic therapies was included within the monitoring for MTX or administration costs. Costs for hospitalization and joint replacement were assumed to increase as the HAQ-DI score increased and were derived from a previous study [28] and inflated to 2015 costs using the National Health Service pay and prices index [31]. The values assumed in the base case are presented in Table 5.

The cost of ACPA testing was not included in the model because it is routinely conducted in clinical practice [32] and EULAR guidelines [33] recommend testing for seropositivity irrespective of the treatment selected. In addition, the exclusion of ACPA testing cost is not expected to change the study findings because, if included, it would have incurred the same cost for both treatment arms.

Outcomes included discounted disaggregated costs, QALY, and incremental cost per QALY gained (incremental cost-effectiveness ratio [ICER]) as well as undiscounted life-years. Costs and outcomes were discounted at 3.5% annually, as specified for NICE reference case [27].

Sensitivity and Scenario Analyses

Univariate sensitivity analysis was used to determine the key drivers in the model; these were then applied to ACPA Q4, because this had shown the lowest ICER for abatacept versus adalimumab. Each variable was varied individually to assess the proportional effect on model results. The variables investigated were abatacept drug cost, abatacept EULAR response rate (good), initial 6-month HAQ-DI score change, and annual HAQ-DI score change while on long-term treatment. Additional scenario analyses were conducted on the basis of different time horizons, the incorporation of an additional (first year) loading dose cost for abatacept, the application of alternative utility mapping equations, and the incorporation of a longer term of treatment (6.17 years) for abatacept.

A PSA was performed for ACPA Q4 for 1000 sets of 1000 patients to assess the impact of parameter uncertainty around major model inputs. Key model parameters were sampled from parametric distributions to generate 1000 estimates of the costs and effects in each arm. EULAR response rates followed beta distributions, nondrug costs, and HAQ-DI score changes; parameters of the utility equation followed normal distributions; mortality relative risk followed a lognormal distribution; and hospitalization costs followed gamma distributions (Table 6).

Table 6 – Parameters considered in PSA (applied to quartile 4).

Parameter	Distribution	Mean	Standard error
ABT and ADA EULAR response rates	Beta	See Table 2	Assumed 10% of mean
Utility mapping algorithm parameters			
a	Normal	0.804	0.05
b1	Normal	0.203	0.08
b2	Normal	0.045	0.03
Mortality per unit HAQ-DI score	Lognormal	1.33	0.13
ABT and ADA HAQ-DI reductions	Normal	See Table 3	See Table 3
Annual cost of hospitalization by HAQ-DI score	Gamma	See Table 5	Assumed 10% of mean

ABT, abatacept; ADA, adalimumab; EULAR, European League Against Rheumatism; HAQ-DI, Health Assessment Questionnaire Disability Index; PSA, probabilistic sensitivity analysis.

Results

Primary Economic Analyses

The primary analysis considered the cost effectiveness of abatacept plus MTX as a first-line treatment after conventional DMARD failure compared with a base-case strategy of adalimumab plus MTX as a first-line treatment in ACPA-positive patients with varying ACPA concentration levels. For patients with poor prognosis (Q3 and Q4), the analysis resulted in increased costs for abatacept but additional benefits (QALYs).

The costs incurred by abatacept treatment compared with adalimumab treatment for patients categorized by ACPA groups are presented in Table 7. With the exception of Q1, treatment with abatacept resulted in higher treatment costs, because of the higher response rates for abatacept and hence higher proportion of patients on long-term therapy, but generally lower hospitalization costs because of various factors, including greater HAQ-DI score reductions after initiating therapy, and delayed disease progression. Treatment and administration/monitoring costs were broadly equivalent for patients who received abatacept and adalimumab across all quartiles.

The QALYs gained with abatacept versus adalimumab tended to increase with increase in ACPA titer groups, ranging from −0.115 QALYs for Q1 to 0.279 QALYs for Q4 (Table 8). The difference between treatments in life-years gained was small and also tended to increase with ACPA titer groups.

In terms of cost effectiveness for Q3 and Q4, the ICER for abatacept (vs. adalimumab) reduced as the baseline ACPA level increased with an ICER of £26,272/QALY in Q3 to £6200/QALY in Q4 (Table 8). In the first ACPA group (Q1), abatacept had a lower QALY gain and a lower cost, resulting in an ICER of £18,397/QALY in the southwest quadrant. In the southwest quadrant, the incremental cost reduction should be much larger to accept an intervention with lower benefits; thus, to be considered cost-effective, the ratios should be higher. In the second ACPA group (Q2), abatacept was dominated because it cost slightly more than adalimumab (+£66) and resulted in a slight decrease in QALYs (−0.009).

Sensitivity Analyses

The consequences of modifying model parameters applied in the sensitivity and scenario analysis for Q4 are presented in Table 9, which presents the range of the ICER between the

Table 7 – Lifetime per-patient costs of treatment with abatacept vs. adalimumab for patients categorized by ACPA quartile.

Quartile	Treatment cost (£)		Administration and monitoring costs (£)		Hospitalization costs (£)		Total lifetime cost (£)	
	ABT	ADA	ABT	ADA	ABT	ADA	ABT	ADA
Q1	50,188	47,680	9519	9488	16,511	16,189	73,710	75,825
Q2	49,212	49,172	9452	9451	18,949	18,923	77,612	77,546
Q3	47,314	45,976	9178	9211	17,949	18,076	74,441	73,263
Q4	50,685	48,491	8939	8971	18,803	19,234	78,428	76,696

ABT, abatacept; ACPA, anticitrullinated protein antibodies; ADA, adalimumab.

different assumptions tested in the analysis. For time horizon, the ICER ranged from £5046/QALY for 5 years to £5954/QALY for 10 years. Changes in the HAQ-DI score reduction on abatacept treatment had the highest impact on the ICER result; even with a 20% decrease in the HAQ-DI score reduction on abatacept, the abatacept treatment strategy remained cost effective at £21,159 per QALY, which was less than the accepted National Health Service threshold for the cost effectiveness of new therapies [34]. Incorporating the loading dose cost for the first year of abatacept treatment and extending the abatacept time on treatment to 6.17 years to reflect a more severe population [23] increased the ICER but the abatacept treatment strategy remained cost effective.

The model was stable when different HAQ-DI score to utility mapping algorithms were applied, in terms of the ICER. Nevertheless, using the HAQ-DI score utility algorithm, which estimated all utilities greater than 0 (0.89 – [0.28 × HAQ-DI]), had a major impact on total QALYs calculated compared with the base case (6.298 vs. 4.343 for abatacept and 6.057 vs. 4.064 for adalimumab), although the incremental difference between abatacept and adalimumab was similar when using the different algorithms (0.241 vs. 0.279, respectively). The analysis indicated that the cost-effectiveness results remained robust in the face of plausible variations of the main assumptions used in the model.

Probabilistic Sensitivity Analysis

In the PSA of abatacept versus adalimumab for Q4 patients, 98.5% of all 1000 simulation results fell in the northeast quadrant of the cost-effectiveness plane, indicating that the abatacept strategy was more effective but also more costly in all simulated runs for the model (Fig. 3). On the basis of the PSA, the probability of each treatment strategy being cost effective at different decision-making thresholds (i.e., willingness to pay per QALY gained) is presented in Fig. 4. There was a 94.2% likelihood that the abatacept strategy was cost effective at a willingness-to-pay threshold of £30,000 per QALY gained.

Discussion

This is the first published economic evaluation to estimate the cost effectiveness of RA treatments stratified by subgroups of patients with RA on the basis of prognostic factor defined by baseline ACPA levels. This model projected abatacept to be a cost-effective alternative to adalimumab in Q3 and Q4 of ACPA-positive patients with RA, showing trends toward increasing incremental total cost and QALY gain with abatacept versus adalimumab with increasing ACPA level. The ICER for abatacept compared with that for adalimumab was the lowest for patients with the poorest prognosis (ACPA Q4 ICER = £6200/QALY). An intervention with an ICER lower than £20,000/QALY to £30,000/QALY gained is generally considered to be cost effective in the UK health care setting [34]. In the group with the lowest ACPA level, the ICERs were in the southwest quadrant, that is, lower cost and lower QALY gains, and therefore the ICERs should be interpreted with caution.

Previous studies have identified serum parameters such as RF and ACPA to be associated with destructive RA [35–38]. Although the predictive value of RF for joint erosion is mixed, the data on ACPA are more uniform, with several studies linking ACPA to erosive disease, comprising structural damage (joint erosions) and radiographic progression [4,7,8,13]. A systematic review by Jilani and Mackworth-Young [13] concluded the presence of ACPA to be a strong predictor of erosive disease. Because established

Table 8 – Cost effectiveness of abatacept vs. adalimumab for patients categorized by ACPA quartile.

Quartile	Difference* in total cost (£)	Life-years (undiscounted)			QALYs			ICER (£/QALY)
		ABT	ADA	Difference*	ABT	ADA	Difference*	
Q1	−2115	28.12	28.14	−0.02	5.546	5.661	−0.115	18,397†
Q2	66	28.32	28.32	−0.01	4.700	4.709	−0.009	Dominated
Q3	1178	26.62	26.61	0.00	4.697	4.652	0.045	26,272
Q4	1732	25.92	25.84	0.08	4.343	4.064	0.279	6200

ABT, abatacept; ACPA, anticitrullinated protein antibodies; ADA, adalimumab; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

* Difference refers to abatacept − adalimumab.

† Lower costs and lower benefits.

Table 9 – Sensitivity analysis of the effect of alternative assumptions (applied to quartile 4).

Analyses	Base case	Sensitivity analysis	Cost per QALY (£)
Base case			6200
Time horizon	40 y	10 y	5954
		5 y	5046
ABT HAQ-DI score reduction	−0.950	−1.14 (+20%)	4365
		−0.76 (−20%)	21,456
ADA HAQ-DI score reduction	−0.750	−0.9 (+20%)	9337
		−0.6 (−20%)	4253
ABT response rate (good)	62.22%	49.78% (−20%)	Dominant
ABT annual cost	£9275	£15,756 (full UK list price)	81,345
		£12,257	39,775
ABT loading dose cost included in first year	£0	£907.20	8770
ABT time on treatment	4.06 y	6.17 y	12,539
Utility equation	$0.804 - 0.203 \times \text{HAQ-DI} - 0.045 \times \text{HAQ-DI}^2$	EQ-5D = 0.89 − (0.28 × HAQ-DI)	6447
		EQ-5D = 0.76 − (0.28 × HAQ-DI)	6299

ABT, abatacept; ADA, adalimumab; EQ-5D, EuroQol five-dimensional questionnaire; HAQ-DI, Health Assessment Questionnaire Disability Index; QALY, quality-adjusted life-year.

RA is a heterogeneous disease, some patients experience aggressive disease in spite of treatment. These patients also have higher use of direct medical resource as well as overall and RA-specific costs [39–41]. Thus, targeting these patients with biologic DMARDs is important.

Reliable markers of prognoses of aggressive RA, such as ACPA, can provide at baseline the rationale for aggressive therapy in patients with a substantial risk of developing destructive disease. In addition to evaluating the clinical benefit of aggressive treatments in patients at risk, one would need to consider the cost-effectiveness of pursuing such a policy. Our analysis was geared toward evaluating the appropriate cost-effective alternative biologic DMARD intervention in managing patients with poor prognosis and thus at risk of disease progression. Similar to our findings, another analysis has also shown biologic DMARDs to be cost effective in patients at risk of rapid disease progression [42]. Our analysis, however, takes this work a step further by specifying the prognostic factors and comparing one biologic DMARD with another, demonstrating that abatacept provided a cost-effective alternative to adalimumab in patients with poor prognosis who had an inadequate response to MTX.

The AMPLE study was chosen as a source of model inputs by way of it being the only head-to-head, randomized, controlled study between two biologics that incorporates radiographic progression end points, provides data on erosions and joint space narrowing in patients with RA, and includes data presented by patient ACPA level [15,16]. The demographic and clinical characteristics of the patients at AMPLE study baseline were balanced across the treatment groups and were considered to be typical for RA studies (the mean age of the patients was 51 years and the mean DAS28-CRP score was 5.5 ± 1.1 in both groups, with equal proportions of patients with moderate and high disease activity in each group [15]). Abatacept and adalimumab provided similarly effective treatment outcomes in patients with RA [15,16]. As

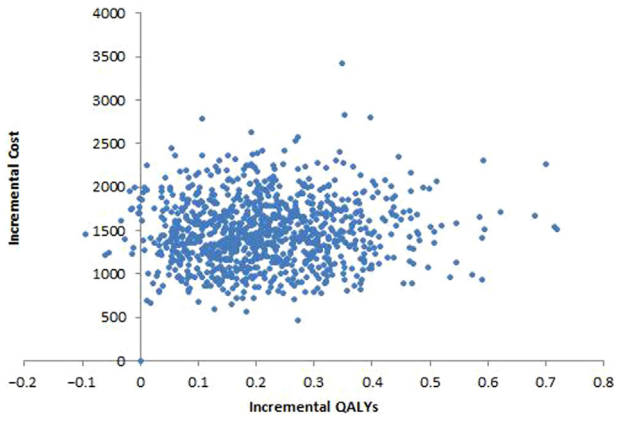

Fig. 3 – Cost-effectiveness plot of probabilistic sensitivity analysis results (abatacept vs. adalimumab). QALY, quality-adjusted life-year.

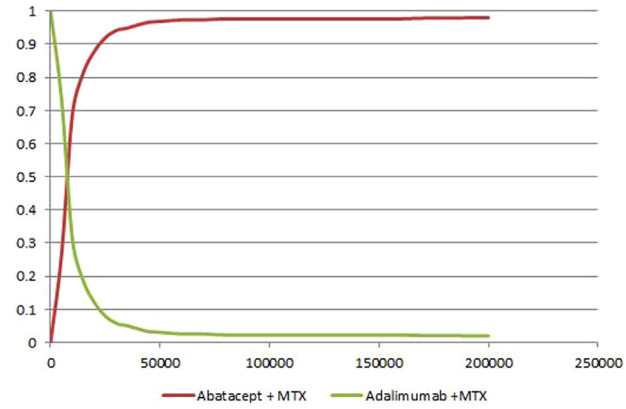

Fig. 4 – Cost-effectiveness acceptability curve (abatacept vs. adalimumab). MTX, methotrexate.

in the AMPLE study, the model compared abatacept with adalimumab; the lack of ACPA quartile data for other treatments currently prohibits running such comparisons for other treatment combinations. Apart from the AMPLE study, data based on real-world RA registries have demonstrated an association between higher ACPA concentrations and improved abatacept efficacy and retention [14,42–45]. Therefore, we believe that the AMPLE study provided the model with reliable comparative efficacy data for a population representative of the general RA population and for two agents where patient ACPA level could be expected to influence outcomes and costs.

A key strength of this model is the application of the approach considered by evidence review groups responsible for assessing the cost effectiveness of RA treatments in the United Kingdom [1,23]. Decision making on the use of treatments for RA in the United Kingdom is based on IPS models, such as the Birmingham rheumatoid arthritis model [20] and the Sheffield rheumatoid arthritis health economic model [21]. As with other IPS models, this cost-effective analysis enabled patient progression while on a certain treatment if a specific disease level was met, allowed treatment sequences to be evaluated rather than single therapy, and incorporated the uncertain duration of treatment effect on each patient [21].

As with any economic evaluation study, it is important to acknowledge the limitations of the analysis and to reflect on the assumptions and data upon which the conclusions have been drawn.

In terms of the patient population characteristics taken from the AMPLE study, although the study population was reasonably large (646 participants), the number of patients in each trial arm by ACPA quartile was relatively small (42–55 participants), which may reduce confidence in the effectiveness estimates by ACPA quartile that were used as inputs.

The present analysis explored the relationship between ACPA level and ICER using ACPA level quartiles and did not attempt to identify any ACPA threshold corresponding to a single ICER value or model outcomes according to ACPA levels of clinical significance. As such, the association is deserving of further study. Such an analysis might require an alternative outcome, such as response rate. Thresholds at which the best response rate occurs could then be investigated using, for example, a receiver-operating characteristic curve to determine the best combination of sensitivity and specificity. This is not possible using the model in its current form because the model uses response rate as an input parameter rather than as an outcome. A future economic analysis might also consider the cost effectiveness of a treatment algorithm incorporating screening for ACPA level and subsequent treatment of a predetermined patient subset versus no screening and the treatment of all patients. The present study evaluated the impact of prognostic factor such as ACPA levels on cost effectiveness and not the impact of a screening strategy.

In addition, the base case assumed that HAQ-DI score progression while on biologic therapy was 0. This assumption is used in most cost-effectiveness models and the literature is mixed because some analyses show that patients with RA treated with a TNF inhibitor have continued disease activity [23]. For patients on palliative care, a constant annual rate of HAQ-DI score progression was assumed. A recent NICE appraisal (Technology Appraisal 375 [28]) has suggested a nonlinear HAQ-DI score progression model, derived from an early RA data registry, for patients on conventional DMARDs and palliative care is a more appropriate reflection of a chronic disease, and that the choice of model to inform HAQ-DI score progression had an impact on ICERs. It is not clear how the use of a cubic representation of HAQ-DI score progression would affect the results of the current model, but it is expected that because the treatment strategy after failure of first-line treatment is the same for both treatment arms, the incremental results would not change greatly.

The utility measures of the EQ-5D were based on a mapping of the HAQ-DI score to utility described by Malottki et al. [23] and used in multiple cost-effectiveness models. Such mapping studies usually overestimate the utilities of bad health states and underestimate the utilities of good health states. It has been suggested that a substantially better estimate of utility is obtained by the inclusion of pain alongside the HAQ-DI than via the HAQ-DI alone [28]. The application of different utility mapping algorithms in this study was investigated in sensitivity analyses and had little impact on the incremental results, but the use of a mapping algorithm incorporating pain as well as the HAQ-DI score should be investigated in future work.

Finally, because of availability of data, the model evaluated abatacept against one anti-TNF agent only (adalimumab) and incorporated clinical data for these two agents only from the observational trial. The model also did not assess the introduction of a second conventional DMARD after MTX failure because the model and the AMPLE trial were reflecting treatment guidelines for the patients with poor prognosis. The limited use of comparators in this study creates an opportunity for further research to assess the cost effectiveness of abatacept versus other conventional and biologic treatment options.

For the next treatment in the sequence (etanercept), it was assumed that the relative difference in EULAR response probabilities observed for adalimumab between the AMPLE study and a recent previous mixed treatment comparison [28] would be similar for etanercept. It is, however, unlikely that this would have favored either abatacept or adalimumab, because patients in each treatment arm moved on to etanercept after failure on the first line of therapy. We tested the impact of these assumptions on the findings via various sensitivity and scenario analyses. Overall, we found that the results were robust in the face of changes in input parameters, yet the opportunity remains to evaluate abatacept against other agents and to increase the clinical data inputs contributing to the robustness of the model.

Conclusions

Abatacept provided a cost-effective alternative to adalimumab in ACPA-positive patients with RA with an inadequate response to MTX. For ACPA-positive patients with higher ACPA levels (Q4 and Q3), higher EULAR response rates for abatacept patients compared with adalimumab patients resulted in higher proportions of patients on long-term therapy resulting in increased treatment costs, but these were partially offset by a greater reduction in disability (HAQ-DI) and lower hospitalization costs. The increased cost per QALY gained for abatacept was lower in those patients with higher ACPA levels. This economic evaluation, therefore, suggests that the use of abatacept in patients with RA with poor prognosis should be seen as a cost-effective approach to the management of RA in the United Kingdom, with clear advantages seen in health-related quality of life.

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