VALUE IN HEALTH ▮ (2017) ▮▮▮–▮▮▮

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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, £6,200/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]. 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

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1098-3015$36.00 – see front matter

http://dx.doi.org/10.1016/j.jval.2017.05.020

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. 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.

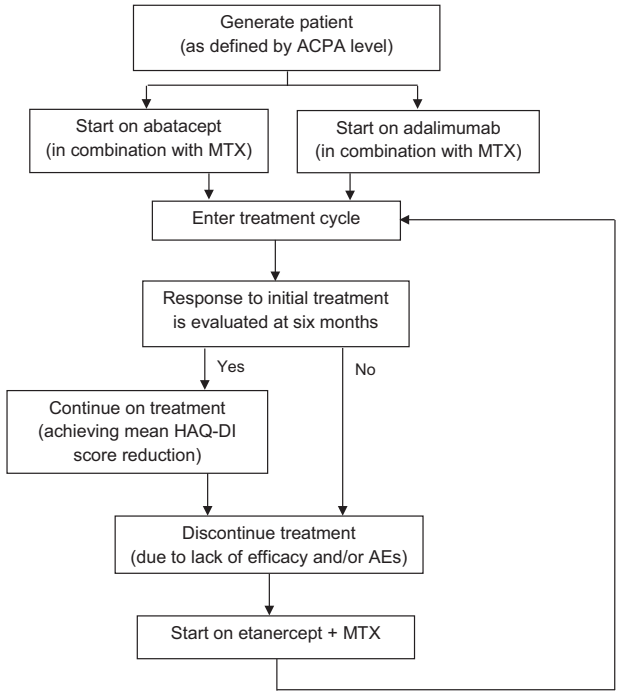

Fig. 1 – Overview of the patient-level simulation model. ACPA, anticitrullinated protein antibodies; HAQ-DI, Health Assessment Questionnaire Disability Index; MTX, methotrexate.

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 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