NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Multiple Technology Appraisal (MTA)

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying anti-rheumatic drugs and after the failure of conventional disease-modifying anti-rheumatic drugs only (Review of Technology Appraisal guidance 130, 186, 224, 234 and a part review of Technology Appraisal guidance 225 and 247)

BMS submission of evidence to NICE

Executive Summary

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Abatacept (ORENCIA®) in combination with methotrexate (MTX) has a UK marketing authorisation for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who responded inadequately to previous therapy with one or more disease-modifying antirheumatic drugs (DMARDs) including MTX or an anti-tumour necrosis factor (TNF). It is administered by intravenous (IV) infusion or subcutaneous (SC) injection.

Efficacy

Intravenous abatacept

Three randomised controlled trials have demonstrated the clinical efficacy of IV abatacept (on a background treatment of MTX) in biologic-naïve RA patients who had an inadequate response to MTX:

1. The AIM (Abatacept in Inadequate responders to Methotrexate) study, a 1-year, Phase III, multicentre, double-blind, placebo-controlled trial.
2. A 1-year, Phase IIb, multicentre, double-blind, placebo-controlled study conducted by Kremer et al.
3. The ATTEST (Abatacept or infliximab versus placebo, a Trial for Tolerability, Efficacy and Safety in Treating rheumatoid arthritis) study, a 1-year, double-blind, double-dummy, placebo- and active-controlled trial that evaluated the efficacy of abatacept or infliximab versus placebo.

All patients completing the 1-year randomised phase of the AIM study and the Phase IIb study were eligible to enter an open-label long-term extension (LTE) period in which all patients received IV abatacept for an additional 4 and 6 years, respectively.

- In the AIM study, IV abatacept (on a background of MTX) demonstrated better efficacy than placebo in improving ACR20 response over 6 months, improving physical function and reducing structural damage progression over 12 months. In addition, IV abatacept significantly reduced disease activity, signs and symptoms, and improved health-related quality of life (HRQoL). Patients who received IV abatacept also reported better sleep quality, less fatigue and fewer days of activity limitation after 6 and 12 months of treatment. Moreover, clinical efficacy, including remission, radiographic non-progression and improvements in physical function and HRQoL that were observed at 1 year, were sustained through 5 years of IV abatacept treatment in the LTE. These sustained efficacy benefits were supported by high retention rates; over 70% of patients originally randomised to IV abatacept who entered the LTE were still participating after 5 years of treatment.

- In the Kremer et al Phase IIb study, 6-month data demonstrated that 10 mg/kg IV abatacept (on a background of MTX) effectively controlled the signs and symptoms of RA and also improved physical function and HRQoL.The 12-month results from this trial demonstrated that 10 mg/kg IV abatacept provided sustained clinical benefits over 1 year as shown by significant improvements in American College of Rheumatology (ACR) responses, functional ability (measured by the modified Heath

Assessment Questionnaire [M-HAQ]) and HRQoL (measured by SF-36). In the open-label LTE period, patients remaining on IV abatacept treatment showed sustained improvements in the signs and symptoms of RA, including disease activity and physical function, for up to 7 years.

- In the ATTEST study, patients treated for 6 months with IV abatacept or infliximab (on a background of MTX), had significant reductions in signs and symptoms of disease (Disease activity score 28 joint count based on erythrocyte sedimentation rate levels [DAS28-ESR]; ACR20, ACR50 and ACR70), and physical function (Health Assessment Questionnaire Disease Index [HAQ-DI]) and HRQoL (SF-36) were improved, when compared with patients who had received placebo. Moreover, the relative efficacy of IV abatacept and infliximab was similar in terms of DAS28-ESR scores, ACR response rates, HAQ-DI responses and HRQoL at Day 197. Similar ACR20 response rates were noted with IV abatacept and infliximab by Day 85. However, between 6 months and 1 year, abatacept responses were maintained, while those with infliximab were not. Furthermore, by Day 365, IV abatacept had a greater numerical difference than infliximab for the reduction in DAS28-ESR and low disease activity state (LDAS), the ACR20 response rate and the HRQoL physical summary.

Subcutaneous abatacept

The clinical efficacy of SC abatacept (on a background treatment of MTX) has been demonstrated in three trials in patients with RA who had an inadequate response to MTX:

1. The AMPLE (Abatacept versus adaliMumab comParison in bioLogic-naivE RA subjects with background methotrexate) study, a 2-year, Phase IIIb, randomised trial that directly compared SC abatacept with SC adalimumab.
2. The ACQUIRE (Abatacept Comparison of Sub(QU)cutaneous versus Intravenous in inadequate Responders to methotrexatE) study, a 6-month, Phase IIIb, randomised, double-blind, double-dummy trial that compared the efficacy of SC abatacept with IV abatacept.
3. The ATTUNE (Abatacept in subjecTs who swiTch from intravenoUs to subcutaNeous thErapy) study, a 12-month, Phase IIIb, open-label, single-arm trial that evaluated efficacy after switching to SC abatacept after long-term (≥4 years) treatment with IV abatacept.

Patients completing the 6-month randomisation phase of the ACQUIRE study were eligible to enter an open-label LTE period in which all patients received SC abatacept for up to 44 months.

- In the AMPLE study, treatment with SC abatacept or SC adalimumab (on a background of MTX) had similar efficacy, with both treatment arms having comparable clinically-meaningful improvements in signs and symptoms of RA, physical function and patient-reported outcomes that were sustained over 1 year. In addition, comparable inhibition of radiographic progression was observed in both groups.

- In the ACQUIRE study, SC abatacept provided efficacy comparable with that of IV abatacept during the 6-month double-blind period. In the LTE period, which lasted up to 44 months, SC abatacept was associated with maintained improvements in clinical and functional efficacy outcomes and high retention rates.

- Results of the ATTUNE study demonstrated that patients can switch from long-term monthly IV abatacept to a weekly fixed dose of 125 mg SC abatacept without experiencing any loss of efficacy.

Safety

Intravenous formulation

The safety of IV abatacept (on a background treatment of MTX) was evaluated in four randomised controlled trials conducted in patients with RA who had an inadequate response to MTX:

1. The AIM study.
2. The Phase IIb study by Kremer et al.
3. The ATTEST study.
4. The ASSURE (Abatacept Study of Safety in Use with other RA thErapies) study.

- Safety data from the 1-year AIM study was consistent with earlier IV abatacept studies. Patients tolerated IV abatacept with similar incidence of adverse events as placebo, with expected higher incidence of serious adverse events, serious infections and discontinuations than placebo. The safety data for IV abatacept from the 4-year open-label LTE period of the AIM study demonstrated that IV abatacept was well tolerated over a total follow-up of 5 years.

- IV abatacept was also well tolerated in the 1-year Kremer et al Phase IIb study, with overall incidence of adverse events and serious adverse events being similar to placebo. Fewer patients discontinued due to adverse events in the 10 mg/kg abatacept group than in the placebo group. Safety data for IV abatacept from the 6-year open-label LTE period of this study further demonstrated that abatacept was well tolerated over a total follow-up of 7 years.

- Although the 1-year ATTEST study was not designed as a head-to-head study, overall IV abatacept had a relatively more acceptable safety and tolerability profile than infliximab, with fewer serious adverse events, serious infections, acute infusional events, and also fewer discontinuations due to adverse events or serious adverse events. Opportunistic infections were relatively uncommon in the study and were mainly observed in the infliximab group, with no opportunistic infections reported in the abatacept group. The safety data for IV abatacept from the 1-year open-label LTE period of the ATTEST study further demonstrated that abatacept was well tolerated over a total follow-up of 2 years.

- Safety data from the 1-year ASSURE study demonstrated that IV abatacept in combination with synthetic DMARDs was well tolerated, being comparable with

placebo, in patients who were inadequate responders to DMARDs and/or biologic therapy. However, IV abatacept in combination with biologic background therapies was associated with an increase in the rate of serious adverse events.

Subcutaneous formulation

The safety of SC abatacept (on a background treatment of MTX) was evaluated in three randomised controlled trials conducted in patients with RA who had an inadequate response to MTX:

1. The AMPLE study.
2. The ACQUIRE study.
3. The ATTUNE study.

In addition, integrated analyses were conducted to evaluate and compare the long-term safety of SC and IV abatacept.

1. In the AMPLE study, the safety profiles of SC abatacept and SC adalimumab were generally similar, other than the occurrence of significantly more local injection site reactions and a higher seroconversion rate in patients treated with SC adalimumab.

2. The ACQUIRE study demonstrated that SC abatacept has a safety profile consistent with that established for IV abatacept, including low incidence of immunogenicity and infrequent injection site reactions.

3. The ATTUNE study demonstrated that patients can switch from long-term monthly weight-tiered IV abatacept to a weekly fixed-dose SC abatacept regimen, with no increased safety concerns or risk of immunogenicity.

Integrated safety data from 1,879 patients for up to 4.5 years (3,086 patient-years of exposure) confirmed that long-term treatment with SC abatacept was well tolerated and did not lead to an increase in infections, malignancies or autoimmune events. The results were comparable with a pooled analysis of IV abatacept safety data from 4,149 patients (12,132 patient-years of exposure).

Therefore, based on the cumulative exposure of 6,028 patients to IV and SC abatacept, the events reported with long-term abatacept treatment were similar to those reported in the short term. There was no increase in incidence rates for any event with increasing exposure, demonstrating that both IV and SC abatacept are well tolerated with a favourable safety profile over the long term.

Cost-effectiveness

BMS have developed a patient-level model to calculate the cost-effectiveness of first-line biologics. The model is based on the Birmingham Rheumatoid Arthritis Model (BRAM). The model considers DAS28 and HAQ score and patients follow a sequence of treatments in accordance with the NICE biologics pathway.

Incremental analysis between the comparators is inappropriate due to the similar QALY gains between treatments. All of the biologics have similar ICERs when compared to DMARDs, at around £30,000/QALY. These results are robust in scenario analyses. Probabilistic sensitivity analysis demonstrates considerable uncertainty as to which treatment is the most cost-effective option.