Indirect treatment comparison of abatacept with methotrexate versus other biologic agents for active rheumatoid arthritis despite methotrexate therapy in the United Kingdom


CRD summary

The authors concluded that abatacept plus methotrexate improved functional status compared with placebo plus methotrexate in UK rheumatoid arthritis patients previously unresponsive to methotrexate. Given differences between included trials, the potential for language bias, and the potential for bias in some included trials, the reliability of the authors' conclusions is unclear.

Authors' objectives

To compare the effectiveness of abatacept and alternative biologic disease-modifying antirheumatic drugs in participants with active rheumatoid arthritis with an inadequate response to methotrexate in the UK.

Searching

MEDLINE, EMBASE, The Cochrane Library and technology appraisals for the UK were searched from January 1980 to October 2010 for articles published in English. Some search terms were reported. Conference reports from the American College of Rheumatology and the European League Against Rheumatism were searched from 2008 to 2010.

Study selection

Eligible for inclusion were randomised controlled trials (RCTs) of methotrexate combined with abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab or placebo in comparison with one another. Eligible participants had rheumatoid arthritis and a previous inadequate response or intolerance to at least one conventional disease-modifying antirheumatic drug. It appeared that studies had to be conducted on participants receiving the recommended dosage of drugs licensed in the UK. Outcomes eligible for inclusion were change from baseline score on the Health Assessment Questionnaire (HAQ) and the American College of Rheumatology (ACR) 20/50/70 response criteria at six months. Further details of the ACR response criteria were reported in the paper.

Included trials evaluated abatacept (10mg/kg every four weeks) compared with placebo plus methotrexate or the following disease-modifying antirheumatic drugs in combination with methotrexate; infliximab (3mg/kg every eight weeks), adalimumab (40mg alternate weeks), certolizumab (200mg alternate weeks), etanercept (25mg twice weekly) or golimumab (50mg every four weeks). The mean age of participants ranged from 48 to 57.2 years; the proportion of women ranged from 66% to 87.3%. The mean years since diagnosis ranged from 4.5 to 13 years. The mean tender joint count ranged from 21 to 34.2; the mean swollen joint count ranged from 12 to 22.6. The proportion of participants taking non-steroidal anti-inflammatory drugs ranged from 72% to 88%; the proportion taking corticosteroids ranged from 53% to 71.5% (where reported).

Two reviewers independently selected the studies for review.

Assessment of study quality

The authors did not appear to formally assess the quality of included studies. They commented on aspects of comparability between included studies which may have affected the reliability of results.

Data extraction

The mean and standard deviation (SD) of the health assessment questionnaire change from baseline were extracted for each group and used to calculate differences in mean change with 95% credible limits (CrL). Where standard deviations were not available, they were estimated based on other available statistical data or by taking the average of all other reported standard deviations. The number of participants with a 20%, 50% and 70% response according to ACR criteria were extracted for each group and used to calculate relative risks (RR) with 95% credible limits.

One reviewer performed the data extraction. A second reviewer checked the data.
Methods of synthesis
Results were pooled using a random-effects Bayesian network meta-analysis (for indirect treatment comparisons) with placebo plus methotrexate as the common comparator. A non-informative prior distribution was used. Expected absolute mean change from baseline for HAQ and expected absolute ACR 20/50/70 probability of response, with 95% credible limits, were calculated. Statistical heterogeneity was assessed using deviance information criteria.

Sensitivity analyses were conducted by removing one trial population with no or no recent exposure to methotrexate, and by excluding participants from one arm of a trial concerning a site where there were protocol violations.

Results of the review
Twenty-one documents reporting on 11 double-blind placebo RCTs were included for analysis (number of participants unclear). The authors gave a qualitative report on comparability of trials. They found that some trials provided escape or rescue therapy or withdrew patients who did not respond from the trial. Inclusion criteria for participants varied between trials and included people with less advanced rheumatoid arthritis in some trials. Differences between trials were also observed in disease duration and number of swollen or tender joints.

Health Assessment Questionnaire (HAQ) scores: Abatacept plus methotrexate significantly reduced HAQ scores from baseline compared with placebo plus methotrexate (difference -0.30, 95% CrL -0.42 to -0.16). The expected absolute change from baseline for HAQ scores was for abatacept (-0.57, 95% CrL -0.69 to -0.43) was better than placebo (-0.27, 95% CrL -0.30 to -0.24). Abatacept was as effective other biologic agents in reducing HAQ scores from baseline (point estimates of relative differences in mean HAQ change from baseline ranging from -0.11 to 0.09).

American College of Rheumatology (ACR) response criteria: Abatacept plus methotrexate resulted in significantly more participants demonstrating an improvement in functional status according to ACR criteria at the 20% level (RR 1.90, 95% CrL 1.24 to 2.57), 50% level (RR 2.62, 95% CrL 1.24 to 4.95) and at the 70% level (RR 3.72, 95% CrL 1.50 to 10.52) compared with placebo plus methotrexate. Abatacept had a numerical advantage over etanercept (for 20% and 50% ACR response) and infliximab (for 20%, 50% and 70% ACR criteria response), but not when compared with adalimumab, certolizumab, and golimumab (for all ACR criteria). However, the credible limits for all these results crossed 1, which indicated no statistical difference in ACR response criteria between the different treatments.

Sensitivity analysis that removed one trial with participants without prior or recent methotrexate exposure did not significantly alter the results.

Authors' conclusions
Abatacept in combination with methotrexate improved functional status compared with placebo plus methotrexate. Improvement was at a level comparable to other recommended biologic agents in patients with rheumatoid arthritis previously unresponsive to methotrexate in the UK.

CRD commentary
The review addressed a clear question. Inclusion criteria were well defined. Several relevant databases were searched and attempts were made to identify unpublished data. Publication bias was not assessed and could not be ruled out. Publications in languages other than English were excluded, which introduced the risk of language bias. Appropriate steps were taken in the study selection and data extraction stages to minimise the risk of reviewer error and bias.

A formal quality assessment was not performed, so the quality of the included trials was unclear. In some studies rescue therapy or study withdrawal was used for non-responders, which may undermine the reliability of the results. The number of participants was not reported, so the amount of data on which the findings were based was unclear. The authors identified differences in trial inclusion criteria and patient characteristics that may have undermined the strength of the findings. Given the differences between trials, it was unclear whether it was appropriate to combine the trials in a meta-analysis. Several of the review authors were employees of Bristol-Myers Squibb (manufacturers of abatacept and funders of the review) at the time of writing.

In light of differences between included trials, the potential for language bias, and the potential for bias in some included trials, the reliability of the authors' conclusions is unclear.
Implications of the review for practice and research

Practice: The authors stated that abatacept was a suitable alternative to other disease-modifying antirheumatic drugs.

Research: The authors did not state any implications for further research.

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