Comparative effectiveness and safety of biological treatment options after tumour necrosis factor alpha inhibitor failure in rheumatoid arthritis: systematic review and indirect pairwise meta-analysis
Schoels M, Aletaha D, Smolen JS, Wong JB

CRD summary
The review concluded that new treatments for rheumatoid arthritis after inadequate response to tumour necrosis factor inhibitors provided significant improvements in efficacy with good safety. The limited number of trials and each trial investigating a different treatment mean that these conclusions may not be reliable.

Authors’ objectives
To compare the efficacy and safety of biological treatments for rheumatoid arthritis after inadequate response to tumour necrosis factor alpha inhibitors.

Searching
MEDLINE, The Cochrane Library and ClinicalTrials.gov were searched from inception to March 2011. Bibliographies of identified publications were searched.

Study selection
Eligible studies were randomised controlled trials of patients with rheumatoid arthritis who had inadequate response to tumour necrosis factor alpha inhibitors. Trials had to compare a novel biological treatment combined with synthetic disease-modifying antirheumatic drug (DMARD) with placebo containing synthetic DMARD only. Studies had to report either efficacy or safety.

The selected studies were of adults. Four treatments were included: abatacept, golimumab, rituximab and tocilizumab. Most patients also received methotrexate. All patients had active disease but the definition of this varied across trials. Average Disease Activity Scores at baseline ranged from 6.3 to 7.0. The average age of patients was 53. Most patients (74% to 84%) were female. Efficacy was defined according to the American College of Rheumatology at the 20%, 50% and 70% levels (ACR20, ACR50 and ACR70). Safety outcomes analysed were adverse events, serious adverse events or infections at eight weeks or more. Only full publications written in English were included.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
Trial quality was assessed using the Jadad scale (minimum score zero, maximum 5).

The authors did not state how many reviewers carried out the quality assessment.

Data extraction
For analyses of efficacy, data were extracted from trials on the response rate on the ACR20, ACR50 and ACR70 scales. Numbers of adverse events and serious adverse events were extracted for the analysis of safety.

The authors did not state how many reviewers carried out the data extraction.

Methods of synthesis
Trials were synthesised using random-effects meta-analyses. Efficacy was assessed in terms of the odds ratio, with 95% confidence interval (95% CI), of achieving a response on the ACR scales after 24 weeks. Safety was assessed in terms of the risk difference or the relative risk (RR), with 95% CIs, in risk of adverse events. Heterogeneity was assessed using Cochran's Q test and the I² statistic. Different active treatments were compared for efficacy and safety using indirect meta-analysis methods.

Results of the review
Four trials were included (1,873 patients, range 393 to 520). Each trial investigated a different treatment. All trials were judged to be of good quality (Jadad scores from 3 to 5). Follow-up time was 24 weeks.

All treatments were more effective than placebo. When combining all trials, the odds ratio for ACR20 was 4.90 (95% CI 3.42 to 7.04), the odds ratio for ACR50 was 7.20 (95% CI 4.70 to 11.02) and the odds ratio for ACR70 was 7.43 (95% CI 3.77 to 14.61). Indirect comparisons showed no differences between treatments on the ACR50 and ACR70 scales but on the ACR20 scale response rates were lower for golimumab than for other treatments. Heterogeneity was not reported.

Adverse event rates were similar for treatments when compared to placebo (RR 1.0, 95% CI 0.9 to 1.1). In indirect comparisons, golimumab had a lower risk of adverse events than other treatments and acute reactions to infusions were higher for the first rituximab infusion than for other treatments.

Results from further sensitivity and subgroup analyses were reported.

**Authors' conclusions**

New treatments for rheumatoid arthritis after inadequate response to tumour necrosis factor inhibitors provided significant improvements in efficacy with good safety when compared to placebo. All treatments appeared to have similar effects.

**CRD commentary**

This review appeared reasonably well conducted but reporting of the review process was limited. Suitable sources were searched but the review was limited to published papers in English and publication and language biases could not be ruled out given the small number of included trials.

Appropriate statistical methods were used to synthesise results. As the authors noted, the limited number of trials and each trial investigating a different treatment made the validity of the results uncertain, particularly for indirect comparisons of treatments.

The authors' conclusions are reasonably cautious but the problems noted by the authors and potential for bias mean that the results may not be reliable.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors suggested that trials that distinguish between patients with inadequate response and those with other reasons for termination of treatment would be useful.

**Funding**

Schering-Plough, USA.

**Bibliographic details**


**PubMedID**

22294630

**DOI**

10.1136/annrheumdis-2011-200490

**Original Paper URL**

http://ard.bmj.com/content/71/8/1303.abstract

**Indexing Status**
Subject indexing assigned by NLM

MeSH
Abatacept; Antibodies, Monoclonal /therapeutic use; Antibodies, Monoclonal, Humanized /therapeutic use; Antibodies, Monoclonal, Murine-Derived /therapeutic use; Antirheumatic Agents /therapeutic use; Drug Substitution; Female; Humans; Immunoconjugates /therapeutic use; MEDLINE; Male; Middle Aged; Randomized Controlled Trials as Topic; Rheumatic Fever /drug therapy; Rituximab; Treatment Failure; Treatment Outcome; Tumor Necrosis Factor-alpha /antagonists & inhibitors

AccessionNumber
12012035687

Date bibliographic record published
24/08/2012

Date abstract record published
08/11/2012

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.