Immunogenicity of monoclonal antibodies against tumor necrosis factor used in chronic immune-mediated inflammatory conditions: systematic review and meta-analysis

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CRD summary
This review found that the development of antibodies against anti-TNF monoclonal antibodies increase risk of treatment discontinuation and hypersensitivity and may decrease clinical response. Combining monoclonal antibodies with other agents reduced the development of antibodies. The evidence was variable in quantity and quality, but the main conclusions appear reliable.

Authors' objectives
To assess the influence of antibodies against biological treatments on the efficacy and safety of such treatments for immune-mediated chronic inflammatory diseases.

Searching
MEDLINE, EMBASE, The Cochrane Library and Web of Knowledge were searched between 2000 and March 2012 for articles published in English, Spanish, French, Italian or Portuguese. Broad search terms were reported. The authors conducted citation searching and sought abstracts from European League Against Rheumatism (EULAR) and American College of Rheumatology conferences held between 2001 and 2011.

Study selection
Eligible studies were experimental or observational studies that measured the influence of antibodies against biological treatments on the efficacy (response to treatment) and safety of the biological treatments for certain immune-mediated chronic inflammatory diseases (as stated in the review). Other outcomes of interest were reported in the review. Case reports were excluded from the review.

Participants of included studies had rheumatoid arthritis, ankylosing spondylitis, Crohn’s disease, ulcerative colitis, psoriasis, psoriatic arthritis, inflammatory bowel disease or juvenile idiopathic arthritis. Mean duration of the condition ranged from two to 18.1 years; mean ages of patients ranged from 11.1 to 61.6 years (where reported). Some studies recruited people previously treated with another biologic agent but previous treatment was often not reported. Current treatments included anti-tumour necrosis factor monoclonal antibodies (infliximab, adalimumab, golimumab, etanercept and certolizumab), rituximab or abatacept. Most studies included concomitant treatment (mostly methotrexate). Various tools were used to measure outcomes in different health conditions.

Two reviewers independently screened studies for inclusion.

Assessment of study quality
The authors created a 30-item checklist to assess study quality, based on criteria proposed by Hayden et al. to assess the quality of prognostic studies. Scores ranged between zero and 100 (100 indicated absence of risk of bias).

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

Data extraction
Data were extracted to calculate odds ratios and their 95% confidence intervals for outcomes in patients with antibodies (seropositive) versus those without antibodies (seronegative) against biological agents.

The authors did not state how many authors performed the data extraction.

Methods of synthesis
Meta-analyses were performed when at least three studies reported on an outcome. Odds ratios and 95% confidence intervals were pooled for seronegative and seropositive patients (DerSimonian and Laird random-effects model). Statistical heterogeneity was measured using the I² statistic (I²>40% indicated high statistical heterogeneity). Statistical
heterogeneity was explored through sensitivity analyses and meta-regression (as detailed in the review).

Where meta-analysis was not possible, data were presented as a narrative synthesis. Data were presented by outcome, type of condition and biologic treatment. Publication bias was assessed through visual inspection of funnel plots and use of Egger's test.

**Results of the review**

Sixty-four studies (13,982 participants) were included in the review: 30 randomised controlled trials (RCTs), 23 prospective and 11 retrospective observational studies. Thirty-seven studies (60%) scored higher than 70% on quality assessment. Where reported, follow-up duration ranged from six to 196 weeks.

**Response:** A statistically significantly worse response to treatment (measured using EULAR criteria) was observed at six months in seropositive patients with rheumatoid arthritis taking infliximab or adalimumab (OR 0.03, 95% CI 0.01 to 0.21; three studies; \(I^2=49.6\%\)) and at six to 12 months (OR 0.03, 95% CI 0.00 to 0.30; three studies; \(I^2=71.1\%\)). There were no statistically significant differences in response between patients with rheumatoid arthritis, with and without antibodies, when using the American College of Rheumatology 20 response (three studies; \(I^2=62.8\%\)).

Similarly, no statistically significant differences in response to treatment were observed in patients with spondyloarthopathies or inflammatory bowel disease. Seropositive patients with rheumatoid arthritis, psoriasis or inflammatory bowel disease showed a non-statistically significantly higher rate of loss of response to treatment compared to seronegative patients (OR 3.0, 95% CI 0.99 to 9.09; three studies; \(I^2=31.8\%\)).

**Safety:** Seropositive patients (regardless of condition) showed statistically significant higher rates of hypersensitivity compared to seronegative patients (OR 3.97, 95% CI 2.36 to 6.67; 16 studies; \(I^2=62.5\%\)). Seropositive patients with rheumatoid arthritis showed statistically significantly higher rates of discontinuation of treatment compared to seronegative patients (OR 3.53, 95% CI 1.60 to 7.82; three studies; \(I^2=34.5\%\)). Concomitant treatment with disease modifying anti-rheumatic drugs (DMARDs) statistically significantly reduced the risk of becoming seropositive (OR 0.32, 95% CI 0.25 to 0.42; 17 studies; \(I^2=0\%\)).

Results from meta-regression and other secondary outcomes were reported in the review. There was evidence of publication bias for response in patients with rheumatoid arthritis but no evidence of bias for other outcomes.

**Authors' conclusions**

Development of antibodies against anti-TNF monoclonal antibodies decreased clinical response in patients with rheumatoid arthritis and increased risk of discontinuation of treatment and development of hypersensitivity. Combining anti-TNF monoclonal antibodies with DMARDs reduced the development of antibodies and associated risk; therefore, anti-TNF antibodies may not be advisable as monotherapy. Information was limited regarding other biologic agents and other immune-mediated chronic inflammatory diseases.

**CRD commentary**

The review question was broad but supported by appropriate inclusion criteria. A satisfactory number of sources were searched for relevant data but there was potential for language bias as some language restrictions were applied. Formal assessment of publication bias indicated some evidence of bias but only a small number of studies were assessed. Study quality was assessed but details were not provided. Study selection was performed in duplicate but it was unclear whether this was the case for other stages of the review process so reviewer error and bias could not be ruled out.

A large evidence base was presented but this resulted in significant variability across studies in terms of patients, treatments, outcomes and outcome measures. This was reflected in the high levels of statistical heterogeneity for most outcomes. The authors went some way to explore sources of heterogeneity and only pooled data where they considered the evidence to be sufficient. However, numbers of studies and sample sizes for meta-analyses in outcomes relating to treatment response were generally small.

The authors acknowledged some limitations of the review, including variability in defining and measuring outcomes and use of odds ratios which may not have been the best estimate to use. Most studies focused on infliximab and adalimumab (which have the highest rate of immunogenicity) so the findings may not be generalisable to other drugs. The authors suggested that the findings should be interpreted with caution given the presence of potential publication bias.
bias and heterogeneity.

The authors’ conclusions reflect the evidence and are suitably cautious. However, potential for bias in the review process and limitations of the evidence (including small numbers of studies and sample sizes, and significant heterogeneity across studies) suggest the findings should be interpreted cautiously as they may not be reliable, particularly for outcomes related to efficacy.

**Implications of the review for practice and research**
The authors did not state any implications for practice and further research.

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