A systematic review and meta-analysis of anti-adhesion molecule therapy in patients with active Crohn's disease

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CRD summary
The review found that anti-adhesion molecule therapy significantly improved remission rates and clinical response rates compared to placebo in patients with active Crohn's disease and had no significant difference in adverse events. The authors' cautious conclusions accurately reflected both the results and limitations of the review, and may be considered reliable.

Authors' objectives
To evaluate the safety and effectiveness of anti-adhesion molecule therapy in patients with active Crohn's disease.

Searching
PubMed, EMBASE, BIOSIS Previews, the Cochrane Library and Science Citation Index were searched from inception to May 2009 for publications in English; search terms were reported.

Study selection
Randomised controlled trials (RCTs) that compared anti-adhesion molecule therapy with placebo in adult patients with active Crohn's disease were eligible for inclusion. Studies were excluded if they were of steroid-refractory or steroid-dependent Crohn's disease, were designed to evaluate gene polymorphisms and serological markers or they used combined treatment. One study was excluded because the outcome was health-related quality of life.

Outcomes extracted were clinical remission rates, response rates and adverse events; the first two of these were primary outcomes in the included studies. Remission was defined in most studies as having a Crohn's Disease Activity Index (CDAI) score of 150 or less. The reviewers defined a response as a decrease in the CDAI score of at least 70 points from baseline. Treatment regimes included natalizumab (a humanised monoclonal antibody, dose 3mg/kg to 6mg/kg or 300mg), ISIS-2302 (an antisense phosphorothioate oligodeoxynucleotide, dose 0.5mg/kg to 2mg/kg, where reported) and MLN002 (a monoclonal antibody, dose 0.5mg to 2mg, where reported); one study evaluated maintenance therapy (of natalizumab). Study duration, where reported, ranged from two to 10 weeks. Mean age of participants in included studies ranged from 26 to 39 years. Mean baseline CDAI score ranged from 258.0 to 303.9. Mean duration of Crohn's disease ranged from 5.7 to 10.1 years.

Two independent reviewers performed study selection.

Assessment of study quality
Methodological quality was assessed by two reviewers independently using the Jadad score. The criteria used included randomisation, blinding, withdrawals and drop-outs. Jadad scores ranged from 0 to 5. A score of 2 or lower was classified as low quality and 3 or higher was classed as high quality.

Data extraction
The numbers of events for each outcome were extracted using a standardised extraction sheet in order to calculate risk ratios (RR) and 95% confidence intervals (CI).

Two independent reviewers extracted data. Disagreements were resolved by discussion; if agreement could not be reached the three other reviewers were consulted and the final decision was based on majority vote. Authors were contacted for missing information.

Methods of synthesis
Risk ratios were pooled using a fixed-effects model when statistical heterogeneity was not present and a random effects
model in the presence of significant heterogeneity (p<0.05). Between-study heterogeneity was determined using the $X^2$ test and $I^2$ statistic. Publication bias was not assessed due to the low number of included studies.

Some sensitivity analyses were performed. Smaller studies (less than 100 participants) were excluded; this was not possible for type of anti-adhesion therapy due to the limited evidence presented.

**Results of the review**

Seven relevant RCTs were identified: 2,228 participants (range 20 to 905) comprised 1,549 treated with anti-adhesion molecule therapy and 679 controls. The Jadad score was 4 for two RCTs and 5 for five RCTs.

Pooled analysis found a significant reduction in remission rates (RR 1.31, 95% CI 1.12 to 1.52, $I^2$=22%, fixed-effects model; seven RCTs) and a modest significant improvement in clinical response rates (RR 1.26, 95% CI 1.05 to 1.50, $I^2$=71%, random-effects model; five RCTs) for anti-adhesion molecule therapy compared to placebo. Subgroup analysis that excluded the two smallest studies did not change the overall conclusion for remission rates.

There was no significant difference in adverse events for anti-adhesion molecule therapy compared to placebo (RR 1.03, 95% CI 0.98 to 1.08, $I^2$=0%, fixed effects model; five RCTs).

The authors considered that there was insufficient evidence to draw conclusions on whether remission could be maintained using anti-adhesion molecule therapy.

**Authors’ conclusions**

Anti-adhesion molecule therapy, which could prevent leucocyte recruitment, was effective in treating active Crohn’s disease. Current anti-adhesion molecule agents were safe and well tolerated. Because of the small number of studies in the meta-analysis, the results should be interpreted with caution.

**CRD commentary**

The review addressed a well-defined question in terms of participants, interventions and study design, but did not clearly define the eligible outcomes. Relevant databases were searched, but for only articles published in English and the search for unpublished studies was not extensive; therefore, some relevant studies may have been missed. Publication bias was not assessed due to the small number of relevant articles identified. Study quality was assessed with suitable criteria. Efforts were made to reduce error and bias throughout the review process. Relevant study details were reported, but there was little data on the placebos used. Statistical heterogeneity was assessed and there was evidence for heterogeneity with some outcomes. The statistical method used for meta-analysis of RCTs was appropriate. Subgroup analyses were not performed for type of anti-adhesion therapy, which was a concern since the different types had different modes of action. The included studies, although few, were of fairly high quality. A sensitivity analysis that omitted the smaller studies was carried out. In view of the low number of studies identified, the authors’ cautious conclusions accurately reflected both the results and limitations of the review, and may be considered reliable.

The authors declared that there were no conflicts of interest.

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

**Practice:** The authors suggested that anti-adhesion molecule therapy should be considered as an addition to therapeutic therapies, especially with patients for whom primary anti-TNF therapy had failed.

**Research:** The authors identified a need for further multicentre studies of longer duration and with larger numbers of patients to assess the efficacy and safety of anti-adhesion molecule therapy. Evidence needed to be updated regularly to allow informed judgements on whether or when anti-adhesion molecule therapy was justified.

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