Mesalamine in the maintenance treatment of Crohn's disease: a meta-analysis adjusted for confounding variables
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Authors' objectives
To assess the effectiveness and tolerability of mesalamine in maintaining remission of quiescent Crohn's disease, and to determine strategies for its optimal use.

Searching
MEDLINE was searched from 1986 to 1997 using the following MeSH terms: 'Crohn's disease', '5-aminosalicylic acid', 'mesalamine' or 'mesalazine'. Studies reported in any language were considered. The reference lists of all available primary studies, review articles and congress abstracts were also checked.

Study selection
Study designs of evaluations included in the review
Published randomised controlled trials (RCTs) comparing mesalamine with a control group receiving either placebo or no treatment. Full papers and abstracts were retrieved. The numbers of treated and untreated patients reported had to be consistent with intention to treat methodology.

Specific interventions included in the review
Mesalamine, also known as mesalazine or 5-aminosalicylic acid, compared with placebo or no treatment. Mesalamine was given in either of two formulations (microsphere and pH-dependent release), at a dose of between 1 and 4 g/day for between 4 and 48 months.

Participants included in the review
People 18 years or older with quiescent Crohn's disease, which was defined as a Crohn's Disease Activity Index (CDAI) of less than 150.

Outcomes assessed in the review
Crude rates of clinical relapse, defined as either a CDAI of greater than 150 or as an increase from 60 to 100 points of the baseline value, were assessed.

How were decisions on the relevance of primary studies made?
Each RCT was reviewed using a list of predefined pertinent issues that concerned characteristics of the patients and treatments. It was implied, but not stated, that three investigators independently reviewed each trial.

Assessment of study quality
The quality criteria of Nicolucci et al. (see Other Publications of Related Interest no.1) were used to assess validity. These assessed randomisation, blinding, compliance, withdrawals, sample size calculations, response evaluation, side-effects and complications, and external validity. Each RCT was evaluated and scored by three independent investigators who had not participated in the trials they evaluated. Any discrepancies among the reviewers were resolved by discussion.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.
Methods of synthesis

How were the studies combined?
Where the response rate was not reported in the trial, it was calculated according to intention to treat.

The overall risk difference between the frequencies of the events (clinical relapse) in treated and untreated patients were calculated using the method of DerSimonian and Laird (see Other Publications of Related Interest no.2). The overall risk difference was tested for significance using a Mantel-Haenszel chi-squared test. The number-needed-to-treat was also used as a measure of treatment effect.

How were differences between studies investigated?
The Qw test of heterogeneity was used to assess whether the variation of treatment effect across trials was greater than that expected by chance. If heterogeneity was detected in the direction or magnitude of effect and if the statistical test was significant, any increase in the pooled risk difference was not accepted as evidence of benefit, even if it reached statistical significance.

Sensitivity analyses were performed using meta-analyses on the core group with the following exclusions: RCTs with surgically-induced remission; RCTs with medically-induced remission; RCTs with both medically- and surgically-induced remission; RCTs with a follow-up of less than 12 months; RCTs published in abstract form; RCTs assessing the mesalamine microsphere formulation; RCTs assessing the mesalamine pH-dependent release formulation; RCTs reporting the highest and the lowest treatment benefit; RCTs with methodological quality scores of 66% or less.

Multivariate models were developed to examine which study characteristics influenced the observed results. A stepwise logistic regression model was developed using symptomatic relapse rate as the dependent variable.

The effect of quality score on the estimate of mesalamine effectiveness was assessed by repeating the analysis using the quality score to weight the studies, as described by Detsky et al. (see Other Publications of Related Interest no.3).

Results of the review

Fifteen RCTs with a total of 2,097 participants (1,049 received mesalamine and 1,048 were controls) were included: there were 13 full papers and 2 abstracts.

Methodological quality: the scores were variable across the studies (range: 45 to 100%).

The pooled estimate of the treatment effect was significant: the overall risk difference was -6.3% (95% confidence interval, CI: -10.4, -2.1, p=0.0028). The number-needed-to-treat was 16. There was no significant heterogeneity among the studies (Qw=12.9, p=0.53).

The overall rate of adverse events was 13.7% in the mesalamine group and 14.9% in the control group (not significant). The most frequent adverse effects were of a gastrointestinal nature.

When separate meta-analyses were performed for surgically-induced remission (4 RCTs) and medically-induced remission (10 RCTs), the pooled risk difference was significant in the postsurgical setting (overall risk difference -13.1%, 95% CI: -21.8, -4.5) but not in the medical setting (overall risk difference -4.7%, 95% CI: -9.6, 2.8).

The multivariate model (12 RCTs, 1,543 participants) predicted that the probability of clinical relapse was significantly lowered by mesalamine treatment, with increasing proportions of patients with ileal disease, surgically-induced remission, or prolonged disease duration. No significant relation was found between the treatment effect and the drug dosage used.

Sensitivity analysis based on methodological quality: 4 RCTs with a quality score of less than 66% were excluded; this had no significant effect on the results.

Authors’ conclusions

Mesalamine may be recommended for maintaining remission of quiescent Crohn's disease. The benefit was mainly
observed in the postsurgical setting, and in patients with ileitis and with prolonged disease duration.

**CRD commentary**
The research question was well-defined. The search was clearly described and was not limited to English language publications, although searching an additional database and searching for unpublished data may have yielded more relevant studies. Handsearching of relevant journals may also have been useful in such a specialist area. Some details of the individual studies were reported, and a quality assessment was performed and used to examine the effect of the quality of study design on the effect size (no significant difference). The studies were appropriately pooled in a meta-analysis and additional sensitivity analyses were conducted. The authors' conclusions seem appropriate.

**Implications of the review for practice and research**
The authors suggest that additional large-scale RCTs investigating the efficacy and tolerability of a long-term mesalamine regimen could be useful in a postsurgical setting. They also suggest that further large-scale multicentre RCTs in high-risk patients with medically-induced remission, which investigate the efficacy and safety of long-term high-dose (4 g/day) mesalamine regimens, may prove useful if improved criteria to predict relapse become available.

**Bibliographic details**

**PubMedID**
9352848

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Anti-Inflammatory Agents, Non-Steroidal /therapeutic use; Crohn Disease /drug therapy; Double-Blind Method; Humans; Mesalamine /adverse effects /therapeutic use; Randomized Controlled Trials as Topic; Retrospective Studies

**AccessionNumber**
11997001344

**Date bibliographic record published**
31/08/1999

**Date abstract record published**
31/08/1999

**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.