5-aminosalicylates prevent relapse of Crohn's disease after surgically induced remission: systematic review and meta-analysis

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CRD summary
The review concluded that mesalamine was of modest benefit compared with no therapy or placebo in preventing relapse in Crohn's disease patients in remission after surgery. The review was generally well conducted and the authors’ conclusions reflect the evidence and seem reasonable.

Authors' objectives
To determine the efficacy and safety of 5-aminosalicylates (5-ASA) in preventing relapse of Crohn's disease once remission has been surgically induced.

Searching
MEDLINE (1966 to April 2010), EMBASE (1984 to April 2010), Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 2, 2009) and the Cochrane Inflammatory Bowel Disease Group Specialist Trials Register were searched for articles in any language. Search terms were reported. Abstract books of conference proceedings between 2002 and 2010 were handsearched. Reference lists of relevant studies were searched and experts in the field were contacted.

Study selection
Randomised controlled trials (RCTs) of 5-ASA (any dose) versus placebo or no treatment in adult patients (>90% of patients aged over 16 years) with luminal Crohn's disease who were in remission after an intestinal resection were eligible for inclusion. Treatment had to last at least six months. Trials had to report assessment of relapse of disease activity at the last point of assessment in the trial, preferably using the Crohn's Disease activity index (other measures were permissible). The first period of any relevant crossover trial was included.

The included trials studied sulphasalazine (3mg daily) and mesalamine (2.4mg to 4mg daily) in various European and North American centres. Most studies used placebo as comparator. Disease distribution, where reported, included ileal, ileocolonic and colon. Relapse was defined by clinical, radiographic and/or endoscopic evidence. The duration of therapy ranged from 33 weeks to three years. Only two studies recruited patients undergoing their first resection.

Two reviewers independently performed study selection. Disagreements were resolved by consultation with a third reviewer.

Assessment of study quality
Trial quality was assessed using the Cochrane Handbook risk of bias tool to appraise randomisation, blinding, allocation concealment, intention-to-treat, selective outcome reporting and withdrawals/drop-outs.

Two reviewers independently performed quality assessment. Disagreements were resolved by discussion with a third reviewer.

Data extraction
Data were extracted on relapse and adverse events on an intention-to-treat basis and used to calculate relative risks (RRs) and 95% confidence intervals (CIs).

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Methods of synthesis
A random effects meta-analysis was used to calculate pooled relative risks and 95% CIs. Statistical heterogeneity was assessed using the $I^2$ statistic. The number needed to treat (NNT) was calculated. Sensitivity analysis was conducted.
according to dosage and duration of therapy, compliance with therapy, duration of disease, risk of bias, region of study and new onset disease. Publication bias was assessed using funnel plots and Egger's test.

**Results of the review**
Eleven RCTs were included in the review (1,282 patients). Trial sample sizes ranged from 20 to 324 patients. Four trials were deemed to be at low risk of bias. Most trials did not clearly define the method of randomisation, allocation concealment and blinding.

Compared with control, mesalamine had a statistically significantly lower risk of relapse (RR 0.80, 95% CI 0.70 to 0.92, NNT=10, I²=0%; six RCTs) and there was no difference with sulphasalazine (RR 0.97, 95% CI 0.72 to 1.31, I²=28%; five RCTs). When mesalamine and sulphasalazine trials were pooled there was a borderline statistically significant decrease in the risk of relapse compared with control (RR 0.86, 95% CI 0.74 to 0.99, NNT=13, I²=35%; 11 RCTs). There was no statistically significant difference in the risk of adverse events with mesalamine compared with control (RR 0.98, 95% CI 0.69 to 1.40; three RCTs).

Sensitivity analyses did not significantly alter results. There was no evidence of publication bias.

**Authors' conclusions**
Mesalamine was of modest benefit compared with no therapy or placebo in preventing relapse in Crohn's disease patients in remission after surgery.

**CRD commentary**
Inclusion criteria for the review were clearly defined. Several relevant data sources were searched without language restrictions. Publication bias was assessed and not detected. Attempts were made to reduce reviewer error and bias throughout the review. Quality assessment indicated the variable quality of the included trials (which the authors acknowledged), although a better discussion of the individual quality items would have aided interpretation. Trials were combined using a random-effects meta-analysis and statistical heterogeneity was assessed and explored in sensitivity analysis, which was appropriate.

The review was generally well conducted and the authors' conclusions reflect the evidence and seem reasonable.

**Implications of the review for practice and research**
**Practice:** The authors stated that in individuals with quiescent disease after a first surgical resection, who would probably not be considered for or were contraindicated long-term immunosuppressive therapy, mesalamine may be a safe and effective option compared with no treatment.

**Research:** The authors stated that further research on mesalamine in postoperative Crohn's disease should try to identify subgroups of patients who derive the most benefits.

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