A meta-analysis of the efficacy of sulfasalazine in comparison with 5-aminosalicylates in the induction of improvement and maintenance of remission in patients with ulcerative colitis

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CRD summary
This review concluded that there was no difference in the efficacy and tolerability of sulfasalazine compared to mesalamine or olsalazine for treatment of ulcerative colitis. Withdrawal due to adverse events was lower with balsalazide than sulfasalazine confident, but conclusions could not be made that balsalazide was better. The authors’ conclusions were appropriate, but potentially important clinical differences were not considered.

Authors' objectives
To compare the efficacy and tolerability of sulfasalazine and 5-aminosalicylates in the management of ulcerative colitis.

Searching
Pubmed, EMBASE, Cochrane Central Register of Controlled Trials, Scopus and Web of Science were searched up to April 2008 without language restrictions; search terms were provided. Reference lists of retrieved articles were scanned.

Study selection
Controlled trials (parallel design only) that compared the efficacy and/or tolerability of sulfasalazine and sulfasalazine and 5-aminosalicylates in adults with ulcerative colitis were included. Only oral formulations were eligible. The outcomes of interest were overall improvement, relapse rate (definitions provided), total adverse events and withdrawals due to adverse events. The 5-aminosalicylates assessed in the included studies were mesalamine, olsalazine and balsalazide; the dose varied within and across these drugs. The daily dose of sulfasalazine ranged from 1.5g to 3g. Duration of treatment ranged from four to 48 weeks. The mean age of participants ranged from 32.5 to 49 years. The authors reported that definitions of remission and improvement varied across the studies, as did the clinical or endoscopic index used to diagnose ulcerative colitis. Three reviewers independently assessed studies for inclusion.

Assessment of study quality
Description of randomisation, blinding and dropouts were assessed using the Jadad scale. The possible score range was from 0 to 5. Studies with a score of 3 or more were classified as high quality. Study quality appeared to be assessed independently by three reviewers (this was not stated explicitly).

Data extraction
The number of patients classified as overall improved and relapsed were extracted, as were the number of adverse events and withdrawals due to adverse events; the relative risk (RR) and 95% confidence interval (CI) were calculated. Three reviewers independently extracted data; there were no disagreements.

Methods of synthesis
Meta-analysis (stratified by drug) was used to obtain a pooled relative risk and 95% CI; fixed-effect analysis where studies were homogenous and random-effects analysis where there was statistical heterogeneity. Heterogeneity was assessed using Cochran’s Q test and L’Abbe plots. Funnel plots (not displayed) and Kendall's test were used to assess presence of publication bias.

Results of the review
Twenty controlled trials (n at least 2,177) were included: 19 were classified as good quality (Jadad score of 3 or more).

Sulfasalazine versus mesalamine: Based on the pooled relative risk, there was no statistically significant difference between the two drugs in overall improvement (four trials), relapse (six trials) total adverse events (five trials) or withdrawals due to adverse events (eight trials).

Sulfasalazine versus olsalazine: There was no statistically significant difference between the two drugs in overall
improvement (three trials), relapse (five trials) total adverse events (five trials) or withdrawals due to adverse events (five trials).

**Sulfasalazine versus balsalazide**: There was no statistically significant difference between sulfasalazine and balsalazide in overall improvement (two trials), but there was a statistically significant reduction in withdrawals due to adverse events with balsalazide compared to sulfasalazine (RR 0.17, 95% CI: 0.06 to 0.49, p=0.0012; three trials).

There was no statistically significant heterogeneity in any of the analyses and no evidence of publication bias.

**Authors' conclusions**
Sulfasalazine did not differ from mesalamine or olsalazine in terms of efficacy and tolerability in the treatment of ulcerative colitis. Although withdrawal due to adverse events was lower with balsalazide than sulfasalazine, further trials that compared these two drugs were required before convincing conclusions could be made.

**CRD commentary**
The authors had clearly stated inclusion criteria and a number of relevant databases were searched for relevant studies. There were no language restrictions, but no specific attempts were made to locate unpublished studies. Analysis suggested there was no publication bias, but this may have been limited by the small number of studies in the analysis. Appropriate review methods were used to assess error and bias. Quality was assessed. The analysis seemed appropriate. There was no evidence of statistical heterogeneity, but there appeared to be clinical differences between the studies (such as drug dose and duration of treatment) that were not explored. The authors' conclusions were appropriate, but potentially important clinical differences were not explored.

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

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

**Research**: The authors stated that further trials that compared the effectiveness and safety of sulfasalazine and balsalazide were required.

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