The efficacy of oral 5-ASAs in the treatment of active ulcerative colitis: a systematic review

Kane S V, Bjorkman D J

CRD summary
This review assessed the efficacy of oral 5-aminosalicylic acid (5-ASA) agents for the treatment of mild to moderate active ulcerative colitis. The authors concluded that mesalamine is superior to placebo and that 5-ASA products appear as effective as sulfasalazine, but there is no difference in efficacy between any of the 5-ASA preparations. The authors' conclusions are likely to be robust.

Authors' objectives
To assess the efficacy of oral 5-aminosalicylic acid (5-ASA) agents for the treatment of mild to moderate active ulcerative colitis (UC).

Searching
MEDLINE and EMBASE were searched from 1980 to 2002 without any language restrictions; the search terms were reported. In addition, the bibliographies of studies that focused primarily on induction of remission were checked, and proceedings from the annual meetings (1991 to 2002) of the American Gastroenterological Association and the American College of Gastroenterology were searched. Investigators in the field were also contacted, as were the manufacturers of all oral 5-ASA compounds available in the USA.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with a parallel-group design were eligible for inclusion.

Specific interventions included in the review
Studies that compared an oral 5-ASA (mesalamine, balsalazide or olsalazine) with placebo, sulfasalazine, or other 5-ASA agents were eligible for inclusion. The interventions assessed were 5-ASA versus placebo, 5-ASA versus sulfasalazine, and different 5-ASA preparations compared with each other. Studies of rectal preparations or combination therapies were excluded. The duration of treatment ranged from 4 to 12 weeks across the trials.

Participants included in the review
Studies of adults with mild to moderate active UC were eligible for inclusion. Studies of participants with Crohn's disease were excluded.

Outcomes assessed in the review
Studies that reported an outcome for clinical improvement or remission were eligible for inclusion.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed studies for inclusion. Any disagreements were resolved by discussion and consensus.

Assessment of study quality
The quality of the primary studies was assessed according to criteria defined by Guyatt et al., which assessed methods of allocation concealment, blinding, length of follow-up, the reporting of withdrawals, and analyses by intention-to-treat (see Other Publications of Related Interest). Two reviewers independently assessed the quality of the included studies. Any disagreements were resolved by discussion.

Data extraction
Two independent reviewers abstracted the data. Any disagreements were resolved by discussion and consensus. Data were abstracted on the number of patients who evidenced clinical improvement or remission within each of the studies.

**Methods of synthesis**

**How were the studies combined?**

The studies were grouped according to the intervention and combined in a narrative.

**How were differences between studies investigated?**

Differences between the studies were discussed in relation to the intervention (dose and length of treatment) and the outcome measures assessed.

**Results of the review**

Nineteen RCTs (n=2,208) were included.

All 19 trials were blinded, 10 had adequate allocation concealment, 13 had undertaken an intention-to-treat analysis and 16 had adequate follow-up. The percentage of withdrawals ranged from 3 to 50% across the trials.

Delayed-release mesalamine versus placebo (2 RCTs, n=245): both RCTs showed that higher doses of mesalamine significantly improved response compared with placebo. The first RCT found that 4.8 g/day mesalamine significantly increased complete or partial response compared with placebo (74% versus 18%, P<0.001; number-needed-to-treat 2) but found less difference between lower dose mesalamine and placebo (27% versus 18%, P not reported). The second trial found that 2.4 and 1.6 g/day mesalamine significantly increased complete or partial response compared with placebo (49% and 43% for higher and lower dose, respectively, versus 23% with placebo, P=0.003 and P=0.031 for drug versus placebo in per protocol analysis). Controlled-release mesalamine versus placebo (1 RCT, n=374): medium and higher (2 and 4 g/day) doses of controlled mesalamine were significantly more beneficial than placebo in terms of remission, complete relief, or a marked improvement in symptoms. There were no significant differences between low-dose (1 g/day) mesalamine and placebo.

Olsalazine versus placebo (4 RCTs, n=216): the results of the trials comparing olsalazine versus placebo were mixed. Two of the RCTs showed no significant differences between treatment with olsalazine and placebo; the other two showed borderline significant differences relative to placebo, but the differences were based on a small number of participants and, therefore, were difficult to interpret.

Balsalazide versus placebo (1 RCT, n=180): there were no significant difference in response rate between treatment with balsalazide (4.5 or 6.75 g/day) and placebo.

Sulfasalazine versus delayed-release mesalazine, controlled-release mesalamine, balsalazide, olsalazine or mesalazine (7 RCTs, n=600): there were no significant differences between treatment with sulfasalazine and any of the comparators in terms of any of the outcomes assessed.

Olsalazine versus mesalazine (1 RCT, n=168): there was significant difference between treatments in remission rates.

Asacol (mesalamine) versus balsalazide (3 RCTs, n=428): two of the studies showed no significant differences between asacol and balsalazide on any of the outcomes assessed; the third study found that balsalazide significantly increased remission rates compared with asacol (62% versus 37%, P<0.05).

**Authors' conclusions**

The studies suggested that mesalamine was superior to placebo for treating active UC. In addition, 5-ASA products appeared as effective as sulfasalazine, but the available data did not suggest a difference in efficacy between any of the 5-ASA preparations.

**CRD commentary**
The review question was reasonably defined in terms of the interventions, participants, study designs and outcome measures. The search was adequate, and efforts were made to locate unpublished studies and to minimise language bias. The methods of the review were reported clearly, and two reviewers were involved in the study selection, quality assessment and data extraction processes; this should have minimised reviewer bias and errors in the review process. The validity assessment tool used to assess the quality of the studies was appropriate.

The authors provided sufficient details of the primary studies (in both the tables and text) to allow the reader to assess whether the conclusions presented are consistent with the evidence reviewed. The use of a narrative synthesis was appropriate given the differences between the studies. Some differences between the studies were explored in the text, and the authors appropriately discussed some of the limitations of the evidence base reviewed. Overall, the authors' conclusions were consistent with the results of the primary studies and are likely to be robust.

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

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**Bibliographic details**

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**Other publications of related interest**
Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? JAMA 1994;271:59-63.

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