Role of 5-aminosalicylic acid (5-ASA) in treatment of inflammatory bowel disease: a systematic review

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Authors' objectives
To perform a systematic review of the efficacy of 5-aminosalicylic acid (5-ASA) compounds (oral and topical) in the treatment of inflammatory bowel disease (IBD), both ulcerative colitis (UC) and Crohn's disease (CD), in the acute phase for inducing remission and for the prevention of relapses or recurrences. Also, to evaluate the influence of several factors (such as dosage schedule, disease localisation and type of formulation) on the efficacy of 5-ASA therapy in IBD.

Searching
PubMed and the Cochrane Controlled Trials Register were searched to August 2000. The search terms (all fields) used were 'ulcerative colitis' or 'Crohn's disease', and any of the following terms: 'mesalamine', 'mesalazine', '5-ASA', '5-aminosalicylic acid'. The references from reviews and meta-analyses on the treatment of IBD with 5-ASA, and from the articles selected for the study, were also examined. Articles published in any language were considered.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies which included at least one branch of treatment consisting of a 5-ASA formulation (oral or topical) were eligible for inclusion. The other branch could include placebo or another active regimen for the treatment of IBD. Various doses of oral formulations of 5-ASA (mesalamine, olsalazine and balsalazide) were assessed in the included studies for both the acute-phase and maintenance treatment. For UC, the duration of oral treatment ranged from 4 to 8 weeks in the acute phase, and from 4 to 18 months for maintenance of remission; the durations were 6 to 16 weeks and 4 to 24 months, respectively, for CD.

The topical formulations assessed for UC included suppositories, foam enemas, and liquid enemas. The duration of treatment ranged from 2 to 8 weeks in the acute phase, and from 6 to 24 months in maintenance of remission.

The control group included placebo, sulfasalazine, Plantago ovata, Escherichia coli preparation, different formulations, bismuth, steroids, ciprofloxacin and no treatment.

Participants included in the review
Studies that included patients with IBD, including both UC and CD, were eligible for inclusion.

Outcomes assessed in the review
Studies that evaluated acute-phase treatment (outcomes unspecified), or the prevention of relapses or recurrences, were eligible for inclusion.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The quality of the clinical trials was assessed on the basis of randomisation and double-blinding. The authors do not state how many of the reviewers performed the quality assessment.
Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

The data were extracted under the following headings: the number of patients; the formulation of 5-ASA; dose; control group; the duration of treatment; randomised; double-blind; results or relapse rate.

Methods of synthesis
How were the studies combined?
A narrative synthesis was undertaken.

How were differences between studies investigated?
The studies were grouped according to whether they assessed 5-ASA in the acute-phase or in maintenance of remission, and whether the patients had UC or CD.

Results of the review
UC: 13 RCTs (n=1,344) assessed the efficacy of oral 5-ASA in acute-phase treatment; 20 RCTs (n=2,927) assessed the efficacy of oral 5-ASA in maintenance of remission; 20 RCTs (n=1,714) assessed the efficacy of rectal 5-ASA in acute-phase treatment; 4 RCTs (n=151) assessed the efficacy of rectal 5-ASA in maintenance of remission.

CD: 7 RCTs (n=765) assessed the efficacy of oral 5-ASA in acute-phase treatment; 9 RCTs (n=1,477) assessed the efficacy of oral 5-ASA in maintenance of medically-achieved remission; and 6 RCTs (n=870) assessed the efficacy of oral 5-ASA in maintenance of post-operative remission.

The results of meta-analyses of 5-ASA in IBD were also included.

Ulcerative colitis.
Acute-phase oral treatment: compared with placebo, statistically significantly better results with 5-ASA were reported in 3 RCTs; these differences were not significant in 4 other studies. Newer 5-ASA formulations seemed to have similar efficacy to the older sulfasalazine for the treatment of acute UC. High doses of 5-ASA seemed to achieve better results in the acute treatment of UC, although the exact dosage schedule with each 5-ASA formulation remains unknown. The location of the disease did not seem to affect the response to therapy in some studies. The efficacy of 5-ASA in UC with regards to the drug formulation remains unclear. A meta-analysis reported that 5-ASA was superior to placebo with regard to all measured outcome variables.

Prevention of relapses of UC with oral treatment: 4 of the 6 studies demonstrated 5-ASA to be statistically significantly better than placebo. 5-ASA and sulfasalazine seemed to have similar efficacy in the long-term (at least 12 months) maintenance of remission of UC. Although there were some data suggesting the benefits of using high doses of 5-ASA for preventing relapses of UC, the issue was unclear. There are insufficient data at present to conclude whether one 5-ASA formulation was better than another to maintain remission of UC. The location of the disease did not seem to affect the response to therapy in one study.

Acute-phase topical treatment of UC: all 4 studies comparing 5-ASA suppositories with placebo demonstrated better results with 5-ASA preparations. Four more studies comparing 5-ASA liquid enema and placebo obtained similarly favourable results. Topical 5-ASA were at least as effective, and probably more effective, than topical steroids for the treatment of distal UC. Topical 5-ASA and oral sulfasalazine appeared to be equally effective in the treatment of active distal UC, although patients treated with 5-ASA reported earlier improvement. A 1 g 5-ASA enema seemed to be sufficient for patients with mild to moderately active distal UC.

Prevention of relapses of UC with topical treatment: topical 5-ASA formulations were effective not only for the treatment of acute UC but also for maintenance of remission.

Crohn's Disease.
Acute phase oral treatment: 2 out of 3 studies showed significantly better results with 5-ASA than placebo. One out of 3 studies reported that steroids were superior to 5-ASA in the treatment of CD; the other 2 studies reported non significant differences. When prescribing 5-ASA formulations for the acute-phase treatment of CD, high doses of these drugs should be used. Some studies suggested that, for the treatment of acute CD, different 5-ASA formulations may be chosen depending on the location of the disease.

Prevention of relapses or recurrences of CD with oral treatment: there were insufficient data for the comparison of 5-ASA with placebo in maintenance of medically-achieved remission. The risk of clinical recurrence of CD may be significantly reduced by 5-ASA maintenance treatment in patients with surgically induced remission. However, the magnitude of the overall effect was small. The use of higher dosages of 5-ASA in maintenance treatment seemed reasonable.

**Authors' conclusions**

**Ulcerative colitis:**

newer 5-ASA formulations seem to have similar efficacy to the older sulfasalazine for the treatment of acute UC;

high doses of 5-ASA seem to achieve better results in the acute treatment of UC, although the exact dosage schedule with each 5-ASA formulation remains unknown;

the disease location of UC does not seem to affect the response to therapy;

the efficacy of different 5-ASA formulations in UC is unclear;

5-ASA and sulfasalazine seem to have similar efficacy in the long-term (at least 12 months) maintenance of remission of UC, and therefore, the choice between the two drugs would depend on factors such as cost or safety, rather than effectiveness;

the benefits of using high-doses of 5-ASA are still unclear;

there are currently insufficient data to conclude whether one 5-ASA formulation is better than another to maintain remission of UC;

topical 5-ASA (as suppositories, foam or liquid enema) are at least as effective, and probably more effective, than topical steroids for the treatment of distal UC;

a 1 g 5-ASA enema seems to be sufficient for patients with mild to moderately active distal UC; and

topical 5-ASA formulations are effective for both the treatment of acute UC and for the maintenance of remission.

**Crohn's disease:**

when prescribing 5-ASA formulations for the acute-phase treatment of CD, high doses of these drugs should be used;

some studies suggest that, for the treatment of acute CD, different 5-ASA formulations may be chosen depending on the location of the disease;

the risk of clinical recurrence may be significantly reduced by 5-ASA maintenance treatment in patients with surgically induced remission;

the length of previous remission of CD does not seem to be useful in clinical practice for predicting the response to 5-ASA for the maintenance of remission in a particular patient; and

adverse events after prolonged-release mesalamine do not appear to be dose-related, the use of higher dosages seems to be reasonable in maintenance treatment.
CRD commentary

The methodology of this systematic review was poor. The authors reported a clear enough review question, but given the broad subject area under review, the inclusion criteria were inadequate and poorly described. The search was not particularly thorough; only two databases were searched and the search terms used were limited. It is possible that some important publications were missed. The authors did not report the process of, or the number of reviewers who carried out the study selection and data extraction. Although only RCTs were included in the review, the quality of the included studies was poorly addressed. Factors relating to internal and external validity were not addressed by the authors' chosen method of appraisal. Some details of the primary studies were tabulated, but participant details (such as age and gender) were missing. In addition, the authors did not include details of the meta-analyses they included. The method of pooling was inadequate; the authors did not attempt statistical pooling although this would have been appropriate. The conclusions of the review were not presented in a clear manner and caution should be exercised when interpreting the results of the review.

Implications of the review for practice and research

Practice: The authors report a series of implications for practice within the text of the review.

Research: The authors state implications for both UC and CD.

The authors state that future studies should assess the following in UC: the role of differences in the cost and tolerance between sulfasalazine and 5-ASA for oral acute-phase treatment and maintenance of remission; the effect of disease location on the response to therapy; the efficacy of 5-ASA depending on the drug formulation for the oral acute-phase treatment and for the prevention of relapse; and the efficacy of different dosage schedules in comparison to one another for the oral prevention of relapse.

The authors state that more research is needed to clarify which different 5-ASA formulations may be chosen, depending on location, for the treatment of acute CD. Further research should also be undertaken to assess whether 5-ASA is effective for the maintenance of 'medically achieved' and 'postoperative' remission in CD. Studies specifically designed to compare several dosage schedules in the same group of patients are needed.

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