High mucosal healing rates in 5-ASA-treated ulcerative colitis patients: results of a meta-analysis of clinical trials

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CRD summary
The review concluded that 5-aminosalicylate preparations achieved mucosal healing in nearly 50% of patients with ulcerative colitis with no significant differences between the various preparations. The synthesis focused on relatively few poorly reported studies of unknown size and unclear reliability. The results should be considered with caution.

Authors' objectives
To systematically compare the effects of different preparations of 5-aminosalicylates on mucosal healing rates in ulcerative colitis.

Searching
PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) were searched. Searched dates were not reported. Search terms were listed. Only full-text publications in English were considered for inclusion.

Study selection
Randomised controlled trials that reported on mucosal healing after 5-aminosalicylate (5-ASA) monotherapy preparations used to treat patients with mild to moderate ulcerative colitis were included. Mucosal healing was defined in 19 different ways across the studies. Included patients were of an average 40 to 42 years and more than half were male. Mean duration of the ulcerative colitis prior to treatment was around 63 months. 5-ASA was given in a variety of formulations including tablets or granules (oral treatment) and suppositories, foam or enema (rectal treatment). Treatment lasted between two and 12 weeks.

Two reviewers independently selected studies for inclusion. Disagreements were resolved by discussion and involvement of a third reviewer.

Assessment of study quality
The reviewers did not appear to formally assess study quality but the presence or absence of blinding was noted in the study details table (appendix).

Data extraction
Study details, definitions of mucosal healing, drug dosage and numbers achieving mucosal healing as defined in the original articles were extracted by an unknown number of reviewers. Reviewers noted whether an endoscopic measurement of mucosal healing was made.

Methods of synthesis
A random-effects model was used to calculate risk ratios and associated 95% confidence intervals for mucosal healing rates comparing different formulations and dosages. Oral and rectal treatments were considered in separate subgroups. Statistical heterogeneity was assessed using $I^2$ and $X^2$.

Results of the review
Forty-nine studies (90 treatment arms) were included in the review. Out of 6,490 patients, 3,977 received oral preparations and 2,513 received rectal formulations. The reported study details did not make it clear how many trials were placebo-controlled or used blinded outcome assessors.

Based on the definitions in the primary studies, 43.7% of patients with ulcerative colitis who were treated with 5-ASA achieved mucosal healing. Within the subgroups, 36.9% receiving oral treatment and 50.3% receiving rectal treatment achieved mucosal healing.

There was a significantly higher rate of mucosal healing success in patients treated with oral 5-ASA preparations at a
dosage of at least 3g compared with less than 3g (RR 1.19, 95% CI 1.07 to 1.32; Ι²=0%; nine trials). No such differences were noted in the two available rectal studies.

It was not possible to directly compare treatment duration in terms of efficacy in achieving mucosal healing with the available data. There appeared to be little difference between short (<6 weeks) versus long (>6 weeks) treatment periods in the rectal group and a slight tendency for high rates of mucosal healing in longer term oral treatment groups.

Direct comparisons of granulate versus tablet oral treatment found no significant differences (2 trials). There were no significant differences in mucosal healing rates when comparing 5-ASA foam versus enema rectal preparations (5 trials).

Authors' conclusions
5-ASA preparations achieved mucosal healing in nearly 50% of patients with ulcerative colitis. There were no significant differences between the various 5-ASA agents in either oral or rectal treatment groups.

CRD commentary
This review addressed a clear question with appropriate inclusion criteria. The limited database search and restriction to full text papers in English may have introduced language and/or publication bias by missing potentially eligible studies. Reporting of the review processes was unclear and while study selection was performed by more than one reviewer it was not clear that this was also the case during data extraction stages.

The included studies were not formally assessed for methodological quality and the manner of study detail reporting made it difficult to judge their reliability or similarity. It was not clear how the overall figures for mucosal healing were calculated (simple addition can produce a misleading result). The limited statistical analyses seemed appropriate but in places it was difficult to establish which trials were being compared.

The authors drew firm conclusions based on a poorly reported selection of studies of uncertain methodological quality. The meta-analyses contained relatively few studies and these were of unknown size and unclear reliability. The results should be considered with caution.

Implications of the review for practice and research
Practice: The authors stated that 5-ASA should be considered the first-line therapy for patients with mild to moderate ulcerative colitis irrespective of disease extension and 5-ASA formulation.

Research: The authors did not make any recommendations for research.

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