Efficacy of topical 5-aminosalicylates in preventing relapse of quiescent ulcerative colitis: a meta-analysis
Ford AC, Khan KJ, Sandborn WJ, Hanauer SB, Moayyedi P

CRD summary
This review concluded that topical mesalazine appeared to be safe and was effective in preventing relapse of quiescent ulcerative colitis. As no trials had a low risk of bias, the authors’ conclusions could be considered to be over optimistic and their reliability is uncertain.

Authors’ objectives
To assess the efficacy of topical 5-aminosalicylates, compared with placebo, in preventing relapse of quiescent ulcerative colitis.

Searching
MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Inflammatory Bowel Disease Group Trials Register were searched, without language restrictions, to July 2011; search terms were reported. Unspecified conference proceedings from 2002 to 2011 were searched. Reference lists of identified articles were examined to identify further studies.

Study selection
Randomised controlled trials (RCTs) comparing the effects of any dose of topical 5-aminosalicylates with placebo in adults (90% of participants older than 16 years) with quiescent ulcerative colitis, were eligible. Treatment had to be for at least six months, and relapse of disease activity had to be reported as an outcome (at the study’s last time point). Adverse events were assessed. The first periods of placebo crossover trials were eligible.

Where reported, the mean duration of disease ranged from five to seven years. Just under half of the trials recruited patients with disease confined to the rectum; one trial included patients with extensive disease. The levels of prior relapse and remission varied across trials, but most were of patients in sustained remission. All trials used mesalazine (5-aminosalicylic acid). Doses varied across trials; most administered it once daily. Treatment lasted from six to 24 months; most trials gave treatment for one year. All but one of the trials were conducted in the USA or Italy.

Abstracts were selected by one reviewer. Articles were assessed by two reviewers independently and disagreements were resolved by discussion with a third reviewer.

Assessment of study quality
The risk of bias was assessed by evaluating levels of risk for the following: method of randomisation, allocation concealment, level of blinding, losses to follow-up, use of intention-to-treat analysis, and selective reporting of outcomes.

Two reviewers independently assessed the risk of bias, with disagreements resolved by discussion with a third reviewer.

Data extraction
Intention-to-treat data from the last assessments of trials were extracted to calculate relative risks and 95% confidence intervals. Data were extracted for a predefined hierarchical list of methods used to assess relapse (details provided in the paper). Authors were contacted for missing data, where necessary.

Two reviewers independently extracted the data.

Methods of synthesis
Meta-analyses were performed to calculate pooled risk ratios with 95% confidence intervals, using a random-effects model. The number needed to treat (NNT) was calculated. Heterogeneity was assessed using $I^2$ and $X^2$. A number of sensitivity analyses were planned if the data were available. Publication bias was assessed using a funnel plot and the
Egger test where there were 10 or more trials in the meta-analysis.

Results of the review
Seven trials were eligible, including 555 patients (range 25 to 157). No trials were judged to be at a low risk of bias. Allocation concealment and randomisation methods were unclear in six trials and were stated in one trial. All trials were described as being double-blind.

There were significantly fewer relapses of disease activity with topical mesalazine, compared with placebo (RR 0.60, 95% CI 0.49 to 0.73; I² = 21%; seven RCTs; NNT=3, 95% CI 2 to 5). Two trials reported the mean time to relapse; both suggested longer times for mesalazine (one had statistically significant results and the other did not).

There were no significant differences between topical mesalazine and placebo in the rates of at least one adverse event (six RCTs) or in anal canal pain during enema or suppository insertion (four RCTs).

Authors' conclusions
Topical mesalazine was effective in preventing relapse of quiescent ulcerative colitis, with no greater number of adverse events than placebo. Most trials included only patients with left-sided disease or proctitis, and its efficacy in patients with more extensive disease was unknown.

CRD commentary
This review addressed a clear question and was supported by reproducible eligibility criteria. Attempts to identify all relevant trials in any language were undertaken by searching electronic databases and checking references. Attempts were made to identify unpublished trials. Suitable methods were employed to reduce the risks of reviewer error and bias for the processes of data extraction and quality assessment, but only one reviewer screened abstracts for inclusion. The risk of bias was evaluated, but the full results were not provided; none of the trials were judged to be at a low risk of bias. Sufficient trial details were provided and appropriate methods were used to pool the data and to assess and investigate heterogeneity.

As no trials had a low risk of bias, the authors’ conclusions could be considered to be over optimistic and their reliability is uncertain.

Implications of the review for practice and research
Practice: The authors stated that their results supported the recommendation for first-line topical 5-aminosalicylate use for relapse prevention in patients with left-sided disease. The efficacy of topical mesalazine in patients with more extensive quiescent ulcerative colitis was not known.

Research: The authors expressed a need for studies of patient preference for drug administration, and on whether the dose, delivery system, or timing (intermittent versus continuous) of treatments influenced their efficacy or tolerability.

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