Azathioprine and 6-mercaptopurine for the prevention of postoperative recurrence in Crohn's disease: a meta-analysis

CRD summary
This review concluded that purine analogues were more effective than placebo in preventing clinical and endoscopic postoperative recurrence in Crohn's disease patients, but were associated with a higher rate of adverse events leading to drug withdrawal. Despite some shortcomings, this was generally a well-conducted review and the authors' conclusions appear reliable.

Authors' objectives
To evaluate the efficacy and safety of purine analogues in the prevention of postoperative recurrence in Crohn's disease.

Searching
MEDLINE, the Cochrane Library and EMBASE were searched for full papers without language restrictions to September 2008; search terms were reported. Additional references were sought through handsearching abstracts from annual meetings of Digestive Disease Week and United European Gastroenterology Week between 2005 and 2007. References of review articles, meta-analyses and published randomised controlled trials were searched.

Study selection
Controlled trials that compared purine analogues (azathioprine, 6-mercaptopurine) with a treatment without proven clinical or endoscopic efficacy (placebo or mesalamine) in adult patients with Crohn's disease were eligible for inclusion. Studies were also required to report data on clinical and/or endoscopic recurrence and methodology for defining clinical and/or endoscopic recurrence to be eligible for inclusion. Outcomes included adverse events that led to drug withdrawal and clinical and endoscopic recurrence at one and two years; severity was defined according to Rutgeerts' score (i2-4 for severe and i3-4 for very severe endoscopic recurrence). Trials that compared placebo or mesalamine with active arms that did not include a purine analogue were excluded. Drug regimens varied in the included studies. Purine analogues included: azathioprine 2mg/kg/day to 2.5mg/kg/day or 6-MP 50mg/day. Control arms included metronidazole 250mg tid or ornidazole bid, 5-aminosalicylates 4g/day and mesalamine 3g/day.

The authors did not state how the studies were selected for the review.

Assessment of study quality
Two reviewers independently assessed the quality of the included trials using the Jadad scale; studies with a score of 3 or more were classified as high quality. Disagreements were resolved through discussion.

Data extraction
Two reviewers independently extracted data to derive relative risks (RR) for the outcomes of interest; disagreements were resolved through discussion or through consultation with two other reviewers. Authors or pharmaceutical companies were contacted for missing or unpublished data or to obtain exact data.

Methods of synthesis
Pooled relative risks and their 95% confidence intervals (CI) were calculated using a DerSimonian and Laird random-effects model. The Peto method was also used to combine data, but the results were not presented. The number-needed-to-treat (NNT) was calculated. Cochran's Q test was used to assess statistical heterogeneity between the trials. Analyses were based on intention-to-treat. Sensitivity analysis was used to explore the impact of excluding studies that used mesalamine as the control group, which restricted the analysis to placebo-controlled studies. Publication bias was assessed using funnel plots and Egger test. Bias was assessed according to Cochran's method.
Results of the review
Four controlled trials met the inclusion criteria (n=433) and compared azathioprine (n=151) or 6-mercaptopurine (n=47) with control arms (placebo with or without antibiotic induction therapy or mesalamine, n=235). Study quality was scored at least 3 in all studies. Factors that affected bias, adequate sequence generation, blinding and incomplete outcome data were addressed in three studies and allocation concealment in two. Study duration ranged from 12 to 24 months.

Compared with controls, purine analogues were significantly more effective in preventing clinical recurrence at one year (RR 8%, 95% CI 1 to 15; four studies; NNT=13) and two years (RR 13%, 95% CI 2 to 24; two studies; NNT=8) and for preventing severe endoscopic recurrence (RR 15%, 95% CI 1.8 to 29; three studies; NNT=7), but they were not effective in the prevention of very severe endoscopic recurrence. The rate of adverse events leading to drug withdrawal was higher in patients treated with purine analogues than for controls (17.2% versus 9.8%; p=0.021).

In the sensitivity analyses, efficacy of purine analogues at one year was superior to that of placebo for the prevention of both clinical (RR 13%, 95% CI 1.8 to 25, p=0.025; NNT=7) and endoscopic recurrence (RR 23%, 95% CI 9 to 37; NNT=4).

Publication bias was assessed and found to be absent.

Authors' conclusions
Purine analogues are more effective than placebo in preventing both clinical and endoscopic postoperative recurrence in Crohn's disease, but were associated with a higher rate of adverse events leading to drug withdrawal.

CRD commentary
The review addressed a clear question supported by appropriate inclusion criteria. Limited study details were reported and so it was uncertain how generalisable the findings were. Several relevant sources were searched without language restrictions. It was unclear whether unpublished studies were sought; some studies may have been missed. Publication bias was assessed and found to be absent (although the number of included studies was probably too small to assess publication bias). Two reviewers performed data extraction and quality assessment, which reduced potential for error and bias; it was unclear whether such methods were applied to study selection. Study quality was assessed using established criteria, but the individual results were not reported; a summary of factors that impacted bias were reported, which were similar to quality criteria. It appeared that appropriate methods were used to pool trials, although the analyses were based on a small number of trials. Heterogeneity was assessed and found to be absent. Sensitivity analyses were conducted to assess the impact of restricting analysis to placebo-controlled studies. Despite some shortcomings, such as uncertainty over study selection and the small number of studies, this was generally a well-conducted review and the authors' conclusions appear reliable.

Implications of the review for practice and research
Practice: The authors stated that azathioprine/6-mercaptopurine should be considered in high-risk patients who commenced prophylaxis within two weeks of surgery.

Research: The authors did not state any implications for further research.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.