Meta-analysis: the efficacy of azathioprine and mercaptopurine in ulcerative colitis

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CRD summary
The review concluded that azathioprine/mercaptopurine were effective for prevention of relapse in ulcerative colitis compared to placebo. The authors’ conclusions appeared appropriate. However, quality assessment and meta-analyses were restricted to RCTs and so it was not possible to assess the reliability of overall findings.

Authors' objectives
To assess the efficacy of azathioprine and mercaptopurine for induction and maintenance of clinical remission of ulcerative colitis.

Searching
MEDLINE, EMBASE (up to May 2008) and The Cochrane Library (Issue 1 2008) were searched. Reference lists of identified articles and reviews were handsearched. No language restrictions were applied. Search terms were reported.

Study selection
Studies that evaluated oral azathioprine or mercaptopurine for induction and/or maintenance of ulcerative colitis clinical remission were eligible for inclusion. For the meta-analysis, randomised controlled trials (RCTs) had to compare azathioprine or mercaptopurine with placebo or 5-aminosalicylic acid. Concomitant treatments with other immunomodulators (for example, methotrexate or cyclosporine) or biologic agents (for example, infliximab) were excluded.

Most of the included RCTs evaluated azathioprine compared to placebo, sulfasalazine or mesalazine. The prescribed dose of azathioprine used in most studies was 2.5mg/kg (range 1.5 to 2.5mg/kg). Only one study evaluated mercaptopurine compared to aminosalicylates. The prescribed dose was 1.5 mg/kg. Azathioprine/mercaptopurine was generally indicated for either induction or maintenance only. The patient population varied and included steroid-dependent patients, newly diagnosed patients and patients with acute proctocolitis. In most of the uncontrolled studies, azathioprine/mercaptopurine was indicated for induction and maintenance of remission; these studies included both steroid-dependent and steroid-resistant patients. Where reported, the prescribed dose range of azathioprine in most of these studies ranged between 2mg/kg and 2.5mg/kg and mercaptopurine dose ranged from 0.85mg/kg to 90mg per day.

Two reviewers independently selected studies. Any disagreements were resolved by consensus.

Assessment of study quality
The Jadad scale was used to assess the quality of RCTs. Scores were allocated for the criteria of randomisation, double blinding and description of withdrawals and dropouts culminating in a composite score between 0 (low quality) and 5 (high quality). There was no reported quality assessment for uncontrolled studies.

Two reviewers independently quality assessed the studies. Any disagreements were resolved by consensus.

Data extraction
Data were extracted to calculate the odds ratio (OR) or mean percentage success of treatment (defined as the induction or maintenance of clinical remission) and number needed to treat (NNT), all with associated 95% confidence intervals (CI).

Data extraction was performed by two reviewers independently. Any disagreements were resolved via consensus.

Methods of synthesis
For RCTs, odds ratios were combined in fixed-effect and random-effects meta-analyses. Efficacy was analysed on an intention-to-treat basis. Heterogeneity was assessed using the $X^2$ and $I^2$ tests. For uncontrolled studies, mean percentage efficacy of azathioprine/mercaptopurine was calculated as a weighted mean with corresponding 95% CIs.

Subgroup analyses were performed separately for controlled studies (based on azathioprine/mercaptopurine indication for induction or maintenance of clinical remission, control group, study quality) and uncontrolled studies (based on steroid resistance or steroid dependence status and azathioprine/mercaptopurine indication for induction or maintenance of clinical remission).

**Results of the review**

Seven RCTs ($n=408$) and 30 uncontrolled studies ($n=1,632$) were included. Six of the seven RCTs were higher quality studies (scored 3 or higher on Jadad scale). Mean follow-up period ranged from three to 18 months (controlled studies) and from three to 58 months (uncontrolled studies).

**Controlled studies:** Maintenance of clinical remission in ulcerative colitis was statistically significantly higher in patients treated with azathioprine/mercaptopurine compared to placebo (OR 2.59, 95% CI 1.26 to 5.3; three RCTs), but not compared to 5-aminosalicylates. Absolute risk reduction was 23% and the number needed to treat to prevent one recurrence was five (compared to placebo). There was statistically significant heterogeneity between studies that compared azathioprine/mercaptopurine versus 5-aminosalicylates.

There was little beneficial effect of azathioprine/mercaptopurine (OR 1.59, 95% CI 0.59 to 4.29; four RCTs) for induction of remission of ulcerative colitis. When only higher-quality studies were considered (studies that scored 3 or higher), azathioprine/mercaptopurine was beneficial for maintenance of remission (OR 2.44, 95% CI 1.42 to 4.17), but not for induction (OR 1.21, 95% CI 0.6 to 2.41). Subgroup analysis results for placebo-controlled trials were presented.

**Uncontrolled studies:** Mean efficacy of azathioprine/mercaptopurine in ulcerative colitis patients was 65% (95% CI 62% to 67%; 30 studies). Subgroup results on studies where azathioprine/mercaptopurine was prescribed for steroid resistance showed a mean efficacy rate of 66% (95% CI 59% to 73%). The mean efficacy rate for induction was 65% (95% CI 55% to 75%) and for maintenance was 76% (95% CI 71% to 81%).

**Authors’ conclusions**

Azathioprine/mercaptopurine was effective for prevention of relapse in ulcerative colitis compared to placebo.

**CRD commentary**

This review focused on a clear research question. Inclusion criteria were well defined in terms of population, intervention and outcomes. The literature search appeared adequate as it covered several databases and manual searches of reviews and identified articles were performed for further studies. Articles published in any language were eligible for this review, which minimised the risk of language bias. However, there were no apparent attempts to identify unpublished studies, which may have introduced publication bias. There were sufficient attempts to minimise bias and errors during the review process. Methods of syntheses appeared appropriate to the included study designs, although the quality of most of the included studies was not reported. The authors’ conclusion reflects the evidence from RCTs, but the reliability of the overall findings is unclear.

**Implications of the review for practice and research**

**Practice:** The authors stated that thiopurine immunosuppressants represented the first option in managing steroid-resistant and steroid-dependent ulcerative colitis.

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

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