A systematic review of the clinical effectiveness of azathioprine in patients with ulcerative colitis

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CRD summary
This reasonably well-conducted review examined the effectiveness and safety of azathioprine for induction and maintenance of remission in ulcerative colitis patients. The authors concluded that azathioprine may be effective in maintaining remission, but there is insufficient evidence that it is effective in inducing remission and further research is needed. These conclusions are likely to be reliable.

Authors' objectives
To assess the effectiveness and safety of azathioprine (AZA) and 6-mercaptopurine (6MP) in the induction and maintenance of remission in ulcerative colitis.

Searching
MEDLINE (1966 to March 2003), the Cochrane Library (Issue 1, 2003) and Japana Centra Revuo Medicina (1981 to March 2003) were searched; some search terms are given. References from retrieved studies and reviews were also used.

Study selection

Study designs of evaluations included in the review
Randomised controlled trials (RCTs) that were blinded and placebo-controlled were eligible for inclusion in the review.

Specific interventions included in the review
Oral AZA or 6MP therapies with a minimum duration of 1 month for the induction of remission, or 3 months for the maintenance of remission, were eligible for inclusion. The studies included in the review administered AZA at a dose of 100 mg/day or 2.0 to 2.5 mg/kg per day for between 1 month and 1 year. The following therapies were administered concomitantly: prednisolone; and prednisolone with sulfasalazine or mesalazine.

Participants included in the review
Patients with a diagnosis of active or quiescent ulcerative colitis aged over 18 years were eligible for inclusion in the review.

Outcomes assessed in the review
The primary outcomes eligible for inclusion were the induction of remission and the maintenance of remission. The definitions employed in the primary studies were accepted for these outcomes. Secondary outcomes that were eligible for inclusion were the presence of a steroid-sparing effect and adverse drug reactions.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed studies for relevance. Any disagreements were resolved by consensus.

Assessment of study quality
The validity of the studies was assessed using the Jadad scale, focusing on randomisation, double-blinding, and the description of withdrawals and drop-outs. The authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data on induction of remission, maintenance of remission, and adverse drug reactions were extracted. Odds ratios (ORs) were calculated for each outcome.

**Methods of synthesis**

How were the studies combined?
The studies were combined in a meta-analysis to calculate pooled ORs with 95% confidence intervals (CIs). The analysis was performed using both fixed-effect and random-effects models and weighting studies by sample size.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Q statistic. Pooled estimates using the fixed-effect model were reported only where significant heterogeneity (P>0.1) was not detected. Differences between the studies were also briefly discussed in the narrative synthesis.

**Results of the review**

Four RCTs with 244 patients were included in the review.

Two studies (n=130) assessed induction of remission. The pooled OR for the response to AZA compared with placebo was 1.45 (95% CI: 0.68, 3.08).

Four studies (n=205) assessed maintenance of remission. The pooled OR for the response to AZA compared with placebo was 2.26 (95% CI: 1.27, 4.01).

No study reported steroid-sparing effect outcomes.

All studies assessed some adverse drug reactions.

The pooled OR for AZA compared with placebo was 2.09 (95% CI: 0.38, 11.57) for bone marrow suppression (4 studies, n=232).

The OR for AZA compared with placebo was:

- 2.05 (95% CI: 0.18, 23.59) for leucopenia (1 study, n=80),
- 3.08 (95% CI: 0.12, 77.80) for gastrointestinal disturbance (1 study, n=80),
- 5.43 (95% CI: 0.25, 118.96) for mild acute pancreatitis (1 study, n=50),
- 3.12 (95% CI: 0.12, 80.40) for jaundice (1 study, n=50),
- 0.19 (95% CI: 0.01, 4.09) for excessive hair loss (1 study, n=80),
- 3.08 (95% CI: 0.12, 77.80) for generalised erythematous rash (1 study, n=80), and
- 4.36 (95% CI: 0.47, 40.20) for withdrawal (2 studies, n=85).

**Authors' conclusions**

AZA might be useful in the maintenance of remission in ulcerative colitis patients when both effectiveness and safety are considered. It was unclear whether AZA is effective in the induction of remission or in producing steroid-sparing effects.

**CRD commentary**
The review question and the inclusion criteria were both extremely clear. The search was adequate, although the authors did not state whether any language restrictions were applied or whether they searched for unpublished studies; both of these factors may be potential sources of bias in the review. The authors used an appropriate tool to assess validity but, although they reported using appropriate measures to minimise bias and errors when selecting studies for the review (i.e. two independent reviewers performed the process), they did not report using such measures in the quality assessment and data extraction processes.

There appeared to be little clinical heterogeneity between the studies. The authors also assessed statistical heterogeneity. The authors' decision to employ a meta-analysis to generate pooled estimates was appropriate, and the analysis appears to have been well conducted. However, subtotals for particular event categories may be a better measure of adverse drug reactions than the overall pooled OR. The authors' cautious conclusions appear justified by the evidence included in the review.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further clinical trials on the effectiveness of AZA, in both the induction and maintenance of remission in patients with ulcerative colitis, are required.

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