Thiopurine-induced myelotoxicity in patients with inflammatory bowel disease: a review

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CRD summary
This review evaluated thiopurine-induced myelotoxicity in inflammatory bowel disease patients and concluded that both azathioprine and mercaptopurine were safe in the long term. In light of the uncertain quality of the included studies, a paucity of study details, a lack of reporting of review methods and significant variation across studies, the authors' conclusions should be interpreted with caution.

Authors' objectives
To evaluate thiopurine-induced myelotoxicity in patients with inflammatory bowel disease.

Searching
MEDLINE and EMBASE were searched without language restrictions to September 2007; search terms were reported. Reference lists of relevant articles were searched manually to identify additional articles.

Study selection
Eligible studies evaluated the incidence of thiopurine-induced myelotoxicity in patients with inflammatory bowel disease. Interventions in the included studies comprised azathioprine (range 1mg/kg to 3mg/kg) or mercaptopurine (range 0.71mg/kg to 1.9mg/kg). Outcomes comprised the cumulative incidence of myelotoxicity and incidence rate of myelotoxicity. Drug-induced leukopenia definitions varied, but the cut-off point for the number of leukocytes was generally set at 3–4x10^9/L and the number of neutrophils at 1.5x10^9/L. Participants in included studies had Crohn's disease, ulcerative colitis or indeterminate colitis. Duration of follow-up ranged from 12 days to 27 years.

The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The cumulative incidence of myelotoxicity and incidence rate of myelotoxicity per patient-years of follow-up with 95% confidence intervals (CI) were calculated for each study.

The authors did not state how many reviewers carried out the data extraction.

Methods of synthesis
Studies were pooled using a random-effects (DerSimonian and Laird) model and weighted by the inverse of the variance. Heterogeneity was assessed using the $X^2$ and $I^2$ tests. Presence of heterogeneity defined as $p<0.1$ or $I^2>50\%$. Subgroup analyses was undertaken post hoc to take account of the duration of follow-up and drug dose.

Results of the review
A total of 67 studies (n=8,900, range 10 to 739) were included in the review; there was some discrepancy in the number of studies and patient numbers between the tables and the text. Where stated, proportions with drug-induced leukopenia ranged from 0% to 39% and severe drug-induced leukopenia from 0% to 5.7%.

Cumulative incidence of azathioprine/mercaptopurine-induced myelotoxicity was 7% (95% CI 6% to 8%). The incidence rate (per patient and year of treatment) of drug-induced myelotoxicity was 3% (95% CI 3% to 4%). Cumulative incidence of death due to azathioprine-induced bone marrow suppression was 0.06% (95% CI 0.02% to 0.17%). The risk of death amongst inflammatory bowel disease patients who developed myelotoxicity was 0.94% (95%
CI 0.32% to 2.70%). Significant heterogeneity was present for these analyses.

Cumulative incidence of severe myelotoxicity was 1.1% (95% CI 0.85% to 1.50%). The incidence rate of severe drug-induced myelotoxicity was 0.9% (95% CI 0.70% to 1.20%). The cumulative incidence of infections among azathioprine/mercaptopurine-induced myelotoxicity patients was 6.5% (95% CI 3.20% to 9.80%).

Analyses for studies of ≤12 months duration yielded an incidence rate of drug-induced myelotoxicity of 11%.

**Authors' conclusions**
The incidence rate of myelotoxicity in patients with inflammatory bowel disease was approximately 3% per patient per year of treatment and reflects the long-term safety of azathioprine and mercaptopurine treatments.

**CRD commentary**
The review question was clear. Inclusion criteria were specified for participants, intervention and outcome, but not for study design. Two relevant databases were searched without language restrictions, which reduced potential for language bias. It was unclear whether unpublished studies were sought, so some studies may have been missed. The authors stated neither how studies were selected for the review nor how many reviewers performed the data extraction, so the potential for reviewer bias and error could not be assessed. There was no formal assessment of study quality. Data were pooled using meta-analysis, but in the presence of significant heterogeneity meant that summary measures did not reflect the variability of the studies. Uncertain quality of the included studies, a paucity of study details, a lack of reporting of review methods and significant heterogeneity limited interpretation of the results presented and the authors' conclusions should be interpreted with caution.

**Implications of the review for practice and research**
**Practice:** The authors stated that regular monitoring of leukocyte count should be performed throughout the duration of azathioprine/mercaptopurine therapy. Several factors unrelated with thiopurine methyltransferase activity may be responsible for azathioprine myelotoxicity in leukopenia cases and systematic blood controls should be done in these patients.

**Research:** The authors stated that an optimal monitoring schedule for bone marrow toxicity should be established and that more studies were required to evaluate the economic aspects of thiopurine methyltransferase monitoring. Further investigations on the role of thiopurine methyltransferase activity assay prior to initiating thiopurine therapy were necessary to rationalise dosing and minimise adverse effects.

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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.