Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine
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CRD summary
This review found that individuals with inflammatory bowel disease treated with azathioprine or 6-mercaptopurine have four times the risk of developing lymphoma compared with the general population. These results were based on observational studies, with few observed lymphoma cases, thus the true effect of immunomodulator treatment is uncertain.

Authors' objectives
To determine whether immunomodulators, such as azathioprine or 6-mercaptopurine (6-MP), increase the risk of developing lymphoma in individuals with inflammatory bowel disease (IBD).

Searching
MEDLINE was searched for articles published in English; the search terms were reported. The reference lists of identified articles were also checked. Only papers published in full were included.

Study selection
Study designs of evaluations included in the review
Cohort studies designed to evaluate cancer as an adverse outcome following treatment with azathioprine or 6-MP were included.

Specific interventions included in the review
Studies of azathioprine or 6-MP were eligible for inclusion. The dosages ranged from 1.65 mg/kg per day to 106 mg/day for azathioprine, and from 12.5 to 100 g/day for 6-MP. The mean duration of treatment was between 12.5 months and 4.4 years.

Participants included in the review
Individuals with IBD were included in the review. Where reported, the proportion of participants with Crohn's disease or ulcerative colitis ranged from 43 to 67% and from 33 to 57%, respectively. Disease stage varied widely amongst the included participants.

Outcomes assessed in the review
The included outcomes were incidence of lymphoma and incidence of non-Hodgkin lymphoma.

How were decisions on the relevance of primary studies made?
Two reviewers assessed the retrieved articles; consensus was reached by discussion.

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

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 the observed and expected numbers of patients with lymphoma and the type of lymphoma were extracted. The standardised incidence ratio (SIR) of lymphoma was either extracted or calculated for each study.
Methods of synthesis
How were the studies combined?
Studies were combined in a meta analysis; pooled SIRs and 95% confidence intervals (CIs) were estimated by summing the observed and expected numbers of lymphomas across studies. In addition, the pooled relative risk (RR) and 95% CI of lymphoma were calculated using Mantel-Haenszel techniques for studies that compared treatment with no treatment.

How were differences between studies investigated?
Statistical heterogeneity was assessed using Poisson regression. A P-value of less than 0.05 was taken as being statistically significant. The authors conducted sensitivity analyses to assess the effect of individual studies on treatment effects and heterogeneity statistics.

Results of the review
Six cohort studies (3,891 participants) were included in the review. These ranged in size from 238 to 1,465 participants.

The overall incidence of lymphoma compared with the general population was SIR 4.18 (95% CI: 2.07, 7.51), with a total of 11 cases of lymphoma. Statistically significant heterogeneity was shown; this heterogeneity was explained by the extreme results of 2 studies.

A significantly increased risk of developing lymphoma was associated with patients with IBD treated with azathioprine or 6-MP (RR 2.92, 95% CI: 1.05, 8.13; 3 studies). No statistical heterogeneity was found.

The overall incidence of non-Hodgkin lymphoma compared with the general population was SIR 3.92 (95% CI: 1.78, 7.47), with a total of 9 cases of non-Hodgkin lymphoma.

Authors' conclusions
Individuals with IBD treated with azathioprine or 6-MP have approximately four times the risk of developing lymphoma. However, it is unclear whether this increased risk is a consequence of the medication, the severity of the underlying disease, or a combination of these.

CRD commentary
The research question was supported by clear inclusion criteria relating to the intervention, outcome and study design. The literature search was limited to one electronic database and restricted to articles published in English. No attempt was made to locate unpublished material or to assess publication bias. This means that we cannot be certain that all relevant studies were included in the review. Two reviewers appeared to select primary studies for inclusion, although it is not known whether this process was independent. The authors do not report how the data were extracted or whether validity was assessed, thus it was not possible to assess the likelihood of reviewer error or bias being introduced at these stages. Very few participant or setting details were provided, making it difficult to assess the generalisability of the findings.

SIRs were calculated from event rates in the general population. Therefore, it might be useful to know more about the population on which these are based. The data were synthesised by meta-analysis and statistical heterogeneity was assessed. However, clinical differences between the studies, in terms of study design, treatment duration and length of follow-up exist, which may mean that a quantitative summary was not appropriate. In addition, very few lymphomas were identified (11 in 3,891 participants) and the rates were low in each study (range: 0 to 3).

The authors acknowledged that their results were based on observational studies and, as such, the true effect of treatment is uncertain. It was also unclear whether the increasing risk may be due to other factors, such as the severity of the underlying disease.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors did not explicitly state any implications for further research. However, they noted that there is insufficient information about how the risk of lymphoma changes when therapy is discontinued and whether the risk is dose related.

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