Meta-analysis of risk of malignancy with immunosuppressive drugs in inflammatory bowel disease
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CRD summary
This review concluded that the administration of immunosuppressive agents was unlikely to increase the risk of malignancy in patients with Crohn’s disease or ulcerative colitis. Although the review methodology was generally sound, methodological weaknesses in the included studies and data analysis make the reliability of the authors’ conclusions uncertain.

Authors’ objectives
To compare the risks of developing malignancy between patients with inflammatory bowel disease (IBD) treated with immunosuppressive agents and those not treated with immunosuppressive agents.

Searching
MEDLINE (1966 to September 2006), the Cochrane Library (Issue 3, 2006) and Japana Centre Revuo Medicina (1981 to September 2006) were searched; the search terms were reported. The reference lists of all retrieved articles were also checked. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Cohort studies with a minimum of 1 year’s follow-up were eligible for inclusion.

Specific interventions included in the review
Studies of immunosuppressive agents for the treatment of IBD that provided information on the duration of therapy were eligible for inclusion. The included immunosuppressants were azathioprine, 6-mercaptopurine, methotrexate and cyclosporine. Doses varied between the studies. The duration of treatment ranged from 1 to 7.4 years.

Participants included in the review
Studies of patients with IBD were eligible for inclusion. Where reported, the mean age of the participants ranged from 31 to 41 years. The majority of studies included patients with Crohn’s disease (CD) and/or ulcerative colitis (UC).

Outcomes assessed in the review
Studies that reported development of malignancy as a predetermined end point were eligible for inclusion. The studies included in the review assessed follow-up from between 1.8 and 17.4 years.

How were decisions on the relevance of primary studies made?
Three reviewers independently selected the studies and resolved any disagreements through discussion.

Assessment of study quality
The validity of the studies was assessed using the 27-item scoring system of Downs and Black. The system evaluated reporting, external validity, internal validity-bias, internal validity-confounding and power. Quality was considered high (score 20 or more), moderate (score 10 to 19) or low (score 10 or less). Only studies of moderate or high quality were included in the analysis. Three reviewers independently conducted the validity assessment. When there were disagreements among the quality scores reported, the lowest score was adopted.

Data extraction
At least two reviewers independently extracted the data. The incidence of malignancy was extracted and transformed into events per person-years.

Methods of synthesis
How were the studies combined?
The risk of developing malignancy was calculated using a general variance-based method and expressed as the weighted mean difference with the 95% confidence interval. Data were also analysed using the odds ratio with 95% confidence interval, but these were not presented. Subgroup analyses were conducted for patients with CD or UC, and the development of different types of malignancy. For studies with no control group, data were obtained from a population-based study (see Other Publications of Related Interest) and used as control group data.

How were differences between studies investigated?
Heterogeneity was assessed using the Q statistical test (p<0.05 considered significant). When significant statistical heterogeneity was present, a random-effects model was used.

Results of the review
Nine cohort studies (4,039 patients) were included.

Two studies had quality scores of 20 and were classified as high quality. The remaining studies had scores of between 14 and 19 and were classified as moderate quality. Six of the 9 studies had no control group.

There was no evidence of an increased risk of developing malignancy in patients who received immunosuppressive agents compared with who did not, in the overall population or in subgroups of patients with CD or UC. No significant relationship was found between length of exposure to immunosuppressive therapy and weighted mean difference in the incidence of development of malignancy. There were no increases in the risk of any particular type of malignancy in patients with IBD, regardless of administration of immunosuppressive agents in such patients.

Authors' conclusions
The administration of immunosuppressive agents was unlikely to increase the risk of malignancy in patients with CD or UC.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Only three databases were searched for studies and this might have resulted in relevant studies being missed. No specific attempt was made to locate unpublished studies, thus raising the possibility of publication bias. Language restrictions were not applied during the search, thereby reducing the risk of language bias. The study selection, validity assessment and data extraction processes were all conducted in duplicate, which reduces the potential for reviewer bias and error. Validity was assessed using an established checklist, although only the composite score was presented and few study details given; this makes it difficult for the reader to judge the validity of the studies for themselves. Six of the 9 included cohort studies did not have control groups and the authors used data from a population-based study to provide control data for the analyses; no details of this study or reasons for its selection were provided. Treatment regimens and length of therapy differed substantially between the studies. Given such clinical heterogeneity, the pooling of studies might not have been appropriate. Although the review methodology was generally sound, the evidence available was limited and there were methodological weakness in both the included trials and the data analysis, making the reliability of the authors’ conclusions uncertain.

Implications of the review for practice and research
Practice: The authors stated that the lack of evidence of an increased risk of malignancy in patients with IBD with immunosuppressive agents means that colonoscopic surveillance of patients with UC receiving immunosuppressants may not be recommended.

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

Funding
Not stated.

Bibliographic details
Masunaga Y, Ohno K, Ogawa R, Hashiguchi M, Echizen H, Ogata H. Meta-analysis of risk of malignancy with...

PubMedID
17200426

DOI
10.1345/aph.1H219

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Cohort Studies; Humans; Immunosuppressive Agents /adverse effects; Inflammatory Bowel Diseases /drug therapy /epidemiology; Neoplasms /chemically induced /epidemiology; Risk Factors

AccessionNumber
12007000794

Date bibliographic record published
07/01/2008

Date abstract record published
03/11/2008

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.