Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis

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CRD summary
The authors concluded that anti-tumour necrosis factor agents combined with immunomodulators was associated with an increased risk of non-Hodgkin's lymphoma in adult patients with Crohn's Disease, but that the absolute risk of these events was low. Given the uncertain quality of included studies, and potential concerns about their synthesis, the extent to which the authors’ conclusion is reliable is unclear.

Authors' objectives
To evaluate the effect of anti-tumour necrosis factor agents on the rate of non-Hodgkin's lymphoma in adult patients with Crohn's disease.

Searching
MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1950 to 2007. Meeting abstracts were searched via the Web of Science (1996 to 2007); there were no search limits. Search terms were reported. Reference lists of relevant articles were scanned. ClinicalTrials.gov was searched for further studies. Unpublished data were sought from clinical trialists and selected pharmaceutical companies.

Study selection
Randomised controlled trials (RCTs), prospective or retrospective cohort studies, or case series of consecutive patients of adults with Crohn's disease, treated with infliximab, adalimumab, or certolizumab pegol, were eligible for inclusion in the review. Induction and maintenance studies were accepted. Eligible studies were required to report adverse outcomes, and have a minimum median follow up of 48 weeks.

Comparator data were obtained from the Surveillance Epidemiology and End Results (SEER) cancer registry, and a meta-analysis of patients treated with 6-mercaptopurine or azathioprine. The mean age of included patients was 36.9 years, and had a mean duration of Crohn's disease of 9.3 years. The most frequently reported drug was infliximab, and an average of 66% of patients were taking concomitant immunomodulators.

Two independent reviewers selected studies for inclusion, and disagreements were resolved by discussion.

Assessment of study quality
Quality assessment of the included studies was not deemed relevant, although attrition was measured.

Data extraction
Data were extracted to enable the calculation of standardised incidence ratios (SIR) and 95% confidence intervals (CI). This was carried out by two independent reviewers, and disagreements were resolved by discussion. Authors were contacted for missing or patient-level data, where necessary.

Methods of synthesis
Standardised incidence ratios and 95% confidence intervals were pooled in a meta-analysis (the method was not reported). The analysis compared with SEER data was adjusted for age and gender. Sensitivity analysis was conducted by removing studies with a drop-out rate of more than 15%. Sub-group analysis was performed to take account of the different study designs. The exploration of publication bias was not deemed relevant.

Results of the review
Twenty-six studies (n=8,905 patients; 21,178 patient years of observation) were included in the review. There were nine RCTs (n=3,399 patients), three cohort studies (n=4,122 patients) and 14 case series (n=1,384 patients). Mean follow-up was 74 weeks, and the drop-out rate ranged from 0 to 33%. Sensitivity analysis was reported only for males.
Rate of lymphoma: A statistically significant higher risk of non-Hodgkin's lymphoma was reported in anti-tumour necrosis factor treated patients (SIR 3.23, 95% CI 1.5 to 6.9; 13 cases; absolute rate 6.1 non-Hodgkin's lymphomas per 10,000 patient-years) compared with the expected rate in SEER cancer registry (SIR 1.9 per 10,000 patient-years). The majority of patients with non-Hodgkin's lymphoma had previously been exposed to immunomodulators. The increase in non-Hodgkin's lymphoma was not statistically significant when compared to the meta-analysis of patients treated only with immunomodulators. Men had a consistently higher rate of non-Hodgkin's lymphoma, and this was statistically significant for those aged between 20 and 54 (SIR 5.4, 95% CI 1.3 to 18.1).

Sensitivity and subgroup analyses: When two studies with drop-out rates greater than 15% were excluded, the risk of non-Hodgkin's lymphoma was increased in men of all ages (SIR 9.4, 95% CI 1.8 to 12.3). In specific age categories, this remained statistically significant in those aged between 55 and 64 years (SIR 16.8, 95% CI 2.0 to 64.4; absolute rate 72 per 10,000 patient-years). In sub-group analysis, the rate of non-Hodgkin's lymphoma was significant for case series designs (SIR 9.4, 95% CI 1.35 to 104.0), but this was driven largely by one study.

Significant heterogeneity of the non-Hodgkin's lymphoma rate was reported amongst the studies, with twenty studies reporting no cases.

Authors' conclusions
The use of anti-tumour necrosis factor agents combined with immunomodulators was associated with an increased risk of non-Hodgkin's lymphoma in adult Crohn's disease patients, but the absolute risk of these events was low.

CRD commentary
The review question was clear, and this was supported by clear and potentially reproducible inclusion criteria. The search strategy covered a number of relevant sources of published and unpublished data, and further bias was minimised by no search limits. It appeared that only published studies or meeting abstracts were included. The decision not to explore publication bias appeared justified on the basis of analysing rare event data. Adequate attempts were made to minimise errors and bias in the selection of studies and data extraction.

A formal quality assessment of studies was not conducted on the basis of irrelevance to the comparator data and use of objective outcomes. Justification for this decision is questionable. Study details were adequately provided. Given that the method of synthesis was not fully reported, it was not clear to what extent this was appropriate in the presence of significant variation.

Given the potential methodological limitations identified above, the extent to which the authors' conclusion is reliable is unclear.

Two of the authors disclosed potential conflicts of interest in terms of their associations with drug companies.

Implications of the review for practice and research
Practice: The authors stated that the risks of using anti-tumour necrosis factor agents should be weighed against the substantial benefits associated with treatment, and this should be tailored for individuals.

Research: The authors stated that prospective studies are required. The monitoring of drug side effects should be applied in large inception cohorts of patients with Crohn's disease that are currently being developed.

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