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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BACKGROUND & AIMS: Although anti–tumor necrosis factor (TNF) therapy can effectively treat Crohn's disease (CD), there is concern that it might increase the risk of non-Hodgkin's lymphoma (NHL). A meta-analysis was performed to determine the rate of NHL in adult CD patients who have received anti-TNF therapy and to compare this rate with that of a population-based registry and a population of CD patients treated with immunomodulators. **METHODS:** MEDLINE, EMBASE, Cochrane Collaboration, and Web of Science were searched. Inclusion criteria included randomized controlled trials, cohort studies, or case series reporting on anti-TNF therapy in adult CD patients. Standardized incidence ratios (SIR) were calculated by comparing the pooled rate of NHL with the expected rate of NHL derived from the Surveillance Epidemiology & End Results (SEER) database and a meta-analysis of CD patients treated with immunomodulators. **RESULTS:** Twenty-six studies involving 8905 patients and 21,178 patient-years of follow-up were included. Among anti-TNF treated subjects, 13 cases of NHL were reported (6.1 per 10,000 patient-years). The majority of these patients had previous immunomodulator exposure. Compared with the expected rate of NHL in the SEER database (1.9 per 10,000 patient-years), anti-TNF treated subjects had a significantly elevated risk (SIR, 3.23; 95% confidence interval, 1.5–6.9). When compared with the NHL rate in CD patients treated with immunomodulators alone (4 per 10,000 patient-years), the SIR was 1.7 (95% confidence interval, 0.5–7.1). **CONCLUSIONS: The use of anti-TNF agents with immunomodulators is associated with an increased risk of NHL in adult CD patients, but the absolute rate of these events remains low and should be weighed against the substantial benefits associated with treatment.**

Crohn's disease (CD) is a chronic inflammatory bowel disease that affects approximately half a million people in the United States.[1] Patients are most commonly diagnosed in young adulthood, but others might not develop symptoms until they are older. Symptoms range from mildly active disease with occasional diarrhea and rectal bleeding to severely active disease that might result in 10–20 bloody bowel movements per day, associated abdominal pain, and the possible need for surgery. Many patients are refractory to standard treatments and require the addition of anti–tumor necrosis factor (TNF) agents. Anti-TNF agents can be very effective for improving symptoms and inducing remission of CD[2,3] and have shown promise in improving quality of life and decreasing the rates of hospitalizations and surgery.[4,5] The currently available anti-TNF drugs for the treatment of CD include infliximab (IFX), adalimumab (ADA), and certolizumab pegol (CTZ).

Shortly after anti-TNF agents became widely available, concern was raised of a possible association with an increased risk of lymphoma, specifically non-Hodgkin's lymphoma (NHL).[6] Studies aimed at quantifying potential risk among CD patients have arrived at estimates ranging from no increased risk (TREAT registry)[7] to a 1.5% absolute annual risk of lymphoma.[8] CD, in and of itself, does not appear to have an increased risk of lymphoma,[9,10] but patients with CD treated with immunomodulators such as azathioprine and 6-mercaptopurine (6MP) might have a 4-fold increased risk.[11] The magnitude of lymphoma risk added by the anti-TNF agents has been a matter of much debate.

For patients and physicians to make better informed treatment decisions regarding anti-TNF drugs, it is critical to understand the balance of risks and benefits. The current spectrum of risk estimates makes it very difficult to use the data in a meaningful way. This meta-analysis systematically evaluates the NHL rate among adult CD patients exposed to anti-TNF agents in a study setting. This rate is compared with the rate in externally derived controls including a population-based cancer registry and a pooled cohort of CD patients treated with immunomodulators without anti-TNF exposure.

Methods

Data Sources and Searches

A literature search was conducted by using the databases MEDLINE via Ovid (1950–October 2007), EMBASE (1974–2007), and Cochrane Reviews/CENTRAL (1990–2007), and meeting abstracts were searched via Web of Science (1996–2007). The search terms included "Crohn's" and related terms "Infliximab," "Ada-

Abbreviations used in this paper: ADA, adalimumab; CD, Crohn's disease; CI, confidence interval; CTZ, certolizumab pegol; IFX, infliximab; 6MP, 6-mercaptopurine; NHL, non-Hodgkin's lymphoma; RCT, randomized controlled trial; SD, standard deviation; SEER, Surveillance, Epidemiology & End Results; SIR, standardized incidence ratio; TNF, tumor necrosis factor.

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limumab," "Certolizumab pegol," and related pharmaceutical names. There were no limits used in our search strategy.

Additional search methods. Additional search methods included a manual review of reference lists of relevant articles and an electronic search of ClinicalTrials.gov. Inflammatory bowel disease clinical trialists and relevant pharmaceutical companies were contacted to determine whether additional unpublished safety data or updated results were available that would meet inclusion criteria.

Study Selection

Studies were included for analysis if they met the following inclusion criteria: study design of randomized controlled trials (RCTs), prospective or retrospective cohort studies, or case series of consecutive patients (to avoid selection bias); published articles or meeting abstracts; treatment included IFX, ADA, or CTZ; population of adult patients with CD; clearly reported adverse outcomes; and a minimum of a median follow-up of 48 weeks. There was no minimum study size, and both induction and maintenance studies could be included. Two reviewers (C.S., S.M., or S.P.) independently evaluated each of the articles for eligibility. Disagreement regarding eligibility was resolved by joint review and discussion between the authors.

Data Extraction

Data from all eligible studies were extracted by 2 independent reviewers (C.S., S.M., or S.P.) by using a standardized data abstraction form. This electronic data collection form (Excel; Microsoft, Redmond, WA) included study design, population size and median age, median time of follow-up, duration of disease, gender, specific anti-TNF agent, method of delivery and dosage, percent taking immunomodulators, dropout rate, and number of NHL cases. A second section of the data abstraction form included details of the patients who developed NHL. Discrepancies between the 2 reviewers were resolved by joint review and discussion between the authors. Corresponding authors were contacted to obtain any necessary missing data from the original publications.

Data Synthesis and Analysis

Pooled summary estimates. To calculate the total rate of NHL, we summed the number of lymphomas in all of the included studies and divided by the total number of patient-years. Patient-years were calculated by converting the follow-up time from weeks to years and multiplying by the total number of subjects.

The expected rate of NHL among subjects not exposed to anti-TNF agents was derived from 2 sources, the Surveillance Epidemiology & End Results (SEER) cancer registry[12] and a meta-analysis of patients treated with 6MP or azathioprine (Kandiel et al[11]). The analysis by Kandiel et al included both CD and ulcerative colitis patients and reported both Hodgkin's lymphoma and NHL. Therefore, the numerator used to calculate the Kandiel rate was only NHL in CD patients, and denominator was patient-years of follow-up in CD patients treated with 6MP or azathioprine. Relative rates were calculated as standardized incidence ratios (SIR), first comparing the pooled NHL rate from anti-TNF studies with population-based NHL rates from SEER and then with the study by Kandiel et al by using the STATA "IR" command (STATA 10.0, College Station, TX).

To adjust for age and gender in the SEER comparisons, we had to develop age- and gender specific lymphoma rates from our data. Age categories were chosen to match those reported in SEER. To determine the exact age distribution of patients within included studies, investigators were contacted for patient level data. When these data were not available,[13–25] we calculated an estimated distribution by deducing age structure on the basis of the available mean or median age and the given standard deviation (SD). If the SD was not provided, it was estimated by dividing the range by 4 or the interquartile range by 1.35.[26] When neither the range nor interquartile range was provided for a study, it was imputed as the average SD from all studies.[26] Assuming a normal distribution, medians were handled as mean age. Once mean age and SDs were ascertained for each study, with STATA 10.0, a random normal age and gender distribution was calculated. If the generated distribution did not include the entire range of study participants, the random distribution program was run until a representative group resulted. By using the actual or estimated age and gender distributions for each study, we calculated age-/gender-specific patient-year denominators and finally categorical NHL rates to make direct comparisons with SEER. SIRs were then calculated for each age/gender category. Because age and gender distribution was not available uniformly for the CD patients included in the meta-analysis by Kandiel et al,[11] we performed a pooled analysis only and did not calculate age- and gender-specific comparisons to this patient population like we did with SEER.

Sensitivity and subgroup analyses. To address the concern that NHL rates might be underestimated if patients who drop out of studies are more likely to have or develop lymphoma, a sensitivity analysis was performed by removing studies that had a dropout rate >15%. Because different study designs might attract or enroll different types of subjects and likely have different intensity of treatment or follow-up, subgroup analyses were performed on the basis of the design of included studies.

Results

Description of Studies

Results of search. Our initial electronic search of MEDLINE identified 644 potentially relevant publications. Af-

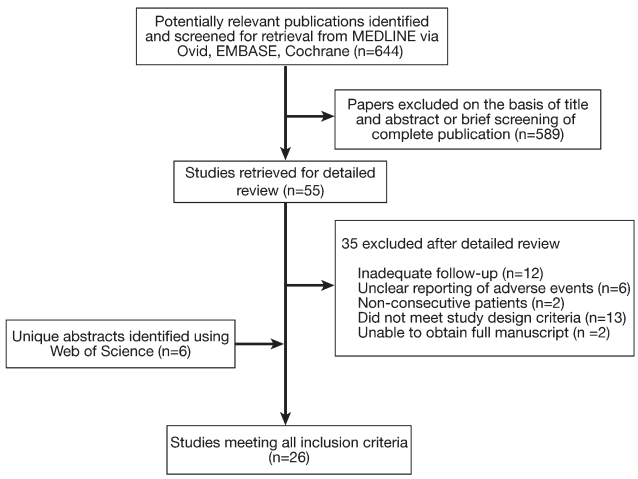

Figure 1. Flow diagram of the studies identified in search, and reasons for study exclusion.