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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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Abstract

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 immuno-modulator 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.

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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 CD2,3 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,” “Adalimumab,” “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 registry12 and a meta-analysis of patients treated with 6MP or azathioprine (Kandiel et al11). 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. After eligibility screening by abstract and title, 55 articles were obtained for more detailed review, of which 35 were excluded for reasons shown in Figure 1. A search of Web of Science identified 6 additional abstracts. If meeting abstracts were identified that included more recent and updated information than a previously published article, data from the meeting abstract replaced those of the full article.[7,13,27] Ultimately, 26 studies met our inclusion criteria. A review of EMBASE, Cochrane Reviews/ CENTRAL, ClinicalTrials.gov, and contact with relevant pharmaceutical companies and experts in the field yielded no additional studies. Data from one study identified through our MEDLINE search were updated after experts indicated that new data were available.[7]

Characteristics of included studies—Twenty-six studies involving 8905 patients were included in this review. As shown in Table 1, nine were RCTs,[2,13,14,17,27–31] three were cohort studies,[3,7,32] and 14 were case series of consecutive patients.[8,20–25,34–40] Patients had a mean age of 36.9 years and a mean duration of CD of 9.3 years. Twenty-two of the included studies involved IFX, 3 involved ADA, and 1 involved CTZ. An average of 66% of participants across the studies were concomitantly taking immunomodulators. The mean duration of follow-up was 74 weeks, with a dropout rate ranging from 0%–33%.

Rate of Lymphoma

There were a total of 13 lymphomas in 21,178 patient-years of observation, yielding a rate of 6.1 NHLs per 10,000 patient-years. When compared with the expected rate of NHL in all age groups combined in SEER (1.9 per 10,000 patient-years), as shown in Table 2, the SIR was 3.23 (95% confidence interval [CI], 1.5–6.9). Table 3 shows the age- and gender-specific NHL rate and SIR as compared with the expected NHL rate from SEER. In both this meta-analysis and SEER, male patients consistently have a higher rate of NHL. Although the crude NHL rate among anti-TNF exposed subjects increased with age, the age- and gender-specific SIR was only significant for male patients between the ages of 20 and 54, with an SIR of 5.4 (95% CI, 1.3–18.1). When compared with the observed rate of NHL in CD patients treated with immunomodulators alone from the study by Kandiel et al[11] (3.6 per 10,000 patient-years), the SIR was 1.7 (95% CI, 0.5–7.1).

There was significant heterogeneity of the rate of NHL across studies. Twenty of the included studies did not have any patients with NHL, whereas 6 reported at least 1 case. The highest rate was seen in the study by Ljung et al.[16] Figure 2 displays the variation of the relative risk of NHL in individual studies compared with SEER.

Characteristics of Patients With Lymphoma

Table 4 shows the characteristics of the 13 patients with NHL. The mean patient age was 52 years (range, 24–79 years). Twelve of the patients with NHL were treated with IFX, and 1 was treated with ADA. Because of the heterogeneity of trial design (mixed group of anti-TNF naïve and maintenance patients), we are unable to confidently give a range of the dose and number

of doses each of these patients received during their lifetime. The subtype of NHL is shown in Table 4. Patient outcomes were available for 12 of the patients with NHL, and at the time of most recent follow-up, 6 had died as a result of lymphoma or its related treatment.

Sensitivity and Subgroup Analyses

The results of our sensitivity analysis excluding anti-TNF studies with a dropout rate greater than 15% are shown in Table 5. The sensitivity analysis is shown only for male patients, because the SIR for female patients did not meet significance in any age category. Excluding the 2 studies with a high dropout rate (Lichtenstein et al7 and Ardizzone et al20) increased the overall absolute risk of NHL to 9.4 per 10,000 patient-years, with an SIR of 9.4 (95% CI, 1.8–12.3). The NHL rate and corresponding SIRs again increased as patients got older, but the only age category in which the SIR reached statistical significance was in men ages 55–64 years.

Subgroup analyses to evaluate the NHL rates in anti-TNF treated patients across different study designs are shown in Table 6. In 9 randomized control trials, there were 2 lymphomas observed in 3860 patient-years, yielding an incidence rate of 5.2 per 10,000 patient-years. In the 3 cohort studies including 15,192 patient-years, there were 7 lymphomas, resulting in an incidence rate of 4.6 per 10,000 patient-years. Finally, in the 14 case series, 4 lymphomas were observed in 2215 patient-years, yielding an incidence rate of 18.8 per 10,000 patient-years. Only the case series remained statistically significant, with an SIR of 9.4 (95% CI, 1.35–104.0).

Discussion

Anti-TNF drugs for the treatment of CD appear to be associated with an increased risk of NHL. Although the increased risk is statistically significant when compared with the general population, the absolute risk remains small (6.1 per 10,000 patient-years). When compared with CD patients taking immunomodulators alone, there is a nonstatistically significant increased rate of NHL for those exposed to anti-TNF agents.

The baseline risk of NHL increases with age and is male-predominant.[41] Therefore, when communicating the NHL risk to patients, conversations should be tailored for individuals. Although the SEER age categories are still fairly broad, it is possible to discuss more specific observed and expected rates for patients, depending on their age and gender, as opposed to our overall summary estimate.

We excluded the 2 studies with a greater than 15% dropout rate for the sensitivity analysis because we were concerned that these studies might not accurately represent the risk of lymphoma in their patient populations. Despite the fact that 6 of the observed lymphomas were then excluded, the disproportionate contribution of patient-years from the TREAT registry[7] dramatically decreased the denominator, thereby increasing the NHL rate across all groups. Although statistical significance was only reached for one age category (men ages 55–64 had an SIR of 16.8), there is a dramatic increase in the absolute rate and SIR as patients get older. Because of infrequent anti-TNF use in older patients in the included studies, our analysis might be underpowered to detect a statistically significant difference in those older than 65 years.

Subgroup analyses were performed to determine whether the risk of lymphoma changed across different study designs. Patients in RCTs probably do not characterize the average patient receiving anti-TNF agents (ie, patients in early clinical trials might be sicker than those who received the medication after Food and Drug Administration approval), but they might correspond to a group at a higher risk of disease and treatment-related complications. On the other hand, clinical trials oftentimes exclude those with significant comorbidities, so it is unclear which direction the bias might favor. The case series might be more representative of patients treated with anti-TNF agents in clinical practice and embody a broad range of patients

worldwide who have been treated in more diverse treatment settings. This subgroup had the highest rate of lymphoma, 18.8 per 10000 patient-years, which is nearly 2 per 1000 or 1 per 500 patient-years. This high rate was mostly driven by the study by Ljung et al,[16] which had 3 cases in only 202 patient-years. This study is the outlier in Figure 2 contributing significantly to the heterogeneity among the included studies. Although the SIR for the case series is statistically significant, it is with wide CIs based on the relatively small sample.

These results contribute to the growing body of knowledge about the risk of NHL in patients with CD, but some confounding might be present. The disease itself does not appear to carry an increased risk of lymphoma,[9,10] although this is controversial.42 It is important to note that almost all of the NHL patients had current or prior exposure to 6MP or azathioprine. Therefore, our rates of NHL are really reported rates of exposure to a combination of anti-TNF and immunomodulator therapy. Although numerically higher, this combination rate is not statistically higher than the Kandiel immunomodulator rate. This begs the question whether the major contributors to the increased risk are the immunomodulators or anti-TNF drugs. Patients in the study by Kandiel et al[11] overall had a longer period of follow-up than those included in the 26 studies for this analysis. Although we do not know whether NHL risk accumulates over time, it is possible that our estimate for immunomodulator alone is an overestimate of what the 1-year incidence would be. However, a recent large French analysis of the lymphoma rate with immunomodulator exposure (but very little anti-TNF exposure) corroborates the possibility that immunomodulators are significantly contributing to the risk.[43] On the basis of our analysis we cannot comment on the NHL risk associated with anti-TNF monotherapy. There simply have not been enough patients treated with anti-TNFs without immunomodulators to make any meaningful conclusions. Another possibility for confounding is radiation exposure. CD patients are potentially exposed to harmful levels of diagnostic radiation from repeated radiographic imaging,44 which might be associated with an increased risk of lymphoma.45 We were not able to ascertain the amount of radiation exposure in this analysis.

The most important limitation to this study is the lack of an ideal comparison group. Because the most common study design for anti-TNF agents includes an initial induction phase in which all patients receive active treatment, the control arms in the RCTs are not true placebo groups. A recent analysis compared adverse events between active and control arms in these anti-TNF RCTs and did not find a difference in lymphoma rates,[46] but because of the above reason we do not believe that this was an adequate comparison to anti-TNF unexposed patients. The case series did not have controls by design, and although the cohort studies did have matched controls, the selective nature of patient enrollment is concerning. Although suboptimal, we chose SEER as a comparator on the basis of the knowledge that the largest study of lymphoma risk in CD patients did not show an increased baseline risk when compared with the general population.[10] Because SEER is a US database and the included studies are international, we explored the variation of NHL rates worldwide. Although there is significant variation in the incidence of Hodgkin's lymphoma, the rate of NHL across continents is similar.[47] Therefore, we believe that SEER is a reasonable representation for comparison.

The time horizon of 1 year was used to give enough time for adverse outcomes to develop, but we do not know whether the lymphoma risk will continue (or accumulate) as time progresses. Dosing data are incomplete, and the question of how much exposure is needed to increase the risk of lymphoma remains unanswered, but it is concerning that at least 4 of the patients had received only 1 infusion of an anti-TNF agent. This might mean that even 1 dose is enough to increase the lymphoma risk, or alternatively, it might raise questions about the biologic plausibility of these cases being attributed to a single episode of exposure.

We did not calculate quality scores for the included articles. Because our primary outcome was an objective event (eg, lymphoma), we did not believe that classic measures of quality such as blinded outcome assessment would have an impact on reporting. In addition, because we did not use the comparison groups from the studies, details of the randomization process seemed less relevant. Concerns regarding attrition were investigated by the sensitivity analysis, and although sampling bias related concerns regarding generalizability remain, the inclusion of multiple study designs might attenuate these problems. A formal analysis of publication bias was not performed because we believed that plotting a "treatment effect" against sample size was not practically relevant to our analysis of rare adverse events. However, we did have a range of included studies, with the smallest study having 13.3 patient-years and the largest having 10,796 patient-years. The smallest study that identified a case of lymphoma included 67.4 patient-years.

Patients, parents of patients, and physicians are concerned about the risk of lymphoma and have different thresholds for how much risk they are willing to accept.[48–50] These results will help us understand the risk of NHL associated with anti-TNF and immunomodulator therapy and facilitate decisions about when it is most appropriate to use these agents. Although these estimates are a helpful step in determining treatment risks, further prospective data are necessary for a more accurate assessment. Large inception cohorts of patients with CD are being developed, and it will be critical to build monitoring of drug side effects into these programs.

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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

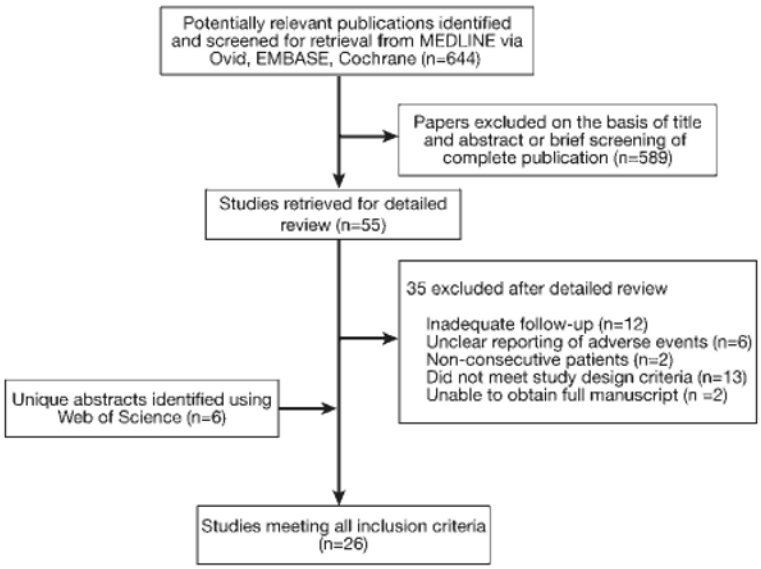

Figure 1.
Flow diagram of the studies identified in search, and reasons for study exclusion.

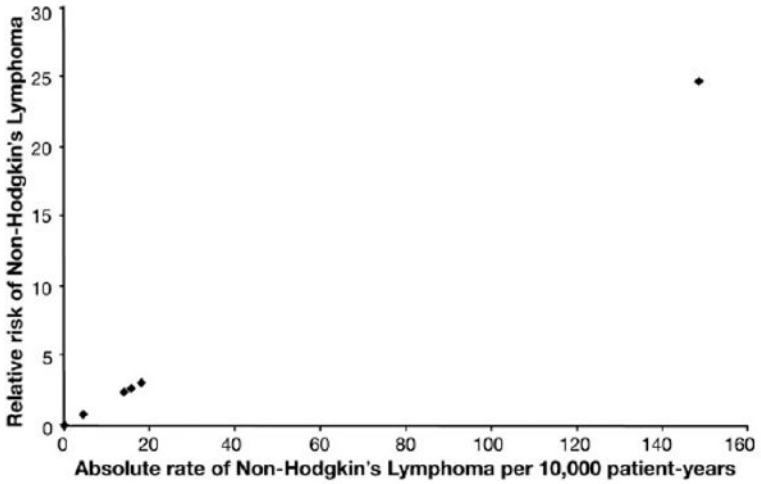

Figure 2.

Heterogeneity among the studies. The relative risk of NHL (compared with SEER) is plotted against the absolute rate per 10,000 patient-years for each study. Twenty of the 26 studies did not have any reported cases of lymphoma. The outlier study with the highest rate is Ljung et al.[16]

Table 1

Characteristics of Included Studies

Study	Year	Publication type	N	CD duration (*y*)[a]	Anti-TNF agent	% on IM[b]	Median follow-up (*wk*)	Patient-Years[c]	% Drop out	Number of NHL
RCT										
Colombel et al[27] (P3/4)	2007	Abstract	905	6	CTZ	NR	53	922.4	NR	0
Colombel et al[13] (OLE)	2007	Abstract	1169	NR	ADA	46.6	58	1299	1	0
Sandborn et al[18]	2007	Full	276	8.7	ADA	30.5	56	552	1.8	1
Lemann et al[15]	2006	Full	57	4.8	IFX	100	52	57.0	3.5	0
Schroder et al[31]	2006	Full	19	8.9	IFX	100	48	17.5	0	0
Mantzaris et al[14]	2004	Abstract	45	NR	IFX	53	60	51.9	0.04	0
Sands et al[3]	2004	Full	282	11.5	IFX	34.4	54	292.8	0	0
Hanauer et al[2]	2002	Full	573	8.2	IFX	29	54	595.0	0	0[d]
Rutgeerts et al[17]	1999	Full	73	10.4	IFX	35	48	67.4	0	1
Cohort										
Lichtenstein et al[7]	2007	Abstract	3396	10.7	IFX	49	201	13,126	21	6
Biancone et al[32]	2006	Full	404	9.5	IFX	53	109	846.8	0	0
Doumit et al[33]	2004	Abstract	322	13.7	IFX	88.2	104	644	0	1
Case series										
Carbone et al[21]	2007	Full	34	NR	IFX	48	52	159.5	0	0
Peyrin-Biroulet et al[36]	2007	Full	52	11	ADA	71	52	52.0	0	0
Hyder et al[23]	2006	Full	22	6	IFX	95	91	38.5	0	0
Pacault et al[40]	2006	Abstract	137	NR	IFX	NR	150	395.2	NR	0
Talbot et al[24]	2005	Full	21	6	IFX	57	87	35.1	0	0
Choi et al[22]	2005	Full	13	8.3	IFX	84.6	57	14.3	0	0
Ardizzone et al[20]	2004	Full	20	9	IFX	23.2	67	25.8	33	0
Colombel et al[35]	2004	Full	500	8	IFX	85	74	711.5	0	1

Study	Year	Publication type	N	CD duration (*y*)[a]	Anti-TNF agent	% on IM[b]	Median follow-up (*wk*)	Patient-Years[c]	% Drop out	Number of NHL
Rodrigo et al[37]	2004	Full	44	7.6	IFX	89	72	60.9	0	0
Schroder et al[38]	2004	Full	12	11.5	IFX	100	57.6	13.3	0	0
Seiderer et al[19]	2004	Full	92	8.4	IFX	82	113	199.9	0	0
Ljung et al[16]	2003	Full	191	NR	IFX	51	55	202.0	0	3
Kinney et al[25]	2003	Full	117	13.3	IFX	48	52	117.0	9.6	0
Cohen[34]	2000	Full	129	13.5	IFX	54	52	129.0	0	0

Abbreviations: IM, immunomodulator; N, total number exposed to anti-TNF; NR, not reported; P3/4, PRECISE 3/4; OLE, open label extension of GAIN and CHARM trials.

[a] Disease duration based on best estimate from available data; mixed reporting of mean and median.

[b] Patients taking concomitant IMs (azathioprine, 6MP, methotrexate) during study.

[c] Calculated by converting follow-up time from weeks to years and multiplying by total N.

[d] There was one NHL from Hanauer et al, but also reported in Ljung et al.

Table 2

Rate of NHL for SEER, Immunomodulator, and Anti-TNF Treated Patients

	NHL rate per 10,000 pt-yrs	SIR	95% CI
SEER all ages	1.9	—	—
IM alone[a]	3.6	—	—
Anti-TNF vs SEER	6.1	3.23	1.5–6.9
Anti-TNF vs IM alone	6.1	1.7	0.5–7.1

Abbreviation: IM, immunomodulator; pt-yrs, patient years.

[a] IM alone is the rate of NHL in CD patients from the Kandiel meta-analysis.[11]

Table 3

Age- and Gender-Specific NHL Rate and SIR

Age	Pooled NHL rate per 10,000 pt-yrs	SEER NHL rate per 10,000 pt-yrs	SIR	95% CI
20–54				
Male	5.9	1.1	5.4	1.3–18.1
Female	3.1	0.8	3.8	0.7–15.9
55–64				
Male	23	4.3	5.4	0.6–20.5
Female	8.5	3.2	2.7	0.1–15.9
65–74				
Male	27	8.4	3.2	0.1–18.4
Female	20.9	6.3	3.3	0.1–19.1
75+				
Male	91.5	13.2	6.9	0.2–39.3
Female	0	9.26	—	—

Table 4

Characteristics of Patients With NHL

	Age (*y*)	Gender	Agent	IM use	Type of NHL	Died & related to NHL[a]
1	70	M	IFX	AZA	B cell	NR
2	25	M	IFX	AZA	NK cell	Yes
3	79	M	IFX	No	B cell	Yes
4	24	F	IFX	NR	B cell	No
5	47	M	IFX	MTX	NR	Yes
6	61	M	IFX	H/o IM use	B cell	Yes
7	54	M	IFX	AZA	Parotid[b]	No
8	71	F	IFX	NR	B cell	No
9	55	F	IFX	AZA	NR	No
10	51	F	IFX	AZA	NR	No
11	42	F	IFX	AZA	T-cell	Yes
12	32	M	IFX	6MP	T-cell[c]	Yes
13	61	M	ADA	AZA	NR	No

Abbreviations: AZA, azathioprine; H/o, history of; IM, immunomodulator; MTX, methotrexate; NK, natural killer; NR, not reported.

[a] At last reported follow-up.

[b] No other information available.

[c] This T-cell lymphoma was a hepatosplenic T-cell lymphoma.

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Table 5

Sensitivity Analysis Excluding Studies With Drop-Out >15%[a]

Age (men)	Sensitivity analysis	NHL rate per 10,000[b]	SEER rate per 10,000[b]	SIR	95% CI
All	All studies	6.1	1.9	3.23	1.5–6.9
	>15% loss excluded	9.4		9.4	1.8–12.3
20–54	All studies	5.9	1.1	5.4	1.3–18.1
	>15% loss excluded	7.3		6.7	0.7–30.6
55–64	All studies	23	4.3	5.4	0.6–20.5
	>15% loss excluded	72		16.8	2.0–64.4
65–74	All studies	27	8.4	3.2	0.1–18.4
	>15% loss excluded	106		12.6	0.3–72.3
75+	All studies	91.5	13.2	6.9	0.2–39.3
	>15% loss excluded	370		28	0.7–159.1

[a] Excluding Lichtenstein 2007[7] and Ardizzone 2004

[b] per 10,000 patient-years.

Table 6

Subgroup Analysis by Study Design

Design	Lymphomas	Patient-Years	NHL rate per 10,000 pt-years	SIR*	95% CI
RCT	2	3860	5.2	2.6	0.19–35.7
Cohort	7	15,192	4.6	2.3	0.44–22.7
Case series	4	2125	18.8	9.4	1.35–104.0

*SIR compared with SEER.