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Is there truly a risk of lymphoma from biologic therapies?

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Abstract

The treatment of psoriasis has undergone a revolution with the advent of biologic therapies, including infliximab, etanercept, adalimumab, efalizumab, and alefacept. Biologics are generally safe and well tolerated. However, there has been concern over the risk of lymphoma with use of these agents due to their immunosuppressive properties. This review summarizes the current evidence in regards to lymphoma risk with biologic therapy obtained from case reports and case series, observational studies, clinical trials, and meta-analyses. The majority of data for T-cell inhibitors comes from case reports and relatively small, short term clinical trials. In addition to published case reports and case series, TNF- α inhibitors have also been studied extensively in large cohort studies and meta-analyses of clinical trials derived primarily from the rheumatoid arthritis population. Current data are not sufficient to completely rule out an increased risk of lymphoma associated with biologics, nor has a causal relationship between lymphoma and biologics been well established. Short- to intermediate-term treatment with biologics (e.g. up to 4 years) appears to be very safe with respect to lymphoma risk, especially with TNF- α inhibitors in which their potential risks appear to be well defined. Continued vigilance is warranted, however, in the appropriate patient, the risk-to-benefit profile of psoriasis treatment with respect to lymphoma risk appears highly favorable.

Keywords

lymphoma; biologics; TNF inhibitor; alefacept; efalizumab; infliximab; adalimumab; etanercept; psoriasis; pharmacovigilance

Introduction

Psoriasis is a common, chronic inflammatory disease of the skin and joints which is associated with impairment in health related quality of life even in mild cases and excess cardiovascular risk and all-cause mortality in patients with severe disease.^{1–5} The pathophysiology of psoriasis involves excess Th1 and Th-17 lymphocyte activity, increased activity of antigen presenting cells, production of inflammatory cytokines such as TNF- α and IFN- γ , epidermal hyper-proliferation, and angiogenesis.^{6, 7} In the last decade, the treatment of psoriasis has undergone a revolution with the advent of biologic therapies which selectively target and suppress inflammatory pathways involved in the pathogenesis

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of psoriasis. Biologics are generally very safe and well tolerated therapies; however, due to their immunosuppressive properties, the risk of lymphoma associated with these agents has been of potential concern.⁸⁻¹¹

Psoriasis is the only dermatologic condition in which biologics are approved for use by the Food and Drug Administration. The biologic agents used for this disease include the TNF- α inhibitors, etanercept, infliximab, and adalimumab, as well as T-cell inhibitors efalizumab and alefacept.¹² The TNF- α inhibitors also have several other indications outside of dermatology. Efalizumab and alefacept, which inhibit T-cell function through the binding of CD11a and CD2, respectively, are indicated for use only in plaque psoriasis (see Table 1).¹³⁻¹⁴ In addition to the treatment of psoriasis, these drugs are often used off-label in a variety of other inflammatory conditions within dermatology with varying success.¹⁵⁻¹⁶

Examining the risk of lymphoma with biologic use is complicated by several factors. First, although lymphoma is of public health importance (it is the fifth most common cause of cancer), it is statistically rare, affecting about 1 in 5000 people per year.¹⁷⁻¹⁸ Therefore, very large studies are necessary in order to yield adequate statistical power to detect clinically significant lymphoma risks of biologics. Second, many patients treated with biologics have received immunosuppressants such as methotrexate, cyclosporine, or azathioprine, either in the past, or concurrently with biologics, which themselves potentially can increase the risk of lymphoma. Consequently, it is difficult to determine which drug, or combination of treatments, meaningfully impacts lymphoma risk. Finally, the disease indications for biologics themselves may be associated with an increased risk of lymphoma due to the chronic lymphoproliferation which characterizes these conditions.¹⁹⁻²⁰ For example, rheumatoid arthritis, psoriasis, and inflammatory bowel disease (IBD) have all been shown to be associated with an increased risk of lymphoma in some, but not all studies.²¹⁻²⁵ This association can lead to channeling bias (also called confounding by indication or protopathic bias), a form of selection bias in which the indication for the treatment under study is itself a risk factor for the outcome of interest.²⁶

The purpose of this review is to evaluate evidence of lymphoma risk from biologics based on a variety of approaches ranging from case reports/case series, observational cohort studies, randomized controlled trials, and meta-analyses of randomized controlled trials (RCT). The most scientifically valid evidence is generally derived from clinical trials and in some instances, well-controlled observational studies. The TNF- α inhibitors, infliximab and etanercept, have been approved for use in rheumatoid arthritis and Crohn's disease for over 10 years. Thus, most of the better designed studies evaluating the risk of lymphoma with biologics are derived from studies of patients with RA or IBD treated with TNF- α inhibitors.

Search Strategy

We searched EMBASE and MEDLINE from inception to January 2009 for case reports, case series, observational studies, clinical trials, and meta-analyses using combinations of the following key words: "biologic," "lymphoma," "hematologic," "malignancy," "infliximab," "etanercept," "adalimumab," "alefacept," "efalizumab," "TNF," "tumor necrosis factor," "psoriasis," "Crohn's disease," and "rheumatoid arthritis." For clinical trial data, we additionally searched the pertinent US Food and Drug Administration (FDA) database (<http://www.fda.gov>) and the Prescribing Information documents for each biologic agent. We included all published case reports and case series that described the development of lymphoma during biologic therapy, as well as data from published FDA reports. Unpublished case reports (e.g. those only reported to the FDA) were excluded. Seven observational studies analyzed the risk of lymphoma in patients treated with biologic agents, all of which are included in this review. For controlled and open-label extension clinical

trials, we included only those published reports that specifically examined lymphoma risk and pooled data from multiple studies. For the meta-analyses, we included studies that assessed the risk of malignancy and/or the risk of lymphoma associated with biologic therapy. The risk of lymphoma associated with biologics under investigation for psoriasis, and not yet approved by the FDA at the time our search was conducted, is not included in this review.

Evidence from Case Reports and Case Series

Case reports are primarily useful for safety signal detection. A safety signal is defined by the World Health Organization as “A set of data constituting a *hypothesis* that is relevant to the rational and safe use of a drug in humans.” Case report data need to be interpreted with caution and they are not a reliable means of assessing the incidence of a potential safety issue due to serious under-reporting of events in the MedWatch system.²⁶ Overall, we identified 27 published case reports²⁷⁻⁴⁸ and an additional 48 reports in three case series, ⁴⁸⁻⁵¹ for a sum of 75 cases describing the development of lymphoma in patients during treatment with one or more biologic (see Table 2 and Table 3). The three case series were based on records obtained from the FDA's Adverse Event Reporting (AER) and MedWatch databases.⁴⁹⁻⁵¹⁻⁵² Of special interest is the cluster of 18 patients reported to the FDA who developed hepatosplenic T-cell lymphoma (HSTCL), an extremely rare malignancy.⁵² Except for 1 patient who had received monotherapy with adalimumab for rheumatoid arthritis, all patients had been exposed to infliximab and had IBD. The large majority of the patients were young males (16/18 male, median age of 22) and almost all (17/18) were receiving combined thiopurine/anti-TNF treatment. Two of these patients were receiving adalimumab along with infliximab and a thiopurine. As there is no effective therapy for HSTCL, all cases were fatal. HSTCL is a rare clinicopathological entity, usually of cytotoxic, $\gamma\delta$ T-cell origin.⁵³ Although the incidence of this disease is unknown, about 200 cases have been reported since its first description in 1981. About one-third of the cases have been associated with immunosuppression, with the majority having occurred *de novo*.⁵⁴⁻⁵⁵

Excluding HSTCL, most of the published case reports occurred in patients with RA (29 out of the remaining 57). For all diseases combined, B-cell non-Hodgkin's lymphomas (NHL) comprised the majority of the types of lymphomas reported (34/57), with large B-cell lymphoma being the most common (15/57). Overall, 13 case reports did not specify the type of B-cell NHL. Cutaneous T-cell lymphoma (CTCL) and Hodgkin's lymphoma also occurred, with 9 and 7 case reports, respectively. Overall, 40 out of 65 patients (61.5%) with a case report detailing their treatment history were receiving concomitant immunosuppressive therapy.

In 6 case reports of patients who developed lymphoma or a lymphoproliferative disorder (LPD) the condition spontaneously regressed after withdrawal of all systemic agents, demonstrating reversibility.³⁴⁻³⁵⁻³⁷⁻⁴⁶⁻⁴⁹ One patient was missing information regarding alternate therapy, but 4 out of the remaining 5 patients were on concomitant systemic immunosuppressive therapies (2 with MTX, 1 with cyclosporine, 1 with MTX and prednisone, and 1 with MTX and another biologic), which were stopped as well when the lymphoma occurred. Reversibility has also been well-documented in the context of lymphomas associated with MTX and cyclosporine therapy.⁵⁶⁻⁵⁷ Notably, 2 deaths were reported in patients in whom a previously diagnosed NHL considered to be in remission recurred upon initiation of etanercept therapy.⁴⁹ No information was given regarding the time interval between lymphoma remission and the start of etanercept. Conversely, there have also been case reports of individuals with a history of lymphoma, LPD, and multiple myeloma receiving biologic therapy without any adverse events.²⁸⁻³⁴⁻⁵⁸⁻⁵⁹ Moreover,

there is a case report of an individual being successfully treated with alefacept for patch-stage, biopsy-proven mycosis fungoides which was refractory to other treatments.⁶⁰

There have been at least 10 published case reports (12 including 2 case reports within a case series without detailed information) of lymphoma or a LPD developing specifically in psoriasis patients.^{28, 29, 33, 34, 37, 44, 48, 49, 61} Nine patients were receiving 1 biologic agent at the time of diagnosis of lymphoma (3 with efalizumab, 3 with etanercept, 2 with infliximab, and 1 with alefacept). The remaining 3 patients were receiving two concomitant biologic agents (2 with efalizumab and infliximab and 1 with efalizumab and etanercept, along with MTX). The majority were male (8/10), and the most common type of lymphoma was CTCL (4/10). The 4 cases of CTCL occurred in patients receiving alefacept, infliximab, etanercept, and dual therapy with infliximab and efalizumab. The other types of lymphoma included cases of 2 unspecified B-cell NHLs, 1 LPD, 1 EBV positive large B-cell lymphoma, 1 Hodgkin's lymphoma, and 1 gastric MALT lymphoma. 3 cases were missing information regarding other treatments, but 4 out of the 9 patients with detailed treatment histories were receiving dual immunosuppressive treatment at the time of the diagnosis of lymphoma, with 3 out of the 4 receiving two concomitant biologic agents and 1 patient receiving cyclosporine concomitantly with infliximab. Two cases were known to be fatal

In a few case reports of lymphoma developing in patients with psoriasis, the authors felt that the lymphoma had been present before the start of biologic therapy, and that the treatment allowed the lymphoma cells to grow unopposed.^{44, 62, 63} In two of these cases, an initial diagnosis of psoriasis was made which was retrospectively proven to be CTCL by biopsy. Both lymphomas rapidly progressed after initiation of biologic therapy (etanercept in one case and efalizumab in the other). In another case, a patient with presumed psoriasis refractory to all treatments received alefacept and later developed large T-cell lymphoma arising as a transformation of mycosis fungoides. Thus, caution should be used in any patient with a lymphoproliferative disorder in remission, uncertain immune status, or any suspicion of occult malignancy. In addition, skin biopsies should be considered in patients with clinical features suggestive of CTCL or in patients whose disease fails to respond or gets worse during treatment with a biologic.

Evidence from Observational Cohort Studies

Several large observational studies have assessed the risk of lymphoma in association with TNF- α inhibitor therapy, all using patients with rheumatoid arthritis as their study population. In general, these studies compared TNF- α inhibitor treated patients to varying reference groups of RA patients. Mean durations of TNF- α inhibitor treatment ranged from 1.0 to 3.7 years. Several studies also computed standardized incidence ratios (SIR), which compared the lymphoma risk in patients receiving TNF- α inhibitors to the general population. The SIR is the ratio of the observed to the expected new cases of cancer, with the expected number of new cases being derived from population-based registries, such as the Surveillance, Epidemiology and End Results (SEER) database (see Table 4). RA has been consistently associated with an increased risk of lymphoma that is positively correlated with measures of inflammatory activity independent of treatment.^{21, 23} Accordingly, we expect the SIR to be elevated in these study populations.

Wolfe et al conducted a prospective cohort study of 18,752 patients enrolled in a U.S. national RA database from 1998-2002.⁶⁴ Of these patients, 8614 were receiving infliximab or etanercept. They found an elevated SIR in the TNF- α inhibitor treatment group (2.9; 95% CI 1.7, 4.9) compared to the overall study population (1.9; 95% CI 1.3, 2.7). The authors concluded that lymphoma is increased in RA compared with the general population, but noted that the RA patients receiving TNF- α inhibitor therapy during this time represented

those with the most severe disease. As this study lacked a control group with RA, they could not rule out the possibility that disease activity played an important role in their findings (e.g. channeling bias).

In an update of this article in 2007, Wolfe et al expanded their study population to 19,562 patients with 89,710 person-years of follow-up.⁶⁵ They also compared the risk of lymphoma in RA patients who received TNF- α inhibitor therapy (etanercept, infliximab, and adalimumab) to those who did not receive TNF- α inhibitor therapy, and found an adjusted odds ratio (OR) of 1.0 (95% CI 0.6, 1.8; [p = 0.875]). Furthermore, they found that the combination of TNF- α inhibitor therapy and MTX did not increase the risk of lymphoma (OR of 1.1 (95% CI 0.6, 2.0; [p=0.710])). In another study, the same authors assessed the risk of all types of malignancy with biologic therapy (infliximab, etanercept, adalimumab, and anakinra), and found that use was associated with an increased risk for non-melanoma skin cancer OR of 1.5 (95% CI 1.2, 1.8; [p < 0.001]) and melanoma (OR of 2.3 (95% CI 0.9, 5.4; [p = 0.70])), but not with lymphoma OR of 1.0 (95% CI 0.6, 1.8; [p = 0.967]) or any solid tumors.⁶⁶ The association with melanoma, however, was not statistically significant, and therefore, could be due to chance.

Using data from southern Sweden registries, Geborek et al examined whether TNF- α inhibitors increased cancer risk in patients with RA.⁶⁷ They compared 757 patients treated with etanercept or infliximab to 800 RA patients with conventional anti-rheumatic treatment from 1999-2002. In the TNF- α inhibitor group, 5 lymphomas were identified in 1603 person-years at risk (SIR of 11.5 (95% CI 3.7, 26.9)), and 2 lymphomas were identified in the reference group with 3948 person-years at risk (SIR of 1.3 (95% CI 0.2, 4.5)). After adjusting for age, sex, and disease severity, the hazard ratio was 5.0 (95% CI 0.9, 27.9; [p = 0.06]). However, as noted by Franklin et al in an accompanying editorial,⁶⁸ this value must be interpreted with caution due to the limited number of observations (7 lymphomas total) and relatively short follow-up period, both of which are reflected in the wide CI. Additionally, the authors noted that the small number of lymphomas likely limited their ability to adjust for disease severity.

Another study using data from Swedish registries by Askling et al compared RA patients receiving TNF- α inhibitor therapy to two separate cohorts in an attempt to adjust for channeling bias: an inpatient cohort of prevalent RA patients and an outpatient cohort of incident RA patients.⁶⁹ The SIR for the inpatient (1.9; 95% CI 1.7, 2.1) and outpatient (2.0; 95% CI 1.0, 3.5) cohorts were found to be similar. Compared with the prevalent and incident RA cohorts, the adjusted relative risk of lymphoma in the TNF- α inhibitor cohort was 1.1 (95% CI 0.6, 2.1). Interestingly, the authors also examined the characteristics of the 9 lymphomas identified in the TNF- α inhibitor cohort. They found that the distribution of subtypes of lymphoma was similar to that seen in RA patients naïve to TNF- α inhibitor treatment and that only 1 of the 9 lymphomas was EBV positive, thus providing some evidence against immunosuppression as the cause.^{70, 71}

Combining information from a large health care utilization database from 3 regions in the US and Canada, Setoguchi et al conducted a cohort study of RA patients above 65 years of age.⁷² They identified a cohort of 1152 patients treated with biologic agents, as well as a cohort of 7306 patients treated with MTX, but never with biologics. After adjusting for region, age, sex, and RA drug use, a comparison of the two cohorts revealed an HR of 1.11 (95% CI 0.51, 2.37) for lymphoproliferative disorders. In addition, using RA-related surgery, extraarticular manifestations, and a C-reactive protein test ordered as markers of disease severity, the authors found that biologic users had overall more severe RA than MTX users.

Asklund et al recently published a study evaluating lymphoma risk with TNF- α inhibitor therapy.⁷³ Using the Swedish Biologics Register and other Swedish registries, the authors assembled a cohort of 6604 TNF- α inhibitor treated RA patients, as well as a comparison group of 67,743 TNF- α inhibitor naïve RA patients. Overall, 336 lymphomas occurred in the TNF- α inhibitor naïve group compared to 26 lymphomas in the TNF- α inhibitor therapy group, yielding a non-significant increase in lymphoma risk with an adjusted RR of 1.35 (95% CI 0.85, 2.11). Stratifying this data, the authors found that the slightly increased RR was entirely accounted for by those patients starting TNF- α inhibitor therapy from 1998-2001 (RR of 1.62), while those patients who started therapy 2002-2006 had a decreased RR of 0.90. Unfortunately, no CI was reported for these stratified RR. Of note, there was a linear trend of declining disease severity among patients at the start of TNF- α inhibitor therapy from 1999 through 2006, suggesting that channeling bias may have contributed to the reported RR in the 1998-2001 TNF- α inhibitor treatment group. Additionally, the authors found no evidence of any difference in relative risk between the three TNF- α inhibitors (etanercept, infliximab, and adalimumab) which ranged between 1.2 and 1.5; however, the authors noted that precision was limited and the CIs were not reported.

Evidence from Controlled Clinical Trials, Open-Label Extension Trials, and Meta-Analyses

Gathering evidence from clinical trials is challenging. Reports of lymphoma in individual clinical trials are rare due to the infrequent nature of malignancy and the relatively brief duration of clinical trials. Thus, individual clinical trials have not been adequately powered to detect differences in rates of lymphoma between placebo and treatment groups. Therefore, the most useful information derived from clinical trials in regards to lymphoma risk with the use of biologics is from studies or reports that have pooled results across trials.

In response to the numerous reports of lymphomas through post-marketing passive surveillance programs, the FDA convened a meeting in March 2003 to summarize safety information for all of the TNF- α inhibitors.⁷⁴⁻⁷⁷ The available data from controlled portions of clinical trials was presented. During etanercept trials, 1 lymphoma developed in the treatment group (n = 2502), and none developed in the placebo group (n = 921). In trials with infliximab, 6 lymphomas developed in the treatment group (n = 2421), while none were observed in the placebo group (n = 489). Similarly, in trials with adalimumab, no lymphomas occurred in the placebo group (n = 690), but 2 were observed in the treatment group (n = 1380). However, none of these differences were statistically significant.

Several studies pooled together data from RCT and open-label extension trials to examine lymphoma risk. As there are no placebo groups in extension trials, the lymphoma rates were compared to the general population using SIR. This approach has the advantage that safety data are actively collected in these studies, avoiding the problem of serious under-reporting of adverse events in the passive, spontaneous reporting system (e.g. MedWatch).²⁶ The 2003 FDA report included combined data from RCT and open-label extension trials for each TNF- α inhibitor. The calculated SIR were 2.31 (95% CI 0.85, 5.03) for etanercept with 7364 person-years of follow-up, 6.98 (95% CI 2.56, 15.19) for infliximab with 4116 person-years of follow-up, and 5.42 (95% CI 2.6, 10.0) for adalimumab with 5760 person-years of follow-up.

More recently, Schiff et al analyzed safety data for adalimumab treated patients from randomized control trials, open label extensions, and 2 phase IIIb open label trials through April 2005.⁷⁸ This analysis included 10,050 patients with 12,506 patient-years of follow-up. Overall, 15 lymphomas were observed, with an incidence rate of 0.12/100 person-years. The

SIR compared to the SEER database was 3.19 (95% CI 1.78, 5.26), consistent with rates reported in RA patients naïve to TNF- α antagonists.²¹

In a review of malignancies observed with efalizumab, Leonardi et al pooled patient data from 14 phase III placebo-controlled, open-label clinical trials involving 2980 patients treated with efalizumab.⁷⁹ In patients treated with efalizumab, 3 cases of LPD were reported in 2558 patients-years of follow-up, yielding an incidence rate of 0.12 per 100 patient years. This rate was within the range of lymphomas reported in 2 external cohorts of patients with moderate to severe psoriasis (0.17 and 0.13), identified through insurance claims databases. Unfortunately, odds ratios with 95% CI's were not reported. There were 0 cases of LPD in placebo-treated patients; however, there were only 185 patients-years of follow-up in this group. To our knowledge, there have been no published pooled clinical trials to date that have assessed the risk of lymphoma specifically with the use of alefacept.

There have been several meta-analyses of RCT that have pooled together data from multiple TNF- α inhibitors to evaluate the safety of these drugs (see Table 5). This approach has the advantage of improving the statistical power to detect potentially meaningful increases in the risk of lymphoma associated with these agents. However, clinical trials often have shorter durations of follow-up in placebo groups compared to treatment groups due to higher rate of treatment failure in the former. This could potentially lead to false estimates as it hinders the assessment of adverse events in the control group.

Bongartz et al conducted a meta-analysis of 9 randomized, placebo-controlled trials of infliximab and adalimumab in patients with RA, with 3493 patients receiving treatment and 1512 patients receiving placebo.⁸⁰ They found that the OR for overall malignancy was 3.3 (95% C.I. 1.2, 9.1), and that the most common malignancy was non-melanoma skin cancer. Additionally, the risk of malignancy was found to be dose-related, with an increased OR 4.3 (95% CI 1.6, 11.8) for high-dose TNF- α inhibitor therapy. They did not calculate a separate OR for lymphoma; however, lymphoma was the second most frequent malignancy reported, with 10 cases observed in the treatment group and 0 in the placebo group. This meta-analysis has been criticized because the analyses did not adjust for duration of exposure and that the study did not include etanercept.⁸¹ This report was later supplemented with additional trials, which resulted in a decreased OR for overall malignancy of 2.4 (95% C.I. 1.2, 4.8).⁸²

Bongartz et al later conducted another meta-analysis specifically to evaluate etanercept.⁸³ Pooling together 9 clinical trials with 2244 patients who received etanercept (2484 person-years) and 1072 who received placebo (1051 person-years), the authors found a hazard ratio of 1.84 (95% CI 0.79, 4.28) for the etanercept group compared to placebo. They used individual patient data (IPD) survival analysis to adjust for higher loss to follow-up in the control groups. Malignancies were diagnosed in 26 patients receiving placebo and 7 in the control group. Due to the wide CI, the results were not statistically significant. There was only 1 case of lymphoma (Hodgkin's lymphoma) in the etanercept treated group, and none in the placebo group. The authors performed additional analyses to assess the effect of time period of exposure and dose, and found that it did not significantly impact the results of the study. They also assessed completeness of follow-up and attrition, and found that 42.2% of patients in the control arms discontinued study treatment versus 25.6% in the treatment group. However, follow-up data beyond the date of discontinuation were available for 90.8% in treatment arms versus 92.7% in the control arms. The most common reasons for early discontinuation in both groups were adverse events and lack of efficacy.

To assess the safety of the three most commonly used TNF- α inhibitors, Leombruno et al analyzed data derived from 18 randomized trials for etanercept, infliximab, and

adalimumab, involving 8808 RA subjects.⁸⁴ Over an average of 0.85 years of treatment, 5 lymphomas were observed in the treatment group (4099 patients with 3805 person-years), while 1 lymphoma was observed in the placebo group (2672 patients with 2124 person-years). In this study, 57% of patients were reported to have been receiving concomitant therapy with methotrexate. With recommended doses of TNF- α inhibitor agents, the authors found no significant increase in the odds of lymphoma (OR of 1.26 (95% CI 0.52, 3.06)). In addition, the authors analyzed the effect of high doses of adalimumab and infliximab (mean dose of 49 mg/week for adalimumab and 1.16 mg/kg/wk for infliximab). They found a higher risk of serious infection (OR of 2.07 (95% CI 1.31, 3.26)), but risk of death, serious adverse events, overall malignancy, and lymphoma (OR of 1.14 (95% CI 0.28, 4.61) with 1621 patient-years of follow-up derived from 8 RCTs) were not increased.

In the only meta-analysis to analyze Crohn's disease patients specifically, Peyrin-Biroulet et al pooled data from 21 luminal Crohn's disease trials to compare the overall and individual safety of 6 TNF- α inhibitors (infliximab, adalimumab, certolizumab, etanercept, oncept, and CDP571).⁸⁵ There were 3341 patients in the TNF- α inhibitor groups and 2051 patients in the control groups with a median follow-up time of 24 weeks. There was no reported difference in overall malignancies between the TNF- α inhibitor treated group ($n = 8$) and the control group ($n = 8$), with a relative risk difference of -0.14% (95% CI -0.4, 0.2; [$p = 0.309$]). Unfortunately, this study did not report the types of malignancies observed.

Discussion

The advent of biologic therapies has dramatically advanced the treatment of psoriasis. Nevertheless, the risk of lymphoma associated with these agents remains controversial. The T-cell inhibitors alefacept and efalizumab have relatively limited (e.g. adequately powered) long-term safety data with respect to malignancy. The observation of lymphomas associated with T-cell inhibitors in case reports and clinical trials indicates the need for appropriately powered long-term follow-up studies to determine the risk of lymphoma associated with these agents.

Compared to T-cell inhibitors, the TNF- α inhibitors have been extensively studied across multiple indications (primarily RA and IBD). Case reports have established that lymphomas may regress in some patients with withdrawal of immunosuppressive therapy. Case reports have also indicated that an extremely rare, but universally fatal lymphoma (e.g. hepatosplenic) may occur in patients treated with the antibody TNF- α inhibitors, particularly when used in combination with thiopurines in patients with IBD. As mentioned previously, many of the systemic immunosuppressive agents used in severe RA, IBD, psoriasis, and other chronic inflammatory diseases have been associated with an increased risk of lymphoma.⁸⁶⁻⁹¹ Prior to this case series, there had been 6 cases of HSTCL reported in patients treated with a thiopurine utilized alone for IBD. These observations seem to suggest that there may be a synergistic effect with infliximab and thiopurines, although it is also possible that the heightened awareness of this rare disease resulted in an increase in reported cases above that seen with thiopurines alone. It is likely that the absolute risk of HSTCL associated with TNF- α inhibitors is very low, given that they have not been observed outside of spontaneous reports. To date, there is no evidence of these agents inducing HSTCL in patients with psoriasis, where combination therapy with thiopurines is rare.

Data from observational studies, clinical trials, and meta-analyses have generally indicated a favorable risk profile of TNF- α inhibitors with respect to lymphoma. Observational studies have generally not found an increased risk of lymphoma above what is expected for the disease being treated. Additionally, these large studies generally have narrow 95% confidence intervals and they are, therefore, able to rule out all but very slight increases in

risk associated with these agents. Meta-analyses of randomized controlled studies, which limit the concerns of channeling bias associated with observational studies have also failed to show a statistically significant risk of lymphoma with TNF- α inhibitors. Although meta-analyses of RCT are considered the gold standard of evidence based medicine, in this instance, they are poorly suited to fully address lymphoma risk due to the short duration of exposure to these agents as well as relatively limited statistical power to rule out associations which may be clinically important. Additionally, the existing evidence from observational studies and clinical trials is primarily derived from the RA and IBD populations where combination therapy with other immunosuppressants is more often used. Therefore, the generalizability of these results to the psoriasis population is uncertain.

Conclusions

In summary, current data are not sufficient to rule out an increased risk of lymphoma associated with biologics, nor has a causal relationship between lymphoma and biologics been well established. Short-term treatment with biologics (e.g. up to 4 years) appears to be very safe with respect to lymphoma risk, especially with TNF- α inhibitors in which their potential risks appear to be well defined. Continued vigilance is warranted; however, in the appropriate patient, the risk to benefit profile of biologic treatment of psoriasis with respect to lymphoma risk appears highly favorable.

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Table 1

Indications for Biologic Agents used for Psoriasis

Drug	Mechanism of Action	Indication	Year of FDA Approval
Etanercept	TNF- α antagonist	Rheumatoid Arthritis	1998
		Juvenile Idiopathic Arthritis	1999
		Psoriatic Arthritis	2002
		Ankylosing Spondylitis	2003
		Plaque Psoriasis	2004
Infliximab	TNF- α antagonist	Crohn's Disease	1998
		Rheumatoid Arthritis	1999
		Ankylosing Spondylitis	2004
		Psoriatic Arthritis	2005
		Ulcerative Colitis	2005
		Plaque Psoriasis	2006
Adalimumab	TNF- α antagonist	Rheumatoid Arthritis	2003
		Psoriatic Arthritis	2005
		Ankylosing Spondylitis	2006
		Crohn's Disease	2007
		Juvenile Idiopathic Arthritis	2008
		Plaque Psoriasis	2008
Alefacept	T-cell inhibitor	Plaque Psoriasis	2003
Efalizumab	T-cell inhibitor	Plaque Psoriasis	2003

Table 2**Patient and Treatment Characteristics in Case Reports**

Characteristic (n = 75 unless otherwise noted)^a	No. (percentage)
Sex (n = 73) ^b	
Male	48 (65.8)
Female	25 (34.2)
Age, y (n = 73) ^b	
Mean (median) [25 th percentile, 75 th percentile]	50.4 (55) [34, 66]
Drug	
Infliximab	41 (54.7)
Etanercept	22 (29.3)
Efalizumab	3 (4)
Adalimumab	3 (4)
Alefacept	1 (1.3)
Efalizumab + infliximab	2 (2.7)
Adalimumab + infliximab	2 (2.7)
Efalizumab + etanercept	1 (1.3)
History of systemic therapy (Prior or concomitant) (n = 68) ^c	
None	5 (7.4)
At least 1 systemic therapy	63 (92.6)
Alternate biologic therapy	8 (11.8)
Methotrexate	29 (42.6)
Systemic corticosteroids	26 (38.2)
Azathioprine	23 (33.8)
6-Mercaptopurine	10 (14.7)
Cyclosporine	5 (7.4)
Mycophenolate mofetil	1 (1.5)
Unknown	7 (10.3)
Concomitant systemic therapy (n = 65) ^d	
None	25 (38.5)
At least 1 systemic therapy	40 (61.5)
Alternate biologic therapy	5 (7.7)
Methotrexate	18 (27.7)
Systemic corticosteroids	17 (26.2)
Azathioprine	12 (18.5)
6-Mercaptopurine	9 (13.8)
Cyclosporine	1 (1.5)
Mycophenolate mofetil	0
Unknown	10 (15.4)

Characteristic (n = 75 unless otherwise noted) ^a	No. (percentage)
Disease	
Rheumatoid arthritis	29 (38.7)
Crohn's disease	24 (32)
Psoriasis	12 (16)
Ankylosing spondylitis	3 (4)
Ulcerative colitis	3 (4)
Dermatomyositis	1 (1.3)
Other/not specified	3 (4)

^aThis number includes 18 reported cases of hepatosplenic T cell lymphoma.

^b2 cases did not report sex or age of patient.

^cSeven case reports did not include information regarding prior or concomitant systemic therapies.

^dTen case reports did not include information regarding concomitant systemic therapies or did not differentiate between prior and concomitant therapies.

Table 3**Lymphoma Characteristics in Case Reports**

Characteristic (n = 75 unless otherwise noted)	No. (percentage)
Time since first exposure to biologic and development of lymphoma, months (n = 61)	
Mean (median) [25 th percentile, 75 th percentile]	11.8(8), [2, 17]
Type of lymphoma	
B-cell non-Hodgkin's lymphoma (NHL): Total	34 (45.3)
Large cell	15 (20)
Mantle cell	3 (4)
MALT	2 (2.7)
Burkitt's	1 (1.3)
Plasmablastic	1 (1.3)
Other/not specified	12 (16)
T-cell lymphoma: Total	29 (38.7)
Hepatosplenic T-cell lymphoma	18 (24)
Cutaneous T-cell lymphoma	9 (12)
Not specified	2 (2.7)
NHL Not specified	2 (2.7)
Hodgkin's Lymphoma	7 (9.3)
Multiple myeloma	1 (1.3)
Cases of lymphoproliferative disorders (LPD)	2 (2.7)
Outcomes:	
Cases that resolved without treatment after discontinuing immunosuppressants	6 (8)
Remission/Regression with therapy	17 (22.7)
Fatal Cases	24 (32)
Unknown	28 (37.3)

Observational Studies

Table 4

Author	Study years	Biologic therapies	Disease	Anti-TNF- α Treatment Group				Reference Group				Comparison of Anti-TNF- α and Reference Groups (95% CI)		
				No. of Lymph.	No. of pts	Person-years of follow-up	SIR (95% CI) ^e	No. of Lymph.	No. of pts	Person-years of follow-up	SIR (95% CI) ^e			
Wolfe et al ⁶⁴	1998-2002	Inf, etan	RA	14	8,614	10,012	2.9 (1.7,4.9)	29	18,574	29,314	1.9 (1.3,2.7)	All RA patients / all treatments		
Wolfe et al ⁶⁵	1998-2006	Inf, etan, ada	RA	43	10,815	----	----	50	8,747	Overall: 89,710 ^b	Overall: 1.8 (1.5,2.2)	Anti-TNF- α naïve RA patients	Adjusted Odds Ratio ^c	1.0 (0.6,1.8) p = 0.71
Wolfe et al ⁶⁶	1998-2005	Inf, etan, ada, anakinra	RA	23	2,221	----	----	22	3,680	----	----	Anti-TNF- α naïve RA patients	Adjusted Odds Ratio ^d	1.0 (0.5,2.0)
Geborek et al ⁶⁷	1999-2002	Inf, etan	RA	5	757	1,603	11.5 (3.7, 26.9) ^e	2	800	3,948	1.3(0.2,4.5) ⁱ	Anti-TNF- α naïve RA patients	Adjusted Hazard ratio ^f	5.0 (0.9, 27.9) p = 0.06
Askling et al ⁶⁹	1990-2003	Inf, etan, ada	RA	9	4,160	9,715	2.9 (1.3, 5.5) ^g	319	53,067	297,102	1.9 (1.7, 2.1) ^k	All RA patients / all treatments	Adjusted Relative Risk ^h	1.1 (0.6,2.1)
Setoguchi et al ⁷²	1994-2004	Inf, etan, anakinra	RA	4	1,152	2,940	----	54	7,306	30,300	2.2 (1.71,2.87) ^j	RA patients with MTX use and no biologic use	Adjusted Hazard Ratio ^j	1.11 (0.51,2.37)
Askling et al ⁷³	1998-2006	Inf, etan, ada	RA	26	6,604	26,981	----	336	67,743	365,026	----	Anti-TNF- α naïve RA patients	Adjusted Relative Risk ^k	1.35 (0.82,2.11)

^aSIR = Standardized Incidence Ratio. Compared rates in TNF- α treatment group with population rates using the US National Cancer Institute SEER (Surveillance, Epidemiology, and End-Results) database unless otherwise noted.

^bPerson-years of follow-up and SIR were reported for all study participants, and were not reported separately for the TNF- α treatment group and comparison group.

^cAdjusted for initial age, sex, education level, smoking, health insurance, and initial values for age, Health Assessment Questionnaire score, prednisone use, and lifetime count of DMARDs.

^dAdjusted for age, sex, education, smoking, baseline Patient Activity Scale score, and baseline prednisone use.

^eCalculated using cancer incidence in the South Swedish healthcare region, stratified for sex, age, and calendar year.

^fAdjusted for age, sex, and disease severity.

^gCompared to the Swedish Population Register.

^hAdjusted for age, sex, and duration of disease.

S_{IR} in this study was computed using entire study population, including those in the TNF- α treatment group and those in the reference group.

j Stratified Cox proportional hazards model by region, with study time as a time scale and adjustment for RA drug use and propensity score as a continuous variable.

k Adjusted for attained age and calendar time.

Meta-analyses of Clinical Trials for TNF- α Inhibitors

Table 5

Author	Study years	Biologic therapies	Study type	Disease	Median Duration of Exposure (Wks)	TNF- α Treatment Group				Placebo Group				Comparison Value: Treatment to Placebo (95% CI)
						No. of Malign.	No. of Lymph.	No. of patients	No. of Malign.	No. of Lymph.	No. of patients	Comparison Type		
Peyrin-Biroulet et al85	1997-2007	Inf, ada, etan, onerecept, cert, and CDP57 ^a	Meta-analysis of 21 RCTs ^b	CD	24	8	----	3,341	8	----	2,015	Risk difference for malignancy ^c	-0.14% (-0.4, 0.2) p = 0.309	
Bongartz et al80	1998-2005	Inf, ada	Meta-analysis of 9 RCTs	RA	26	24	10	3,494	2	0	1,512	Odds Ratio for malignancy ^r	3.3 (1.2,9.1)	
Bongartz et al83	1997-2006	Etan	Meta-analysis of 9 RCTs	RA	24	26	1	2,244	7	0	1,072	Hazard Ratio for malignancy ^r	1.84 (0.79,4.28)	
Leombruno etal84	1999-2007	Inf, ada, etan	Meta-analysis of 17 RCTs	RA	38.4	50	5	----	15	1	----	Odds Ratio for Lymphoma	1.26 (0.52,3.06)	

^aCDP571 is a humanized anti-tumor necrosis factor-alpha monoclonal antibody.

^bRCT = Randomized controlled trial

^cThese meta-analyses did not analyze lymphoma risk separately.