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A comprehensive review and evaluation of the side effects of the tumor necrosis factor alpha blockers etanercept, infliximab and adalimumab

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For more than 5 years, infliximab and etanercept have been utilized to treat rheumatoid arthritis and Crohn's disease. There is therefore much post-approval data on their side effects. A variety of Medline searches were done at the beginning of June 2004 using the terms 'etanercept', 'infliximab' and 'adalimumab' and the words 'lymphoma', 'infection', 'congestive heart failure', 'demyelinating disease', 'lupus', 'antibodies', 'injection site reaction', 'systemic', 'side effects' and 'skin'. Approximately 150 articles were so identified. In addition, FDA and manufacturers' data obtained by internet searches using Google were reviewed. The important side effects that have been most extensively related to TNFα blockers include: lymphoma, infections, congestive heart failure, demyelinating disease, a lupus-like syndrome, induction of auto-antibodies, injection site reactions, and systemic side effects. The risk of these side effects is very low. Nevertheless, it is important for clinicians to be aware of these side effects when prescribing therapy. (*J Dermatol Treat* (2004) **15:** 280–294)

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Introduction

There are three approved biologic therapies that block the activity of tumor necrosis factor alpha (TNFα). They are etanercept (Enbrel), a dimeric fusion protein blocking the effect of TNFα; infliximab (Remicade), a chimeric monoclonal receptor antibody; and adalimumab (Humira), a human monoclonal TNFα antibody. Infliximab and etanercept have been approved and used respectively for more than 5 years to treat rheumatoid arthritis and Crohn's disease. Therefore, there is much post-approval data on their side effects. This article will survey the side effects of TNFα blockers reported in the literature and the package insert for etanercept,[1] infliximab[2] and adalimumab,[3] with a particular focus on etanercept and infliximab.

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The important side effects that have been most extensively related to TNFα blockers include: infections, lymphoma, congestive heart failure, a lupus-like syndrome, induction of auto-antibodies and injection site reactions. Some aspects of these side effects and uses of these medications are compared in Table I.

This article will discuss the class of agents of TNFα blockers generally and then each TNFα blocker specifically as it relates to these side effects. The data in this article were assembled using a variety of Medline searches done in June 2004 using the terms 'etanercept', 'infliximab' and 'adalimumab', and the words 'lymphoma', 'infection', 'congestive heart failure', 'demyelinating disease', 'lupus', 'antibodies', 'injection site reaction', 'systemic', 'side effects' and 'skin'. Approximately 150 articles were identified and reviewed. In addition, the Food and Drug Administration (FDA) and manufacturers' data obtained by internet searches using the Google search engine were reviewed. (Figure 1)

	Etanercept	Infliximab	Adalimumab
PPD test required	No	Yes	No
Worsens CHF, NYHA III–V	Minimal evidence	Some evidence	No evidence
Infusion can cause anaphylaxis	No	Yes	No
Approved to treat Crohn's disease	No	Yes	No
Generation of clinically significant medication neutralizing antibodies	No	Yes	No

PPD test=purified protein derivative test; CHF=congestive heart failure; NYHA=New York Heart Association.

Table I

Comparison of some side effects and indications of TNFα blockers[1,2,3]

Evaluation of safety data and side-effect reports

The evaluation of side effects of medications is complicated. In large well-designed, well-monitored, placebo-controlled, clinical studies, powered with a number of patients sufficient to detect efficacy differences, side effects can be established with some surety in a population with a given disease. Such clinical studies are referred to as Phase III studies. After a medication is approved and used by the general population, its safety is monitored in so-called Phase IV studies (post-marketing studies). The safety assessment that goes on in these Phase IV studies is more amorphous than that conducted in Phase III studies because reporting is more inexact. Adverse events can occur randomly in larger groups and thus because there is no control group in Phase IV studies, one cannot be sure which side effects are due to a medication that is used and which side effects are due to chance, i.e. some intrinsic quality of the population with a disease or some other uncontrolled factor(s).

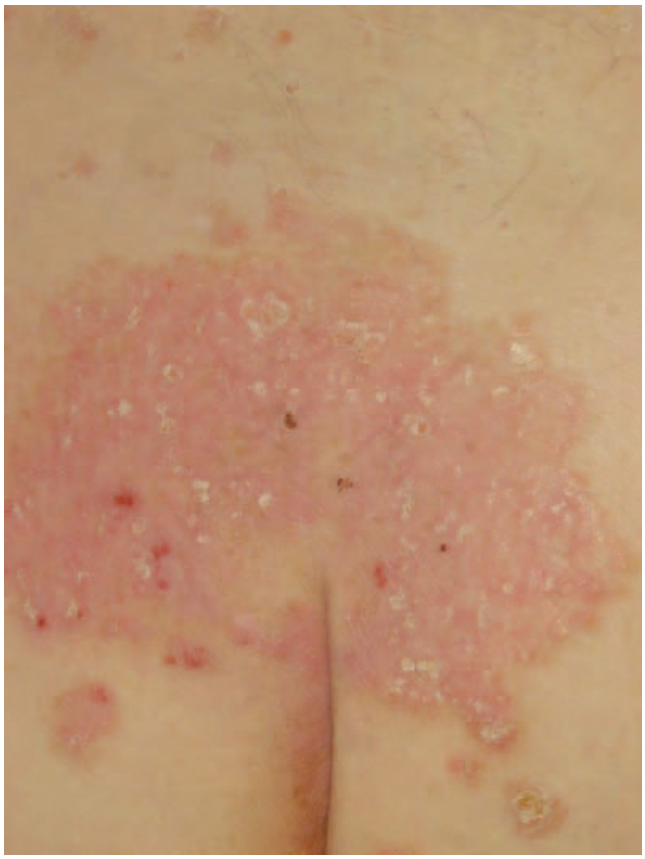

Figure 1

Stable plaque psoriasis on the sacrum.

This review cites all the data that were found regarding medication side effects; however, case reports of side effects in one or several patients must be evaluated based on an understanding of their anecdotal nature. Additionally, it should be noted that side effects in one population (e.g. patients with rheumatoid arthritis) cannot strictly be compared with side effects in another population (e.g. patients with psoriasis) because a patient's underlying disease state shapes the host response to external stimuli and may lead to different population side effect profiles.

The FDA has assembled data on the side effects of TNFα blockers. In 2001, the FDA published the first such post-marketing data.[4] These data will be discussed in this article. The FDA published additional data on these medications that it assembled in March of 2003, which are also summarized in this article.[5] An excellent series of lectures on these medications is available from Medscape[6] and the side effects of TNFα blockers have been surveyed recently by Cush.[7]

Lymphoma

The specific but immunosuppressive effects of TNFα blockers engendered a desire by the FDA to actively monitor their possible role in the induction of malignancy, in particular lymphoma.[8] The FDA summarized the clinical trial experience data in 2003 (Table II).[5] When considering these data it must be noted that the incidence of lymphoma is increased (approximately doubled) in patients with rheumatoid arthritis[9] and psoriasis.[10]

In 2002, scientists from the FDA further explicated the link between TNFα blockers and lymphoma and reported 26 cases of lymphoproliferative disorders following treatment with etanercept (18 cases) and infliximab (eight cases).[11] In all, 81% of cases were

	Etanercept	Infliximab	Adalimumab
Treated/exposure			
patient numbers	3389	1298	8729
patient years	8336	2458	7885
Total number of lymphomas	9	4	13
Hodgkin's	3	1	1
non-Hodgkin's	6	3	12
mean time to onset	21 months	10–19 months	21 months
Standardized incidence ratio compared with general population	3.47	6.4	4.35

Table II

Lymphoma clinical trial experience[5]

non-Hodgkin's lymphomas. The interval between the initiation of therapy with etanercept or infliximab and the development of lymphoma was very short (median 8 weeks). In two instances (one infliximab, one etanercept), lymphoma regression was observed following discontinuation of anti-TNFα treatment, in the absence of specific cytotoxic therapy directed toward the lymphoma.

The FDA asked an advisory panel to review the evidence linking the TNFα blockers to an increased risk of lymphoma. In March 2003, summarizing the panel's findings, the panel's chairman stated, "There are not enough numbers to say there's causality, but there's enough to say there may be a signal."[12] Some have reviewed the data relating lymphoma and TNFα blockers and denied a link between TNFα blockers and lymphoma.[13]

Lymphoma – etanercept

The only linkage of lymphoma to etanercept appeared in the 2002 FDA case series mentioned above. Thus, it remains unclear whether there is an increased incidence of lymphoma in patients using etanercept.[14] Information relating to lymphoma as a side effect of etanercept is not mentioned in its package insert.[1]

Lymphoma – infliximab

As stated, the 2002 FDA case series reported lymphoma in eight patients taking infliximab. Others postulated that use of infliximab in Crohn's disease is associated with an increase in lymphoma risk of around fivefold compared with non-immunosuppressive use, and tenfold compared with the general population.[15] Non-Hodgkin's lymphoma occurred in a patient with refractory dermatomyositis who had been treated with infliximab.[16] The risk of lymphoma is not listed in the package insert of infliximab.[2]

Lymphoma – adalimumab

Adalimumab has only recently been approved and most data that relate its side effects come from clinical trials. Among 2468 patients treated in clinical trials with adalimumab for a of 24 months, 48 malignancies of various types were observed, including 10 patients with lymphoma.[3] The standardized incidence ratio (SIR) (ratio of observed to age-adjusted expected in the general population) for malignancies was 1.0 (95% CI, 0.7, 1.3) and for lymphomas was 5.4 (95% CI, 2.6, 10.0).[3] An isolated report linking adalimumab and lymphoma has been published.[17]

Non-lymphoma cancers

There does not appear to be any linkage between the use of TNFα blockers and the development of non-lymphoma malignancies. Only isolated case reports exist of the development of non-lymphoma cancers while these medications are being taken.

Non-lymphoma cancers – etanercept

It seems that entanercept does not increases the incidence of non-lymphoma malignancy. The package insert notes that in 3 years during clinical trials the incidence of non-lymphoma malignancies has not increased with extended exposure to etanercept[1] and is similar to that expected when projected from the National Cancer Institute's Surveillance, Epidemiology and End Results database.[18]

One initial report linked the rapid onset of cutaneous squamous cell carcinoma in patients with rheumatoid arthritis treated with etanercept.[19] However, a larger series did not support the linkage between etanercept and the development of cutaneous squamous cell cancer.[20] A case of acute myelogenous leukemia following etanercept therapy has been reported.[21]

Non-lymphoma cancers – infliximab

There is no clear linkage between the use of infliximab and the development of non-lymphoma skin cancer. In trials, cancers did occur, including non-Hodgkin's B-cell lymphoma, breast cancer, melanoma, squamous, rectal

adenocarcinoma and basal cell carcinoma, but at a rate no higher than in the general population.[2] Acute leukemia has occurred after infliximab therapy.[22] The acute development of multiple squamous cell carcinomas and keratoacanthomas in a patient receiving infliximab for rheumatoid arthritis has been reported.[23]

Non-lymphoma cancers – adalimumab

In clinical trials, non-lymphoma malignancies observed during the use of adalimumab were breast, colon–rectum, uterine–cervical, prostate, melanoma, gallbladder–bile ducts, and other carcinomas. These cancers did not occur at a rate higher than in the general population.[3]

Infections

Infections occur at a higher rate among those who use TNFα blockers. The most common kind of infection that occurs is the upper respiratory infection but more serious infections can also occur, which will be considered in the next section. The FDA summarized data relating to significant infections, systemic side effects and etanercept and infliximab in 2001 (Table III).[4]

Infections – etanercept

The most common side effects linked to etanercept use in clinical trials are non-upper respiratory tract infections followed by upper respiratory infections. The maker of etanercept puts the general infection rate with etanercept over an entire course of therapy at 35% in placebo-controlled trials.[1]

Etanercept is associated with serious bacterial infections. Multifocal septic arthritis and osteomyelitis caused by group A streptococcus has occurred in a child receiving etanercept.[24] In addition, orbital myositis in a rheumatoid arthritis patient during etanercept treatment has been reported.[25] Etanercept can also facilitate viral infections and has been linked to a case of viral pneumonia.[26] It has also been linked to fungal infections in particular histoplasmosis[27] and toxoplasmosis.[28] There has been a report of a case of disseminated sporotrichosis in a 49-year-old man who was treated with multiple immunosuppressants, including etanercept and infliximab for arthritis.[29] Pulmonary aspergillosis in a patient with rheumatoid arthritis treated by etanercept has been noted.[30] Finally, a case of recurrent *Mycobacterium xenopi* infection presenting as Pott's disease in a patient receiving etanercept for severe rheumatoid arthritis has been described.[31]

Infections – infliximab

Physicians, when examining patients who have used infliximab, should have a high index of clinical suspicion for the occurrence of infections.[2] Pre-existing deep fungal and mycobacterial infections are contraindications to the use of infliximab and residence in areas where these infections are endemic should engender cautious use of these agents.[2]

Infectious agent or adverse event	Infliximab (n ~170 000 worldwide)	Etanercept (n ~104 000 worldwide)	Historic population: incidence rate (historic)
Mean age (years)	53	56	–
Mycobacterium tuberculosis	84	11	USA 8.2/100 000 patient years
M. avium intracellulare	0	6	NA
M. marinum	0	1	NA
M. kansasii	0	1	NA
Histoplasmosis	9	1	NA
Listeria monocytogenes	11	1	NA
Pneumocystis carinii	12	5	NA
Aspergillosis	6	2	NA
Candidiasis	7	3	NA
Cryptococcosis	2	3	NA
Coccidioidomycosis	2	0	NA
Pancytopenia	15	12	NA
Aplastic anemia	0	4	RA 5.7–8.2/100 000 patient years
Multiple sclerosis: total	6	14	NA
Multiple sclerosis: new diagnosis	3	6	4/100 000 patient years
Optic neuritis	4	3	5/100 000 patient years
Seizures	29	26	35/100 000 patient years
Lupus-like disease	4	4	NA
Colonic perforations	NA	13	NA
Lymphoma	10	18	NA

Table III

Infections, systemic side effects and TNFα blockers — 2001 data[4]

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