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Safety of Tumour Necrosis Factor-α Antagonists

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Abstract

Tumour necrosis factor-α (TNFα) is a proinflammatory cytokine that is synthesised by a variety of cell types in response to infectious or inflammatory stimuli. Although TNFα plays an adaptive role in immune protection and wound healing at 'physiological' levels, excess TNFα production can lead to adverse consequences. TNFα is a pivotal cytokine involved in the pathogenesis and progression of rheumatoid arthritis (RA). TNFα antagonists have been shown to be effective in the treatment of signs and symptoms of RA and the US FDA has approved three TNFα antagonists, etanercept, infliximab, and most recently, adalimumab, for the treatment of RA. However, differences have emerged, with respect to their demonstrated efficacy in other diseases (e.g. Crohn's disease). Worldwide, over half a million patients have been treated with TNFα antagonists and concerns regarding their safety have been raised.

There is a risk of reactivation of granulomatous diseases, especially tuberculosis, with all three agents and appropriate measures should be taken for detection and treatment of latent infections. An association between non-Hodgkin's lymphoma and treatment with TNFα antagonists has been reported, although patients with active, long-standing RA are already known to have an increased incidence of non-Hodgkin's lymphoma. No associations with solid tumours have been found to date. The biological plausibility of lymphomas associated with immunomodulatory agents raises concern and vigilance is appropriate until the relationship is fully characterised. Large phase II and III trials have shown a detrimental effect of TNFα antagonists in advanced heart failure and these agents should be avoided in this population. Rare case reports of drug-induced lupus, seizure disorder, pancytopenia and demyelinating diseases have been noted after TNFα antagonists and continued vigilance is warranted in patients on TNFα antagonists for the development of these diseases. At present there is no evidence implicating TNFα antagonists with embryotoxicity, teratogenicity or increased pregnancy loss.

The paradigm of the treatment of rheumatoid arthritis (RA) has shifted since the discovery in 1988 that levels of tumour necrosis factor-α (TNFα) are elevated in synovial fluid from patients with RA.[1,2] It is still unclear how the disease process is initiated, but synovial tissue is invaded by B cells, CD+ T cells and macrophages that lead to tissue destruction.[3,4] Macrophages release TNFα along with interleukin (IL)-1, IL-6 and a variety of other cytokines.[5] TNFα and IL-1 cause endothelial cells and fibroblasts to up-regulate the expression of cell adhesion molecules.

To prevent the inflammatory and destructive changes of RA, a number of agents designed to

inhibit TNFα have been developed. The US FDA has approved three TNFα antagonists for the treatment of RA: etanercept, infliximab, and most recently, adalimumab. The manner in which these products block TNFα differ in that etanercept is a soluble receptor while infliximab (chimeric) and adalimumab (fully human) are monoclonal antibodies. All three have shown efficacy in clinical trials of RA. Differences have emerged, however, with respect to their demonstrated efficacy in other diseases and with respect to certain aspects of their safety profiles. This review will examine in brief the structural and pharmacological differences between the agents, their efficacy in RA and other diseases, and the differences and similarities in safety between the three agents. The data presented in this review have been collected from published data, the package inserts of the three individual TNFα antagonists,[6-8] individual case reports or series, the MedWatch postmarket adverse event surveillance system supported by the FDA, and the 4 March 2003 FDA advisory committee meeting.[9] As MedWatch is a passive surveillance system, it is highly likely to underestimate the true incidence of adverse events following TNFα antagonist exposure. These data should be interpreted with that caveat in mind. Medline and the Cochrane Library electronic databases were searched to 1 September 2003. The keywords included 'tumor necrosis factor antagonists', 'infliximab', 'etanercept', 'adalimumab' 'safety' and 'side effects'. No language, date or age restrictions were applied. Proceedings from the American College of Rheumatology and European Congress of Rheumatology meetings were searched for the years 2001 and 2002. American College of Rheumatology 2003 meeting abstracts were also reviewed. The reference lists from the published clinical trials and review articles were reviewed to identify any additional studies. The recent Food and Drug Administration update[9] was accessed on 1 September 2003 to enrich our search for recent clinical trials.

1. Structural and Pharmacological Comparison of the TNFα Antagonists

TNFα interacts with two distinct receptors; TNF-RI, a 55 kDa receptor (also known as p55), and TNF-RII, a 75 kDa receptor (p75).[10] Etanercept is a recombinant fusion protein composed of two soluble TNF-RII (p75) receptors attached to the Fc portion of human IgG1.[11] The two sTNF arms bind to TNFα in the body and prevent its interaction with TNF receptors on cell surfaces. Etanercept binds equally well to lymphotoxin-α (LTα) and TNFα, in a similar fashion to the human p75 TNFα receptor; the significance of this interaction has not been clarified.[12] It binds to TNFα in a one-to-one complex, with the TNFα trimer, occupying two of three receptor sites on the TNF molecule. Scallon et al.[13] showed that the binding of etanercept to TNF is relatively unstable, with a fast rate of association and dissociation. They also demonstrated that the TNF that dissociates from etanercept is still bioactive. Etanercept has peak absorption at 51 hours, a mean half-life of 68 hours (4.3 days), and a binding affinity of 10^{10}/mole.[14] Etanercept is administered subcutaneously at a dosage of 25mg twice a week.

Infliximab is a chimeric monoclonal antibody against TNFα, with murine variable and human IgG1 and κ constant regions.[15] Its size (149kDa) and structure are similar to antibodies that occur in nature. Each molecule of infliximab is able to bind to two molecules of TNFα; in addition, up to three infliximab molecules can bind with each TNF homotrimer, so that all three receptor-binding sites on TNF are blocked.[13] Infliximab forms a relatively stable complex with the TNF molecule, with a binding affinity of 1.8×10^9/mole, and a Koff (the half-life of the drug/TNF complex) of 6.29×10^{-5}. The biological half-life of infliximab is 8–9.5 days. It is administered intravenously, with a dosage of between 3 and 10 mg/kg every 8 weeks.[6] Adalimumab is a fully human monoclonal antibody TNFα, constructed using phage technology. Adalimumab also forms relatively stable complexes with the TNF molecule, with a binding affinity of

2.3×10^{10}/mole, and a Koff of 4.54×10^{-5}. Its half-life is 10–13.5 days.[16] It is administered at a dosage of 40mg subcutaneously every other week. Much like infliximab, adalimumab has been shown to bind both soluble and membrane-bound TNFα. *In vitro*, at a high density (similar to infliximab), adalimumab has demonstrated its ability to fix complement and lyse cells. The applicability of this *in vitro* data to human disease is not known.

2. Efficacy of TNFα Antagonists

All three TNFα antagonists have been successfully utilised in treating clinical signs and symptoms and retarding radiographic progression in RA.[17-19] Etanercept has received FDA approval for the treatment of psoriatic arthritis, ankylosing spondylitis and polyarticular juvenile RA based on well designed randomised controlled studies.[8,20-22] Infliximab has also been shown to be efficacious in the treatment of psoriatic arthritis[23] and ankylosing spondylitis[24] in randomised controlled studies. Controlled trials of infliximab in juvenile RA have not yet been reported.

Studies of infliximab and etanercept, however, have not shown similar results in the treatment of Crohn's disease.[25] Infliximab has proven efficacious in the treatment of both active Crohn's disease and fistulising Crohn's.[25] In active Crohn's disease, infliximab was efficacious in both reducing disease activity and inducing remissions based on the Crohn's disease activity index (CDAI). In contrast, studies of etanercept have not shown clinical benefits.[26] It has been shown that infliximab induces monocyte apoptosis in patients with Crohn's disease, one possible mechanism for the effectiveness of infliximab in this disease.[27,28]

3. Safety of TNFα Antagonists and Infections

3.1 Vaccination

There has been a debate in the literature about whether a nonspecific immunisation might exacerbate the manifestations of existing autoimmune disease via activation of an inflammatory reaction.[29] There are case reports in patients with hepatitis B and influenza vaccinations which are somewhat suggestive of this;[30,31] however, results from the large immunisation programmes and epidemiological studies have been negative.[32,33] The current data strongly suggests that the benefits of vaccination outweigh the possible risks.

Patients with different rheumatic conditions, when given pneumococcal vaccination, had a lower B-cell immune response compared with patients not on biologics.[34] However, patients receiving both adalimumab and etanercept have demonstrated a favourable response to pneumococcal vaccination showing a doubling of titre to three of four antigens tested, similar to patients on methotrexate.[35] Patients treated with etanercept have also shown acceptable immune responses to influenza vaccine.[8] Although the immunocompromised patients should be encouraged to receive yearly inactivated influenza vaccine, FluMist®™ [1] (a live attenuated influenza vaccine), is contraindicated in immunosuppressed patients.[36]

3.2 Bacterial Infections

3.2.1 General Bacterial Infections

In the clinical trials, the use of all three TNFα antagonists was associated with infections requiring treatment. Most of the infections were minor, treated with either outpatient antibiotic therapy and/or temporary withdrawal of the drug. The most commonly reported infections were of the respiratory tract (including sinusitis, pharyngitis, and bronchitis) and

1 Use of trade names is for product identification purposes only and does not imply endorsement.

the urinary tract. In the infliximab clinical studies, treated infections were reported in 36% of patients on infliximab compared with 26% in the placebo-treated group.[6] No increased risk of serious infections or sepsis was seen in the Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT)[17] or A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen (ACCENT)[25] trials. The risk of serious infections (requiring hospitalisations or parenteral antibiotics) in the infliximab studies for both Crohn's disease and RA was 6.2% compared with 6.8% in the placebo group (Crohn's disease 5.2% in the infliximab group versus 1.8% in the placebo group, RA 8.1% in the infliximab versus 9.0% in the placebo group).[37] In trials of etanercept versus placebo, 35% of patients in the treatment group developed infections compared with 32% in the placebo group.[8] In trials comparing etanercept plus methotrexate to methotrexate alone, 64% in the etanercept group developed an infection compared with 72% in the methotrexate group. Serious infections occurred in 1% of the patients in both the etanercept and placebo groups.[8] In adalimumab studies, 52.7% adalimumab patients developed infections compared with 46.7% in the placebo-treated group. The incidence of serious infections was 1.7% in the adalimumab group versus 1.4% in the placebo group.[7]

The risk of serious infections in RA patients in the pre-TNFα antagonist era was 0.03–0.09 cases/patient-year.[38,39] The incidence of serious infections in the clinical trials with TNFα antagonists is as follows: etanercept 0.04/patient-year,[8] adalimumab 0.04/patient-year[7] and infliximab 0.06/patient-year.[9]

Summary

TNFα antagonists are associated with an increased risk of serious infections compared with the general population but the rate is similar to RA patients treated with other disease-modifying agents in the pre-TNF era. When serious infections occur, TNFα antagonists should not be started or should be discontinued.[9] Treatment with these agents can be resumed after the infections have been treated adequately.[40]

3.2.2 Tuberculosis

In animal models, TNFα plays an important role in the host response to tuberculosis, particularly in granuloma formation and in the containment of latent disease.[41] In addition, administration of TNFα antagonist caused reactivation of tuberculosis in murine models of latent infection.[42] TNFα is important in mediating macrophage apoptosis after bacillary infection. Even though there were only two cases of tuberculosis reported in clinical trials of infliximab,[6] there have been 295 cases of infliximab-associated tuberculosis reported as of August 2002.[9,43] This gives an estimated rate of 37 cases per 100 000 (86 cases/233 547 exposed) and 150 cases per 100 000 in Europe (156 cases/103 335 exposed).[9] As of March 2002, 36 tuberculosis cases/~150 000 treated have been reported with etanercept giving a rate of approximately 24 cases per 100 000 patients treated.[9] In comparison, the background rate of tuberculosis in RA patients in the US is estimated to be 6.2 cases per 100 000 person[44] and 20 cases per 100 000 person[45] in Europe.

In a detailed evaluation of 70 cases of tuberculosis treated with infliximab,[41] it was found that 56% of these had extrapulmonary tuberculosis, and 79% of the cases received one or more concurrent medications (corticosteroids alone or in combination with methotrexate). The median interval from start of infliximab to onset of tuberculosis was 12 weeks (range 1–52 weeks). Interestingly, 91% of the cases were from countries with a low incidence of tuberculosis. Suggestion of an association between treatment with infliximab and development of tuberculosis is strengthened by the close temporal association to infliximab administration, the higher estimated rate of tuberculosis compared with the background rates in RA patients, and the laboratory evidence linking susceptibility to tuberculosis with decreases in TNFα activity.[41]

Using the FDA's MedWatch programme, 25 cases (17 from the US) of tuberculosis seen with use of etanercept were recently reported in abstract form.[46] The median period from the first dose of etanercept to the diagnosis of tuberculosis was 11.5 months (range 1–20 months). Fifty-two percent had extrapulmonary disease. The investigators attribute the difference in apparent incidence of tuberculosis reactivation between the two agents to the different ways in which the two agents neutralise TNFα and to the proportionately higher use of etanercept in the US than in Europe.[41]

There were 13 cases of tuberculosis seen with adalimumab during 4870 patient-years of clinical trials; most of these cases occurred within the first 8 months of initiation of therapy.[7] Eight of these cases occurred in the phase I and II development programme where supratherapeutic doses were used. During the phase III study, where the 40mg every other week dose (currently approved FDA dose for the treatment of RA) was used and tuberculosis prophylaxis was instituted, five more cases occurred.[9]

Although postmarketing cases of tuberculosis have been reported for both etanercept and infliximab, the data suggest, but do not prove, that the risk of tuberculosis is different for the two agents. In voluntary reporting systems, the reporting rate among infliximab users is several-fold higher than the incidence in the general US population. In addition, more cases of tuberculosis have been seen among patients not otherwise considered at risk of tuberculosis. Tuberculosis has also been seen in the clinical trials of infliximab and adalimumab. These findings led to a black box warning by the FDA in the infliximab and adalimumab inserts.[6,7] Etanercept has a bold warning, but no black box warning regarding tuberculosis.[8] For etanercept, postmarketing cases of tuberculosis have been uncommon, with a reporting rate similar to or a little higher than the US incidence. Most patients who developed tuberculosis were considered to be at high risk for other reasons. Also, no cases of tuberculosis have been seen through October 2002 in etanercept trials of patients with RA either in the US or Europe (total 3280 patients).

In North America, the purified protein derivative (PPD) is usually used to screen for tuberculosis, but some questions about this practice, rather than chest films, have recently been raised. It appears that RA, *per se*, decreases PPD responses. A recent study showed a poor response to intermediate (5μ) PPD in RA patients compared with healthy controls (median size of PPD response in RA 4.6mm versus 12mm in controls, $p < 0.001$); the inadequate response was independent of the disease duration, activity and background disease-modifying antirheumatic drugs.[47] On the other hand, it does not appear that TNFα antagonists decrease the PPD response *per se*. For example the number of positive responses did not decrease in an RA population before and after 1 year of infliximab.[48]

Summary

Reactivation of tuberculosis can occur with TNFα antagonists. Patients should be evaluated with a PPD test and/or a chest x-ray, if needed.[49] Patients with evidence of latent tuberculosis should be treated before TNFα blocking agents are used.[49] PPD skin test criteria for patient receiving TNFα antagonists have recently been published.[50] Some authorities suggest that TNFα antagonists may be started as soon as antituberculosis treatment is started, although this approach needs further evaluation.

3.2.3 Other Bacterial Infections

Other published postmarketing individual case reports of bacterial infections associated with the use of TNFα include listerosis,[51] atypical mycobacteria, cutaneous nocardiosis, fatal *Streptococcus pneumoniae* sepsis with necrotising fasciitis, severe bilateral pneumonia due to *S. pneumoniae*, fatal α-haemolytic group A streptococcus sepsis with necrotising fasciitis, and sepsis due to *Staphylococcus aureus* (table I).[9,52]

Table I. Opportunistic infections seen with infliximab and etanercept

Infections	Infliximab[a]	Etanercept[b]
Aspergillosis	26	7
Candidiasis	59	73
Cryptococcus	7	7
Coccidioidomycosis	13	1
Cytomegalovirus	20	8
Histoplasmosis	37	2
Infectious mononucleosis	12	5
Listeria monocytogenes	29	2
Nocardiosis	8	2
Pneumoocystis carinii	44	5[52]
Tuberculosis	295	36
Atypical mycobacteria	37	11

a 365 000 patients exposed as of March 2003.[9,43]

b >150 000 patients exposed as of December 2002.[43,53]

3.3 Fungal Infections

3.3.1 Histoplasmosis

Histoplasmosis has been observed in many immunocompromised states. As of June 2002, there were 37 cases of histoplasmosis reported in the US among patients receiving infliximab and two with etanercept.[43] Detailed evaluation of ten cases by the FDA[54] showed that all cases resided in histoplasmosis endemic areas and received concomitant immunosuppressive medications in addition to the TNFα antagonist. Patients treated with infliximab presented with histoplasmosis within 1 week to 6 months of the first dose. Nine patients required treatment in an intensive care unit and one died. Based on an estimated 150 000 patients receiving infliximab (as of August 2001) and about 96 500 patients receiving etanercept (as of April 2001) in the US, the rate of histoplasmosis following treatment with infliximab and etanercept was estimated to be about 6 in 100 000 and 1 in 100 000, respectively. Cases of histoplasmosis were also seen with adalimumab in the clinical trials (table I).[7]

Pneumocystis carinii pneumonia (PCP) is a common opportunistic infection in immunocompromised persons. As of June 2002, there have been 44 cases of PCP in the US following the use of infliximab[43] and five cases of PCP following etanercept.[52] The ages of the cases ranged from 15 to 67 years (median 56.5 years) and the time to onset from the start of treatment to the diagnosis of PCP averaged 1 month for infliximab and 2 months for etanercept. There were six deaths among the 15 cases.

3.3.2 Other Fungal Infections

TNFα plays a central role in the recruitment of neutrophils into the lungs in response to pathogens such as *Aspergillus fumigatus* and *Cryptococcus neoformans*.[55] There have been individual case reports and reports to the FDA of pulmonary aspergillosis and cryptococcal infection in patients treated with TNFα antagonists.[9,43] Other opportunistic infections, including systemic candidiasis and coccidioidomycosis[43,56] have also been reported to the FDA.[9]

Summary

Patients treated with TNFα antagonists, especially infliximab, may have an increased risk of reactivation of granulomatous fungal infections. Patients living in high-risk areas should be monitored closely. Unlike tuberculosis, guidelines have not been developed to screen or treat latent fungal infection before initiating the anti-TNFα therapy.

Many opportunistic infections have been documented but their incidence is extremely low (table I).

The lesson to be learned is that for infections where host defences are particularly macrophage dependent, physicians should exercise careful vigilance, especially in areas of high disease prevalence, while using anti-TNFα agent.

3.4 Viral Infections

The antiviral activity of TNF has long been recognised.[57,58] A literature search produced few case reports of viral infections following the use of TNFα antagonists in RA or Crohn's disease patients.[59] However, there have been reports of opportunistic viral infections (e.g. herpes simplex and herpes zoster) submitted to the FDA following the

use of infliximab and etanercept.[9] As of 30 June 2001, 94 cases of viral infections were reported to the FDA following the use of infliximab and 553 cases following etanercept use.[60] The great majority of the viral infections with etanercept were reported by patients with influenza and other common viral illnesses.

3.4.1 HIV

Elevated TNFα levels have been associated with HIV infection.[61] Furthermore, TNFα stimulates HIV replication and has been correlated with HIV viral load.[61,62] Etanercept effectively treated HIV-associated psoriatic arthritis and reduced TNFα levels.[63] Infliximab decreased TNFα levels in six patients with HIV without any effect on their viral loads[64] and was successfully used in a patient with HIV-associated Reiter's syndrome.[65] Treatment with antiretrovirals has no impact on the TNFα levels.[57]

3.4.2 Hepatitis C

Patients with concomitant RA and hepatitis C virus (HCV) infection treated with TNFα antagonists have recently been reported.[66] The mean HCV viral load, liver functions and albumin over 34 months did not differ significantly from baseline in a group of 22 RA patients ($p > 0.05$). A pilot study in HCV patients receiving standard of care treatment (ribavirin and interferon-α-2b) were randomised to either etanercept 25mg twice a week (19 patients) or placebo (25 patients).[67] At 6 months, 67% of the etanercept group had an undetectable hepatitis C RNA level compared with 32% in the placebo group and 61% had normalisation of their alanine aminotransferase (ALT) compared with 48% in the placebo arm ($p < 0.05$ for both).

3.4.3 Hepatitis B

TNFα, which is induced by hepatitis B virus antigens, is supposed to be beneficial for viral clearance[68] and there is a theoretical concern of hepatitis B reactivation in a chronic carrier. Hepatitis B reactivation in a chronic carrier and fulminant hepatitis in a patient with hepatitis B treated with infliximab have been reported.[69,70]

3.4.4 Summary

There is little convincing evidence that TNFα antagonists predispose to an increased incidence of viral infections, although their mechanism of action should make one keep this possibility in mind when treating patients with the TNFα antagonists. Preliminary evidence suggests a beneficial role of the TNFα antagonists in hepatitis C. TNFα antagonists should be used very carefully in patients with HIV (for fear of activation of infections) and probably avoided in the hepatitis B carrier state due to the risk of reactivation of their hepatitis B.

4. Safety of TNFα Antagonists and Non-Infectious Conditions

4.1 Injection/Infusion Site Reaction

Injection site reactions (ISRs) have been seen with both etanercept and adalimumab in their clinical trials. Etanercept was associated with ISRs in 37% of patients versus 7% in the placebo arm.[18] Seven percent of patients experienced redness at previous injection sites when subsequent injections were given.[8] None of the patients discontinued the drug due to ISRs. The ISRs usually occur in the first month of treatment and decrease with time. The reactions are believed to be T-lymphocyte-mediated, delayed-type hypersensitivity reactions with decrease in intensity over time possibly due to induced tolerance.[71]

Adalimumab had 20.9% ISRs versus 14% in the placebo arm in the clinical trials.[72] ISRs caused 0.3% of patients to discontinue the drug, which was the same as in the placebo group.

Infliximab was associated with a 22% infusion reaction rate versus 9% in the placebo arm in their clinical studies. An infusion reaction was defined as any adverse event occurring during an infusion or within 2 hours after infusion. Among 935 patients treated in clinical trials, 3% patients had nonspecific

fever and chills, <1% of infusions were serious, which included anaphylaxis and hypotension.[6] Only 2.5% discontinued treatment due to these reactions in clinical trials.[37]

4.1.1 Summary

ISRs are common with both etanercept and adalimumab and usually occur in the first month of treatment and decrease with time. Infliximab is associated with mild infusion reactions requiring either a decrease in the rate of infusion or pretreatment with a histamine H_1 receptor antagonist with or without low-dose parenteral glucocorticoids.[6,73] Patients with anaphylactic reactions to infliximab should not receive another dose of infliximab.

4.2 Demyelination

Although data from animal studies have shown mixed effects of TNFα inhibition in the treatment of disorders characterised by CNS demyelination,[74] human studies in patients with multiple sclerosis (MS) have shown a deleterious effect of anti-TNFα therapy. Infliximab was evaluated in two patients with rapidly progressive MS. Both patients had an increase in the number of gadolinium-enhancing lesions observed on magnetic resonance imaging and an increase in their cerebrospinal fluid (CSF), IgG and lymphocytes.[75] Also, in a randomised, double-blind study in patients with MS, lenercept (a soluble p55 TNF-receptor-immunoglobulin G fusion protein) was associated with more clinical exacerbations of their MS than placebo.[76] Neurological deficits were also worsened in subjects receiving lenercept. The exact mechanism of this detrimental effect of the TNFα antagonism in demyelinating disease is unclear, but it may be a class effect.

Nineteen cases suggestive of CNS demyelination in the presence of TNFα inhibition have been reported from the passive surveillance system in the FDA's Adverse Event Reporting System (AERS) database.[77] Seventeen cases followed the use of etanercept, and two followed infliximab use, with a mean duration of 5 months (range from 1 to 15 months) between initiation of the therapy and onset of neurological symptoms. Discontinuation of the drug led to partial or complete resolution of symptoms. One patient exhibited a positive rechallenge phenomenon; however the worsening coincided with the ending of a corticosteroid taper. As of September 2001, there have been nine cases of MS (three new cases) and four cases of optic neuritis reported among 170 000 patients exposed to infliximab (7.6 cases/100 000 exposed). With etanercept, 14 cases of MS (four new cases) and three cases of optic neuritis/ 104 000 exposed. A recent update through August 2002 reported a total of 64 cases of demyelinating disorders after the use of infliximab. These were divided into four subgroups: (i) central demyelination (21 cases); (ii) Guillain-Barré syndrome/chronic inflammatory demyelinating polyradiculoneuropathy (9 cases); (iii) neuropathy (37 cases); and (iv) transverse myelitis (1 case).[9] New data on etanercept have not been published. Three cases of demyelination (one case of optic neuritis and two cases of paraesthesias) have been reported with adalimumab in clinical studies.[9] For a historical perspective, the incidence rate of new cases of MS and optic neuritis is 4 and 5/100 000 patient-years, respectively in the general population.[53]

4.2.1 Summary

Instances of demyelinating-like disorders have been reported with TNFα antagonists. The incidence of demyelinating diseases does not appear to be increased in patients on TNFα antagonists compared with the background rate,[77] although data are available in terms of the number of patients exposed to TNFα antagonists, rather than in terms of patient-years of response. For safety, however, these agents should be stopped if a patient develops demyelinating-like disorder and should be avoided in patients with pre-existing demyelinating diseases.

4.3 Seizure Disorder

Seizure disorder has been reported in 29/170 000 exposed and 26/104 000 exposed with infliximab

and etanercept, respectively.[53] These data are sparse, anecdotal, and without valid comparison or control and, as per the safety update by the FDA on TNFα antagonists, a pre-existing seizure disorder does not seem to be a contraindication to TNFα therapy.

4.4 Congestive Heart Failure

4.4.1 Clinical Trial Data

TNFα has been shown to be over-expressed in myocardial tissue in heart failure and is thought to cause progression of the disease by virtue of its direct toxic effect on the heart and circulation.[78] An increasing serum TNFα level is correlated with a worse New York Heart Association (NYHA) functional class for congestive heart failure (CHF), an increase in hospitalisations due to CHF, and an increase in mortality.[79] Initial data from preclinical and pilot studies were encouraging, showing some anecdotal efficacy of TNFα antagonist therapy in the treatment of CHF.[80]

Etanercept was evaluated in two large, randomised, phase III, placebo-controlled trials to look at its effect on patients with congestive heart failure: the Randomized Etanercept North American Strategy to Study Antagonism of Cytokines (RENAISSANCE) trial and the Research into Etanercept Cytokine Antagonism in Ventricular Dysfunction (RECOVER) trial. The two studies were of a similar design; RENAISSANCE was performed in North America and RECOVER was performed in Europe, Israel and Australasia. Overall, 25 countries were involved. The studies were combined and presented as the Randomized Etanercept Worldwide Evaluation (RENEWAL) study.[9,81] The main inclusion criteria was NHYA II–IV for at least 2 months and left ventricular ejection fraction of <30%. There were three treatment groups in the RECOVER study (1123 patients): placebo and etanercept 25mg administered once a week or twice a week. The three treatment groups in the RENAISSANCE study (925 patients) were placebo and etanercept 25mg administered two or three times a week. Both studies were terminated early because interim analysis did not show any benefit of etanercept on morbidity or mortality. For the RENAISSANCE study, the key finding was a trend towards higher mortality in etanercept-treated subjects, a concern heightened by the apparent dose-response relation. Specifically, mortality rates were 14.2, 17.9, and 19.8% in the placebo, etanercept twice a week, and etanercept three times a week treatment groups, respectively. The mortality rate for the placebo, etanercept once a week, and etanercept twice a week treatment groups in RECOVER trial were 8.8, 5.9, and 7.2%, respectively.

Infliximab was evaluated in a pilot study Anti-TNF alpha Therapy Against *C*hronic Heart Failure (ATTACH). CHF was defined as an ejection fraction ≤35% and patients were required to have NYHA class III, IV CHF. There were three treatment groups, placebo, infliximab 5 mg/kg or infliximab 10 mg/kg and the agent was administered by intravenous infusion at week 0, week 2 and week 6.[82] Overall, 150 patients were recruited. There were strong trends towards an increase in the percentage of patients with worsening clinical status with increasing infliximab dose, largely due to an increase in deaths or hospitalisation for heart failure at weeks 14 (primary endpoint) and 28. One year all cause mortality showed that four (8.2%) patients in the placebo arm died compared with four (8%) in the 5 mg/kg arm and eight (15.7%) in the 10 mg/kg arm.[81] The mortality rate for patients receiving the highest doses of infliximab was statistically greater than that observed in the placebo arm.

4.4.2 Postmarketing Data

The FDA recently reported 47 cases of new and/or worsening CHF using their MedWatch AERS.[83] After TNFα antagonist therapy, 38 patients developed new-onset CHF and nine patients experienced CHF exacerbation. Of the 38 patients with new-onset CHF, 19 (50%) had no identifiable risk factors. Ten patients aged <50 years developed new-onset heart failure after receiving TNFα antagonists. After TNFα antagonist therapy was discontinued

and heart failure therapy was started in these ten patients, three had complete resolution of heart failure, six improved, and one died.

4.4.3 Summary

Patients who are on high doses of etanercept and infliximab, should be monitored carefully for signs and symptoms of CHF. Patients with NHYA class III, IV CHF who are given high doses of TNFα antagonists have an increased relative risk of worsening heart failure and mortality. Based on the data in section 4.4.1 and 4.4.2 and what we believe is the use of good clinical judgement, we believe that patients with well compensated, mild CHF (NYHA class I and II) and a concomitant indication for use of TNFα antagonist should have a Doppler echocardiogram performed. Patients with a normal ejection fraction (usually felt to be >50%) can receive this therapy with fully informed discussion with the patient and close monitoring for any clinical signs or symptoms of worsening of the heart failure. TNFα antagonists should be avoided in patients with a decreased ejection fraction. This implies but does not require that one should do an echocardiogram in patients with a history of CHF in whom TNFα antagonist therapy is being considered. In patients who develop new-onset heart failure on TNFα antagonists, the TNFα antagonists should be stopped and the patients should be evaluated for other causes of heart failure. We recommend against the reintroduction of the TNFα antagonist therapy in these patients.

4.5 Autoantibodies and Drug-Induced Lupus

TNFα is clearly an important component of the inflammatory response, and concentrations are raised in systemic lupus erythematosus. However, in New Zealand black and New Zealand white F1 mice, exogenous TNFα actually delays the onset and progression of systemic lupus erythematosus, implying a potentially protective role.[84]

In the Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) trial, 62% of patients developed a positive antinuclear antibody (ANA) compared with 27% of placebo-treated patients. Anti-double-stranded DNA (dsDNA) developed in 15% of infliximab-treated patients compared with none in the placebo arm. Most of the anti-dsDNA associated with infliximab are IgM isotype. In the clinical studies, six patients developed systemic lupus erythematosus-like syndrome, which improved on stopping the biological therapy.[6] Children (n = 24) with a variety of rheumatological diseases were treated with infliximab. A total of 16.7% (4/24) of the patients developed anti-dsDNA antibodies during treatment with infliximab; however, none of them developed clinical signs and symptoms of systemic lupus erythematosus.[85]

Longitudinal assessments of ANA and antibodies against dsDNA were done during the regulatory approval process for etanercept. During 6-month clinical trials, 11% of 323 patients treated with etanercept became positive for ANA, and 15% and 3% developed antibodies against dsDNA by radioimmunoassay and *Crithidia luciliae* assay, respectively, compared with 5% for ANA and 4% and none in the placebo group, respectively; no patients, however, developed clinical autoimmune disease.[8] Twenty-two case reports of lupus-like syndromes have recently been reported with etanercept in the form of case reports, series and FDAs AERS.[86,87]

Adalimumab has a 12% rate of positive ANA compared with placebo (7%). No data on dsDNA have been reported. One patient developed systemic lupus erythematosus-like syndrome and improved on discontinuation of the drug.[7]

Most cases of drug-induced lupus with TNFα antagonists had skin and pleuropericardial involvement along with positive anti-dsDNA, anti-Smith and/or anti-histone antibodies as their manifestation.[86,87] No patient thus far has developed neurological or renal disease.

4.5.1 Summary

Patients treated with TNFα antagonists have an increased incidence of developing a positive ANA and dsDNA. Although antibodies develop to all

TNFα antagonists, they may develop more frequently to infliximab, a chimeric antibody. The presence of these antibodies does not presage systemic lupus erythematosus-like disease (which is rare and reversible) and does not preclude their use.

4.6 Malignancies

4.6.1 Lymphoma

Patients with RA have been shown to have an increased risk of lymphoma, especially non-Hodgkin's lymphoma.[88,89] Several epidemiologic studies have demonstrated that the risk of lymphoproliferative cancers is increased several-fold over the general population, with the upper boundary of the relative risk as high as 26-fold for patients with severe active RA. A recent study reviewed cases of lymphoma in RA patients from 1964 to 1984 and found a predominance of diffuse large B cell lymphoma (a type of non-Hodgkin's lymphoma).[90] These patients had either little or no exposure to immunosuppressive agents, a risk for developing lymphomas. Other factors that may contribute to an increased risk of lymphoproliferative malignancies include infection with Epstein-Barr virus, high disease activity, widespread joint involvement, advanced age, poor functional class, and prolonged RA duration.[91,92]

The age-adjusted incidence of lymphoma in the US from 1995 to 1999 was 22.2/100 000 (19.4/100 000 for non-Hodgkin's lymphoma and 2.8/100 000 for Hodgkin's lymphoma.[93] Recently, using the MedWatch postmarket AERS by the FDA, a study estimated the incidence of lymphoma with etanercept and infliximab.[94] The investigators reported 19 cases/100 000 patients treated with etanercept and 8 cases/121 000 or 6.6 cases/100 000 treated with infliximab. The majority of cases (81%) were of non-Hodgkin's lymphomas. The interval between initiation of therapy with etanercept or infliximab and the development of lymphoma was short (median 8 weeks). In two instances (one infliximab, one etanercept) lymphoma regression was observed following discontinuation of treatment with TNFα antagonists, in the absence of specific cytotoxic therapy directed toward the lymphoma. The number of biopsy-proven lymphoma cases from the latest update from the recent FDA advisory committee meeting is 70 and 95 subsequent to etanercept and infliximab treatment, respectively, with a predominance of diffuse large B cell subtype of non-Hodgkin's lymphoma.[95] This gives a rate of 0.03/100 patient-years for etanercept and 0.017 for infliximab and is similar to the expected rate in the population (0.03/100 patient-years), although this may be an underestimate due to under-reporting.[93] The recent update by the FDA also calculated the standardised incidence ratio (SIR) for lymphomas with all the TNFα antagonists (table II). In the clinical trials for both the Crohn's disease and RA population with infliximab (2421 patients with 4148 patient-year follow-up) reported a SIR of 6.98 for

Table II. Observed and expected cases of lymphomas seen in the clinical trials with three tumor necrosis factor-α (TNFα) antagonists[9]

Population	n	Patient-years of follow-up	Median patient-years of follow-up	Observed cases	Expected cases[a]	SIR	SIR 95% CI
Adalimumab	2468	4870	2.4	10	1.80	5.42	2.6, 10
Etanercept	3389	7364	2.2	6[b]	2.6	2.31	0.85, 5.03
Infliximab	2421	4148	1.37	6	0.86	6.98	2.56, 15.19
Infliximab (ASPIRE[c])	743	702.6	0.78	0	0.17	0	0

a Cancer rates used were 1992–1999 Surveillance, Epidemiology and End Results (SEER) rates.

b Three more cases were diagnosed after a follow-up period (total of nine cases with SIR = 3.47).

c Active Controlled Study of Patients Receiving Infliximab for Treatment of Rheumatoid Arthritis Early Onset (ASPIRE) study of infliximab in early rheumatoid arthritis (RA) [methotrexate-naive] preliminary results.[9]

SIR = standardised incidence ratio (incident cases in the trials divided by the expected incidence in the general population for an age, gender and race-matched cohort [not in RA population] from SEER database).

lymphomas. In the placebo arm of these studies (489 patients with 691 patient-year follow-up), no cases of lymphomas were seen. It should be noted, however, that the number of patients was considerably smaller and median duration of follow-up was shorter in the placebo group (median follow-up 0.32 years) than in the treated group (median follow-up 1 year). The recently completed clinical trial of infliximab in methotrexate-naive early RA patients (743 patients with 702.6 patient-year follow-up) with 0.78 year follow-up did not reveal any cases of lymphoma.[9]

The rate of lymphomas seen with adalimumab in the preregulation studies was ten cases per 2468 patients treated with the TNFα antagonists, giving a standardised incidence ratio of 5.4 (expected 1.85, 95% CI 2.6, 10).[7,95] This safety database was much larger than available at the time of approval of the other two TNFα antagonists, which may have resulted in more cases of lymphomas than seen with the other TNFα antagonists. Available data are thus insufficient to determine whether adalimumab increases the incidence of lymphomas but the FDA has required the sponsors of adalimumab to acquire a large safety database to provide better estimates of adverse events.

4.6.2 Summary

The safety of TNFα antagonists is currently unknown with regard to the development of lymphomas. One to three cases of lymphomas were diagnosed in the treated groups for each TNFα antagonist versus none in the control groups (six lymphomas versus none across all controlled studies). The biological plausibility of lymphomas associated with immunomodulatory agents, along with the data presented, raises concerns about potential causality. Continued vigilance is warranted until any relationship of these agents to the lymphoproliferative disorders incidence is fully characterised.

4.6.3 Solid Tumours

Certain other malignancies such as breast, colon, cervical, prostrate, melanoma, gall bladder, squamous- and basal-cell carcinoma have been reported with use of TNFα antagonists. These have not exceeded the age- and sex-matched incidence in the US population. Malignancies, other than lymphomas, are not increased in patients treated with these agents.[9]

4.7 Immunogenicity

Treatment with TNFα antagonists can be associated with the formation of antibodies against the individual agents. These data need to be interpreted in terms of the variability and accuracy of methods used in the articles cited.

An average of 10% of RA patients develops human anti-chimeric antibodies (HACA) to infliximab.[6] The presence of the antibody is associated with a higher rate of infusion reactions (defined as reaction occurring within 2 hours of infusion). Among 25 patients with HACA and 125 controls without HACA, infusion reactions occurred in 11% of HACA-positive patients and 3% HACA-negative patients while American College of Rheumatology (ACR) 20% response was equal for the two groups (from the ATTRACT study).[6]

In a recent prospective study, 125 patients with Crohn's disease receiving infliximab infusion 5 mg/kg for the first time were evaluated for antibodies to infliximab and their relationship to infusion reactions and clinical efficacy.[73] There were technical issues relating to the antibody assay as well as clinical problems relating to the definition of clinically important antibody concentrations, making associations between the presence and concentration of antibody and efficacy or toxicity very tenuous. The comparability of previously published methods to methods used in this study is not known. Also, cut points for significant titres of antibodies were chosen ex *post facto* and arbitrarily. Beyond that, however, a high percentage of patients (approximately 47%) developed HACA in the Crohn's disease population after a single infusion. Concomitant use of immunosuppressives reduced the apparent immunogenic response.

In adalimumab clinical trials, 5% of RA patients developed antibodies to adalimumab. Patients using concomitant methotrexate had a lower rate of antibody formation than patients using adalimumab as monotherapy (1% versus 12%). The ACR 20% response was numerically but not statistically lower among antibody-positive patients than antibody-negative patients (30% versus 50%, p = 0.1).[9]

In etanercept clinical trials, <5% of patients developed antibodies, all of which were non-neutralising.[8] Results were similar with psoriatic arthritis, ankylosing spondylitis and juvenile RA.[8]

4.7.1 Summary

Infliximab, a chimeric antibody, clearly results in a higher incidence of HACA. The implication of this difference on efficacy is unclear, although these antibodies are associated with increased adverse events in some cases. Concomitant use of methotrexate reduces immunogenic response to both infliximab and adalimumab.[6,9] No neutralising antibody was seen with etanercept.

4.8 Haematological

4.8.1 Aplastic Anaemia, Pancytopenia

Four cases of aplastic anaemia have been reported with the use of etanercept as of September 2001.[53] The historical background incidence is 5.7–8.2 patients/100 000 patient-years with an increased incidence of aplastic anaemia in RA (odds ratio = 7.6, 95% CI 2.6, 23). Fifteen and 12 cases of pancytopenia have been reported with infliximab and etanercept, respectively, as of September 2001.[53]

4.8.2 Summary

As the incidence of haematological disorders is rare, if patients on TNFα antagonists develop aplastic anaemia or pancytopenia, these agents should be stopped and patients should be evaluated for evidence of other underlying disease.[40]

4.9 Vasculitis

4.9.1 Leukocytoclastic Vasculitis

Twenty-eight cases of leukocytoclastic vasculitis (LCV) obtained from the FDA MedWatch programme were recently presented in an abstract form.[96] Sixteen were associated with etanercept administration and 12 followed infliximab administration. Sixteen of the 28 (57.1%) were biopsy-proven cases, and the others apparently had skin lesions that were reported to be clinically typical for LCV (i.e. palpable purpura, distribution on the lower extremities). Twenty-one of 28 (75%) patients had complete resolution or marked improvement of skin lesions upon stopping TNFα antagonist therapy and eight patients experienced recurrence (positive rechallenge phenomenon) of LCV upon restarting TNFα antagonist therapy.

4.9.2 Summary

In patients who develop LCV, TNFα antagonists should be stopped. This is most likely a hypersensitivity reaction, as TNFα antagonists have been used to treat other vasculitides (e.g. Wegener's granulomatosis).[97]

5. Safety of TNFα Antagonists and Pregnancy

All TNFα antagonists are categorised as pregnancy category B. In the mouse model, TNFα intervention has shown that preimplantation development and pregnancy can be restored to normal, proving its fundamental role in early pregnancy.[98] However, increased production of TNFα has been associated with recurrent spontaneous abortions, infertility relating to endometriosis and pre-eclampsia.[99-102] Using an elegant mouse model of antiphospholipid syndrome, TNFα was shown to be a mediator of fetal damage.[103] TNFα induces cyclooxygenase (COX)-2 gene expression in early pregnancy[104,105] and TNFα antagonists can inhibit COX-2. Since cyclooxygenases are important in blastocyst implantation, endometrial vascular permeability, and the uterine decidualisation process

and marked inhibition of COX-2 by high doses of both indomethacin and selective COX-2 inhibitors (celecoxib ≥80 mg/day and rofecoxib ≥10 mg/kg/day) produced pre- and post-implantation losses and reduced embryo/fetal survival in rats and rabbits.[106,107] It is theoretically possible that TNFα antagonists could interfere with implantation and ovulation.

However, no evidence of embryotoxicity or teratogenicity was observed in developmental toxicity studies conducted in animals at very high doses and case reports both in RA and Crohn's disease of successful pregnancy with both etanercept and infliximab have been published.[108,109] The experience with infliximab in human pregnancy has been published in abstract form.[110] As of October 2001, there were 59 pregnancies identified in conjunction with exposure to infliximab. Of the 36 patients with known outcomes, 26 (72%) resulted in live births, five (14.3%) in miscarriages, and five (14.3%) in therapeutic termination. Of the 26 live births, two infants had complications. One preterm infant (gestational age 23 weeks) died 3 weeks following birth and another infant had surgical correction of tetralogy of Fallot. The incidence of live births, miscarriages and therapeutic terminations are similar to those observed in a national cohort of healthy women (62, 16 and 22%, respectively).[110] Thus despite potential problems theoretically, there is no actual evidence at present that TNFα antagonists decrease fertility or induce miscarriages.

6. Conclusion and Recommendations

1. Controlled clinical trials of all three TNFα antagonists have not consistently shown an increased risk of infections compared with RA patients treated with immunosuppressives in the pre-TNFα antagonists era, although serious infections have been uncommonly associated with their use.

2. Reactivation of granulomatous infections is a concern with inhibition of TNFα and appropriate measures should be taken for detection and treatment of latent infection before initiating therapy with all of these agents.

3. Patients should be vaccinated against common encapsulated organisms before the initiation of the TNFα antagonists.

4. The relationship of TNFα antagonists to non-Hodgkin's lymphoma is unclear. The biological plausibility of lymphomas associated with immunomodulatory agents, along with the data presented, raises concerns about potential causality. Continued vigilance is warranted until any relationship of these agents to the lymphoproliferative disorders incidence is fully characterised. There is no evidence linking TNFα antagonists with a higher incidence of solid tumours.

5. TNFα antagonists should be avoided in patients with pre-existing demyelinating disease.

6. TNFα antagonists should be avoided in advanced CHF (NYHA class III-1V) and in patients with NYHA I and II with reduced ejection fraction (<50%). TNFα antagonists should be used with great caution in NYHA class I and II with normal ejection fraction.

7. Drug-induced lupus, cutaneous lupus or pancytopenia have rarely been reported with TNFα antagonists and patients should be monitored for clinical signs of systemic lupus erythematosus, vasculitis or for pancytopenia.

8. At present there is no evidence implicating TNFα antagonists with embryotoxicity, teratogenicity or increased pregnancy loss, although caution, as usual, is warranted.

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