The safety of etanercept for the treatment of plaque psoriasis

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Abstract: Effective treatment with etanercept results from a congregation of immunological signaling and modulating roles played by tumor necrosis factor-alpha (TNF-alpha), a pervasive member of the TNF super-family of cytokines participating in numerous immunologic and metabolic functions. Macrophages, lymphocytes and other cells produce TNF as part of the deregulated immune response resulting in psoriasis or other chronic inflammatory disorders. Tumor necrosis factor is also produced by macrophages and lymphocytes responding to foreign antigens as a primary response to potential infection. Interference with cytokine signaling by etanercept yields therapeutic response. At the same time, interference with cytokine signaling by etanercept exposes patients to potential adverse events. While the efficacy of etanercept for the treatment of psoriasis is evident, the risks of treatment continue to be defined. Of the potential serious adverse events, response to infection is the best characterized in terms of physiology, incidence, and management. Rare but serious events: activation of latent tuberculosis, multiple sclerosis, lymphoma, and others, have been observed but have questionable or yet to be defined association with therapeutic uses of etanercept. The safe use of etanercept for the treatment of psoriasis requires an appreciation of potential adverse events as well as screening and monitoring strategies designed to manage patient risk.

Keywords: etanercept, psoriasis, demyelination, tumor necrosis factor, lymphoma, tuberculosis, infection, safety

Characterizing the safety of a drug is rarely simple and never complete. Both short and long-term drug safety profiles require episodic, critical reviews of available information. Episodic reviews are necessary to survey case reports and put previous summaries into perspective. Critical evaluation is important to determine relevance, veracity, and adequacy of available information. Etanercept is no exception.

The short-term safety of etanercept is well established by rigorous clinical trials in rheumatoid arthritis, psoriatic arthritis, and psoriasis (Leonardi et al 2003; Papp 2004; Keystone 2005; Kavanaugh et al 2006). Registries, now abundant in the rheumatology arena, are resources for assessing long-term risk and harm (Sokka 2004). Psoriasis registries should provide useful data over the next few years. Nonetheless, information extracted from registries must be put into context. The underlying disease may have epidemiologic characteristics different from the target disease. And, by their nature, registries are not as restrictive or as selective as controlled trials (Krishnan and Fries 2004). There is a treatment bias: treatment tends to be given to a sicker population. There may be a confounding indication: not every enrollee fulfills appropriate diagnostic criteria. Biased patient selection, good or bad, may exaggerate effectiveness or safety. In addition, patients enrolled in clinical registries have few if any restriction on concurrent therapy thus confounding drug-drug interactions and attribution of efficacy or adverse effects. On the other hand, registries are thought to be more reflective of
real world experience. In addition, registries often provide larger number of patients, long periods of observation and data collection compared with registration trials.

Case reports will identify unanticipated adverse events attributed to etanercept but are limited by the potential for inappropriate association of cause and effect. Etanercept is an effective therapy for psoriasis: effectiveness is advantageous to its adoption as a new therapy. This advantage is potentially offset by heightened scrutiny, off-label use, and sub-standard post marketing reports of adverse events.

In this review, every effort is made to provide a balanced appraisal of risk. Pathophysiology and likelihood of association are considered as complements to incident reports when evaluating safety (Mulrow et al 1997; Ioannidis et al 2006). Where assessment of risk is hampered by insufficient epidemiologic data, provisional estimates or cautionary comments are inserted.

Background

TNF-alpha, often referred to as tumor necrosis factor (TNF), is one member of the TNF superfamily of cytokines (Zhou et al 2002). TNF was initially described as a hemorrhagic necrosis factor produced by lipopolysaccharide-stimulated tumours. We now appreciated that TNF is a ubiquitous cytokine expressed by many cell types and having activity in innate and adaptive immune pathways (Zhou et al 2002). As a consequence of its important immunological function, TNF plays a central role in acute and chronic inflammation (Liz-Grana and Carnota 2001; Pfeffer, 2003). The variety of immunological and metabolic processes affected by TNF-alpha, the functions of soluble and membrane bound TNF-alpha, and interactions between members of the TNF superfamily are impacted by the molecular activity of TNF-inhibitors such as etanercept. Both unanticipated risks and unanticipated benefits may arise through long-term high frequency exposure to a TNF-inhibitor. Given the unique molecular characteristics of each TNF-inhibitor, we expect common risk-benefit profiles and differences.

Etanercept is a dimeric fusion protein produced using recombinant genetic programming of Chinese hamster ovary cells. The protein has a molecular weight of 150 kDa and consists of two 75 kDa TNF-alpha receptors linked to the Fc portion of human immunoglobulin G1 (Dembic et al 1990; Mohler et al 1993).

Clinical study reports are sufficiently detailed to provide short term safety data, but none are powered to identify rare events. The National Data Bank for Rheumatic Diseases and the publicly available BIOBADASER are examples of registries that provide excellent longitudinal information on patients with rheumatologic diseases treated with TNF-antagonists.

The structure of this review is as follows: Broad categories of adverse events are identified. Within each category there may be specific, noteworthy concerns. Inciting observations and scientific rationale preface each general and specific category. Data relevant to the category are presented accompanied by brief commentary. Comparative data for TNF-antagonists as a group are avoided where possible to limit the scope of the review.

Mechanisms of action

Tumor necrosis factor-alpha engages in many aspect of immunological function. By its activity on TNF-alpha, etanercept will impact immunological and inflammatory processes ranging from innate and extrinsic immunological response, cellular trafficking, acute and chronic inflammation, fever, and neuroendocrine regulation (Gruss and Dower 1995). TNF interacts with glucocorticoids to regulate Toll-like receptor 2 gene expression (Hermoso et al 2004).

The precise mechanisms of action of TNF-antagonists are not known. Certainly etanercept binds to free, soluble, or non-membrane-bound TNF-alpha but etanercept also has activity against the p55 receptor TNF-beta, also called lymphotoxin (Williams and Griffiths 2002; Keystone and Dinarello 2005). Contrary to the effects on TNF-alpha, the activity of etanercept against p55 may stimulate immunoreactivity (Han et al 2005) in addition to having effects on B-, T-, NK-cells and lymphoid architecture (Spahn et al 2005). Moreover, there is evidence that both etanercept and infliximab induce apoptosis in macrophages, but not lymphocytes within rheumatoid arthritis (RA) joints (Catrina et al 2005). In general, the effects of etanercept are mediated by its binding of soluble TNF-alpha, but other TNF-antagonist activities are recognized. The implications of accessory TNF-antagonist activities are not known. Etanercept has peak absorption at 51 hours and a mean half-life of 68 hours (Korth-Bradley et al 2000).

Whether or not TNF is an intrinsic pyrogen remains controversial (Steffler et al 1996; Luheshi et al 1997; Dinarello 2005). In the mouse model, TNF does not appear to have pyrogen activity (Dinarello 2005). Nonetheless, resolving the question for humans is significant as fever is a common, early, ubiquitous sign of infection and infections remain the most prominent safety concern during treatment with TNF-antagonists.
A more complex role is reflected in the effects TNF may have on neuroendocrine response. Pituitary and hypothalamic response are potentiated when TNF is present in high levels (Turnbull and Rivier 1999). The neuroendocrine effects of TNF may be reflected in the psychological state of patients experiencing chronic inflammatory disease (Tyring et al 2006).

**Adverse events**

**Injection site reactions**

Mechanical processes such as poor injection technique, irritation, or immunologically mediated inflammatory processes associated with either drug or excipients cause injection site reactions. Foreign proteins may cause direct or indirect inflammatory response (Shepherd 2003). It is not surprising that injection site reactions are by far the most common side effect associated with etanercept.

Studies evaluating etanercept for the treatment of RA report a high incidence of injection site reactions with 34%–37% of etanercept-treated patients compared with 7%–10% of controls reporting reactions (Lebwohl 2002; Fleischmann and Yocum 2004). The high incidence in the RA population contrasts with a much lower incidence seen in psoriasis studies: 14%–20% (Leonardi et al 2003; Papp 2004; Papp et al 2005). Why there are stark differences in the incidence of injection site reactions between RA and psoriasis populations is not known.

Injection site reactions with 25 mg doses of etanercept are mild, well tolerated, self-limiting, and tend to occur early in the course of therapy (Zeltser et al 2001; Papp 2004). Irritation during and briefly following injection is very common with the 50 mg single dose compared with the 25 mg dosing formulation. Occasionally, persistent reactions of moderate severity are noted. Persistent reactions are characterized by erythematous, indurated, and urticarial like plaques (Edwards et al 2003). The histology of etanercept injection site reactions is consistent with a delayed-type hypersensitivity reaction (Werth and Levinson 2001; Zeltser et al 2001). Delayed and recall injection site reactions are infrequent but tend to be somewhat more severe than typical etanercept-associated injection site reactions (Zeltser et al 2001; Rajakulendran and Deighton 2004). Significant and severe injection site reactions are rare with etanercept regardless of dose (Papp 2004).

**Infection**

Clinical trials and post-marketing experience suggest that infection is the most common significant category of adverse events experienced by patients treated with etanercept. Less common infections including tuberculosis and opportunistic infections, specifically histoplasmosis and listeriosis, are considered separately.

TNF is involved in the immune response to bacterial and viral infections (Imanishi 2000; Herbein and O’Brien 2000). More specifically, TNF plays an essential role in host response to intracellular pathogens (Choy and Panayi 2001). The important role of TNF in immune response to intracellular organisms is further supported by TNF-deficient animal models (Marino et al 1997). For Gram-positive and Gram-negative infections, clearance of organisms may be impeded by TNF-suppression (Takashima et al 1997; O’Brien et al 1999; Rijneveld et al 2003; Moore et al 2003, 2005). Clinical studies, registries, and case reports confirm that host response to infection is the most common significant safety concern in patients treated with etanercept.

Serious infection is defined within studies and for safety monitoring as one requiring intravenous antibiotics or hospitalization (Keystone 2004). The incidence of serious infections in patients treated with etanercept varies according to the population treated, severity of disease, concomitant medication, and adherence to a definition of serious infection. Some report serious infections as those requiring systemic therapy.

During the clinical trial development of etanercept, the observed serious infection rate in the RA population was 0.03–0.04 serious infectious events per patient-year (SIE/pt-yr), equal to rates seen in placebo controls (Cush 2004a 2004b). Post-marketing surveillance across all indicated diseases has shown the rates of SIE with etanercept and infliximab to be 0.007 SIE/pt-yr (confidence interval [CI] 0.03–0.09/pt-yr). Significant under-reporting with post-marketing surveillance is expected but confounding effects include a less well defined treated population, inclusion of indications other than those reported in the clinical studies, and thus these rates may be substantially more common in the RA population (Cush 2004a, 2004b).

Within the RA population, an increased risk of serious infection is seen in patients having extra-articular manifestations of RA, presence of comorbid diseases, and immunosuppressive therapy (Doran et al 2002a). These infections tend to be upper respiratory, skin, and urinary tract infections.

Tumor necrosis factor-antagonist therapy may increase the risk of infection in the RA population. Reports of the number of infection-related adverse events per 100
patient-years during an 18 month period show that etanercept had a rate of 22.6 (18.7–27.2) events per hundred years compared with controls (those receiving disease modifying and remitting drugs [DMARDs]) with a rate of 6.8 (5.0–9.4) per hundred patient years (Listing et al 2005). The rates for serious infections were 6.4 (4.5–9.1) and 2.3 (1.3–3.9) for etanercept and control groups respectively. Adjusting for case-patient mix, the rates of serious infection were similar for etanercept and infliximab. These results suggest there is an increased risk of infection in those treated with TNF-antagonists. This study is limited by small numbers, a short observation period, and bias in populations: those on anti-TNF cannot be the same population as those on DMARDs since general patients with more severe disease are treated with TNF-antagonists, which introduces potential bias in the study populations.

It is certain that TNF-antagonists exacerbate septicemia with increase in mortality among septic patients on etanercept (Fisher et al 1996; Baghai et al 2001).

Patients developing new infections while on etanercept should be closely monitored and discontinued in those with serious infections or sepsis. Etanercept should not be initiated in patients with active infections including chronic or localized infections. Caution should be exercised when initiating etanercept in patients with a history of or predisposition to frequent recurrent infections.

**Mycobacterium tuberculosis**

Susceptibility to mycobacterium tuberculosis (TB) impacted by multiple factors including age, environment, immune status, and microbial virulence (Mitsos et al 2003) and genetic susceptibility (Abel and Casanova 2000; Casanova and Abel 2002). Latent tuberculosis remains a significant global health concern with nearly 30% of the world population infected (Jasmer et al 2002). TNF is necessary for cell recruitment, granuloma formation, and clearance of mycobacterial infection (Roach et al 2002). Recent clinical results demonstrating reactivation of latent TB in patients receiving anti-TNF monoclonal antibody therapy solidifies the importance of TNF in host response to TB (Keane et al 2001; Keane 2004, 2005).

The role of TNF in initial host response and subsequent confinement of TB organisms is complex and not completely elucidated. TNF regulates chemokine induction that in turn orchestrates cell recruitment, granuloma formation, and clearance of mycobacterial infection (Roach et al 2002; Stenger 2005). Mice lacking TNF mount delayed chemokine response and cellular infiltrate. Subsequent high chemokine production produced disorganized T-cell and macrophage responses capable of producing high levels of interferon-gamma but unable to protect against fatal TB infections 28 days post inoculation. Wild mouse strains survived 16 weeks or longer. The response of TNF-deficient mice exposed to mycobacteria anticipates the prominent role TNF plays in the initial response to infection and subsequent maintenance of granulomas. In large part, mortality results from unchecked type-1 inflammatory response producing tissue necrosis (Zganiacz et al 2004). Animal models also suggest there are differences in the activity of membrane-bound and -free TNF in acute and chronic response to TB (Olleros et al 2005; Saunders et al 2005). TNF is also required to maintain latency of TB (Botha and Ryffel 2003). Thus, the role of TNF in immune response to TB is poly-modal: initiate inflammatory response, regulate and suppress the inflammatory response, and maintain chronic immunological response.

RA patients on etanercept showed a linear incidence of TB infection (Wallis et al 2004a, 2004b) suggesting that acquisition of TB was related to exposure and not re-activation of latent infection. Infliximab-treated patients demonstrated an accelerated incidence of TB infection in keeping with activation of latent disease (Wallis et al 2004a, 2004b). While the incidence of TB in patients on etanercept may not be significantly greater than the background rate, treatment with etanercept does alter the clinical presentation of TB (Arend et al 2003; Gardam et al 2003). Approximately half of patients treated with etanercept who develop clinical TB present with extra-pulmonary manifestations including disseminated TB. The expected rate of extra-pulmonary TB in immunocompetent hosts is less than 15% (Dye et al 1999).

In summary, there is no scientific data in support of screening for latent TB prior to initiating therapy with etanercept. However, patients treated with etanercept who acquire infection with TB are more likely to have atypical presenting signs and symptoms. Etanercept-treated patients developing TB may be at increased risk of severe and potentially fatal infection. Screening for active TB with a chest X-ray is medically prudent. A more cautious approach is to screen for latent and active TB by chest X-ray (CXR) and tuberculin (PPD) testing prior to initiating etanercept in patients at high risk. Based upon minimal data, but highlighting the need for extreme safety, some suggest a CXR and PPD prior to introducing any immunosuppressive treatment (CDC 2004; Keane 2005).
Opportunistic infections
Opportunistic infections occur in patients on TNF-blocking agents (Jarvis and Faulds 1999; Garrison and McDonnell 1999; Mease et al 2000; Doran et al 2002a, 2002b; Netea et al 2003; Elkayam et al 2004), but these are rare (Keystone 2004).

Histoplasmosis is an uncommon opportunistic infection endemic to many regions of the world (Cano and Hajjeh 2001). Normal host defense to infection is dependent upon TNF expression (Smith et al 1990; Zhou et al 1998). Infection with histoplasmosis may be exacerbated in patients on therapy with TNF-antagonists, but lack of control comparators and cases occurring in histoplasmosis-endemic regions of the US make any conclusions tentative (Lee et al 2002). Less certain is the question of risk of reactivation of latent infection with histoplasmosis. This uncertainty is highlighted by reports of disseminated histoplasmosis occurring in patients on low-dose methotrexate (Berry 1969; Witty et al 1992; LeMense and Sahn 1994; Voloshin et al 1995; Roy and Hammerschmidt 2000; Arunkumar et al 2004).

Listeria monocytogenes is an uncommon but ubiquitous, opportunistic, intracellular pathogen causing gastroenteritis, meningitis, encephalitis, and septicemia (Hamon et al 2006). TNF is essential to effect normal host response to listeria (Havell, 1989, Rothe et al 1993; Kanaly et al 1999; Dinarello 2003; Torres et al 2005) and treatment with etanercept may predispose patients to infection (Schett et al 2005). Infection with listeria is reported in patients treated with TNF-antagonists and particularly etanercept (Slifman et al 2003; Eilers 2005; La Montagna and Valentin 2005; Nadarajah and Pritchard 2005; Rachapalli and O’Doughty 2005; Schett et al 2005). What is not evident is whether there is a real increased risk of infection or a modification of clinical presentation and host response (Pagliano et al 2004). Given that etanercept does affect lymphotoxin (Williams and Griffiths 2002) and that lymphotoxin is essential in providing normal immune response to listeria (Eilers et al 2003), the possible increased susceptibility to infection with listeria must be considered.

Rare cases of disseminated sporotrichosis further stress the importance of TNF in maintaining normal host response to infections (Gottlieb et al 2003).

Vaccination
TNF plays a significant role in immune response to pathogens (Herbein and O’Brien 2000) and may therefore modulate host response to vaccination. A number of studies have evaluated response to influenza vaccine in RA patients treated with etanercept. In general, response to influenza vaccine is blunted but not completely suppressed (Fomin et al 2006). The addition of methotrexate further suppresses the response to vaccination (Kapetanovic et al 2006).

Malignancy exclusive of lymphoma
The role of TNF in carcinogenicity and tumor surveillance has not been established. Early cell culture studies indicated that TNF is cytotoxic for certain tumor cell lines (Old 1985; Creasey et al 1986; Palladino, Patton, et al 1987; Palladino, Srivastava, et al 1987). Subsequent studies revealed that, for certain types of malignancies, TNF may act as a growth factor (Freedman et al 1992; Warzocha et al 1995; Filella et al 1996; Warzocha and Salles 1998; Warzocha, Bienvenu, et al 1998; Warzocha, Ribero, et al 1998; Renard et al 1999; Moore et al 1999) and may even enhance the metastatic potential of certain tumors (Balkwill et al 1990; Malik et al 1990).

Review of the clinical studies and registries for TNF-antagonists shows no increase in the incidence of solid tumors in the RA population (Keystone 2003, 2005). Likewise, in the clinical studies evaluating etanercept for the treatment of psoriasis, there is no evidence of increased risk of malignancy (Leonardi et al 2003; Papp 2004; Papp et al 2005). The potential for increased risk of solid tumors in patients receiving concurrent etanercept and alkylating agents must be considered (Mukhtar and Luqmani 2005; WGET 2005; Hellmich et al 2006; Stone et al 2006). There are cases of rapidly developing squamous cell carcinomas in RA patients initiating therapy with etanercept (Smith and Skelton 2001). To the contrary, TNF-alpha deficient mice are resistant to cutaneous carcinogenesis (Arnott et al 2002).

Lymphoma
There is a strong association of non-Hodgkin’s lymphoma with Epstein-Barr virus (EBV) infection and immunosuppression (Liebowitz 1998; Meyer et al 2004; Poppema 2005). Approximately 95% of adults are infected with EBV. Many develop subclinical reactivation (Rickinson and Kieff 1996). Members of the TNF superfamily of receptors play a role in pathogenesis of EBV-positive lymphomas arising in immunosuppressed patients, but the role of TNF-alpha is not established (Liebowitz 1998; Herbein and O’Brien 2000). Chronic inflammation produces elevated TNF levels, which in turn produce indirect alterations in immunological function (Khan 2006; Weyand et al 2006) and modulatory effects of TNF on T-cell surveillance (Baran-Marszak et al 2006).
Confounding the role of TNF in the development of lymphoma is the association of chronic inflammatory processes and lymphoma (Kato et al. 2003; Chang et al. 2005). The potential association of TNF, TNF-antagonism, and the development of lymphomas is confounded by epidemiologic surveys showing a strong trend in risk in patients with psoriasis (Hannuksela-Svahn et al. 2000; Gelfand et al. 2003, 2006) though these findings are not substantiated by larger surveys (Smedby et al. 2006). The association of lymphoma and rheumatoid arthritis appear more certain (Baecklund et al. 1998, 2003, 2004, 2006; Ekstrom et al. 2003).

There are case reports of lymphoma developing in patients receiving TNF-antagonists (Brown et al. 2002). Of the 26 cases reported, 18 developed in patients on etanercept. The mean time to onset of lesions after commencing therapy was 8 weeks. Data from an RA registry suggests an increased risk of lymphoma in patients treated with TNF-antagonists or methotrexate compared with those who are not (Wolfe and Michaud 2004b). There is, however, a strong selection bias in that those receiving anti-TNF therapy tend to be the most severely affected patients, a cohort already known to have a greater risk of lymphoma (Baecklund et al. 1998) and that the strongest association is not with therapy but the underlying RA itself (Baecklund et al. 2006). In addition, two cases of cutaneous and systemic T-cell lymphoma progressed rapidly after initiating TNF-blockade: one with etanercept and one with infliximab (Adams et al. 2004). Both cases were described as rapid in onset with fulminant courses: extensive cutaneous, and systemic involvement resulting in death within months of diagnosis.

While there are numerous case reports of lymphoma developing in patients treated with etanercept, the relative risk of lymphoma remains constant for RA patients regardless of therapy with TNF-antagonists (Keystone 2005). The high incidence of lymphoma in RA patients makes risk assessment complex. The lower incidence of lymphoma in the psoriasis population may be instrumental in the assessment of risk associated with long-term treatment with etanercept.

**Central nervous system demyelination events**

We have some understanding of the incidence of multiple sclerosis (MS) in the general population: women more commonly affected, there are regional variations in incidence and prevalence (Ebers and Sadovnick, 1993, Magnano et al. 2004). Incidence in the general population is approximately 6 per 100,000 per year with a prevalence of nearly 85/100,000. An increased in risk of MS is reported in individuals with affected first degree relatives (Sadovnick et al. 1993).

MS is uncommon. Furthermore, assessments may be complicated as not all instances of magnetic resonance imaging (MRI) findings consistent with demyelination are MS (Koller et al. 2005a). Instances of chronic, inflammatory, demyelinating polyneuropathy are usually peripheral, but may include cortical and optic nerve demyelination. Interestingly, MS appears to be a Th1 disorder mediated by cytokines including TNF and evinces many of the pathogenic pathways active in psoriasis (Koller et al. 2005b).

The putative relationships between TNF, TNF-antagonism, and MS are not obvious. Many theoretical reasons support TNF-antagonist activity induces demyelization (Magnano et al. 2004). Equally supportive arguments support the contrary: TNF-antagonism does not increase the risk of MS and may potentially be of therapeutic value (Magnano et al. 2004). Reporting bias of case reports (Magnano et al. 2004) and potential association with other autoimmune diseases (Midgard et al. 1996) confound the role of TNF-antagonist therapy in the onset or exacerbation of MS.

Much of the current concern over TNF-antagonism and MS results from a single study evaluating lenerecept; a p55, recombinant, soluble TNFR1 receptor protein, for the treatment of relapsing-remitting and secondarily progressive MS (LMS-UBC 1999). The study found no increase in new or active lesions as demonstrated on MRI. However, there was a significant dose-related increase of attack frequency though not attack severity nor attack duration. The contrary response of MS patients treated with lenerecept underscores the difficulty in extrapolating results from animal models. Antibodies to lenerecept did not affect clinical response but did increase rate of drug clearance (Wiendl and Hohlfeld 2002). Two cases of MS patients treated with infliximab demonstrated increased MRI activity but no clinical worsening (van Oosten et al. 1996).

The rarity of MS in psoriasis patients treated with etanercept is highlighted by the rarity of case reports (Sukal et al. 2006). From the rheumatology literature, there are cases temporally related to TNF-suppression, some of which resolved upon withdrawal of treatment (Mohan et al. 2001). MS remains rare and of uncertain causal association with anti-TNF therapy (Mohan et al. 2001; Magnano et al. 2004). Many but not all patients develop recurrent symptoms on re-challenge (Mohan et al. 2001; Cisternas et al. 2002).

There is growing concern among some groups of neurologists who suggest pretreatment MRI scans for all...
patients about to receive a TNF-antagonists (Bellesi et al 2006). Currently, etanercept should be avoided in patients with a personal history of any central nervous system demyelinating disorder and used with caution in patients with a family history of these disorders. Pretreatment MRI may be considered in patients with equivocal histories of neuropathy or signs or symptoms of demyelination and first degree family histories of MS.

**Hematological events**

Rare cases of pancytopenia and aplastic anemia are reported in association with etanercept (Lebwohl 2002). A fatal outcome is reported in some cases (Jarvis and Faulds 1999; Khanna et al 2004). Nonetheless, it is important to review drug and medical history to exclude other potential causes of myelosuppression (Baumelou et al 1993; Marshall et al 2006).

**Hepatitis**

TNF plays a role in host response to hepatitis B and C (Herbein and O’Brien 2000). With 1.8% of the world population infected with hepatitis C virus and 5% infected with hepatitis B, the potential for exacerbation of viral hepatitis associated with TNF-antagonist therapy is noteworthy. While TNF does play a role in viral hepatic infection, the importance of TNF in maintaining suppression of viral replication is not clear (Calabrese et al 2004).

Mixed reports on response of patients with hepatitis B treated with anti-TNF agents correlates with the natural, variable history of the infection (Khanna et al 2003; Calabrese et al 2004; Khanna et al 2004; Lok and McMahon 2004). Nonetheless, TNF plays a primary role in sustaining a normal response to infection with hepatitis B (Schlaak et al 1999; Michel et al 2003; Ostuni et al 2003). Recently, Health Canada issued an advisory related to possible reactivation of hepatitis B in patients receiving anti-TNF therapy. The advisory is based upon a single case report (HPB Canada 2006).

The mechanisms relating to reactivation of hepatitis B are uncertain. Equally uncertain is the association between treatment with TNF-antagonists or other immunosuppressant and hepatitis B reactivation. More likely is reaction upon drug discontinuation or rebound with replication of hepatitis B in hepatocytes upon discontinuation of immunosuppressive therapy (Herbein and O’Brien 2000).

It is suggested that antiviral therapy be initiated prior to initiation of immunosuppressive treatment or to introduce antiviral therapy upon activation of hepatitis (de Franchis et al 2003).

Hepatitis C appears to follow more consistent patterns of infection characteristic of its natural course (Calabrese et al 2004). A small group of hepatitis C-positive RA patients were administered etanercept or infliximab for periods of 3–36 months. None of the patients showed changes in liver enzymes or viral loads (Zein and Zein 2002; Peterson et al 2003).

Elevated liver enzymes may be observed in patients receiving anti-TNF therapy but these observations are confounded by medications or circumstances making the aetiology of elevations uncertain (Schiemann and Kellner 2002; Khanna et al 2003, 2004).

The data currently available suggest etanercept is unlikely to have negative impact and may be protective against morbidity associated with chronic hepatitis C infection. Morbidity associated with chronic infection with hepatitis B virus in the face of treatment with etanercept is not well characterized. Prudent medical practice would support screening for hepatitis B infection prior to commencing therapy with etanercept.

**Lupus-like drug reactions**

Antinuclear antibodies (ANA) and anti-DNA antibodies develop in RA patients treated with etanercept (Watts 2000; De Bandt et al 2003, 2005; Haraoui and Keystone 2006). There also appears to be an increase in anticardiolipin expression in RA patients after 6 months of etanercept (Jonsdottir et al 2004). While serum antibodies are rarely associated with symptoms, there are few cases of etanercept-induced lupus erythematosus (Cairns et al 2002; Shakoor et al 2002; Carlson and Rothfield 2003). In general, etanercept-induced lupus resolves within 6 weeks to 14 months of discontinuation of therapy (Mohan et al 2002). Most frequently, the presentation has signs and symptoms of sub-acute cutaneous lupus (Bleumink et al 2001; Misery et al 2002). Overall, drug-induced lupus appears to be less common in patients treated with etanercept compared with those treated with other TNF-antagonists (Cush 2004c).

There are no surveys indicating the prevalence of ANA and anti-DNA antibodies in the psoriasis population and no data from large clinical studies or registries identifying the risk of autoantibody formation in psoriasis patients treated with etanercept. Personal experience suggests that somewhat less than 10% of psoriasis patients become ANA positive during the first two or three years of treatment. While the
ANA titres are in generally low: less than 1:40, higher titres are observed.

Given the overall lack of association between positive ANA and DNA titres in the general population and those treated with etanercept, screening for autoantibodies prior to treatment with etanercept is unwarranted. However, unless there is exceeding good communication between the dermatologist and other healthcare providers, the authors feel it useful to have a baseline screen for ANA titres with annual or every two year tests for ANA to reduce the risk of other healthcare professionals initiating costly diagnostic procedures based upon incidental and clinically unimportant laboratory results.

Cutaneous reactions
Leukocytoclastic vasculitis has been reported in patients treated with etanercept. Some instances resolve spontaneously while on therapy. Results are mixed on re-challenge with instances of recurrence while others are not (Galaria et al 2000; Mohan et al 2004). The underlying mechanism and association are not clear.

Cases of urticaria have been reported in associated with etanercept (Skytta et al 2000). Possibly more uncommon are cases of psoriasis induced by treatment of RA with etanercept (Sfikakis et al 2005).

Cardiovascular
Congestive heart failure
We do not know the underlying incidence of congestive heart failure (CHF) in the general psoriasis population. More specifically, we do not know the incidence of CHF in the population of patients with moderate to severe plaque psoriasis. There were no cases of CHF in the 6 months etanercept-psoriasis studies (Leonardi et al 2003; Papp 2004; Papp et al 2005). It has been reported that 51 RA patients treated with TNF-antagonists developed CHF (FDA 2003). The mean time to onset was 3.5 months post initiation of therapy. At least half of the cases had pre-existing risk factors for CHF. However, there are data showing that polymorphisms in the promoter region of the TNF gene are associated with cardiovascular complications (Elahi and Matata 2005).

Biologically, there is evidence to support the use of TNF-antagonists for the treatment of CHF (Torre-Amione et al 2000; Cush 2004c). A study to evaluate 3 months of therapy with etanercept for the treatment of New York Heart Association (NYHA) III-IV CHF showed a significant dose-dependent improvement in left ventricular structure and function and a trend towards improvement in patient functional status (Bozkurt et al 2001). A study assessing etanercept at 25 mg, 50 mg, or 75 mg weekly for the treatment of NYHA III-IV CHF was stopped prematurely owing to prespecified stopping rules supporting lack of efficacy. There was no evidence of worsening of outcome, but neither was there relevant benefit on rate of death or hospitalization (Mann et al 2004).

Subsequently, MedWatch reported 47 patients experiencing new or worsening CHF on anti-TNF therapy: 38 developed new-onset (26 etanercept, 12 infliximab); 19 had no identifiable risk factors (12 etanercept and 7 infliximab); 9 experienced exacerbation (3 etanercept, 6 infliximab) (Kwon et al 2003). Of those patients with new onset CHF, 29 were receiving treatment for RA, six for Crohn’s Disease, one for psoriatic arthritis, one for juvenile RA, and one unknown.

Evidence from Arthritis Research Center Foundation registry suggests etanercept may reduce risk of CHF in patients with RA compared with patients not receiving anti-TNF therapy (Wolfe and Michaud 2004a). Overall, heart failure was significantly less common in patients receiving anti-TNF therapy than in other patients (p < 0.05). There was no increase in heart failure observed among patients younger than 50 years.

There is currently insufficient evidence to ascribe a causal association between etanercept and CHF. Evidence from limited clinical studies of patients suffering severe CHF and data from long-term registries suggest no association with the onset of CHF and the use of etanercept. On the contrary, there is evidence supporting a beneficial effect on CHF in patients treated with etanercept.

Cautionary notes
Wound healing
In a small series of 31 patients with RA undergoing foot or ankle surgery, the use of etanercept or infliximab (15 of the 31 patients were treated with standard DMARD therapies) was not associated with an increased risk of post-surgical wound healing or infection (Bibbo and Goldberg 2004). Nonetheless, caution and evaluation of risk-benefit must be considered when patients on etanercept undergo elective surgery.

Insulin resistance and diabetes
Population studies (Zinman et al 1999) and genetic studies (Obayashi et al 2000; Rasmussen et al 2000) suggest TNF-alpha concentrations may play a pathophysiological role in
and are positively correlated with insulin resistance. Though no severe episodes of hypoglycemia were reported in clinical studies evaluating etanercept, appropriate precautions are advisable when introducing anti-TNF therapy in patients with insulin resistance.

Breast feeding and pregnancy
Detectable levels of etanercept are found in breast milk (Ostensen and Eigenmann 2004). The clinical significance of this observation is unknown and complicated by the low gastric proteolytic activity in preterm infants and newborns (Hamosh 1996; Henderson et al 2001).

In mice, TNF plays an essential role in implantation (Tartakovsky and Ben-Yair 1991). Elevated levels of TNF-alpha have been associated with recurrent spontaneous abortions and infertility (Daher et al 1999; Murakami et al 2002). While there are theoretical concerns regarding implantation and ovulation, there is no evidence supporting altered fertility in humans treated with etanercept and likewise no evidence for embryotoxicity or teratogenicity (Khanna et al 2004).

Summary
Characterizing the safety of etanercept in patients with psoriasis is neither simple nor complete. Long term risk associated with use of etanercept will require vigilance (Imperato et al 2004). The identification of rare events requires exposure of tens and hundreds of thousands of patients. The current state of information suggests three broad categories of concern.

Patients receiving etanercept are more prone to infections. The majority of infections are mild: upper respiratory tract infections localized cutaneous abscesses, and cold-like illnesses. Patients may have increased susceptibility to infections by intracellular organisms particularly listeria and tuberculosis. Reactivation of latent infection is not yet supportable. Those acquiring tuberculosis are at increased risk of presenting with atypical or disseminated infection. Patients who become septic and are receiving etanercept are at greater risk of fatality than those who are not.

Prior to instituting therapy with etanercept, a review of risks should be completed. An outline is provided in Table 1. Suggestions for monitoring therapy are outlined in Table 2. Precautions should be maintained during therapy with routine laboratory testing and patient review with special regard to signs and symptoms of infection or adverse effects exacerbated by treatment with etanercept. Patients should be reminded to discontinue therapy with etanercept when treated with antibiotics. Patients should also be aware of the reduced efficacy of vaccination while on treatment with etanercept.

Table 1 Introducing therapy

| Contraindications |
|-------------------|
| Hypersensitive reactions to etanercept |
| Active infection |
| Septic arthritis within 12 months |
| Active or personal history of demyelination |
| Hematological dyscrasia |
| Septicemia |

| Relative contraindication |
|---------------------------|
| Pregnancy or breast-feeding |
| NYHA grade 3 or 4 heart failure |
| First degree relative with history of demyelinating disease |
| Prior hematological dyscrasia |
| Frequent infections |
| Open wounds, chronic or recurrent ulceration |
| Insulin resistance |

Table 2 Initiation and maintenance of therapy

| A. Discontinue during administration of antibiotics |
| B. Consider comorbidity |
| RA: Hypertension (15%) increased risk of CHF; Diabetes (6%) increased risk of hypoglycemia; Cardiac ischemia (4%) (BIOBADASER, June 2003) |
| C. CXR to exclude active TB |
| D. Consider PPD to exclude latent TB (this is suggested for all TNF-antagonists by many. However, there is no evidence supporting activation of latent TB in patients treated with etanercept) |
| E. Surgery: Discontinue etanercept 1–2 weeks prior and recommence 2 weeks following uncomplicated recovery |
| F. Vaccination: discontinue 4 weeks prior to and re-instate 4 weeks post (based upon potential depressed efficacy rather than safety considerations) |
| G. Discontinue in the event of a malignancy with the exception of cutaneous basal cell carcinoma. |
| H. Periodic CBC and ALT (every 3 months) |
| I. Periodic ANA (once yearly) |
| J. Periodic history regarding signs and symptoms of opportunistic infections |
| K. Annual cutaneous examinations for malignancy |
| L. In the event of pregnancy, appropriate review of risk-benefit |

| Abbreviations: ALT, alanine aminotransferase; CBC, complete blood count; CHF, congestive heart failure; CXR, chest X-ray; PPD, tuberculin; RA, rheumatoid arthritis; TB, tuberculosis. |

reminded to discontinue therapy with etanercept when treated with antibiotics. Patients should also be aware of the reduced efficacy of vaccination while on treatment with etanercept.

References
Abel L, Casanova JL. 2000. Genetic predisposition to clinical tuberculosis: bridging the gap between simple and complex inheritance. Am J Hum Genet, 67:274–7.

Adams AE, Zwicker J, Curiel C, et al. 2004. Aggressive cutaneous T-cell lymphomas after TNF-alpha blockade. J Am Acad Dermatol, 51:660–2.
Ektrom K, Hjalgrim H, Brandt L, et al. 2003. Risk of malignant lymphomas in patients with rheumatoid arthritis and in their first-degree relatives. Arthritis Rheum, 48:963–70.

Elahi MM, Matata BM. 2005. Genetic diversity of tumour necrosis factor: implications on cardiovascular complications of polymorphisms at position -308 in the promoter region. The Cardiology, 1:179–88.

Elkayam O, Caspi D, Reiblatt T, et al. 2004. The effect of tumour necrosis factor blockade on the response to pneumococcal vaccination in patients with rheumatoid arthritis and ankylosing spondylitis. Semin Arthritis Rheum, 33:283–8.

[FDA] Food and Drug Administration Briefing Document. 2003. Update on the TNF blocking agents [online]. Accessed on 22 October 2006. URL: http://www.fda.gov/ohrms/dockets/ac/03/briefing/3930B1_01_B-TNF. Briefing.pdf.

Filella X, Blode J, Guillermo AL, et al. 1996. Cytokines (IL-6, TNF-alpha, IL-1alpha) and soluble interleukin-2 receptor as serum tumor markers in multiple myeloma. Cancer Detect Prev, 20:52–6.

Fisher CJ Jr, Agosti JM, Opal SM, et al. 1996. Treatment of septic shock with the tumor necrosis factor receptor:Fc fusion protein. The Soluble TNF Receptor Sepsis Study Group. N Engl J Med, 334:1697–702.

Fleischmann R, Yocum D. 2004. Does safety make a difference in selecting the right TNF antagonist? Arthritis Res Ther, 6(Suppl 2):S12–18.

Forni L, Caspi D, Levy V, et al. 2006. Vaccination against influenza in rheumatoid arthritis: the effect of disease modifying influences including TNF alpha blockers. Ann Rheum Dis, 65:191–4.

Freedman MH, Cohen A, Grunberger T, et al. 1992. Central role of tumour necrosis factor, GM-CSF, and interleukin 1 in the pathogenesis of juvenile chronic myelogenous leukaemia. Br J Haematol, 80:40–8.

Galaria NA, Wether VP, Schumacher HR. 2000. Leukocytoclastic vasculitis due to etanercept. J Rheumatol, 27:2041–4.

Gardam MA, Keystone EC, Menzies R, et al. 2003. Anti-tumour necrosis factor agent and tuberculosis risk: mechanisms of action and clinical management. Lancet Infect Dis, 3:148–55.

Garrison L, McDonnell ND. 1999. Etanercept: therapeutic use in patients with rheumatoid arthritis. Ann Rheum Dis, 58(Suppl 1):165–9.

Gelfand JM, Berlin J, van Voorhees A, et al. 2003. Lymphoma rates are low but increased in patients with psoriasis: results from a population-based cohort study in the United Kingdom. Arch Dermatol, 139:1425–9.

Gelfand JM, Shin DB, Neumann AL, et al. 2006. The risk of lymphoma in patients with psoriasis. J Invest Dermatol.

Gottlieb GS, Lesser CF, Holmes KK, et al. 2003. Disseminated sporotrichosis associated with treatment with immunosuppressants and tumor necrosis factor-alpha antagonists. Clin Infect Dis, 37:838–40.

Gruss HJ, Dower SK. 1995. The TNF ligand superfamily and its relevance to human diseases. Cytokines Mol Ther, 1:75–105.

Hamon M, Bierne H, Cossart P. 2006. Listeria monocytogenes: a model system -308 in the promoter region. The Cardiology, 1:179–88.

Han S, Zhang X, Marinova E, et al. 2005. Blockade of lymphotoxin pathway exacerbates autoimmune arthritis by enhancing the Th1 response. Arthritis Rheum, 52:3026–9.

Hannukasela-Svahn A, Pukkala E, Laara E, et al. 2000. Psoriasis, its treatment, and cancer in a cohort of Finnish patients. J Invest Dermatol, 114:587–90.

Harauvi B, Keystone E. 2006. Musculoskeletal manifestations and autoimmune diseases related to new biologic agents. Curr Opin Rheumatol, 18:96–100.

Havell EA. 1989. Evidence that tumor necrosis factor has an important role in antibacterial resistance. J Immunol, 143:2894–9.

Hellmich B, Lamprecht P, Gross WL. 2006. Advances in the therapy of Wegener's granulomatosis. Curr Opin Rheumatol, 18:25–32.

Henderson TR, Hamosh M, Armand M, et al. 2001. Gastric proteolysis in preterm infants fed mother's milk or formula. Adv Exp Med Biol, 501:403–8.

Herbein G, O'Brien WA. 2000. Tumor necrosis factor (TNF)-alpha and TNF receptors in viral pathogenesis. Proc Soc Exp Biol Med, 223:241–57.

Hermoso MA, Matsuguchi T, Snook C, et al. 2004. Gliocorticoids and tumour necrosis factor alpha cooperatively regulate toll-like receptor 2 gene expression. Mol Cell Biol, 24:4743–56.

HPB Canada. 2006. Dear Healthcare Professional Letter (2006 Jan 18) [online]. Accessed on 15 December 2006. URL: http://www.hc-sc.gc.ca/dbp-mps/medeff/advisories-avis/public/2006/anti-tnf-therapy/cp_e.html.

Imanishi J. 2000. Expression of cytokines in bacterial and viral infections and their biochemical aspects. J Biochem (Tokyo), 127:525–30.

Imperato AK, Smiles S, Abrasion SB. 2004. Long-term risks associated with biologic response modifiers used in rheumatic diseases. Curr Opin Rheumatol, 16:199–205.

Ioannidis JP, Mulrow CD, Goodman SN. 2006. Adverse events: the more you search, the more you find. Ann Intern Med, 144:298–300.

Jarvis B, Faulds D. 1999. Etanercept: a review of its use in rheumatoid arthritis. Drugs, 57:945–66.

Jasmer RM, Nahid P, Hopewell PC. 2002. Clinical practice. Latent tuberculosis infection. N Engl J Med, 347:1860–6.

Jonsdottir T, Forslid J, Van Vollenhoven A, et al. 2004. Treatment with tumour necrosis factor alpha antagonists in patients with rheumatoid arthritis induces anti-CD20 antibodies. Ann Rheum Dis, 63:1075–8.

Kanaly ST, Nashleman M, Hondowicz B, et al. 1999. TNF receptor p55 is required for elimination of inflammatory cells following control of intracellular pathogens. J Immunol, 163:3883–9.

Kapetanovic MC, Saxne T, Szolhalmi A, et al. 2006. Influence of methotrexate, TNF blockers and prednisolone on antibody responses to pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis. Rheumatology (Oxford), 45:106–11.

Kato I, Koenig KL, Baptiste MS, et al. 2003. History of antibiotic use and risk of non-Hodgkin’s lymphoma (NHL). Int J Cancer, 107:99–105.

Kavanaugh A, Tutuncu Z, Catalan-Sanchez T. 2006. Update on anti-tumor necrosis factor therapy in the spondyloarthopathies including psoriatic arthritis. Curr Opin Rheumatol, 18:347–53.

Keane J. 2004. Tumor necrosis factor blockers and reactivation of latent tuberculosis. Clin Infect Dis, 39:300–2.

Keane J. 2005. TNF-blocking agents and tuberculosis: new drugs illuminate an old topic. Rheumatology (Oxford), 44:714–20.

Keane J, Gershon S, Wise RP, et al. 2001. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med, 345:1098–104.

Keystone EC. 2004. Safety issues related to emerging therapies for rheumatoid arthritis. Clin Exp Rheumatol, 22:S148–50.

Keystone EC. 2005. Safety of biologic therapies—an update. J Rheumatol Suppl, 74:8–12.

Keystone EC, Dinarello CC. 2005. Mechanism of action of tumor necrosis factor antagonists. J Rheumatol Suppl, 74:1–2.

Khan G. 2006. Epstein-Barr virus, cytokines, and inflammation: a cocktail for the pathogenesis of Hodgkin’s lymphoma? Exp Hematol, 34:399–406.

Khanra D, McManus M, Forst DE. 2004. Safety of tumour necrosis factor-alpha antagonists. Drug Saf, 27:307–24.

Khanra M, Shirodkar MA, Gottlieb AB. 2003. Etanercept therapy in patients with autoimmunity and hepatitis C. J Dermatol Treat, 14:229–32.

Koller H, Kiesieker BC, Jander S, et al. 2005a. Chronic inflammatory demyelinating polyneuropathy. N Engl J Med, 352:1343–56.

Koller H, Schroeder M, Kiesieker BC, et al. 2005b. Chronic inflammatory demyelinating polyneuropathy—update on pathogenesis, diagnostic criteria and therapy. Curr Opin Neurol, 18:273–8.

Korth-Bradley JM, Rubin AS, Hanna RK, et al. 2000. The pharmacokinetics of etanercept in healthy volunteers. Ann Pharmacother, 34:161–4.

Krishnan E, Fries JF. 2004. Measuring effectiveness of drugs in observational databanks: promises and perils. Arthritis Res Ther, 6:41–4.
Kwon HJ, Cote TR, Cuffe MS, et al. 2003. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. Ann Intern Med, 138:807–11.

La Montagna G, Valentini G. 2005. Listeria monocytogenes meningitis in a patient receiving etanercept for Still’s disease. Clin Exp Rheumatol, 23:121.

Lebwohl M. 2002. New developments in the treatment of psoriasis. Arch Dermatol, 138:686–8.

Lee IH, Siffman NR, Gershon SK, et al. 2002. Life-threatening histoplasmosis complicating immunotherapy with tumor necrosis factor alpha antagonists infliximab and etanercept. Arthritis Rheum, 46:2565–70.

Lemense G P, Sahn SA. 1994. Opportunistic infection during treatment with low dose methotrexate. Am J Respir Crit Care Med, 150:258–60.

Leonardi CL, Powers JL, Matheson RT, et al. 2003. Etanercept as monotherapy in patients with psoriasis. N Engl J Med, 349:2014–22.

Liebowitz D. 1998. Epstein-Barr virus and a cellular signaling pathway in lymphomas from immunosuppressed patients. N Engl J Med, 338:1413–21.

Listing J, Strangfeld A, Kary S, et al. 2005. Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis Rheum, 52:3403–12.

Liz-Quirno M, Gomez-Reino Carnota JJ. 2001. Tumour necrosis factor: genetics, cell action mechanism and involvement in inflammation. Algodol Immunol Clin, 16:140–9.

[LMIS-UBC] The Lenenercet Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group. 1999. TNF neutralization in MS: results of a randomized, placebo-controlled multicenter study. The Lenenercet Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group. Neurology, 53:457–65.

Lok AS, McMahon BJ. 2004. Chronic hepatitis B: update of recommendations. Hepatology, 39:857–61.

Luhehi GN, Steffler A, Turnbull AV, et al. 1997. Febrile response to tissue inflammation involves both peripheral and brain IL-1 and TNF-alpha in the rat. Am J Physiol, 272:R868–86.

Mannino DD, Robinson WH, Genovese MC. 2004. Demyelination and inhibition of tumor necrosis factor (TNF). Clin Exp Rheumatol, 22: S134–40.

Malik ST, Naylor MS, East N, et al. 1990. Cells secreting tumour necrosis factor show enhanced metastasis in nude mice. Eur J Cancer, 26:1031–4.

Mann DL, McMurray JJ, Packer M, et al. 2004. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). Arthritis Rheum, 47:282–9.

Marino MW, Dunn A, Grail D, et al. 2007. Characterization of tumor necrosis factor-deficient mice. Proc Natl Acad Sci U S A, 94:8093–8.

Marshall RW, Marshall VJ, Hull R. 2006. Disease-modifying anti-rheumatic drugs are only one of a number of potential causes of myelosuppression: a careful drug history is necessary to elucidate the cause of an adverse event. Rheumatology (Oxford), 45:362–3; author reply 363–4.

Mease PJ, Goffe BS, Metz J, et al. 2000. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet, 356:385–90.

Meyer TM, Ambinder RF, Stroobants S. 2004. Hodgkin’s lymphoma: evolving concepts with implications for practice. Hematology (Am Soc Hematol Educ Program): 184–202.

Michel M, Duvox C, Hezode C, et al. 2003. Fulminant hepatitis after infliximab in a patient with hepatitis B virus treated for an adult onset still’s disease. J Rheumatol, 30:1624–5.

Midgard R, Gronning M, Riise T, et al. 1996. Multiple sclerosis and chronic inflammatory diseases. A case-control study. Acta Neurol Scand, 93:322–8.

Misery L, Perrot JL, Gentil-Perret A, et al. 2002. Dermatological complications of etanercept therapy for rheumatoid arthritis. Br J Dermatol, 146:334–5.

Mitsos LM, Cardon LR, Ryan L, et al. 2003. Susceptibility to tuberculosis: a locus on mouse chromosome 19 (Tlr4) regulates Mycobacterium tuberculosis replication in the lungs. Proc Natl Acad Sci U S A, 100:6610–15.

Mohan AK, Edwards ET, Cote TR, et al. 2002. Drug-induced systemic lupus erythematosus and TNF-alpha blockers. Lancet, 360:646.

Mohan N, Edwards ET, Cupps TR, et al. 2001. Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. Arthritis Rheum, 44:2862–9.

Mohan N, Edwards ET, Cupps TR, et al. 2004. Leukocytoclastic vasculitis associated with tumor necrosis factor-alpha blocking agents. J Rheumatol, 31:1955–8.

Mohler KM, Torrance DS, Smith CA, et al. 1993. Soluble tumor necrosis factor (TNF) receptors are effective therapeutic agents in lethal endotoxemia and function simultaneously as both TNF carriers and TNF antagonists. J Immunol, 151:1548–61.

Moore RJ, Owens DM, Stamp G, et al. 1999. Mice deficient in tumor necrosis factor-alpha are resistant to skin carcinogenesis. Nat Med, 5:328–31.

Moore TA, Lau HY, Cogen AL, et al. 2003. Anti-tumor necrosis factor-alpha therapy during murine Klebsiella pneumoniae bacteremia: increased mortality in the absence of liver injury. Shock, 20:309–15.

Moore TA, Lau HY, Cogen AL, et al. 2005. Defective innate antibacterial host responses during murine Klebsiella pneumoniae bacteremia: tumor necrosis factor (TNF) receptor 1 deficiency versus therapy with anti-TNF-alpha. Clin Infect Dis, 41(Suppl 3):S213–17.

Mulikayi C, Luangani R. 2005. Current state of tumour necrosis factor alpha blockade in Wegener’s granulomatosis. Ann Rheum Dis, 64(Suppl 4):iv31–6.

Mulrow C, Langhorne P, Grimshaw J. 1997. Integrating heterogeneous pieces of evidence in systematic reviews. Ann Intern Med, 127:989–95.

Murakami T, Okamura C, Matsuzaki S, et al. 2002. Prediction of pregnancy in infertile women with endometriosis. Gynecol Obstet Invest, 53(Suppl 1):26–32.

Nadarajah K, Pritchard C. 2005. Listeria monocytogenes septic arthritis in a patient treated with etanercept for rheumatoid arthritis. J Clin Rheumatol, 11:120–2.

Netae MG, Radstake T, Joosten LA, et al. 2003. Salmonella septicaemia in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: association with decreased interferon-gamma production and toll-like receptor 4 expression. Arthritis Rheum, 48:1853–7.

O’Brien DP, Broles DE, Szalai AJ, et al. 1999. Tumor necrosis factor alpha receptor I is important for survival from Streptococcus pneumoniae infections. Infect Immun, 67:595–601.

Obayashi H, Hasegawa G, Fukui M, et al. 2000. Tumor necrosis factormicrosatellite polymorphism influences the development of insulin dependency in adult-onset diabetes patients with the DRB1*1502-DQB1*0601 allele and anti-glutamic acid decarboxylase antibodies. J Clin Endocrinol Metab, 85:3348–51.

Old LJ. 1985. Tumor necrosis factor (TNF). Science, 230:630–2.

Ollerenshaw MG, Guler R, Vesin D, et al. 2005. Contribution of transmembrane tumor necrosis factor to host defense against Mycobacterium bovis bacillus Calmette-guerin and Mycobacterium tuberculosis infections. Am J Pathol, 166:1109–20.

Lampe AR, Kiermeier M, Eigenmann GO. 2004. Etanercept in breast milk. J Rheumatol, 31:1017–18.

Ostensen M, Eigenmann GO. 2004. Etanercept in breast milk. J Rheumatol, 31:1017–18.

Ostensen M, Eigenmann GO. 2004. Etanercept in breast milk. J Rheumatol, 31:1017–18.

Palladino MA Jr, Patton JS, Figari IS, et al. 1987. Possible relationships between type B diabetes, association with DR3 and DQw1 and susceptibility to Streptococcus pneumoniae infections. Proc Natl Acad Sci U S A, 84:9993–7.

O’Riordan P, Briles DE, Szalai AJ, et al. 1999. Tumor necrosis factor alpha receptor I is important for survival from Streptococcus pneumoniae infections. Infect Immun, 67:595–601.

Obayashi H, Hasegawa G, Fukui M, et al. 2000. Tumor necrosis factormicrosatellite polymorphism influences the development of insulin dependency in adult-onset diabetes patients with the DRB1*1502-DQB1*0601 allele and anti-glutamic acid decarboxylase antibodies. J Clin Endocrinol Metab, 85:3348–51.

Old LJ. 1985. Tumor necrosis factor (TNF). Science, 230:630–2.

Ollerenshaw MG, Guler R, Vesin D, et al. 2005. Contribution of transmembrane tumor necrosis factor to host defense against Mycobacterium bovis bacillus Calmette-guerin and Mycobacterium tuberculosis infections. Am J Pathol, 166:1109–20.

Ostensen M, Eigenmann GO. 2004. Etanercept in breast milk. J Rheumatol, 31:1017–18.

Ostensen M, Eigenmann GO. 2004. Etanercept in breast milk. J Rheumatol, 31:1017–18.
Warzocha K, Bienvenu J, Ribeiro P, et al. 1998. Plasma levels of tumour necrosis factor and its soluble receptors correlate with clinical features and outcome of Hodgkin’s disease patients. *Br J Cancer*, 77:2357–62.

Warzocha K, Ribeiro P, Bienvenu J, et al. 1998. Genetic polymorphisms in the tumor necrosis factor locus influence non-Hodgkin’s lymphoma outcome. *Blood*, 91:3574–81.

Warzocha K, Salles G. 1998. The tumor necrosis factor signaling complex: choosing a path toward cell death or cell proliferation. *Leuk Lymphoma*, 29:81–92.

Watts RA. 2000. Musculoskeletal and systemic reactions to biological therapeutic agents. *Curr Opin Rheumatol*, 12:49–52.

Werth VP, Levinson AI. 2001. Etanercept-induced injection site reactions: mechanistic insights from clinical findings and immunohistochemistry. *Arch Dermatol*, 137:953–5.

Weyand CM, Goronzy JJ, Kurtin PJ. 2006. Lymphoma in rheumatoid arthritis: an immune system set up for failure. *Arthritis Rheum*, 54:685–9.

[WGET] Wegener’s Granulomatosis Etanercept Trial Research Group. 2005. Etanercept plus standard therapy for Wegener’s granulomatosis. *N Engl J Med*, 352:351–61.

Wiendl H, Hohlfeld R. 2002. Therapeutic approaches in multiple sclerosis: lessons from failed and interrupted treatment trials. *BioDrugs*, 16:183–200.

Williams JD, Griffiths CE. 2002. Cytokine blocking agents in dermatology. *Clin Exp Dermatol*, 27:585–90.

Witty LA, Steiner F, Curfman M, et al. 1992. Disseminated histoplasmosis in patients receiving low-dose methotrexate therapy for psoriasis. *Arch Dermatol*, 128:91–3.

Wolfe F, Michaud K. 2004a. Heart failure in rheumatoid arthritis: rates, predictors, and the effect of anti-tumor necrosis factor therapy. *Am J Med*, 116:305–11.

Wolfe F, Michaud K. 2004b. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. *Arthritis Rheum*, 50:1740–51.

Zein CO, Zein NN. 2002. Advances in therapy for hepatitis C infection. *Microbes Infect*, 4:1237–46.

Zeltser R, Valle L, Tanck C, et al. 2001. Clinical, histological, and immunophenotypic characteristics of injection site reactions associated with etanercept: a recombinant tumor necrosis factor alpha receptor: Fc fusion protein. *Arch Dermatol*, 137:893–9.

Zganiacz A, Santosuosso M, Wang J, et al. 2004. TNF-alpha is a critical negative regulator of type 1 immune activation during intracellular bacterial infection. *J Clin Invest*, 113:401–13.

Zhou P, Miller G, Seder RA. 1998. Factors involved in regulating primary and secondary immunity to infection with Histoplasma capsulatum: TNF-alpha plays a critical role in maintaining secondary immunity in the absence of IFN-gamma. *J Immunol*, 160:1359–68.

Zhou T, Mountz JD, Kimberly RP. 2002. Immunobiology of tumor necrosis factor receptor superfamily. *Immunol Res*, 26:323–36.

Zimmer B, Hanley AJ, Harris SB, et al. 1999. Circulating tumor necrosis factor-alpha concentrations in a native Canadian population with high rates of type 2 diabetes mellitus. *J Clin Endocrinol Metab*, 84:27–8.