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

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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 immuno-reactivity (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 (Stefferl 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; Ehlers 2005; La Montagna and Valentini 2005; Nadarajah and Pritchard 2005; Rachapalli and O'Daunt 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 (Ehlers 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 (Mukhtyar 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 immunosupressed 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).

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