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Tumor Necrosis Factor and Granuloma Biology: Explaining the Differential Infection Risk of Etanercept and Infliximab

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Several studies show that the risk of granulomatous infections following therapy with the anti-tumor necrosis factor (TNF) antibody infliximab is higher than after treatment with the soluble TNFRp75 immunoglobulin fusion construct etanercept. Therefore, despite sharing a common target, it is possible that the actual mode of action of the two biologicals differs in vivo. TNF is known to participate in the induction and maintenance of protective granulomas at multiple steps, and evidence supporting a differential inhibition of TNF bioactivity and signaling by the two drugs is discussed.

Tumor necrosis factor (TNF) is a multipotent cytokine that occurs in a monomeric and trimeric soluble and transmembrane form. The soluble form binds to both TNF receptors (p55 and p75), whereas the transmembrane form predominantly signals via TNFRp75 (1). TNF plays an important role in the pathogenesis of inflammatory diseases such as rheumatoid arthritis (RA) and Crohn's disease (CD). Since 1998, two TNF antagonists have increasingly been used to treat these conditions. Infliximab is a chimeric anti-TNF monoclonal antibody with murine variable regions and human IgG1 constant regions that is administered by periodic infusion. It binds diverse TNF moieties, including monomeric and trimeric soluble TNF and transmembrane TNF (2). Infliximab is effective for the treatment of RA and steroid-refractory CD, in which it induces long-term remissions not readily explained by the kinetics of its inhibition of soluble TNF (3). Case reports indicate activity in sarcoidosis and Wegener's granulomatosis (4,5). In contrast, etanercept is a dimeric fusion protein consisting of the extracellular portion of the p75 TNF receptor linked to the Fc domains of human IgG1 that is administered twice or once weekly by injection. Etanercept binds only trimeric TNF and interacts with transmembrane TNF with reduced avidity compared with infliximab (2). Etanercept and infliximab are equally effective in RA; however, etanercept is ineffective in CD and sarcoidosis (6,7).

The increased clinical use of TNF antagonists has been accompanied by increased reporting of granulomatous infectious diseases, including tuberculosis (TB), histoplasmosis, and other less common conditions (8). Granulomas represent a host defense strategy to contain intracellular pathogens whose growth cannot be limited by other cellular immune mechanisms (9). Following ingestion of these indigestible pathogens, macrophages release cytokines, chemokines, and other factors that trigger the influx of successive waves of cells to the site of infection (Fig. 1). Initially the response is non-specific, consisting largely of macrophages, neutrophils, and natural killer cells (10). It later progresses to involve lymphocytes with limited antigenic diversity (eg, $\gamma\delta$ T cells) and ultimately results in the recruitment and expansion of highly antigen-specific populations of CD4 and CD8 T-cells. These cells secrete the macrophage-activating cytokines TNF and interferon gamma (IFNγ), express cytotoxicity against infected macrophages, and release antibiotic peptides via granular exocytosis mechanisms. They may also induce apoptosis or otherwise inhibit intracellular microbial growth via other poorly understood mechanisms involving direct cell contact (11,12).

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Nonetheless, these mechanisms apparently are not often successful in eradicating *Mycobacterium tuberculosis* infection.

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Dr Ehlers has presented data from his own publicly funded research on the role of TNF and lymphotoxin in experimental tuberculosis at several international symposia sponsored by Amgen. Dr. Wallis has served as a consultant for Amgen.
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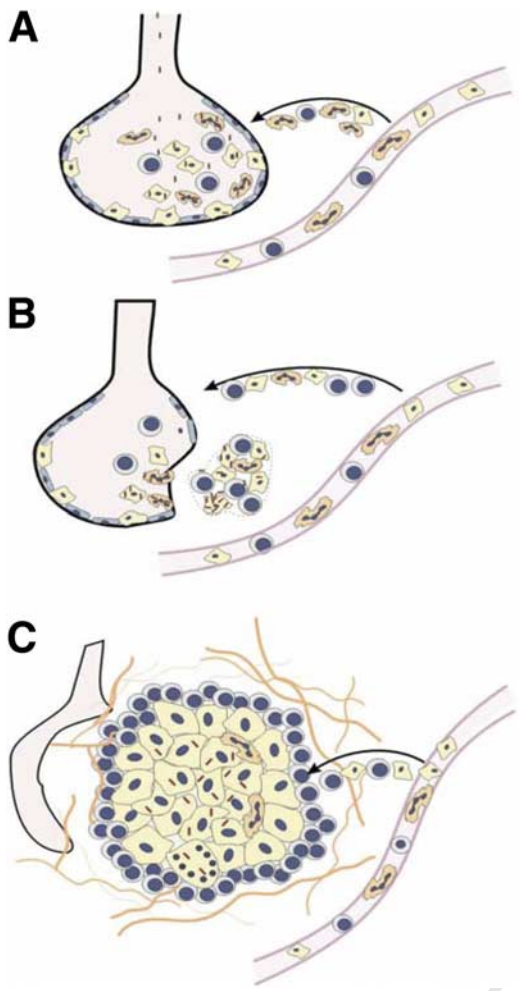

Figure 1 Schematic representation of granuloma induction and maintenance in the lung. (A) Infected macrophages release cytokines and chemokines that induce the recruitment of a mixed (granulocytic and monocytic) cellular infiltrate from the bloodstream into the alveolar and interstitial spaces. (B) The interstitial infiltration becomes predominantly mononuclear in nature and organizes itself into a granuloma with centrally located macrophages and a lymphocytic rim. (C) The fully organized granuloma displaces parenchymal tissue and develops perigranulomatous fibrosis, thereby causing tissue damage. Continuous recruitment of inflammatory cells from the bloodstream is necessary to maintain granuloma structure and contain viable microorganisms persisting in macrophages.

As a result, human mycobacterial immunity is primarily bacteriostatic rather than bacteriocidal, as it results not in sterilization of infected tissues, but in containment of still viable *M. tuberculosis* within granulomas. Maintenance of granulomas is an active process in which cells (both macrophages and T-cells) are continually recruited from the blood (9). Those cells that are not terminally differentiated (such as T-cells) may divide several times in situ before either undergoing apoptosis or returning to the circulation as central memory T-cells. TNF participates in this process at several levels (9,10,13,14). Produced by both macrophages and T-cells, TNF induces antimycobacterial activity in macrophages, promotes the migration of various types of cells to the site of infection, and, under certain circumstances, promotes apoptosis in T-cells. The relative activities of the soluble and cell-associated forms of TNF in these contexts are not fully understood, with the exception that soluble TNF likely is required to establish the cytokine gradient required to promote cell migration.

Given the multiple sites of TNF action in the host's defense against infections, TNF blockade might be predicted to increase the risk of infections, particularly those normally contained by granulomas. Studies in animal models have indeed provided ample support for this: Mice deficient for TNF or one of its receptors (TNFRp55), or in which TNF function was blocked by neutralizing antibodies, were unable to restrain the growth of microorganisms such as *M. tuberculosis*, *Listeria monocytogenes*, or *Histoplasma capsulatum* (12,15). In the case of mycobacterial infections, these mice showed significantly delayed formation of granulomas, and even the granulomas that formed subsequently disintegrated (16,17). When TNF was experimentally neutralized by antibody after well-organized lesions had been established in wild-type mice, the granuloma structure broke down and dissemination of mycobacteria ensued (18). Similarly, blockade of TNF during chronic latent tuberculosis led to reactivation of mycobacterial multiplication and accelerated death of treated mice (19,20). Because both antibacterially active mechanisms and the demarcation of infectious foci are seriously impaired in the absence of TNF signaling, lesions present as disorganized, diffuse, bacteria-laden, necrotizing infiltrations of mixed cellularity in TNF and TNFRp55-deficient mice.

Unexpectedly, early clinical reports of granulomatous infections appeared to indicate a substantially greater risk posed by infliximab than by etanercept (21-23). A recent report by Wallis and coworkers represents the largest, most systematic study of granulomatous infections associated with infliximab and etanercept contained in the US Food and Drug Administration (FDA) Adverse Event Reporting System (AERS), using reports from 1998 through the third quarter of 2002 (24,25). The number of patients treated with infliximab or etanercept during this time was based on data provided by the manufacturers to the FDA. Of the 35,275 distinct reports extracted from the AERS database arising in the US, 255 described granulomatous infections associated with infliximab and 68 granulomatous infections associated with etanercept. The numbers of treated patients were 197,000 and 113,000, respectively. The overall risk of granulomatous infection was 129 per 100,000 infliximab-treated patients compared with 60 per 100,000 for etanercept ($P < 0.001$). Among the infections that occurred significantly more frequently with infliximab were tuberculosis, histoplasmosis, listeriosis, and coccidioidomycosis; trends toward increased risk were apparent for candidiasis, non-TB mycobacterial disease, and nocardiosis. Infliximab treatment also increased the proportion of extrapulmonary TB cases from 8 to 26% ($P = 0.02$).

Two-thirds of the reports contained data indicating the time from starting TNF antagonist to onset of disease. Time to onset was significantly shorter after starting infliximab for TB (96 versus 350 days, $P < 0.001$) and histoplasmosis (66 versus 518 days, $P = 0.022$); this is consistent with the rec-

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ognized importance of reactivation of latent infection in the pathogenesis of these diseases. The risk of TB associated with infliximab was maximal in the first 90 days after starting treatment. If the remaining one-third of TB cases followed a similar distribution, the annualized risk of TB during the first 90 days was 95 cases per 100,000 person-years, compared with 11 per 100,000 person-years for etanercept. For comparison, the reported TB incidence in the US as a whole during this interval was 5 per 100,000 person-years (26).

Thus, despite sharing a common therapeutic target, infliximab is uniquely associated with a high risk of reactivation of latent *M. tuberculosis* infection. This is consistent with the apparent differential therapeutic activities of these two drugs for granulomatous inflammatory conditions and appears to indicate that infliximab, but not etanercept, disrupts established granulomas. Three hypotheses may be proposed to explain these differential effects.

Differential Inhibition of TNF Signaling Events

This hypothesis is based on the differential binding avidities of infliximab and etanercept for soluble versus transmembrane TNF and predicts that inhibition with infliximab would shut down both TNFRp55- and TNFRp75-mediated events, whereas etanercept would leave TNFRp75-mediated signaling at least partially intact (2-27). Since infliximab and etanercept are drugs optimized to bind to human and not mouse TNF, it is difficult to directly address this issue with these reagents in experimental murine models. However, mice deficient in TNF and made transgenic for only the transmembrane form of TNF retained substantial resistance against challenge infections with *M. bovis* BCG or *M. tuberculosis*, arguing that transmembrane TNF signaling via TNFRp75 may provide sufficient antimycobacterial protection under certain experimental conditions (26). In other models of inflammation, host defense mechanisms are severely impaired only in TNFRp55-deficient, but not TNFRp75-deficient, mice (29). In addition, the TNFRp75 seems to be particularly involved in suppressing TNF-mediated inflammatory responses, providing an immunoregulatory feedback loop (29). In corroboration of these findings, studies in murine models of autoimmune diseases have convincingly shown that TNFRp55 signaling is associated mostly with detrimental proinflammatory events, whereas TNFRp75 signaling supports immunomodulatory, disease-ameliorating functions (30).

Differential Power of Neutralizing TNF Bioavailability

Because of its high association and very low dissociation rate, infliximab binds TNF quickly and irreversibly. In contrast, etanercept has both "high-on" and "high-off" binding kinetics, shedding about 50% of soluble TNF and 90% transmembrane TNF within 10 minutes after binding (2). Assuming tissue levels were sufficiently high, infliximab would neutralize all of TNF bioactivity, whereas freely diffusing etanercept would redistribute bioavailable TNF from sites of production to sites of lower concentration.

In the context of granulomatous infections, complete blockade of TNF activity would result in the complete abrogation of inflammatory cell recruitment into the granuloma and a major impairment in macrophage activation. The minimal amount of TNF required to provide sufficient protective functions within the various tissues is of course unknown. However, it is possible that a lower degree of TNF blockade (eg, up to 90%) is still compatible with maintaining both the granuloma structure and the residual antimicrobial macrophage functions in certain circumstances. For example, the rate and success of experimental reactivation of tuberculosis in mice substantially differs depending on the time postinfection, the duration of antimycobacterial treatment, the anti-inflammatory potency of the reactivating regimen, etc., all of which are factors that determine the relative amount and availability of TNF present in the lesion (19,20). This hypothesis therefore argues that a window of opportunity exists in which TNF levels are high enough to sustain the integrity of granulomas but low enough to reduce the activity of some, but not all, chronic inflammatory disease conditions. Assuming that etanercept and infliximab also differ in vivo in terms of their overall efficacy of neutralizing TNF, the differential therapeutic efficacy of these drugs in CD and sarcoidosis might be explained.

Differential Induction of Target Cell Death

Infliximab has been shown to induce apoptosis both in vitro and in vivo, whereas no such reports exist with etanercept. Specifically, infliximab caused apoptosis in monocytes from CD patients, through a caspase-3-dependent pathway, and, in ex vivo studies, increased apoptosis in CD3+ lymphocytes in the lamina propria of colonic biopsies (31,32). Analyses of tissue biopsies in *M. tuberculosis* infected mice following antibody-mediated inhibition of TNF activity also indicated increased apoptotic activity within granulomatous lesions (20), whereas in patients treated with infliximab apoptosis within pulmonary granulomas was apparently decreased (33). If T-cells with specific reactivity against mycobacterial antigens express transmembrane TNF, and if infliximab caused the elimination of these memory cells by inducing apoptosis, reactivation TB would be readily explained by the loss of specifically reactive, IFNγ-producing and macrophage-activating T-cells.

Conversely, a recent phase I study in which etanercept was administered for 1 month as adjunctive treatment to 16 HIV-infected subjects with pulmonary tuberculosis suggested that etanercept may inhibit, rather than promote, T-cell apoptosis (34). The mean baseline CD4 T-cell count was 394 μL. In the absence of specific antiretroviral therapy, CD4 counts rose in these subjects by 96 cells/μL during this treatment, compared with 25 in control subjects ($P = 0.1$). Apoptosis is a recognized mechanism for T-cell depletion in TB and HIV infection; the increased T-cell number observed due to etanercept may be due to its inhibition by etanercept.

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It is also possible that infliximab—having bound to membrane-associated TNF on monocytes or lymphocytes—activates complement or causes antibody-dependent cellular cytotoxicity via its Fc tail (35). This would help explain the relatively high occurrence of disseminated TB in infliximab-treated patients, because the lysed granuloma macrophages would spill *M. tuberculosis* organism into the bloodstream. However, no studies have directly demonstrated target cell lysis by infliximab.

Rheumatology has undoubtedly been revolutionized by the use of TNF-targeted biologics, which provide symptom relief even in cases of treatment-refractory chronic inflammatory disorders (36). The unexpected clinical observation that, despite sharing a common therapeutic target, these drugs differ substantially in efficacy and adverse event profiles has encouraged investigations into the true mode of action in vivo, since more than simple neutralization of TNF appears to be involved. This unprecedented interaction between basic and clinical sciences should ultimately lead to the design of a new generation of TNF-targeted drugs in which therapeutic effects can be maximized, and side effects, such as interference with protective granuloma formation, can be minimized.

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