Immunosuppression Related to Collagen-Vascular Disease or Its Treatment

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Collagen-vascular diseases are associated with immune dysregulation and inflammation, leading to tissue destruction or compromise. Immunosuppression is more commonly associated with the drugs used to treat these disorders than with the diseases themselves. The newest agents being used to treat collagen-vascular diseases are the tumor necrosis factor (TNF)- α inhibitors. U.S. Food and Drug Administration–approved TNF- α inhibitors have differing effects on the immune system, reflecting their potency and mechanisms of action. They are particularly effective in breaking down granulomatous inflammation, which makes them effective treatment for sarcoidosis and Wegener's granulomatosis. This same property makes them likely to break down the host defense mechanism that normally contains pathogens such as mycobacteria and fungi in a dormant state, namely the physical and immunologic barrier formed by granulomas in the lung and elsewhere. The most common infection reported with the TNF- α inhibitors has been tuberculosis, which may manifest as pulmonary and/or extrapulmonary disease, with the latter being more common and severe than usual. *Histoplasma capsulatum*, *Aspergillus*, *Cryptococcus neoformans*, and *Listeria monocytogenes* have also been described in a number of cases, and their frequency is discussed.

Keywords: granuloma; tuberculosis; tumor necrosis factor α

The collagen-vascular diseases (rheumatoid arthritis [RA], systemic lupus erythematosus, Sjögren's syndrome, polymyositis-dermatomyositis, and systemic sclerosis) and the granulomatous vasculitic conditions exemplified by Wegener's granulomatosis are associated with immune dysregulation. There is no known pathogen toward which the resulting inappropriate inflammation and immune response is targeted, although many have been sought. Although the unregulated immune stimulation may result in a propensity for developing pulmonary infections due to, for example, excessive and uncleared pulmonary secretions, these conditions are not generally associated with a specific breakdown in lung defense and infection. Infection is often in the differential diagnosis when a person with RA or systemic lupus erythematosus presents with a pleural effusion or pulmonary nodules, especially if associated with fever. Pulmonary infection may occur if neutropenia develops during long-standing RA as part of Felty's syndrome. Dyspnea and a dry, nonproductive cough are common symptoms of systemic sclerosis and may be complicated by aspiration pneumonia due to esophageal dysmotility resulting in gastric reflux. This may be complicated by bacterial or viral pneumonia. Finally, although the initial evaluation of Wegener's granulomatosis, with its associated pulmonary

infiltrates and cavitary findings, often focuses on infectious etiologies, these patients may not be at particularly high risk for lung infection except as a consequence of progressive lung destruction and physical compromise.

IMMUNOSUPPRESSION RELATED TO DRUGS USED TO TREAT COLLAGEN-VASCULAR DISEASES

Although the collagen-vascular diseases are associated with only moderate and rather nonspecific infections, the therapeutic agents used to control collagen-vascular diseases can result in significant immunosuppression and subsequent pulmonary and systemic infections. Examples of traditional treatment modalities include corticosteroids, methotrexate, and cyclophosphamide. High-dose corticosteroids reduce lymphocyte and antigen-presenting cell function, increasing the risk of unchecked growth of even weakly pathogenic bacteria, viruses, fungi, and mycobacteria. Extensive or disseminated infectious complications may develop with a paucity of inflammatory signs or symptoms. Methotrexate, a folate antimetabolite, interferes with numerous intracellular metabolic processes, particularly affecting cell proliferation. For this reason, it is effective in treatment of a number of malignancies and inflammatory conditions. Even at low doses, methotrexate inhibits the replication and function of T and B lymphocytes and can suppress secretion of proinflammatory cytokines, including interleukin (IL)-1, IFN- γ , and tumor necrosis factor (TNF). It also decreases chemotaxis of neutrophils. The effects are dependent on the dose and length of exposure. Most infections associated with methotrexate are a result of absolute neutropenia. Cyclophosphamide functions as an alkylating agent and is active against many neoplastic diseases and in lupus nephritis, nephrotic syndrome, Wegener's granulomatosis, rheumatoid arthritis, and graft-versus-host disease or graft rejection. Cyclophosphamide also causes lymphopenia (both B cells and T cells) and selective suppression of T- and B-lymphocyte activity.

The newest agents being used to treat collagen-vascular conditions exploit new understanding of the complex cytokine pathways in immune function and dysfunction and the role that certain proinflammatory cytokines play. Although there are a number of cytokines in the proinflammatory immune pathways, inhibition of TNF- α improves several inflammatory conditions, and several TNF- α inhibitors have been U.S. Food and Drug Administration (FDA) approved. These agents can ameliorate the destruction associated with the inflammatory arthritides (RA, juvenile arthritis, ankylosing spondylitis, and psoriatic arthritis). They are also effective against the granulomatous diseases (Crohn's disease, Wegener's vasculitis, and sarcoidosis). The approved TNF- α inhibitors are not identical in structure, composition, or pharmacokinetic properties. They also have differing effects on the different disease entities and have been associated with infectious complications at different rates. The rest of this article focuses on these new agents and associated infectious complications.

TNF- α INHIBITORS: A REVIEW OF AVAILABLE OPTIONS

The TNF- α inhibitors infliximab (Remicade; Centocor, Malvern, PA) and etanercept (Enbrel; Immunex Corporation, Seattle, WA)

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(1, 2) were joined in 2003 by adalimumab (Humira; Abbott Laboratories, Abbott Park, IL; approval 12/30/2002) for treatment of RA. Off- and on-label use of these agents, along with the IL-1 receptor antagonist anakinra (Kineret; Amgen Inc., Thousand Oaks, CA), is increasing. These agents are not identical in their actions or in their efficacy in various conditions, however (2). Infliximab is a chimeric monoclonal antibody that binds to the monomeric and trimeric forms of soluble TNF and binds avidly to transmembrane TNF (3). Etanercept is a fusion protein that binds primarily to soluble TNF, not the transmembrane form of TNF, and the resulting complexes are less stable than those formed by infliximab. Etanercept also binds lymphotoxin, whereas infliximab does not. Etanercept is the only one of these agents with efficacy in the treatment of juvenile RA, where higher levels of lymphotoxin are thought to contribute to the pathophysiology of the disease. Infliximab seems much more effective in the granulomatous diseases such as sarcoidosis, Wegener's vasculitis, and Crohn's disease. All the TNF- α inhibitors (infliximab, etanercept, and adalimumab) have demonstrated efficacy and are indicated for RA. A number of studies are evaluating use of the drugs with and without traditional disease-modifying antirheumatic drugs, such as methotrexate, or with low-dose corticosteroids.

STUDIES EXAMINING THE PATHOPHYSIOLOGY OF INFECTION WITH TNF- α INHIBITORS

Granuloma formation is a common pathologic feature of many of the collagen-vascular diseases, and one measure of the effectiveness of TNF- α inhibitors is their ability to facilitate dissolution of offending granulomatous structures (4). The TNF- α inhibitors are unable to discriminate between pathologic granulomas and granulomas that exist to control certain infectious diseases. Why are granulomas important in human immunity? Although many organisms are dispatched early by activated effector cells, others have evolved mechanisms to resist their effects; prime examples are *Mycobacterium tuberculosis* and fungal pathogens such as *Histoplasma*. If the reactive oxygen and nitric oxide species generated do not kill the organism, secondary mechanisms develop over time to prevent overwhelming infection and death. Granulomas are an example of this "plan B"; they serve as a physical barrier to dissemination of the living organisms (5) and form an environment unfavorable for ongoing replication. A network of cytokines and chemokines form and actively maintain this fallback defense mechanism.

Tuberculosis (TB) granulomas in humans surround the invading bacilli with tissue macrophages, some of which activate and form multinucleated giant cells, and an outer layer of CD4 and CD8 T and B lymphocytes. The bacteria are forced to ratchet down their normal metabolic pathways and replication capacity to survive, but they undergo occasional bursts of activity. This observation is crucial to understanding that if the integrity of the granuloma structure has weakened (as may happen if any of the components actively maintaining the granuloma are compromised), the pathogens remain capable of returning to their replication competent status, causing "reactivation" disease.

TNF is the cytokine most essential for formation and maintenance of granulomas. Macrophages and T cells express TNF in response to interaction with a number of different pathogens. In turn, TNF stimulates the release of IL-1 and other inflammatory cytokines, chemokines, and adhesion molecules, thus recruiting the kind of cells needed to form the granuloma and ensuring that they are optimally activated and as microbicidal as possible (6).

Flynn and colleagues (7) have shown that TNF is required to control infection in their mouse model of acute infection with

M. tuberculosis. Blockage of TNF results in poor or nonexistent granuloma formation. This could be shown in TNF receptor-1 knockout mice or in mice treated with a neutralizing antibody against TNF, reminiscent of current therapeutic options. Furthermore, they have shown that TNF is necessary to maintain the integrity of existing granulomas and found that in their model of chronic latent TB infection, administration of neutralizing antibody against TNF caused rapid reactivation of TB infection, with a marked loss of typical granuloma structure. Although bacterial numbers were not dramatically increased, the granuloma-associated cells migrated to other parts of the lung, leading to larger areas of inflammation-associated damage (8). They hypothesize that TNF may work chiefly by regulating chemokines, which are small molecules that interact with cell surface receptors and direct cell movement. By controlling chemokine production, cells may be compelled to remain tightly centered in a granuloma formation, which helps control the potential pathogen and reins in unnecessary and widespread inflammation.

SPECIFIC PULMONARY INFECTIONS REPORTED WITH TNF- α INHIBITORS

Infliximab has received the most reports of associated infections. There are several possible reasons for this. It seems to be the most potent inhibitor of TNF- α , binding to the soluble and transmembrane forms of TNF- α , thereby preventing the interaction of TNF- α with its two distinct cellular receptors, the p55 and the p75 TNF receptors (3, 9). On the other hand, lack of required reporting of infections coupled with scattered and incomplete registries of patients being treated with the different agents make it difficult to assess the true incidence of infections associated with each agent. Also, each drug has been on the worldwide market for varying lengths of time, infliximab for the longest. Patients receiving infliximab report to an infusion center for each dose, which may enhance detection and reporting of infections compared with the other agents that are self-administered subcutaneously, usually at the patient's home. Establishing case rates of specific infections is also difficult due to differing populations and their underlying burden of latent infections. For example, 38% of postapproval infliximab has been used in Europe and Scandinavia, which have higher background population rates of TB compared with the United States. Etanercept has been used primarily in the United States, which has a lower background rate of latent TB infection, and could at least partially explain the fewer number of TB cases reported with this agent (10).

The pharmacokinetic properties of the TNF- α inhibitors may influence their effect on host immunity and subsequent infections (11). Achieving a balance between allowing enough circulating TNF for immune competence while inhibiting excessive TNF from causing destructive inflammatory conditions is the challenge. Ideally, the inhibitors would be targeted to the tissues where excess TNF is having a deleterious effect, such as the synovium in RA or the gut in Crohn's disease. Because they are not (as is the case with the available agents), the more widespread and complete the inhibition, the more likely there may be associated infectious complications. For example, because infliximab binds soluble and membrane-bound TNF and is given in boluses resulting in very high peak serum levels, it may temporarily shut down the cell-mediated immune system, allowing pathogens to escape immune sequestration (3, 12). In contrast, adalimumab and etanercept, administered subcutaneously on a weekly or bi-weekly basis, achieve a lower peak effect and may be less likely to perturb the immune system, although they might not dampen inflammation enough to halt disease progression or flare.

Another differential effect of the agents is seen in their ability to cause apoptosis. Apoptosis, or programmed cell death, is

critical in the normal immune response because it is the final step that destroys the immune cell that has performed its function and ingested an invading pathogen (13). It is also critical for halting the expansion that normally occurs among peripheral lymphocytes in response to an antigen. In Crohn's disease, inflammation in the gut may result when T lymphocytes in the lamina propria become abnormally resistant to apoptosis. Infliximab seems to induce apoptosis in gut lymphocytes, whereas etanercept does not (14), correlating with clinical studies showing that infliximab, but not etanercept, is effective in Crohn's disease, lending credence to this line of investigation.

INFECTIONS ASSOCIATED WITH TNF- α INHIBITORS

There are numerous and increasing case reports of infections associated with TNF- α inhibitors, but several stand out as having the most numbers of reported instances and should be sought when a patient presents in an intensive care unit or with progressive pulmonary or systemic illness in the setting of treatment with these agents (Table 1) (15, 16).

TB

The most frequently reported serious infection associated with TNF- α inhibitors has been TB. Seventy cases of TB were reported to the FDA's Adverse Event Reporting System in association with infliximab between 1998, when the drug was first licensed, until May 2001. The retrospectively collected cases were described by Keane and colleagues (17). Gomez-Reino and colleagues reported their findings after reviewing a Spanish registry of patients with RA started on biologic modifiers (18). They found 17 culture-confirmed cases of TB among their cohort; all were being treated with infliximab. In another review, Keystone (10) reported that through the first quarter of 2003, there had been 38 postmarketing reports of TB among 230,000 etanercept-treated patients; 95% had been treated in the United States, giving a worldwide rate of approximately 17/100,000 patients exposed, compared with 441 reports associated with infliximab by October 2003 (for Crohn's and RA), giving a case rate closer to 88/100,000 treated (10). During the adalimumab pivotal clinical trials, there were 21 cases reported among their 9,460 enrolled subjects, giving a calculated case rate of 222/100,000.

Although TB is the most frequent and potentially the most severe infection pulmonologists might see associated with these

agents, TB in this setting is highly likely to manifest at an extrapulmonary site. Gomez-Reino reported that 6 of 17 (35%) of their patients developed disseminated or hepatosplenic disease, and 5 of 17 (29%) were reported to have disease affecting the nervous system. In total, 65% had extrapulmonary TB, compared with the usual distribution of 70 to 75% pulmonary and 15 to 20% extrapulmonary disease in community populations from Europe and the United States (18). Only patients with advanced AIDS are reported to have similarly high rates of extrapulmonary disease. In addition, two of the patients died (11%), compared with TB mortality rates of 4.6% in the United States in 2000. Their findings mirror Keane's findings and highlight the fact that clinicians must be alert to the possibility of TB developing rapidly in patients treated with these agents and may present with disseminated disease.

A few guidelines have been published for preventing, diagnosing, and treating TB in patients with RA on anticytokine therapy. Furst and colleagues (19), in the United States, published a set of "preliminary guidelines" that were followed by a letter from rheumatologists in France delineating the different approach they are taking (20). The present author also had the opportunity to offer recommendations in this regard (15), which are influenced by the U.S. experience and by recommendations by groups in the United States, including the Centers for Disease Control, the Infectious Disease Society of America, and the American Thoracic Society (21). More formal guidelines are being formulated by panels of international TB experts, but in the meantime, country- or region-specific guidelines should be developed in conjunction with local TB experts who can define the most current methods of diagnosis, prevention, and treatment compatible with public health policies.

Histoplasmosis

Histoplasmosis is caused by the yeastlike fungus *Histoplasma capsulatum*. Like TB, infection is acquired by the respiratory route, and an intact cellular immune system is required to control latent infection within granulomas. Pulmonary histoplasmosis can be radiographically indistinguishable from TB. In the setting of AIDS, latent infection can reactivate, causing a progressive, potentially fatal illness. It is the most common endemic mycosis in the United States and shows up as an opportunistic infection in transplant recipients (22-24), HIV/AIDS (28), and now with anti-TNF therapy. As with TB, animal models have demonstrated

TABLE 1. INFECTIONS MOST COMMONLY REPORTED IN ASSOCIATION WITH TUMOR NECROSIS FACTOR- α INHIBITOR

Infection	Clinical Manifestation	Prevention	Diagnosis
Tuberculosis	Extrapulmonary or disseminated disease more common	TB skin test	Radiographic or symptom-based search for abnormality
		INH for 9 mo if skin test reactive or if history of reactive skin test or exposure	Biopsy any abnormality and send for AFB smear and culture
Histoplasmosis	Extrapulmonary or disseminated disease more common	Unknown	Radiographic or symptom-based search for abnormality Biopsy any abnormality and send for fungal stain and culture Urinary or serum antigen detection for diagnosis and follow-up for relapse
Cryptococcosis	Meningitis	Unknown	Head CT with contrast Spinal tap for abnormal cells, protein, glucose, and fungal stain and culture CSF for cryptococcal antigen
Aspergillus	Rhino-cerebral or pulmonary	Unknown	Radiographic or symptom-based search for abnormality Biopsy any abnormality and send for fungal stain and culture
Listeria	Sepsis syndrome	Avoid soft cheeses	Send blood and CSF for routine blood culture

Definition of abbreviations: AFB = acid-fast bacilli; CSF = cerebrospinal fluid; CT = computed tomography.

that TNF- α is critical in determining the initial clinical course and disease manifestations and for control of latent histoplasmosis infection (25, 26).

Lee and colleagues (26) reviewed the FDA's Adverse Event Reporting System and reported 10 cases of histoplasmosis, nine associated with infliximab and one with etanercept. Nine of the 10 cases required intensive care treatment, and one patient died. Endemic regions include river valleys of the world between latitudes 45° north and 30° south. The organisms reside in the soil, especially soil with a high concentration of bird excrement, and large outbreaks have been associated with earth moving, major excavations, and recreation in endemic regions.

Wood and colleagues (27) report three patients from Indiana who were being treated for RA. Two patients had received infliximab, and one had received etanercept. All three patients presented with respiratory symptoms and fever, had elevated *Histoplasma* urine antigen titers, and had culture-positive disease or elevated complement fixation titers. Amphotericin B is the drug of choice for moderate to severe histoplasmosis in immunocompromised patients. Using the HIV/AIDS model, chronic suppression with itraconazole would be recommended if further infliximab therapy were necessary.

Aspergillus Species

Aspergillus fumigatus is the usual cause of aspergillosis, although in immunocompromised hosts *A. flavus* and other species can cause invasive disease. The first report of invasive aspergillosis in a patient receiving infliximab was reported as a letter to the editor in April 2001, occurring in a patient being treated for Crohn's disease. Animal models have shown that TNF- α secreted by macrophages is critical for effective innate immunity against *Aspergillus* species for early host defense and later in its role of amplifying neutrophilic production of oxygen free radicals, which effect fungus hyphal damage (28, 29).

Aspergillus has a predilection to invade blood vessels, causing thrombosis and tissue infarction. It causes pulmonary, central nervous system, and disseminated disease in those who are immunocompromised. Voriconazole, a triazole similar to fluconazole and itraconazole, is now considered the drug of choice for invasive aspergillosis, replacing amphotericin B deoxycholate, a toxic and poorly tolerated drug (30). Voriconazole can be administered intravenously or orally, with 90% or greater bioavailability and good penetration into brain tissue and the meninges.

Cryptococcosis

Cryptococcus neoformans, a yeast that is ubiquitous in nature, enters through the respiratory tract, where it may cause pulmonary disease. It is important because it disseminates, causing a chronic but progressive meningitis. A recent case report of pulmonary cryptococcosis is instructive because, like reported cases of TB, it occurred after only three doses of infliximab (31). The patient presented with dyspnea and anemia but was afebrile, and he had no night sweats, chest pain, or weight loss—symptoms classically associated with the effects of TNF during infection. The authors did not report the results of a spinal tap, although most would recommend this be done in an immunocompromised patient because central nervous system disease is common and requires a lengthier course of therapy.

Listeria monocytogenes

Listeria monocytogenes affects those with compromised immune systems due to age (neonates and elderly persons), medications (e.g., chronic corticosteroids), illness (HIV/AIDS), and pregnancy. *Listeria* can be spread by food in all countries and social

strata. Certain foods are more likely to support the growth of *Listeria* if contaminated, such as soft cheeses and unpasteurized milk, but outbreaks have been associated with processed meats (e.g., cold cuts and hot dogs) and frozen desserts.

L. monocytogenes is an intracellular, gram-positive bacillus ("rod"), and mouse studies have repeatedly demonstrated the key role TNF- α plays in its control (32–34). Slifman and colleagues (35) reported on a series of postlicensure adverse events related to *L. monocytogenes* and infliximab and etanercept (35). They reviewed the FDA's Adverse Event Reporting System between 1998 and September 2002 and found 26 patients with culture-positive *L. monocytogenes* infections. Twenty-four cases were infliximab-associated, and two cases were etanercept-related. Eight patients died (seven infliximab, one etanercept). Estimated case rates for listeriosis within the first year of starting infliximab according to FDA reports were approximately 43/1,000,000 and approximately 61/1,000,000 for patients with RA. This compares with overall U.S. rates of 3/1,000,000 or 13/1,000,000 for individuals older than 60 yr.

CONCLUSIONS

Collagen-vascular disorders are being successfully managed with a new class of potent anticytokine agents. Although the agents have a specific target (i.e., inhibition of TNF- α), the targeted cytokine is also critical for maintaining several common pathogens in a sequestered, nonpathogenic state. Successful management of any immunocompromised patients requires a high index of suspicion for infection, frequent clinical assessment, and aggressive diagnostic approaches that include biopsy or sampling of any organ that seems abnormal. Clinical specimens should undergo routine fungal and mycobacterial culture and staining and assessment by a pathologist when appropriate. Patients on TNF- α inhibitors can look relatively well until they are critically ill. Prospective clinical trials are needed to examine potential preventive therapy strategies among the expanding population for whom anticytokine therapy is being offered.

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