

# Invasive Fungal Infections in the Era of Biologics

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## KEYWORDS

- TNF-alpha • Invasive mycoses
- Histoplasmosis • Coccidioidomycosis
- Aspergillosis • Infliximab • Etanercept • Adalimumab

Antagonists of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) have revolutionized the treatment of select inflammatory diseases including rheumatoid arthritis and Crohn's disease. Currently three TNF- $\alpha$  antagonists—adalimumab, etanercept, and infliximab—have been approved worldwide for use for the treatment of various rheumatic diseases.<sup>1</sup> Although these three medications exhibit efficacy in the treatment of autoimmune disorders, they also seem to affect host resistance to infectious pathogens, particularly granulomatous infections.<sup>2</sup> The TNF- $\alpha$  antagonists have been associated with numerous adverse events, of which serious infections and malignancies are the most common.<sup>3</sup> Mycobacterium tuberculosis, histoplasmosis, aspergillosis, listeriosis, cytomegalovirus, coccidiomycosis, nocardiosis, and other serious bacterial infections have been reported in several series and case reports of patients receiving TNF- $\alpha$  antagonist therapy. This article focuses solely on fungal infections associated with the anti-TNF- $\alpha$  therapies.

## ANTI-TUMOR NECROSIS FACTOR- $\alpha$ THERAPIES

Although anti-TNF- $\alpha$  factor therapies target the same cytokine, their mechanisms of action and

therefore efficacy and side effects are different. Infliximab (Remicade) was the first agent approved for treatment of Crohn's disease. Initially, however, it was studied for treatment of rheumatic arthritis (RA). Infliximab is a chimeric molecule that combines the Fc region of human immunoglobulin G1 (IgG1) with the variable region of the mouse antibody against TNF- $\alpha$ . It binds to both membrane-bound and soluble TNF- $\alpha$ , interfering with the binding of TNF- $\alpha$  to its receptor. The loss of bioactivity is a result of binding to soluble TNF- $\alpha$ , whereas binding to membrane-bound TNF- $\alpha$  causes complement- and/or antibody-dependent lysis of cells that express TNF- $\alpha$ , such as lymphocytes and monocytes.<sup>4,5</sup> Infliximab does not inhibit TNF- $\beta$  (lymphotoxin- $\alpha$ ). Infliximab is approved for treatment of RA, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and ulcerative colitis. The usual dose of infliximab is 3 to 5 mg/kg for RA and Crohn's disease, respectively, administered intravenously at weeks 0, 2, and 6 and followed by maintenance infusions every 8 weeks.<sup>6</sup> For patients who do not respond, doses may be escalated to 10 mg/kg.

Etanercept (Enbrel) is indicated for treatment of RA, psoriatic arthritis, ankylosing spondylitis, and polyarticular-course juvenile idiopathic arthritis.<sup>7</sup>

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Etanercept is a soluble dimeric fusion protein that consists of the extracellular ligand-binding portion of the human 75-kDa (p75) TNF receptor linked to the Fc portion of human IgG1. The fusion protein binds to both TNF- $\alpha$  and TNF- $\beta$ , interfering with their ability to interact with their receptors. Unlike infliximab, etanercept can interact only with soluble TNF- $\alpha$ .<sup>4</sup> The usual dose of etanercept is either 25 mg twice weekly or 50 mg once weekly administered subcutaneously.<sup>7</sup>

Adalimumab (Humira) is indicated for RA, Crohn's disease, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis. Adalimumab is a recombinant human IgG1 monoclonal antibody specific for TNF- $\alpha$ ; it does not inhibit TNF- $\beta$ . The usual dose is 40 mg administered subcutaneously every 2 weeks, but the dose may be increased to 40 mg every week if necessary.<sup>8</sup>

#### ROLE OF TUMOR NECROSIS FACTOR- $\alpha$ IN INFECTION

TNF- $\alpha$  plays a central role in the host immune response to infectious pathogens. Alveolar macrophages secrete large amounts of TNF- $\alpha$  in response to antigen presentation. T lymphocytes and natural killer cells produce it to a lesser extent. TNF- $\alpha$  is essential in the recruitment of inflammatory cells to the site of infection and in the formation and maintenance of infectious granulomas. Shortly after fungal or mycobacterial infection occurs, monocytes, dendritic cells, effector T cells, and B cells migrate to the site of infection and organize to form these granulomas. It is thought that the role of infectious granulomas is to contain the pathogen and prevent its spread beyond the original site of infection. If the integrity of the granuloma is disrupted, pathogen replication and dissemination may occur.<sup>9</sup>

Animal studies have demonstrated clearly the relationship between TNF- $\alpha$ , chemokine production, and granuloma formation. In TNF- $\alpha$ -deficient mice, chemokine levels lagged behind those in wild-type mice, leading to delayed or aberrant granuloma formation, increased bacterial replication, and destructive immunopathology.<sup>9,10</sup> In an experimental model of histoplasmosis, anti-TNF- $\alpha$  antibody blocked the T-helper (Th)-1 arm of cellular immunity<sup>11</sup> and prevented the development of a protective immune response.<sup>12</sup> For these reasons, it is not surprising that infections, including invasive fungal infections (IFIs), are a common side effect of the TNF- $\alpha$  inhibitor therapies.

#### INVASIVE FUNGAL INFECTIONS ASSOCIATED WITH TUMOR NECROSIS FACTOR- $\alpha$ INHIBITORS

The true incidence of IFIs associated with the TNF- $\alpha$  inhibitors is unknown for various reasons. Studies reporting on the emergent infections often lack the appropriate denominator, the recipients of anti-TNF agents. TNF- $\alpha$  inhibitors are prescribed commonly in conjunction with other immunosuppressants to help decrease the dose of these additional medications.<sup>13–16</sup> On the other hand, the disease states for which these medications are administered could predispose a patient to infection. For example, a patient suffering from RA is at increased risk of infection, probably because of underlying immune dysregulation.<sup>17</sup> Recently, however, a meta-analysis showed a significant association between TNF- $\alpha$  blockade and serious infections (the trial did not include etanercept). The rates of serious infections were low, on average 6 per 100 patient-years, and there seemed to be no significant difference in the rates of infection with infliximab, etanercept, or adalimumab.<sup>3</sup> Postmarketing studies suggest that the rate of serious infections complicating anti-TNF- $\alpha$  therapies might be much higher than reported in clinical trials evaluating TNF- $\alpha$  blockers.<sup>18</sup>

#### SPECIFIC INVASIVE FUNGAL INFECTIONS

##### *Histoplasmosis*

Histoplasmosis is the most common IFI associated with TNF- $\alpha$  inhibitors. In a recent survey of infectious diseases specialists, histoplasmosis was second only to *Staphylococcus aureus* as the cause of serious infection complicating anti-TNF and other biologic therapies.<sup>19</sup> In most reported cases, patients are from areas in which the fungus is endemic and have received concurrent immunosuppressants. To date 86 cases of histoplasmosis have been reported with some clinical information.<sup>2,11,20–30</sup> The two most common indications for anti-TNF therapy are RA and inflammatory bowel diseases. According to the FDA MedWatch, the complicating anti-TNF agent in most of the 240 patients who had histoplasmosis was infliximab (207 cases), followed by etanercept (17 cases) and adalimumab (16 cases).<sup>31</sup> The type of infection varied from acute pulmonary to extrapulmonary or progressive disseminated histoplasmosis; pulmonary involvement was reported in the majority of cases.<sup>32</sup> Typical presenting signs and symptoms included cough, fever, malaise, dyspnea, and interstitial pneumonitis on chest radiograph. Many of these signs and symptoms also could be caused by the patient's underlying disease state, resulting in

a delay in recognition and therefore treatment of the histoplasmosis.<sup>22</sup> Rapid diagnosis can be achieved most reliably by the urine or serum *Histoplasma* antigen test<sup>32</sup> and cytopathologic analysis of bronchoalveolar lavage (BAL).<sup>11</sup> Most patients were treated with amphotericin B followed by itraconazole. Mortality was nearly 20% in the cases for which that information was available.

### **Coccidioidomycosis**

To date 30 cases of coccidioidomycosis associated with anti-TNF therapy have been reported. Of these, 28 (93%) were associated with infliximab and 2 (7%) with etanercept.<sup>33–38</sup> Bergstrom and colleagues<sup>33</sup> estimated a relative risk of 5.23 for developing symptomatic coccidioidomycosis in patients residing in endemic areas receiving infliximab, as compared with those who are not taking an anti-TNF agent. Pneumonia was present in all cases, and five cases had evidence of disseminated infection. All patients were concomitantly taking methotrexate and/or corticosteroids. The diagnosis was made by positive serologic findings in 11 of the 15 cases for which such information is available. In four cases, the coccidioidomycosis was diagnosed by biopsy (lung, BAL, or skin) or from a culture.<sup>33,34,37</sup> The coccidioidal serology before anti-TNF therapy was negative in all six patients who were tested before initiation of infliximab. Of the 15 patients for whom information on treatment and outcome was available, 14 received antifungal therapy (amphotericin B, itraconazole, or fluconazole) with an attributable mortality of approximately 13% (2/15).<sup>33,34,37</sup>

### **Aspergillosis and Zygomycetes**

Sixty-five cases of aspergillosis associated with TNF- $\alpha$  inhibitor use have been reported to date. Most cases were associated with infliximab (48 cases, 74%), followed by etanercept (15 cases, 23%) and adalimumab (2 cases, 3%).<sup>27,28,39–50</sup> Of the 25 patients for whom the indication was known, 18 received the TNF- $\alpha$  inhibitor for graft-versus-host disease (GVHD) following allogeneic bone marrow transplantation for a hematologic malignancy, 5 for rheumatologic diseases, and 2 for inflammatory bowel disease. Sixty-three of the 65 patients were receiving concomitant immunosuppressant medications. Most patients developed invasive pulmonary aspergillosis and were diagnosed by culture or by biopsy obtained through bronchoscopy. One case was determined by a positive BAL culture result plus positive antigen testing. The overall prognosis was grave: mortality reached 82% in patients who had GVHD.<sup>43,46,47</sup>

Four cases of Zygomycetes infection have been reported in the literature to date.<sup>46,51,52</sup> Three of the four cases were associated with infliximab use (in one patient who suffered from Crohn's disease and in two patients who had GVHD). The fourth case was a patient who had RA who developed orbital cellulitis along with disseminated Zygomycetes infection in association with adalimumab therapy.<sup>52</sup> No patient survived.

### **Candida Infections**

Sixty-four cases of *Candida* infections associated with TNF- $\alpha$  inhibitor therapy have been identified. Of those cases, 84% (54/64) were associated with infliximab, 14% (9/64) with etanercept, and 2% (1/64) with adalimumab.<sup>21,28,39,40,44,47,53–56</sup> The indication for TNF- $\alpha$  therapy was known in 18 cases, 11 of which were GVHD, 5 were inflammatory bowel disease, and 2 were RA. The site of infection varied but included the bloodstream, abscesses, esophagus, oropharynx, and endovascular sites. These *Candida* infections were associated with 50% mortality (in cases for which outcome data were available). Of note, 75% of the patients who died were coinfecting with additional organisms: *Pneumocystis* and *Aspergillus* in one case,<sup>44</sup> a mixed intra-abdominal abscess<sup>21</sup> in another, and a *Salmonella* species in the last case.<sup>55</sup>

### **Cryptococcus Infections**

To date 28 cases of *Cryptococcus* infections associated with TNF- $\alpha$  inhibitor therapy have been reported.<sup>28,57–64</sup> Of the 28 cases, 17 (61%) have been associated with infliximab, 10 (36%) with etanercept, and 1 (3%) with adalimumab. Most patients presented with pneumonia. Additional clinical manifestations that have been noted include fungemia, involvement of the central nervous system, cutaneous infections, tenosynovitis requiring amputation of the involved fingers, and a rare case of *Cryptococcus albidus* infection. Typically *Cryptococcus* infections were diagnosed by biopsy. The infections responded to fluconazole or amphotericin B, and no patients died.

### **Blastomycosis**

Two cases of blastomycosis have been reported in abstract form with very limited information.<sup>38</sup>

### **OTHER AGENTS**

Although anti-TNF agents are considered essential in the treatment of RA, Crohn's disease, and other inflammatory diseases, other biologic agents now are being introduced in clinical use.

Rituximab (Rituxin) is a chimeric murine/human monoclonal antibody against CD20, which is found on mature and pre-B lymphocytes. Binding of rituximab to CD20 causes B-lymphocyte lysis and almost complete depletion of B-cell lineages.<sup>65,66</sup> B-cell depletion usually lasts 3 to 9 months but has been observed for up to 12 to 15 months.<sup>65-67</sup> Initially approved for treatment of certain B-cell non-Hodgkin's lymphomas, following or in combination with other chemotherapeutic regimens, rituximab also is approved for treatment of moderately to severely active RA in combination with methotrexate in adult patients who have had an inadequate response to one or more TNF-antagonist therapies.<sup>65</sup> It is being used increasingly for the treatment of other autoimmune diseases, including autoimmune-mediated thrombocytopenias and lupus.<sup>67</sup>

Although initial oncology trials did not show any increase in serious infections, later publications have suggested an increased risk of infections with rituximab. Although several cases of fungal infections have been reported in patients receiving rituximab for B-cell non-Hodgkin's lymphoma, it often is difficult to attribute these infections solely to rituximab because of concomitant or recent use of cytotoxic chemotherapeutic agents. In a review of 745 patients who had RA and who were receiving either rituximab or placebo, 17 serious infections were observed in the rituximab group compared with seven in the placebo group; none were fungal infections.<sup>68</sup>

*Pneumocystis* pneumonia has been reported in association with rituximab.<sup>69-74</sup> One case of fatal *Pneumocystis* pneumonia was diagnosed in a patient treated with rituximab in addition to methotrexate and low-dose prednisolone for RA. The diagnosis was made by polymerase chain reaction (PCR) on BAL fluid.<sup>73</sup> The increased risk of *Pneumocystis* infection with administration of rituximab was supported further by clinical trials that examined the addition of rituximab to standard chemotherapy for lymphomas. One study reported 10 cases (4.4%) of *Pneumocystis jirovecii* pneumonia in patients receiving rituximab, cyclophosphamide, hydroxydaunorubicin (Adriamycin), vincristine (Oncovin), and prednisone/prednisolone or rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine (Oncovin), etoposide and prednisone, compared with three cases (0.8%) in patients receiving chemotherapeutic regimens that did not include rituximab.<sup>71</sup>

Aspergillosis has been attributed to the use of rituximab in patients who are otherwise immunocompromised because of an underlying lymphoma after solid-organ transplantation,<sup>75</sup> hematopoietic stem cell transplantation,<sup>76</sup> or autoimmune disease.<sup>77</sup> On the other hand, rituximab

was given for more than a year to a patient who had chronic disseminated aspergillosis treated with voriconazole with no evidence of progression of the disease.<sup>78</sup> Disseminated histoplasmosis and mucormycosis also have been reported in association with rituximab use.<sup>79,80</sup>

Abatacept (Orencia) is a fusion protein that binds to CD80 and CD86 receptors on antigen-presenting cells, preventing their interaction with the CD28 receptor on T cells. It mimics the function of naturally occurring cytotoxic T-lymphocyte antigen-4, which results in a decrease in T-cell activation and proliferation. This decrease subsequently affects B-cell function, causing inhibition of TNF- $\alpha$ , interleukin (IL)-2, IL-6, and possibly interferon- $\gamma$ .<sup>66,81</sup> Abatacept has been approved for treatment of patients who have moderately to severely active RA and who have had an inadequate response to more than one disease-modifying anti-rheumatic drug (DMARD) or TNF antagonist. It can be used alone or in combination with DMARDs or TNF- $\alpha$  agonists.<sup>81</sup>

There are few reports of fungal infections related to abatacept therapy. Of 1960 patients who received abatacept, 49 had serious infections, and only one had a fungal infection (pulmonary aspergillosis). This patient had a history of tuberculosis and pulmonary fibrosis and died of aspergillosis and *Pseudomonas* septicemia.<sup>68</sup> Two other studies containing 1286 and 223 patients who had RA observed no fungal infections 6 months after starting abatacept therapy.<sup>82,83</sup>

Natalizumab (Tysabri) is a recombinant monoclonal antibody that competitively binds to alpha-4 integrin, a membrane protein on all leukocytes except neutrophils. It is involved in cell adhesion and leukocyte transmigration across endothelial cells and into peripheral tissues and may interfere with the activation of T lymphocytes.<sup>84</sup> It is approved for treatment of relapsing multiple sclerosis and in moderate to severe Crohn's disease with inflammation that has not responded to conventional therapy. Many of the reports of opportunistic infections associated with natalizumab therapy have focused on three patients in early trials of the agent who developed progressive multifocal leukoencephalopathy (PML), two of whom died. Since that time, larger studies have been performed, one of which showed a 0.1% risk of PML in the 3116 patients studied. Natalizumab was taken off the market for a short time and now carries a black box warning regarding the risk of developing PML.<sup>84</sup> The package insert notes that fewer than 1% of patients receiving natalizumab for Crohn's disease developed opportunistic infections, among which are listed *Pneumocystis jirovecii* pneumonia and

bronchopulmonary aspergillosis. Subsequent studies did not observe any fungal infections.

Anakinra (Kineret) is an IL-1 receptor antagonist that contains a single methionine residue at its amino terminus. It is approved for adults who have RA rheumatoid arthritis and who have not responded to one or more DMARDs. It can be used alone or in combination with DMARDs or TNF inhibitors.<sup>85</sup> Four trials reviewed 2771 patients who had RA arthritis receiving anakinra compared with 729 patients who had similar characteristics receiving placebo. No cases of fungal infection were observed,<sup>68</sup> and no case studies reporting fungal infections were found.

## SUMMARY

With the advent and widespread use of immunomodulating biologic agents, emerging invasive fungal infections are reported increasingly. To date there is no reliable method to screen patients before starting anti-TNF therapy to predict their risk for acquiring fungal infections, partly because most of these infections are de novo infections. Patients should be counseled about avoiding high-risk activities that are associated with the endemic mycosis in their geographic areas. Physicians should maintain a high level of suspicion for endemic fungal infections when patients receiving anti-TNF therapy or other biologics present with pulmonary or systemic infections. Rapid diagnosis and initiation of antifungal therapy are of utmost importance.

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