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Endemic Fungal Infections in Patients Receiving Tumour Necrosis Factor-α Inhibitor Therapy

Jeannina A. Smith and *Carol A. Kauffman*

Division of Infectious Diseases, University of Michigan Medical School, Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, Michigan, USA

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Abstract

Tumour necrosis factor (TNF)-α inhibitors are widely used agents in the treatment of a variety of inflammatory and granulomatous diseases. It has long been appreciated that these agents confer an increased risk of tuberculosis; however, more recently it has been recognized that patients being treated with TNFα inhibitors are also at significant risk for infection with the endemic fungi, in particular *Histoplasma capsulatum*, and when infected, to develop severe disseminated infection. Patients often present in an atypical manner and the symptoms of the fungal infection can be mistaken for those of the underlying disease. Thus, delay in diagnosis and treatment is common, and mortality has been high. In an attempt to increase awareness of this problem, the US FDA issued a 'black box' warning for clinicians in September 2008 to alert providers of the risks of endemic fungal infections in patients treated with TNFα inhibitors. The management of patients who develop endemic fungal infection while receiving TNFα inhibitor therapy should include discontinuation of the TNFα inhibitor and early use of antifungal agents including polyenes and/or azoles according to the Infectious Diseases Society of America guidelines for treatment of these infections in immunocompromised hosts.

1. Role of Tumour Necrosis Factor (TNF)-α in Immunity and Chronic Inflammatory Diseases

Tumour necrosis factor (TNF)-α is a cytokine that is released by many cell types, including macrophages, monocytes and T lymphocytes, and that promotes inflammation through multiple different mechanisms. TNFα activates nuclear factor kappa B, induces interferon (IFN)-γ and several interleukins (IL-1, IL-6 and IL-8), and upregulates adhesion molecules produced by endothelial cells, resulting in enhanced leukocyte extravasation and migration.[1-3] TNFα is critical for effective granuloma formation and maintenance, and is an essential component of host immunity against intracellular pathogens, including mycobacteria and certain fungi.

Aberrant activity of TNFα has been implicated in a number of diseases, including rheumatoid arthritis, juvenile rheumatoid arthritis, inflammatory bowel disease, psoriasis, graft versus host disease, ankylosing spondylitis, uveitis and vasculitis. Because of this, a number of drugs that block the effects of TNFα have been developed for the treatment of these and other inflammatory and granulomatous conditions.[4,5] For many patients, these agents have proved to be extremely effective in dampening the immune response that causes their symptoms. However, use of these agents has been associated with an increased risk of developing certain types of infections. The attributable excess risk for infection has been difficult to elucidate. In part, this is because patients with granulomatous and autoimmune disorders already have impaired immune responses to infection.[6] In addition, individuals with the most severe disease are most likely to receive TNFα inhibitors and, additionally, many of these patients also receive other immunosuppressive agents, making it difficult to ascribe the risk of infection solely to the TNFα inhibitor.

2. Currently Licensed TNFα Inhibitors

Four TNFα inhibitors, infliximab, etanercept, adalimumab and certolizumab, are currently US FDA-approved for clinical use. These agents differ in their structure, pharmacokinetic and pharmacodynamic properties, the mechanism of inhibition of TNFα and other biological activities (table I).

Infliximab (Remicade®) is a chimeric IgG1 monoclonal antibody with human constant and murine variable sequences. It binds to and neutralizes both soluble and membrane-bound TNFα, preventing the binding of TNFα to its receptor. Infliximab also fixes complement, inducing antibody-mediated lysis of cells expressing membrane-bound TNFα, and induces T-cell and monocyte apoptosis. Infliximab does not bind with TNFβ (lymphotoxin). Infliximab was licensed in 1998 and is approved to treat moderate to severe rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease and ulcerative colitis.[4,7] It also has been used for uveitis, psoriasis, hidradenitis suppurativa and sarcoidosis.[7-9]

Etanercept (Enbrel®) is a human soluble TNFα receptor fusion protein composed of the extracellular portion of two TNFα type II (p75) receptors joined to the Fc portion of IgG1. Etanercept binds to soluble TNFα and TNFβ, thereby preventing receptor-mediated activation. Unlike infliximab, etanercept does not fix complement, cause antibody-dependent cytotoxicity, or trigger T-cell or monocyte apoptosis. Etanercept was also licensed in 1998 and is approved to treat moderate to severe rheumatoid arthritis and juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and moderate to severe plaque psoriasis.[5,9,10]

Adalimumab (Humira®) is similar to infliximab in its actions. However, it is a human monoclonal IgG1 antibody, not a chimeric molecule like infliximab. It binds to both soluble and membrane-bound TNFα; it does not bind with TNFβ. Similarly to infliximab, it fixes complement, causes lysis of cells expressing membrane-bound TNFα and induces apoptosis. Adalimumab has been approved to treat rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis.[9,11,12]

Certolizumab pegol (Cimzia®) is a pegylated humanized Fab′ fragment with a high binding

Table I. Properties of the currently licensed tumour necrosis factor (TNF)-α inhibitors

Agent	TNFα binding	TNFβ binding	Fixes complement; antibody-mediated cell lysis	Elimination half-life (days)	Route of administration	Efficacy for granulomatous diseases	Comparative risk of infection with endemic mycoses
Infliximab	Soluble and membrane-bound TNFα	No	Yes	9.5	IV	Yes	Greater
Etanercept	Soluble TNFα	Yes	No	4.2	SC	No	Lesser
Adalimumab	Soluble and membrane-bound TNFα	No	Yes	14	SC	Yes	Greater
Certolizumab	Soluble and membrane-bound TNFα	No	No	14	SC	Yes	Unknown

IV = intravenous; **SC** = subcutaneous.

affinity for TNFα. In contrast to infliximab and adalimumab, certolizumab pegol does not contain an Fc portion and therefore does not fix complement or induce apoptosis of T cells or monocytes. Certolizumab pegol has been approved in the US for Crohn's disease and is under review for the treatment of rheumatoid arthritis.[9,13,14] It is the newest of the TNFα inhibitors, and thus there is little information on adverse effects when compared with the other three agents.

The pharmacological variations among these agents have clinical implications. For example, in the case of granulomatous disorders, such as sarcoidosis, Crohn's disease and Wegener's granulomatosis, etanercept appears to be considerably less effective than infliximab.[15] This indicates that the specific type of TNFα blockade may be important in the therapeutic efficacy of these agents. Etanercept binds primarily to soluble TNFα, whereas infliximab binds to both soluble and membrane-bound TNFα and has broader activities, including complement fixation and induction of apoptosis of cells expressing membrane-bound TNFα.[16] Thus, it is likely that this broader activity of infliximab against T cells and monocytes is reflected in a greater risk for intracellular pathogens that are primarily controlled by these cells. Indeed, this has been seen in the types of infections noted in patients receiving the various TNFα inhibitors.

3. TNFα Inhibitors and Infection with Intracellular Pathogens

All the TNFα inhibitors are associated with an increased risk of infection.[17-21] It appears that the incidence of granulomatous infections is less with etanercept than infliximab and perhaps adalimumab. Rates of development of active tuberculosis have been estimated to be 53.81 per 100 000 persons for infliximab and 28.32 per 100 000 persons for etanercept.[17,18] Among 1200 patients in Europe and 1700 patients in the US to whom adalimumab had been administered, there were eight cases of reactivation tuberculosis in Europe and one case of primary tuberculosis in the US.[19] Two large registries, one in France and the other in Portugal, confirmed rates that were similar for the development of tuberculosis in patients receiving either infliximab or adalimumab, and noted that the rate for etanercept was much lower.[17,22] These observations uniformly suggest that both adalimumab and infliximab confer a greater risk of developing active tuberculosis than does etanercept. A smaller registry in Germany did not show a difference in infection rates between infliximab and etanercept, but no invasive fungal infections were reported and only one case of tuberculosis was seen in a patient receiving infliximab.[23] There is so little clinical experience with certolizumab pegol that the rate of development of infection with intracellular pathogens is unknown.

Other infections associated with the use of TNFα inhibitors, including aspergillosis, candidiasis, bartonellosis, coccidioidomycosis, histoplasmosis, legionellosis, leprosy, listeriosis, non-tuberculous mycobacterial infections, nocardiosis, pneumocystosis and toxoplasmosis, have all been reported more frequently with infliximab than with etanercept.[20] Only cryptococcosis and salmonellosis have been more commonly noted with etanercept than infliximab. In a recent review, 80% of all fungal infections associated with use of TNFα inhibitors were in patients treated with infliximab, versus only 16% with etanercept and 4% with adalimumab.[21] Fungal infections associated with infliximab tended to occur much earlier in the course of therapy (55 days) than those seen with etanercept (144 days).[21]

Several hypotheses have emerged to explain the differences in the risk of infection found with infliximab and adalimumab compared with etanercept. The inability of etanercept to induce apoptosis in monocytes/macrophages and T cells expressing membrane-bound TNFα clearly differentiates this agent from the other TNFα inhibitors.[21] Agents that bind more avidly to the membrane-bound TNFα receptor (TNFR) p75, namely infliximab and adalimumab, appear to have greater disruption of immune regulation than etanercept.[24] Decreased levels of IFNγ have been noted when T cells from patients with tuberculosis associated with infliximab therapy were studied *in vitro*;[25] these effects were not found when cells from etanercept-treated patients were studied. Finally, lysis of TNFα-expressing cells, as noted with infliximab and adalimumab, may persist for long periods, yielding a more lasting effect on the host's ability to inhibit intracellular pathogens.[16]

4. TNFα Inhibitors and Infection with Endemic Mycoses

The most commonly reported endemic fungal infection in patients who have been treated with TNFα inhibitors is histoplasmosis. Among all the endemic mycoses, *Histoplasma capsulatum* is the classic intracellular pathogen. The host response to *Blastomyces dermatitidis* and to *Coccidioides* spp. involves neutrophils, as well as lymphocytes and macrophages, but *H. capsulatum* is contained almost entirely by cell-mediated immunity. This may be the reason for the larger number of cases of histoplasmosis noted with TNFα inhibitor therapy, but there may also be more patients exposed to *H. capsulatum* because of its wider geographical distribution. There have been no reported cases of paracoccidioidomycosis or penicilliosis in patients receiving TNFα inhibitor therapy, and these endemic mycoses are not discussed in this review.

4.1 Histoplasmosis

Histoplasmosis is endemic in the Ohio and Mississippi River valleys of the US and in Central America, and is found occasionally in localized areas in southern Europe, Africa and Asia. Infection is acquired through the inhalation of microconidia and is usually asymptomatic and self-limited in immunologically healthy individuals. However, immunocompromised individuals who are exposed to *H. capsulatum* are at high risk for developing symptomatic histoplasmosis with progression to severe disseminated, often fatal, infection.[26]

Even before TNFα inhibitors became available for clinical use, there was concern that patients would be at risk for severe histoplasmosis. In murine models, it was known that TNFα was vital to the immunological containment of both primary and reactivated histoplasmosis.[27-30] Naive mice develop a rapidly progressive infection when endogenous TNFα is neutralized by anti-TNFα monoclonal antibody.[27,29] The molecular pathogenesis of this increased susceptibility to severe disease has not been clarified, but is likely to involve interactions with the receptors TNFR p75 and TNFR p55 on the cell membrane.[29,31] In immune mice, TNFα inhibitors ablate the protective response to *H. capsulatum* by a different mechanism.[29] It appears that interference with TNFα activity in these animals leads to a dysregulated immune response with marked increases in IL-4 and IL-10, two

cytokines that decrease the cell-mediated immune response.[30]

Soon after the introduction of infliximab and etanercept, two case reports of histoplasmosis in patients treated with these agents were published.[32,33] These reports were followed in 2002 by a postmarketing report of ten cases of histoplasmosis in patients treated with TNFα inhibitors.[34] Nine of these cases were in patients treated with infliximab and one was in a patient treated with etanercept. All patients had received additional concomitant immunosuppressive medications, and all patients resided in an endemic region. Among the infliximab-treated patients, clinical manifestations of histoplasmosis occurred from 1 to 20 weeks after the first, and in some patients only, dose of the drug. Nine of ten patients required admission to an intensive care unit, seven had disseminated histoplasmosis and one died. In an addendum to this report, an additional 12 cases of histoplasmosis were noted, ten of which occurred in patients treated with infliximab. Three of these ten patients died.[34]

Since the initial reports, there have been other reports of patients with histoplasmosis associated with TNFα inhibitor therapy.[21,35-38] The incidence of histoplasmosis in patients treated with TNFα inhibitors has been estimated to be 18.78 per 100 000 persons for infliximab and 2.65 per 100 000 persons for etanercept. That incidence is highly geographically variable and thought to be much higher in endemic areas.[20]

In 2008, the FDA reviewed 240 reports of histoplasmosis in patients who were treated with infliximab (207 cases), etanercept (17 cases) and adalimumab (16 cases); one case was later reported in a patient who was treated with certolizumab pegol.[35] The majority of those reports came from areas in which *H. capsulatum* is endemic. In at least 21 of the 240 reported cases, histoplasmosis was not diagnosed until late in the clinical course, leading to a delay in the initiation of appropriate antifungal therapy; 12 of those 21 patients died.

Whether most cases of histoplasmosis among patients taking TNFα inhibitors are due to reactivated infection or to newly acquired infection is controversial.[32,36,37] Some authors believe that most cases are due to recent acquisition and that reactivation after the use of TNFα inhibitors is rare. This idea is supported indirectly by the fact that the incidence of histoplasmosis in patients using TNFα inhibitors is less than would be expected if reactivation were a common mechanism. Others have asserted that the very rapid onset of manifestations of infection after administration of a TNFα inhibitor, with symptoms occurring as early as 1–4 weeks after the first dose, is suggestive of reactivation. Occurrence in a patient who resides outside the endemic area, but who had previously lived in the endemic area, also speaks to reactivation as a mechanism of disease.[37]

Manifestations of histoplasmosis in patients taking TNFα inhibitors include fever, malaise, dyspnoea and cough. Patients can come to the physician after several weeks of worsening symptoms, but frequently they present acutely ill with a septic picture with hypotension and confusion. Severe hypoxaemia and development of acute respiratory distress syndrome (ARDS) can quickly ensue. Physical examination reveals rales on auscultation of the chest and hepatosplenomegaly is common. Skin lesions, when present, can be pustular, nodular or ulcerated, and painful mouth ulcers can be present. Chest radiographs and CT scans usually reveal diffuse pneumonitis (figure 1). Pancytopenia is common as are elevated liver enzyme tests.

The diagnosis should be quickly sought in the acutely ill patient by obtaining biopsy samples from lung, liver and/or bone marrow.[26] Histopathological examination using methenamine silver stain will reveal the small oval budding yeasts typical of *H. capsulatum* (figure 2). Cultures obtained from these tissues and also from blood are the definitive test, but take several weeks for growth to occur. Another rapid test that should be obtained when the diagnosis of histoplasmosis is a consideration is the urine antigen assay for the capsular polysaccharide of *H. capsulatum*; this assay has proven to be very useful in immunosuppressed patients who are often unable to mount an antibody response.[39]

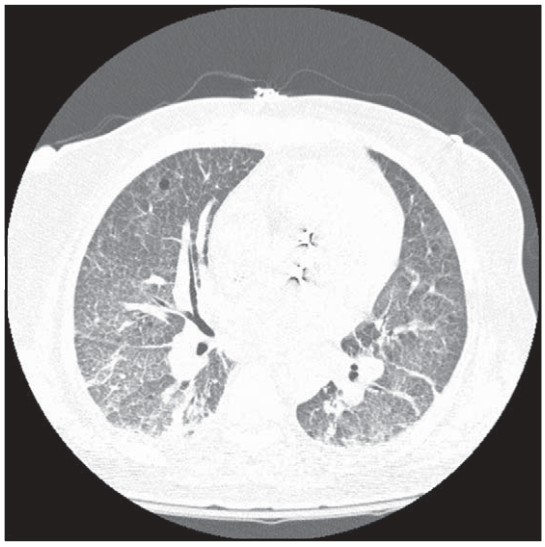

Fig. 1. Chest CT scan of a 53-year-old woman who had rheumatoid arthritis and who had been treated with infliximab and methotrexate. She presented with mental status changes, cough and fever. Anaemia, elevated liver enzymes and diffuse infiltrates on chest radiograph were noted. CT scan shows extensive bilateral reticulonodular infiltrates.

This assay shows cross-reactivity with samples from patients who have blastomycosis.

The Infectious Diseases Society of America (IDSA) updated practice guidelines in 2007 for the management of histoplasmosis.[40] Treatment depends on the clinical manifestations of the disease in individual patients, but it is likely that most patients who are receiving TNFα inhibitors will have severe disease (table II). Patients who have moderately severe to severe acute pulmonary or disseminated histoplasmosis should be treated initially with a lipid formulation of amphotericin B. The usual dosage is liposomal amphotericin B, 3 mg/kg, or amphotericin B lipid complex, 5 mg/kg. It should be emphasized that for patients who are acutely ill with sepsis and ARDS, empirical treatment with a lipid formulation of amphotericin B should be started as quickly as possible after obtaining biopsy of involved tissues, blood cultures for fungi, and urine antigen tests.

After clinical improvement occurs, therapy can be changed to itraconazole 200 mg three times daily for 3 days and then twice daily for a total of 12 months of therapy. Patients who have mild to moderate acute pulmonary or disseminated histoplasmosis can be treated initially with oral itraconazole at the same dosage for a total of 12 months.[40]

The TNFα inhibitor should be stopped as soon as the diagnosis of histoplasmosis is suspected. Only after it has been established by culture methods and measurement of urine *Histoplasma* antigen that the infection is adequately treated should resumption of therapy with a TNFα inhibitor be contemplated. If the TNFα inhibitor is restarted, itraconazole therapy should be continued for as long as the patient receives the immunosuppressive agent.

4.2 Blastomycosis

B. dermatitidis, the thermally dimorphic fungus that causes blastomycosis, is endemic in moist soil with decaying vegetation in the Mississippi and Ohio River valleys, in the Midwestern states and Canadian provinces that border the Great Lakes, in the areas of New York and Canada adjacent to the St Lawrence Seaway, and in certain areas of Africa.[41-45]

Perhaps because immunity involves both neutrophils and T lymphocytes, *B. dermatitidis* has not classically been thought of as causing infection more often in immunosuppressed patients. However, blastomycosis has been increasingly reported in patients who are transplant recipients or have AIDS, and these patients have more severe disease manifestations.[46-49]

There have been few reports of blastomycosis in patients treated with TNFα inhibitor therapy. Seven cases had been reported postmarketing to the FDA Adverse Event Reporting System as of mid 2008.[35] The clinical manifestations of blastomycosis in these patients have not been detailed. However, it is likely that the disease is similar to that described in other immunosuppressed patients, who are more likely to develop widespread dissemination to skin and viscera, including the CNS.[48] Skin lesions in immunosuppressed patients tend to be more pustular and ulcerative than the typical heaped-up chronic lesions seen in patients who are not immunosuppressed. In immunosuppressed patients, the

infection often progresses rapidly and ARDS can occur.[48,49]

The diagnosis of blastomycosis can be established most quickly by sampling involved tissue for histopathological examination. Bronchoscopy with lavage and lung biopsy, and biopsy of a skin lesion are most helpful. Examination of material obtained by biopsy reveals the characteristic large, thick-walled yeasts that have a single broad-based bud. Growth in culture takes several weeks, but provides definitive proof of infection with *B. dermatitidis*.[50] A urinary assay for *B. dermatitidis* antigen is available and, with more experience, could prove to be useful for the rapid diagnosis of this infection in severely ill patients.[51] The urinary antigen test for *B. dermatitidis* shows cross-reactivity in samples from patients who have histoplasmosis.

Updated practice guidelines for the treatment of blastomycosis have been published by IDSA.[52] Because patients receiving TNFα inhibitors are inherently immunosuppressed, most have severe blastomycosis and should be treated initially with amphotericin B (table II). A lipid formulation of amphotericin B at a dosage of 3–5 mg/kg/day or amphotericin B deoxycholate at a dosage of 0.7–1 mg/kg/day is recommended for 1–2 weeks or until improvement is noted. This initial therapy is followed with treatment with oral itraconazole 200 mg three times daily for 3 days and then 200 mg twice daily, for a total of 12 months. Lifelong suppressive therapy with oral itraconazole

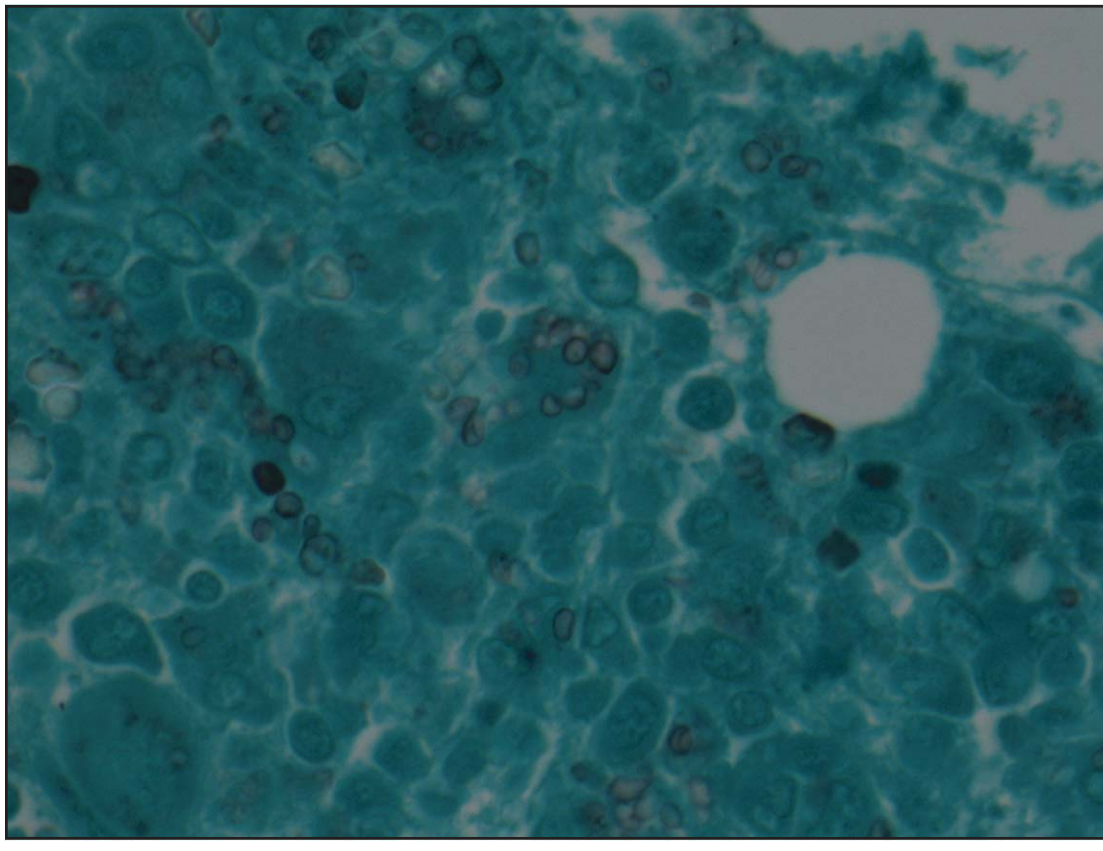

Fig. 2. Bone marrow biopsy from the patient whose chest CT is shown in figure 1. Clusters of small (2–4 μm) oval budding yeasts typical of *Histoplasma capsulatum* are seen using methenamine silver stain. *H. capsulatum* was grown from blood cultures, bone marrow and liver tissue. Urine and serum tested positive for *Histoplasma* antigen.

Table II. Characteristics of endemic fungal infections occurring in patients receiving tumour necrosis factor-α inhibitors

Organism	Endemic areas	Estimated incidence[a]	Diagnosis	Initial therapy	Step-down therapy
Histoplasma capsulatum	Ohio and Mississippi River valleys, Central America, other microfoci	18.78 per 100 000 persons	Histopathological examination of involved tissues Culture blood and involved tissues *Histoplasma* urinary antigen	Lipid AmB 3–5 mg/kg/day	Itraconazole 200 mg tid×3 days, then 200 mg bid for 1 y
Blastomyces dermatitidis	North-central and southern US, Canadian provinces bordering Great Lakes and St Lawrence Seaway, certain areas of Africa	Unknown	Histopathological examination of involved tissues Culture involved tissues *Blastomyces* urinary antigen	Lipid AmB 3–5 mg/kg/day or AmB deoxycholate 0.7–1 mg/kg/day	Itraconazole 200 mg tid×3 days, then 200 mg bid for 1 y
Coccidioides immitis and *C. posadasii*	Sonoran deserts of south-western US, Central and South America	5.58 per 100 000 persons	Histopathological examination of involved tissues Culture blood and involved tissues Coccidioidal antibodies Coccidioidal urinary antigen	Lipid AmB 3–5 mg/kg/day or AmB deoxycholate 0.7–1 mg/kg/day	Itraconazole 200 mg tid×3 days, then 200 mg bid OR fluconazole 400 mg daily for at least 1 y

a Estimated incidence in infliximab-treated patients.

AmB = amphotericin B; **bid** = twice daily; **tid** = three times daily.

200 mg/day may be required for patients in whom immunosuppression cannot be reversed and for patients who experience relapse despite appropriate therapy.

Although not addressed specifically in the guidelines, therapy with the TNFα inhibitor should be discontinued when the diagnosis of blastomycosis is made. Only after the clinician is firmly convinced that the infection is under control should resumption of therapy with the TNFα inhibitor be contemplated. In those in whom it is decided that therapy with a TNFα inhibitor should be restarted, itraconazole should be continued for as long as the patient receives the TNFα inhibitor.

4.3 Coccidioidomycosis

Coccidioidomycosis, caused by *Coccidioides immitis* in southern California and *C. posadasii* in all other areas, is endemic to the deserts of the south-western US and similar desert areas in Central and South America.[53] Most immunocompetent patients have mild or asymptomatic infection, but patients with impaired cell-mediated immunity are at increased risk of developing symptomatic disease.[54-56]

Experimental data provide a rationale for the observed increase in incidence and severity of coccidioidomycosis in patients treated with TNFα inhibitors. In the mouse, TNFα is produced by peritoneal macrophages incubated with coccidioidal spherules.[57] Human peripheral blood mononuclear cells produce TNFα when exposed to spherules as well as arthroconidia of *C. immitis*.[58,59] Thus, blocking the activity of TNFα would be expected to increase the risk of more severe infection with coccidioidomycosis.

The rate of symptomatic coccidioidomycosis in patients receiving TNFα inhibitor therapy has been estimated to be 5.58 per 100 000 persons for infliximab and 0.88 per 100 000 persons for etanercept.[20] Because of the geographical restriction of coccidioidomycosis, this rate is not generalizable to the entire US population. There is currently a clinical trial at the University of Arizona (ClinicalTrials.gov identifier: NCT00796809) to determine the incidence and

calculated risk of coccidioidomycosis in patients receiving various TNFα inhibitory agents.

In the first published series of patients who developed symptomatic coccidioidomycosis while being treated with TNFα inhibitor therapy, 12 patients had received infliximab and one etanercept. Eleven of the 12 patients who had been given infliximab were further immunosuppressed with methotrexate.[60] All patients presented with pneumonia and four also had evidence of dissemination. Eleven patients had IgM and/or IgG anticoccidioidal antibodies, and four had biopsy or culture evidence of coccidioidomycosis. Five patients were hospitalized and two died, one of coccidioidomycosis. Six of these patients had serological studies for coccidioidomycosis performed prior to receiving a TNFα inhibitor, and all six had negative tests. It was therefore postulated that these patients developed new infection with *Coccidioides* spp. Two other patients had a history of coccidioidomycosis in the preceding 2 years and both developed reactivation of infection when given TNFα inhibitor therapy.[60]

A larger series of 31 cases of coccidioidomycosis associated with TNFα inhibitor therapy has been presented in an abstract only.[61] The diagnosis was made by serological tests in 17 patients and by histopathological demonstration of *Coccidioides* spp. or positive culture in the other 14 patients. Cough, fever and fatigue were the prominent symptoms in this cohort.

Rarely, patients who have never travelled to areas endemic for *Coccidioides* spp. and who were treated with TNFα inhibitors have developed coccidioidomycosis. In one case, exposure to the organism was most likely related to dust imported from Arizona with landscaping materials.[62]

The usual manifestations of acute pulmonary coccidioidomycosis are fever, malaise, cough and dyspnoea, and chest radiographs show localized pneumonia. However, in immunocompromised patients, localized infiltrates can quickly progress to diffuse bilateral infiltrates and hypoxaemia.[54,55] The most common sites for dissemination are skin, osteoarticular structures and meninges. Multiple ulcerated and/or nodular skin lesions can appear at any site. Meningeal involvement is manifested initially by headache and confusion; behavioural changes and cranial nerve findings can follow, and this form of coccidioidomycosis is fatal if left untreated. Acute pulmonary coccidioidomycosis also can present with associated rheumatic symptoms, known as 'desert rheumatism', which could lead to treatment aimed at a flare of an underlying rheumatic syndrome, rather than coccidioidomycosis, with subsequent devastating consequences.

The diagnosis of coccidioidomycosis can be established by several means, but the most rapid is through biopsy of affected tissue for histopathological examination. The tissue form of *Coccidioides* spp. is quite distinctive. The spherules are large (50–80 μm in diameter) and can be visualized with haematoxylin and eosin stains, as well as silver stains. Growth in culture is rapid compared with the other endemic mycoses, but is risky for the laboratory staff, who must use special precautions to avoid dispersal of the arthoconidia. In contrast to histoplasmosis and blastomycosis, serological assays appear to be more useful in patients with coccidioidomycosis, even when they are taking TNFα inhibitors.[60,61] A urine antigen assay for *Coccidioides* spp. has been recently developed and could prove to be useful when more experience has accrued with its use.[63]

Guidelines for the treatment of coccidioidomycosis note that patients who are at high risk of complications because of immunosuppression, including the use of TNFα inhibitors, should be treated initially with an amphotericin B formulation[64] (table II). Oral azole agents, fluconazole or itraconazole, usually 400 mg/day, are used for step-down therapy after an initial response to amphotericin B. Azole therapy is continued for at least a year and is given lifelong if the patient remains immunosuppressed. TNFα inhibitor therapy should be promptly stopped when a diagnosis of coccidioidomycosis is suspected. Whether a patient who has been diagnosed as having coccidioidomycosis and has been treated for this can resume therapy with a TNFα inhibitor has not been clarified. At least one patient is known to have relapsed years later

even while receiving itraconazole when infliximab was started.[60] Patients who have CNS infection with *Coccidioides* spp. have a lifelong risk for relapse and must continue receiving azole therapy for life. It would be prudent to avoid resumption of a TNFα inhibitor in such a patient.

5. Prevention of Endemic Mycoses among Patients Receiving TNFα Inhibitor Therapy

Given the propensity for *H. capsulatum*, *B. dermatitidis* and *Coccidioides* spp. to disseminate and cause severe, often fatal, disease in patients who are receiving TNFα inhibitors, prevention of infection should be a goal. However, the approach to prevention is not clear-cut. Prophylaxis for all patients who will be treated with TNFα inhibitors is not an option, given the risk of adverse effects, drug-drug interactions and costs of antifungal agents. A better approach would be to define the patients who are at highest risk of development of an endemic fungal infection and target prophylaxis towards this group. Unfortunately, methods of defining those at highest risk have not been established.

The simplest starting point is to screen for prior exposure to the endemic mycoses. A thorough history should include questions about symptoms that are typical of the endemic mycoses. One should carefully review whether the patient has ever lived in an area in which *H. capsulatum*, *B. dermatitidis* or species of *Coccidioides* are endemic, and whether they had an occupation or vocation that might have put them at increased risk of exposure to one of these fungi.

Screening with antibody titres prior to the initiation of TNFα inhibitor therapy has been suggested as a means of telling whether a patient might be at risk for development of an endemic mycosis. Screening for antibody against *Coccidioides* spp. in patients living in the endemic area has proved useful prior to solid organ transplantation.[55,56] However, no studies have evaluated this approach for coccidioidomycosis or histoplasmosis prior to initiating TNFα inhibitor therapy, and there are several reasons to think that this will not prove effective. Patients who are already immunosuppressed, as are many who will receive TNFα inhibitor therapy, often do not have an effective antibody response. Although antibody titres may remain positive at low titres for several years after infection, more often they become negative within a short time and thus are not sensitive tests. Screening for antibodies will not be useful if most infections are due to new exposure to the fungus.[60] There are no sensitive or specific antibody tests for blastomycosis, but this endemic mycosis presents the lowest risk for patients receiving TNFα inhibitor agents.

Urine and serum antigen assays for the endemic mycoses are useful in patients who have active infection with the endemic mycoses, but these are not useful as screening tests prior to the use of TNFα inhibitors. The IDSA guidelines for the management of histoplasmosis note that urine antigen tests could be useful in the specific instance of a patient who has had a recent documented episode of histoplasmosis and who is about to undergo immunosuppression, as might occur with TNFα inhibitor therapy. In this unusual circumstance, baseline urine antigen levels and follow-up levels every 2–3 months are suggested to help assess for reactivation of histoplasmosis.[40] Detection of antigen should prompt aggressive work-up for active histoplasmosis. There is too little experience with the urine antigen tests for blastomycosis and coccidioidomycosis to recommend similar studies.

Even if patients at highest risk for infection could be defined, it is still not clear whether prophylaxis with an antifungal agent will prevent infection. Prophylaxis has been used in transplant patients who have a history of coccidioidomycosis or positive serology test for *Coccidioides* spp.[55,56] and in individuals with AIDS who reside in highly endemic areas with a documented high attack rate for histoplasmosis.[65] However, there are no similar data for the group of patients treated with TNFα inhibitors, and no formal recommendations have been put forward to use an antifungal agent, such as itraconazole, in this population.

The approach currently used is to strongly advise patients to avoid high-risk activities likely to expose them to endemic fungi and to remind physicians to be vigilant for possible manifestations of endemic fungal infections. Recommendations to patients include avoiding demolition work on old buildings, clean-up activities in attics and basements, and activities that involve disrupting soil in areas endemic for histoplasmosis. Spelunking, or caving, should be forbidden because many caves, even those outside the highly endemic areas, contain microfoci of *H. capsulatum*. Patients who live in the areas endemic for *B. dermatitidis* should avoid outdoor activities that involve disruption of wet or moist soil, especially along riverbanks, and clearing decaying brush and trees. Curtailing hunting, because this activity has been associated with infection with *B. dermatitidis*, should be mentioned to patients for their consideration. In the desert southwest areas of the US in which species of *Coccidioides* are endemic, patients on TNFα inhibitor therapy should stay inside during dust storms and should not indulge in activities, such as digging and riding all-terrain vehicles that are likely to disrupt the desert soil.

Physicians must be informed about the manifestations of infection with the endemic mycoses and realize that the disease may progress rapidly. When infection is suspected, urine antigen testing for the endemic mycoses should be obtained immediately. Biopsy of organs involved, such as skin, lungs, lymph nodes, bone marrow or liver, should be performed promptly, and the pathologist should be asked to look specifically for fungi in the tissues. If there is a strong suspicion for an infection with an endemic mycosis, therapy should not be delayed awaiting the results of the above tests. Empirical therapy with amphotericin B is suggested for any patient who presents with severe pneumonia or sepsis syndrome with no obvious bacterial cause. Given the toxicities of amphotericin B, it is reasonable to use itraconazole in patients who present with less severe or focal disease. However, it must be kept in mind that this agent is only available as an oral formulation that has poor bioavailability, it has many drug-drug interactions and it takes at least a week to reach steady state. Patients on TNFα inhibitor therapy can show rapid clinical deterioration; thus, for most patients receiving TNFα inhibitor therapy, initial amphotericin B therapy is prudent.

6. Conclusions

TNFα inhibitors are an important class of drugs for the treatment of inflammatory and granulomatous disorders. However, use of these agents is associated with an increased risk of infection with the endemic fungi, particularly *H. capsulatum* and *Coccidioides* spp. The greatest risk appears to be with infliximab, followed by adalimumab and then etanercept. Patients who acquire these infections are at risk for severe and/or disseminated disease. Diagnosis may be difficult and therapy delayed because the symptoms of fungal infection can mimic those of some types of diseases for which therapy with TNFα inhibitors is indicated. Therefore, providers should assess the epidemiological risk for development of endemic fungal infections in all patients in whom TNFα inhibitor therapy is contemplated. Patients who are being treated with a TNFα inhibitor and who present with signs and symptoms suggesting a systemic fungal infection, including anorexia, weight loss, malaise, fever, chills, sweats, cough and dyspnoea, should be promptly evaluated for the possibility of infection with an endemic mycosis. Evaluation includes prompt biopsy of involved tissues for histopathological examination for fungi and measurement of urinary fungal antigens. In patients thought to be at risk of endemic fungal infection, empirical antifungal treatment, in most cases with amphotericin B, is recommended after the initial diagnostic studies have been obtained. Early empirical therapy is vital because a delay in antifungal therapy is associated with poor outcomes. As is true for any patient who is receiving immunosuppressive agents, and who presents with signs and symptoms concerning for a serious infection, the TNFα inhibitor should be stopped until the infection has been appropriately treated.

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Correspondence: Dr *Carol A. Kauffman*, Veterans Affairs Ann Arbor Healthcare System, 2215 Fuller Road, Ann Arbor, MI 48105, USA.
E-mail: ckauff@umich.edu