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Life-Threatening Histoplasmosis Complicating Immunotherapy With Tumor Necrosis Factor α Antagonists Infliximab and Etanercept

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Objective. **Two tumor necrosis factor α (TNFα) antagonists were recently licensed in the US. Infliximab was licensed in 1998 for the treatment of Crohn's disease (CD), and since 1999, it has been licensed in combination with methotrexate for treatment of rheumatoid arthritis (RA). Etanercept was licensed in 1998 for treatment of RA and, more recently, for juvenile RA and psoriatic arthritis. Because of potential immunosuppression related to use of anti-TNFα agents, we sought to identify postlicensure cases of opportunistic infection, including histoplasmosis, in patients treated with these products.**

Methods. **The US Food and Drug Administration's (FDA) passive surveillance database for monitoring postlicensure adverse events was reviewed to identify all reports received through July 2001 of histoplasmosis in patients treated with either infliximab or etanercept.**

Results. **Ten cases of *Histoplasma capsulatum* (HC) infection were reported: 9 associated with infliximab and 1 associated with etanercept. In patients treated with infliximab, manifestations of histoplasmosis occurred within 1 week to 6 months after the first dose and typically included fever, malaise, cough, dyspnea, and interstitial pneumonitis. Of the 10 patients with histoplasmosis, 9 required treatment in an intensive care unit, and 1 died. All patients had received concomitant immunosuppressive medications in addition to infliximab or etanercept, and all resided in HC-endemic regions.**

Conclusion. **Postlicensure surveillance suggests that acute life-threatening histoplasmosis may complicate immunotherapy with TNFα antagonists, particularly infliximab. Histoplasmosis should be considered early in the evaluation of patients who reside in HC-endemic areas in whom infectious complications develop during treatment with infliximab or etanercept.**

Tumor necrosis factor α (TNFα) has been identified as a central regulator of inflammation (1), and TNFα-neutralizing agents have been shown to be effective in treating several inflammatory disorders in which TNFα is believed to have an important role (2,3). Infliximab (Remicade) is a chimeric mouse–human monoclonal IgG1 antibody, directed against soluble and cellular TNFα, that blocks the binding of TNFα with its endogenous cell surface TNFα receptor (2). Infliximab was approved by the US Food and Drug Administration (FDA) in October 1998 for the treatment of moderately to severely active Crohn's disease (CD) refractory to conventional therapies and for fistulizing CD. In November 1999, the FDA extended the indication for use of infliximab (in combination with methotrexate) to include treatment of moderately to severely active rheumatoid arthritis (RA) refractory to methotrexate therapy alone. Etanercept (Enbrel), another TNFα antago-

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Table 1. Comparison of infliximab and etanercept*

	Infliximab (Remicade)	Etanercept (Enbrel)
Molecular description	Chimeric monoclonal antibody; human constant and murine variable regions	Human protein; ligand-binding portion of 75-kd TNFR fused to Fc portion of IgG1
Molecular weight	~149 kd	~150 kd
Mechanism of TNFα inhibition	Binds to TNFα and inhibits it from binding with its TNFRs	"Decoy" receptor for TNFα
Affinity for TNFβ	No	Yes
In vitro lysis of cells expressing transmembrane TNFα	Yes	No
Terminal half-life	~8–9.5 days (median values)	4.25 ± 1.25 days (mean ± SD)
Clinical indication	Moderately to severely active CD refractory to other therapies or fistulizing CD; in combination with methotrexate, in moderately to severely active RA refractory to methotrexate alone	Moderately to severely active RA; moderately to severely active polyarticular-course JRA refractory to other therapies; active psoriatic arthritis

* TNFR = tumor necrosis factor receptor; CD = Crohn's disease; RA = rheumatoid arthritis; JRA = juvenile RA.

nist, is a recombinant protein consisting of the extracellular portion of the human TNFα receptor fused to the Fc portion of human IgG1 (3). Etanercept inhibits TNFα activity by serving as a "decoy" TNFα receptor. The FDA approved etanercept for treatment of RA in November 1998, for treatment of polyarticular juvenile RA in 1999, and for treatment of psoriatic arthritis in January 2002. Etanercept is not approved for the treatment of CD. Characteristics of these 2 products are shown in Table 1 (2,3).

Because of the potential immunosuppressive effects of TNFα antagonists, adverse events related to infection are a major concern with use of these agents, although placebo-controlled prelicensure clinical trials did not indicate a clearly higher risk of infection. However, the potential for developing histoplasmosis as a complication of therapy with TNFα-neutralizing agents is consistent with earlier observations of decreased host resistance to *Histoplasma capsulatum* (HC) infection in a murine model (4,5).

Subsequent to licensure, the manufacturer of infliximab and the FDA have received reports of histoplasmosis (as well as other infectious complications) (6). In addition, 2 case reports of histoplasmosis in association with the use of infliximab have been published (7,8). We now report a series of 10 patients (including 2 who were previously described; see refs. 7 and 8) who were residents of HC-endemic geographic regions in the US and who developed histoplasmosis after treatment with either infliximab or etanercept. Physicians should be alert to histoplasmosis as a potentially life-threatening complication of treatment with TNFα antagonists.

MATERIALS AND METHODS

Postlicensure safety of approved or licensed drugs and biologic therapeutic products is monitored by the FDA through its Adverse Event Reporting System (AERS). The AERS receives spontaneous reports of suspected adverse drug reactions from health care professionals and others through the FDA MedWatch program (for details, see http://www.fda.gov/medwatch). Additionally, manufacturers are required to forward information about adverse events that has been reported directly to them for entry into the AERS. However, as with all passive surveillance systems, underreporting of adverse events may occur due to various factors, such as lack of recognition of the association of the event with exposure to the suspected drug or lack of awareness of systematic voluntary postmarketing surveillance of adverse events. Furthermore, information regarding the event may be incomplete at the time of reporting.

We reviewed the AERS database to identify all reports of histoplasmosis associated with use of infliximab or etanercept that were received through July 2001. When necessary, the reporter of the adverse event was contacted to clarify or confirm the information that was submitted.

RESULTS

Through July 2001, the FDA received a total of 10 reports of histoplasmosis associated with use of infliximab (9 cases) or etanercept (1 case) (Table 2). The median age of patients was 43.5 years (range 11–78 years), and 60% were male. Six patients (60%) had RA, and 4 (40%) had CD. All 10 patients received antifungal therapy (usually intravenous amphotericin B); 9 patients recovered, and 1 (patient 4) died. Among the 9 patients who received infliximab (5 with RA, 4 with CD), the presenting signs or symptoms of histoplasmosis, such as fever, malaise, cough, dyspnea, and interstitial pneumonitis on chest radiographs, occurred from within 1 week

Table 2. Clinical charcteristics, manifestations, and outcomes of patients with histoplasmosis reported in this series*

Patient	Age/sex	Indication	Agent	Dose	No. of doses	Time, days†	Clinical presentation and outcome	Diagnostic biopsy, culture, or test
1	52/F	RA	Infliximab	3 mg/kg	3	50–60	Fever, dyspnea, weight loss, diffuse interstitial pneumonitis; recovered	Transbronchial biopsy
2	61/M	RA	Infliximab	3 mg/kg	3	50–60	Fever, malaise, cough, dyspnea, abnormal CXR, BOOP; outpatient management; recovered	Transbronchial biopsy
3	45/F	RA	Infliximab	3 mg/kg	1	30–40	Malaise, pneumonia, hilar lymphadenopathy, hypotension, acute renal failure; recovered	Transbronchial biopsy
4	78/F	RA	Infliximab	3 mg/kg	6	10–20	Fever, malaise, weight loss, interstitial pneumonitis, CHF, shock; died	Open lung biopsy
5	67/F	RA	Infliximab	3 mg/kg	1	10–20	Dyspnea, neutropenia, thrombocytopenia, elevated LFTs; recovered	Transbronchial, liver, and bone marrow biopsies
6	11/M	CD	Infliximab	5 mg/kg	2	5–10	Fever, sinusitis, interstitial pneumonitis, history of acute HC exposure; recovered	Open lung biopsy
7	19/M	CD	Infliximab	5 mg/kg	2	130–150	Fever, cough, night sweats, hepatosplenomegaly, anemia, thrombocytopenia; recovered	Liver and bone marrow biopsies; liver and urine cultures
8	38/M	CD	Infliximab	5 mg/kg	5	150–180	Fever, malaise, cough, myalgia, neutropenia, pulmonary nodules, DIC; recovered	Transbronchial biopsy; blood culture
9	42/M	CD	Infliximab	5 mg/kg	2	50–60	Fever, cough, pulmonary nodules, elevated LFTs, pancytopenia, DIC; recovered	Transbronchial biopsy; blood culture
10	38/M	RA	Etanercept	25 mg	95	320–350	Fever, malaise, weight loss, elevated LFTs, pancytopenia; recovered	Blood IgM anti-HC; urine HC antigen

* Patients 1 and 7 were previously described (see refs. 7 and 8, respectively). In patient 2, histoplasmosis was more indolent than in the other 9 patients; he required hospitalization only for bronchoscopy and biopsy, after which he was managed successfully with itraconzaole as an outpatient; tissue histopathology was interpreted initially as idiopathic bronchiolitis obliterans and organizing pneumonia (BOOP) before a definitive diagnosis of histoplasmosis was made. In patient 4, underlying medical conditions included carcinoma of the breast (treated in 1984), large cell lymphoma of the kidney (treated in 1988), and chronic renal insufficiency; she was treated with itraconazole to avoid possible renal toxicity associated with amphotericin B therapy. In patient 6, fistulizing CD improved remarkably with a single dose of infliximab; he reported that within 24 hours of cleaning an old barn that housed many pigeons, he began to experience fever that was unresponsive to antibiotics; his rapidly deteriorating condition required management in an intensive care unit; he was treated with amphotericin B and recovered. Patient 10 had the only case of etanercept-associated histoplasmosis reported to the FDA as of August 2001; in addition to etanercept, he had received concomitant immunosuppressive medications, including methotrexate and prednisone; he recovered following itraconazole therapy. RA = rheumatoid arthritis; CXR = chest radiographic findings; CHF = congestive heart failure; LFTs = liver function test results; CD = Crohn's disease; HC = *Histoplasma capsulatum*; DIC = disseminated intravascular coagulopathy.

† When >1 dose was given, the approximate time interval (in days) to clinical presentation was measured from the first dose.

to 6 months after receiving the first (or only) dose of infliximab. One case of histoplasmosis associated with use of etanercept was reported: a 38-year-old man (patient 10) developed disseminated histoplasmosis after 11 months of etanercept therapy.

All patients had received at least 1 immunosuppressive medication (e.g., prednisone, methotrexate, and/or azathioprine) in addition to infliximab or etanercept. All resided in states known to be endemic for histoplasmosis: Ohio (2 patients), Tennessee (2 patients), and Alabama, Iowa, Indiana, Kentucky, Louisiana, and Wisconsin (1 patient each) (Figure 1). Nine patients required aggressive treatment in an intensive care unit; 1 patient (patient 2) was successfully managed as an outpatient. A definitive diagnosis of histoplasmosis was based on results of blood cultures or tissue biopsies of lung, liver, and/or bone marrow.

DISCUSSION

This case series of 10 patients suggests that histoplasmosis may be an important complication of

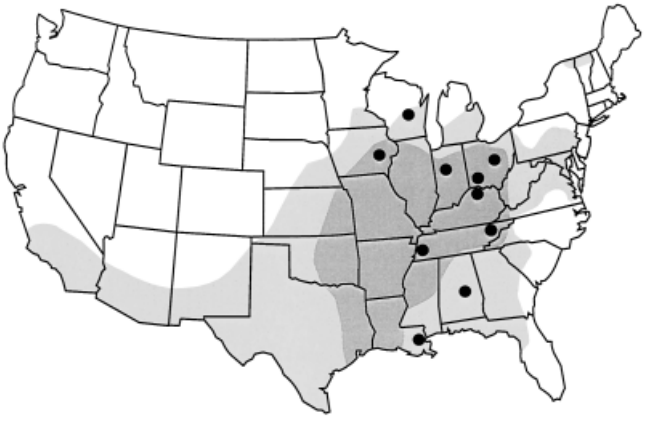

Figure 1. Endemic areas of histoplasmosis in the continental US, based on skin testing, and locations of cases reported in this series. Skin reactivity to histoplasmin was assessed among Navy recruits from the continental US from 1958 through 1969 by Edwards et al (9). Light gray shading indicates the approximate geographic areas with at least 10% prevalence of positive histoplasmin skin test reactivity (induration ≥4 mm diameter), and dark gray shading indicates the approximate areas with at least 60% prevalence. Circles indicate the general locations of the 10 cases in our series.

treatment with TNFα-neutralizing agents, particularly infliximab. The clinical presentation of histoplasmosis (pulmonary, extrapulmonary, or disseminated) may mimic some of the nonspecific signs and symptoms of a patient's underlying RA or CD, which may delay recognition and treatment. When monitoring for complications of TNFα antagonist therapy, early consideration of histoplasmosis in patients who reside in HC-endemic geographic areas may reduce morbidity and mortality. In the US, the most highly endemic areas are in the Ohio and Mississippi River valleys, although HC has also been identified outside of these areas, such as in the northern parts of New York and Vermont (9) (Figure 1).

HC is transmitted by inhalation of mycelial fragments and microconidia of the organism after disturbance of contaminated soil. HC infection is frequently asymptomatic and is generally self-limited in the normal host. Immunocompromised individuals (e.g., persons with cancer, human immunodeficiency virus infection, or those receiving immunosuppressive therapy) who are exposed to HC are at high risk for developing symptomatic histoplasmosis (10,11). Macrophages play a key role in cell-mediated immunity against HC infection. Activated macrophages elaborate a diverse array of cytokines, present microbial antigens to T cells, recruit other immune cells, and serve as the major final effector cells that destroy intracellular HC. Key cytokines identified in mediating the coordinated response against HC include TNFα, interferon-γ, interleukin-3 (IL-3), IL-4, IL-10, IL-12, and granulocyte–macrophage colony-stimulating factor (4,10–14). Thus, inhibition of TNFα activity may also affect the activity of other cytokines.

Because infliximab and etanercept inhibit TNFα activity through different mechanisms, the risk for developing histoplasmosis associated with these 2 agents might also differ. In addition, infliximab, but not etanercept, has been shown in vitro to lyse TNFα-expressing cells (3,15). Furthermore, a recent study suggested that infliximab may induce apoptosis of peripheral monocytes in patients with active CD (16). Thus, it is possible that administration of infliximab may induce lysis of monocytes and macrophages, thereby affecting cytokine secretion or other functions of these cells.

As with all passive surveillance systems, use of the AERS database to detect drug-associated risks is limited by underreporting, the possible presence of unrecognized confounding factors, and the potential for inclusion of coincidental events that are only temporally, not causally, related to the suspect drug. Multiple cases of histoplasmosis have been reported in patients taking methotrexate (17–19) or other immunosuppressive medications frequently used in the treatment of RA and CD. However, the incidence of histoplasmosis in RA and CD patient populations has not been estimated, and it is not known whether RA or CD may be independent risk factors for developing histoplasmosis.

In our case series, 9 of the 10 patients had received infliximab. Through August 2001, ~150,000 patients in the US had been treated with infliximab: ~51,000 (34%) were treated for RA, and ~99,000 (66%) were treated for CD (Centocor, Malvern, PA: personal communication). Through April 2001, ~96,500 patients in the US had been treated with etanercept for RA (Immunex, Seattle, WA: personal communication). In our series, histoplasmosis was reported in 9 patients treated with infliximab (~6 of 100,000) and in 1 patient treated with etanercept (~1 of 100,000).

The observed difference in the reporting rates suggests that patients treated with infliximab may be at higher risk for developing histoplasmosis compared with patients treated with etanercept. Comparisons of reporting rates must be interpreted cautiously, because these rates may be subject to unknown biases (either positive or negative); nonetheless, they may represent a "signal" for further investigation. Other factors that may also have contributed to the observed difference include 1) the use of methotrexate concurrently with infliximab, as

indicated for RA on the product label, but not necessarily with etanercept; 2) the duration of immunosuppression may be more prolonged with infliximab; 3) infliximab-treated patients may be more immunosuppressed than are etanercept recipients for reasons unrelated to the 2 agents; and 4) the efficiency of reporting adverse events associated with infliximab and etanercept may be different.

Consistent with the potential immunosuppressant effects of TNFα antagonists has been the emergence of certain infectious complications associated with these products. In a published series of cases based on the FDA AERS database, through May 29, 2001, tuberculosis was reported in 70 patients treated with infliximab and in 9 patients receiving etanercept (20). Through November 30, 2001, the FDA received 117 reports of infliximab-associated tuberculosis (21). The manufacturer of infliximab added a "Boxed Warning" to the labeling of the product in October 2001, recommending that patients should be evaluated for latent tuberculosis, including a tuberculin skin test, before initiating therapy with infliximab, and that treatment of latent tuberculosis be started before therapy with infliximab. Acute life-threatening histoplasmosis should also be recognized as a potential complication of treatment with TNFα-neutralizing agents, particularly infliximab, in patients who reside in geographic areas where HC is endemic. Because of this potential, a new warning was added to the package insert of infliximab, indicating that for patients who have resided in HC-endemic areas, the risks and benefits of infliximab treatment should be carefully evaluated before beginning treatment.

In our series, we were unable to determine the proportion of patients in whom histoplasmosis represented reactivation of latent infection, acute primary infection, or reinfection. A discussion regarding avoidance of activities related to risks of HC exposure, such as frequent exposure to soil (e.g., cleaning chicken coops, disturbing soil beneath bird-roosting sites) and exploring caves (22), should be considered in patients receiving TNFα antagonists who reside in HC-endemic areas. Health care professionals are encouraged to report clinically important adverse events to the FDA MedWatch program (1-800-FDA-1088 or http://www.fda.gov/medwatch) in order to further define the occurrence of histoplasmosis or other complications associated with use of TNFα antagonists.

Addendum. Since the time this manuscript was written, there were 12 additional cases of histoplasmosis in the US associated with anti-TNFα therapy, resulting in a total of 22 cases through May 31, 2002. Of these 12 new cases, 10 were associated with infliximab (9 patients had arthritis [including 2 with psoriatic arthropathy], and 1 had CD); 2 were associated with etanercept (both patients had RA). Four deaths occurred: 3 were associated with infliximab, and 1 was associated with etanercept. The patients resided in the following states: Indiana (2 patients), Minnesota (2 patients), Kentucky (2 patients), and Maryland, Michigan, Missouri, Ohio, Tennessee, and Texas (1 patient each). The clinical presentation of these patients was similar to the presentations reported in Table 2, except for 1 patient who was diagnosed as having granulomatous hepatitis without evidence of other organ involvement. In addition to the cases occurring in the US, the FDA has received reports of 2 cases of infliximab-associated histoplasmosis occurring outside of the US: 1 from Canada and 1 from Switzerland.

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