OBSERVATION

Fatal Influenza A(H1N1) Respiratory Tract Infection in a Patient Having Psoriasis Treated With Infliximab

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Background: The use of biologic agents represents a remarkable advance for patients with psoriasis and psoriatic arthritis who have experienced an incomplete response to other therapeutic modalities. Decreased mortality and improved quality of life have been reported in patients undergoing treatment with these agents. Increased risk of bacterial, viral, granulomatous, and opportunistic infections also has been associated with the use of these medications. Enhanced patient education, watchful monitoring to promote early detection of infections, discontinuation of the medication when clinical symptoms are identified, and immediate availability of supportive care are advised to balance the benefit of treatment with biologic agents against the potential risk of infection. Herein, we discuss the risk of infection and the monitoring and vaccination guidelines in patients having psoriasis treated with biologic agents.

Observations: A woman with obesity and psoriasis that had previously been successfully treated with efalizumab (Raptiva) for 3 years was started on a regimen of infliximab (Remicade) to treat a flare. She died 1 week after her first infusion of infliximab and was found to have had influenza A(H1N1).

Conclusions: We report the first case to date of a patient with psoriasis who died of influenza A(H1N1) respiratory tract infection while undergoing treatment with infliximab. Further observations are needed to make a causal association.

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TUMOR NECROSIS FACTOR (TNF) is a proinflammatory cytokine produced predominantly by macrophages and T cells that facilitates the onset of a broad spectrum of biologic activity that enhances the inflammatory response and the body’s ability to defend itself against infection. Treatments targeted against TNF represent a remarkable advance in improving the clinical symptoms and in possibly slowing the progression of several diseases.

Elevated levels of TNF have been detected in the serum and the epidermis of psoriatic plaques, in the serum and synovial fluid of patients with rheumatoid arthritis and those with ankylosing spondylitis, and in the serum and gut mucosa of patients with Crohn disease. Elevated TNF levels at the sites of inflammation are the direct cause of tissue damage. Tumor necrosis factor levels are also elevated systematically in these chronic inflammatory diseases. Herein, we report a fatal case of influenza A(H1N1) in a patient with obesity and extensive psoriasis who was found dead 1 week after her initial infusion of infliximab (Remicade) to treat a flare.

REPORT OF A CASE

A 55-year-old woman with psoriasis since childhood had failed treatment with numerous topical therapies. Weighing 94 kg, the patient was obese, with a body mass index (calculated as weight in kilograms divided by height in meters squared) of 49.3. She had an excellent clinical response to efalizumab (Raptiva) therapy, which was administered at a dose of 1 mg/kg of body weight per week for 3 years. She was encouraged to consider other options after reports of cases of progressive multifocal leukoencephalopathy in patients who had been using the medication for more than 3 years. Efalizumab therapy was discontinued, and the patient experienced a severe flare in her psoriasis several weeks later. Because of her weight and data demonstrating lesser responses of psoriasis to other biologic agents, infliximab was initiated at a dose of 5 mg/kg as a therapeutic agent. Friends of the decedent reported that the patient had experienced upper respiratory tract symptoms 4 days after the infusion. She was then discovered dead in her home 1 week after her initial infusion with inflix-
imab. While using biologic agents for her psoriasis, she had received yearly inactivated influenza vaccines and purified protein derivative (PPD) skin tests.

An autopsy revealed no external signs of trauma. Important findings included an enlarged heart and granular kidneys, consistent with chronic hypertension. The larynx and trachea exhibited areas of ulceration with tan-yellow exudate, and the lungs were markedly congested and edematous (2250 g) with scattered areas of firm and hemorrhagic parenchyma. Histologic sections of the lungs revealed vascular congestion and intraparenchymal hemorrhage with hyaline membrane formation, increased interstitial and airspace cellularity, type II pneumocyte hyperplasia, and focal intraalveolar fibrin deposition. These findings were consistent with diffuse alveolar damage, the pathologic correlate of severe acute respiratory syndrome. The laryngeal and tracheal mucosa exhibited acute and chronic inflammation with ulceration, as well as fibrinous exudate and cellular debris, consistent with a necrotizing process. Given the recent outbreak of influenza A(H1N1) in the area and the gross pulmonary findings in the case, there was a high suspicion of this influenza in the patient. Nasopharyngeal swabs were tested by polymerase chain reaction and were positive for novel influenza A(H1N1).

COMMENT

Tumor necrosis factor blockers have demonstrated remarkable results in improving the clinical symptoms of rheumatoid arthritis, psoriatic arthritis, and psoriasis and in inhibiting the progression of disease in patients with rheumatoid arthritis. Sustained and significant increases in physical function and quality-of-life measures have been observed in patients treated with these medications. This improvement has resulted in clinically meaningful functional benefits that include fewer disabilities, higher employment rates, and lower health care costs.

Studies report an increased incidence of serious infections associated with the administration of biologic therapy (anti-TNF agents).

Patients having rheumatoid arthritis treated with TNF antagonists have dramatically decreased mortality, as well as significant and clinically relevant improvement in physical function and quality of life, inhibition of progressive disease, and sustained improvement in the signs and symptoms of inflammation. The British Society for Rheumatology Biologics Register reported a marked reduction in the incidence of myocardial infarction among patients receiving anticytokine agents. A Scandinavian registry reported that treatment with TNF blockers is associated with a 50% lower incidence of first cardiovascular events among patients with rheumatoid arthritis.

The startlingly high 50% decrease in 5-year mortality from cardiovascular events among patients with rheumatoid arthritis who have received TNF blockers compared with other therapies must be balanced against the anticipated adverse effects of these biologic agents, which decrease inflammation and immune response. Although an increase in infections and malignant neoplasms has been reported, the incidence has not reached sufficient clinical significance to decrease the overall mortality rate among patients receiving these medications.

Bongartz et al reported a significant increase in serious infections among patients treated with TNF antagonists, as well as a dose-dependent increase in the risk of malignant neoplasms. Pharmacokinetic investigations have demonstrated that infliximab dosages higher than 3 mg/kg every 8 weeks lead to a high risk of overexposure, with an excessive binding of TNF. Nestorov suggested that lower dosages of the medication should be preferred based on a review of the published clinical trials, which demonstrated a statistically insignificant difference in clinical efficacy between low-dose anti-TNF antibody treatment (adalimumab, 20 mg every other week, or infliximab, 1 mg/kg every 4 weeks) and the substantially higher recommended dosages. Factors that need to be considered in determining the final dosage include medical history, clinical response to previous therapeutic agents, degree of disability, and disease progression. However, Nestorov did not consider the development of antichimeric antibodies, which have been shown to increase in patients treated with low-dose infliximab.

According to Listing et al, the German biologics register (RABBIT [German acronym for rheumatoid arthritis-observation of biologic therapy]) documented a 2.7 to 2.8 times higher incidence of serious infections among patients receiving biologic agents (etanercept or infliximab) compared with control subjects and a 3.3 to 4.1 times higher incidence of adverse events in general. Although almost one-third of the increase in the rate of adverse events could be attributed to differences in individual patient characteristics (eg, age, disease severity, comorbid conditions, and exposure to other immunosuppressive drugs), most of the increase was likely caused by the use of TNF inhibitors. Susceptibility to all types of infections is higher among patients receiving anti-TNF therapy, but the highest incidences of infections are for sepsis, urinary tract infections, bone and joint infections, lower respiratory tract infections (especially pneumonia), bacterial skin infections (erysipelas), and subcutaneous tissue infections. The rate of serious infections associated with the use of biologic agents documented by Listing et al is similar to rates reported by others.

Patients receiving TNF antagonists have chronic inflammatory disease and are already predisposed to infections. This risk increases with age, disease severity, immunosuppression from other therapeutic modalities, and other comorbid conditions. The suggestion that the risk is higher for bacterial infections than for viral infections is anecdotal and requires further confirmation.

In Spain, the risk of tuberculosis was reported to be increased 20-fold among patients treated with infliximab vs control subjects. The risk of granulomatous infection is higher among patients treated with the monoclonal TNF antibodies infliximab and adalimumab than with the soluble TNF receptor fusion protein etanercept; this difference is explained by the different modes of action. The Spanish registry disclosed a 78% decrease in the rate of active tuberculosis among patients treated with biologic agents after screening and management guidelines for latent tuberculosis were initiated.
Our patient described herein was screened by PPD testing before initiation of treatment with a biologic agent, and she was subsequently screened on an annual basis. All PPD test results were negative.

Increased bacterial, viral, granulomatous, and opportunistic infections have been reported in patients receiving TNF antagonists. The desired mechanism of action in TNF antagonists that exerts powerful anti-inflammatory effects, which minimize the symptoms, severity, and progression of inflammatory disease, also blunts the inflammatory response to infection. In addition to older subjects, patients at high risk of developing serious infections include those receiving glucocorticosteroids and those having chronic disorders, more severe manifestations of disease, and comorbid conditions (eg, diabetes mellitus, heart disease, and obesity).

Our patient had developed biopsy specimen–documented herpes zoster during treatment with efalizumab. The literature about the risk of infections in patients treated with TNF antagonists predominantly discusses bacterial infections and tuberculosis. To our knowledge, fewer data are available about the incidence of viral infections among these patients. Herpes zoster has been one of the more commonly reported adverse effects of anti-TNF agents. Strangfeld and Listing observed that treatment with the monoclonal anti-TNF antibodies adalimumab and infliximab is associated with an increased risk of herpes zoster. This risk was independent of age, disease severity, or glucocorticosteroid use and was absent in patients treated with the receptor fusion protein etanercept. The increased risk of herpes zoster due to inflammation associated with disease vs due to treatment with immunosuppressive drugs could not be distinguished in their study.

Several reports of bacterial infection followed by fatal sepsis have heightened concern about the use of TNF antagonists. However, the few randomized controlled trials available are underpowered, and definitive conclusions about the association between sepsis and TNF antagonist treatment cannot be made. In our patient, the temporal relationship and the fact that infliximab is immunosuppressive (with data showing increased upper and lower respiratory tract infections) raise the suspicion of a causal relationship, but no conclusion can be made solely based on this case report.

The recent global presentation of influenza A(H1N1) heightens concern among physicians that this virus may increase the risk of serious infections in patients undergoing treatment with TNF antagonists. The potential for the fast spread of this virus among susceptible populations and the difficulties in developing a vaccine and initiating an inoculation program against this rapidly mutating entity may pose a significant danger to patients receiving this class of medication.

The Medical Board of the National Psoriasis Foundation has set forth guidelines for monitoring and vaccinating patients treated with biologic agents for psoriasis. Intensive patient education to heighten awareness about early symptoms of infection and careful monitoring of patients treated with these medications are essential. Early detection of infection by routine history and physical examination and the initiation of immediate supportive care are critical because the sign-symptom complex may be blunted secondary to the anti-inflammatory effects of these medications. Tumor necrosis factor antagonists should be discontinued when there is clinical suspicion of an infection and should not be reinitiated until the condition of the patient is stabilized.

Evidence is lacking about whether vaccination is effective in preventing serious infections among patients treated with biologic agents, nor is there convincing evidence that vaccination is ineffective. Package inserts for biologic agents give recommendations about vaccination. Before administration of biologic agents, standard vaccines should be administered when appropriate, including the following: tetanus, human papillomavirus, varicella, herpes zoster, influenza, pneumococcal, hepatitis A and B, meningococcal, and measles-mumps-rubella. Thereafter, patients should receive an annual inactivated influenza vaccine.

We are uncertain whether the outcome in the case reported herein would have been better if the patient had received influenza A(H1N1) vaccination before infusion of infliximab (this vaccine was unavailable before her death). With respect to antiviral therapy, given the outcome of this case it may be prudent to advise patients receiving biologic agents to report any upper respiratory tract symptoms early and to consider treatment with antiviral agents such as oseltamivir (Tamiflu). Further observations and studies are needed to make any conclusions.

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