Ask the Expert

Bacterial Infection Risk With TNF-α Therapy

Serious infection as a consequence of disease-related immune system changes and immunosuppressive therapy is a major cause of increased morbidity and mortality in patients with rheumatoid arthritis. Recent media attention has generated substantial interest, in particular in the relationship between bacterial infection risk and tumor necrosis factor–α (TNF-α) antagonists among patients being treated for rheumatoid arthritis.

JEFFREY R. CURTIS, M.D.

The TNF-α cytokine, which is implicated in the synovial inflammation characteristic of rheumatoid arthritis, has a role in controlling systemic infection. As such, it has been hypothesized that blocking TNF-α might lead to an increased rate of intracellular bacterial infection above and beyond the risk observed with older anti-inflammatory and immunosuppressive agents, according to Dr. Jeffrey R. Curtis of the University of Alabama, Birmingham.

The results of recent clinical trials of anti-TNF-α treatment in rheumatoid arthritis have been inconsistent regarding the question of increased infection risk. "Some [of the trials] have demonstrated no increased risk, some have indicated a possible increased risk, and some have demonstrated a statistically significant risk," said Dr. Curtis, who along with colleagues at the University of Alabama and the Center for Health Care Policy and Evaluation in Eden Prairie, Minn., sought a more definitive answer in a retrospective cohort study of rheumatoid arthritis patients from a large U.S. health care organization taking TNF-α blockers (Arthritis Rheum. 2007;56:1125-33).

The investigators compared the incidence of serious bacterial infections among 2,393 rheumatoid arthritis patients treated with TNF-α antagonists, often in conjunction with methotrexate, with that seen in 2,933 patients taking methotrexate alone. Over a median 17-month follow-up, the rate of hospitalization with a confirmed bacterial infection was 2.7% in the TNF-α antagonist group and 2.0% in the methotrexate-only group. "The adjusted hazard ratio of infection among the patients who received TNF-α antagonists was 1.9 [compared with the methotrexate-only patients]," said Dr. Curtis, noting that the incidence of infection was highest within the first 6 months of treatment initiation. "There was a fourfold increased risk of serious infection during this period," he said.

In this month's column, Dr. Curtis discusses the findings of this study and how they should impact the clinical management of patients taking TNF-α antagonists.

Rheumatology News: What is the clinical significance of the increased risk of infection associated with anti-TNF-α therapy reported in your investigation?

Dr. Curtis: Overall, we found about a twofold increased risk of hospitalization for serious infection in the anti-TNF-α users, however, it's important to realize that it's still a relatively small risk—only about three infections per hundred patients. This is similar to the infection risk associated with high-dose steroid use in this population. There's been a lot of attention given to the fact that the relative risk of infection is about double [compared with methotrexate-only patients], but it's two times a fairly small absolute risk.

RN: Why is the risk of infection much higher within the first 6 months of treatment?

Dr. Curtis: There are several possibilities. If a patient gets an infection early in treatment, the doctor is going to stop the drug, essentially weeding out high-risk patients. It is also possible that dosing schedules are important. For example, infliximab is typically given via an induction dosing regimen, whereby the dosing at 0, 2, and 6 weeks is much higher than the subsequent maintenance dosing. As with high-dose steroids, higher doses of anti-TNF-α drugs may open the door to infections.

RN: Which patients are vulnerable to infections related to anti-TNF-α therapy?

Dr. Curtis: Patients with diabetes, chronic kidney disease, chronic obstructive pulmonary disease, older patients and those taking higher doses of prednisone are at greatest risk of infection in general. These risk factors are not unique to those patients treated with TNF-α blockers. In our study, pneumonia accounted for about one-third of cases, followed by cellulitis, soft tissue infections, kidney infections, and bacteremia.

RN: Does the occurrence of a serious bacterial infection preclude continued and/or future use of the TNF-α antagonist?

Dr. Curtis: That's a physician's call because there is no consensus or guidelines. In fact, our group at the University of Alabama has been charged by the American College of Rheumatology with the task of developing guidelines, to be released later this year, for rheumatoid arthritis patients receiving biologics. Right now, the general perception is that the [TNF-α antagonist] should be stopped until the infection is treated and cleared. Many physicians feel comfortable then reinitiating treatment, unless the infection was life threatening. Clearly, the risk of potential harm has to be balanced with the benefit of treatment, and unfortunately there is a paucity of data to answer this question.

RN: The increased infection risk has led to the recommendations for early, aggressive treatment of infections to prevent bad outcomes. Might this lead to potential overtreatment of noninfectious conditions with symptoms that mimic those of early infection and, at the same time, unnecessary discontinuation of effective anti-TNF-α treatment?

Dr. Curtis: It is possible. One concern that is often mentioned is the possibility that a patient or physician might mistake an injection-site reaction—a welt or a wheal—for cellulitis, and as a result stop the anti-TNF-α drug and begin treating the infection, although I think it's unlikely. In contrast, it is perhaps more clinically relevant for early symptoms of a soft tissue infection to be ascribed to just an injection-site reaction, which is why we recommend vigilant monitoring for signs of infection in these patients.

RN: What are the important clinical implications of the increased risk of infection regarding the management of rheumatoid arthritis patients on anti-TNF-α treatment?

Dr. Curtis: It's really about risk-management. First, make sure patients are up to date with their immunizations for influenza and pneumonia before initiating immunosuppressive treatment (including glucocorticoids). Also, [purified protein derivative] testing for tuberculosis should be ordered and depending on individual patient risk, a chest x-ray may be useful. It's also imperative to talk with patients about the fact that if they are on immunosuppressive agents, they need to have a lower threshold about when to call the doctor to report fever or early signs of infection. It's especially important to monitor for signs of infection shortly after treatment has started. ■

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By Diana Mahoney, New England Bureau

Systemic Fibrosis Risk Earns Contrast Agents Boxed Warning

BY ELIZABETH MECHCATIE
Senior Writer

The Food and Drug Administration has requested that a boxed warning explaining the increased risk of nephrogenic systemic fibrosis in patients with renal insufficiency be added to the labels of gadolinium-based contrast agents, according to an alert posted on the agency's MedWatch Web site.

Joint pain is a common finding in patients who develop nephrogenic systemic fibrosis.

The FDA has requested that the manufacturers add this information to the warnings section of the prescribing information of the five marketed gadolinium-based contrast agents (GBCA), which are used to enhance the quality of magnetic resonance imaging.

The risk of nephrogenic systemic fibrosis (NSF) has been associated with exposure to these agents in patients with acute or chronic severe renal insufficiency (glomerular filtration rate less than 30 mL/min per 1.73 square meters) and in patients with acute renal insufficiency of any severity due to the hepatorenal syndrome or in the perioperative liver transplantation period, according to the FDA.

"Healthcare professionals should avoid the use of a GBCA in these patients unless the diagnostic information is essential and not available with noncontrast enhanced magnetic resonance imaging," according to the alert. No cases of NSF have been reported in patients with normal kidney function, or mild to moderate kidney insufficiency.

The agency is advising patients be screened for kidney problems before they receive one of the imaging agents, and the recommended dose should not be exceeded.

Physicians should consider having hemodialysis patients undergo the procedure promptly after a GBCA is administered, according to the FDA. Clearance rates of GBCA have been reported to be as high as 99% after three hemodialysis sessions, although it is not known whether hemodialysis prevents NSF.

NSF—a debilitating and potentially fatal disease identified in 1997, which affects the skin, muscle, and internal organs—has been reported only in patients with acute or chronic severe renal insufficiency. Signs and symptoms include joint stiffness and pain deep in the hip as well as limited range of motion in the arms, legs, hands, or feet.

Whether the risk of NSF is similar for all the agents is not known. Postmarketing reports show that Omniscan (manufactured by GE HealthCare) is the most commonly reported agent, followed by Magnevist (Bayer Schering Pharma) and OptiMark (Mallinckrodt).

GBCAs are used off label for magnetic resonance angiography (MRA), but "some radiologists believe that these agents help provide detailed images of blood vessels," according to the FDA.

The FDA first notified health care professionals about this risk in June 2006, after learning about 25 such reports in Denmark, and updated the information on the risk in December 2006. ■

More information is available at www.fda.gov/medwatch/safety/2007/safety07.htm#Gadolinium. Report adverse reactions to GBCAs to FDA's MedWatch program at www.fda.gov/medwatch.