Follow-Up Extended to 2013

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ly equally effective, with about 75% of patients achieving a good response with the first TNF-alpha drug they use,” he said. “Additionally, there has been some interesting information about switching, in that approximately 50%-60% of patients who failed their first TNF-alpha blocker seem to get a good response when they switch to another one, so we’re pretty encouraged by that.”

With respect to adverse events, “by and large, the side effect profile has been pretty much what we would have expected, but there have been one or two quite interesting and rather uncommon side effects.” One of these has been the onset of psoriasis in a small percentage of patients who received anti-TNF therapy for other rheumatoid diseases, but who had no known history of psoriasis. In a Phase II study, there was no unexpected finding, and the clear evidence demonstrating the efficacy of anti-TNF drugs in the treatment of both psoriasis and psoriatic arthritis, said Dr. Isenberg. The age- and sex-adjusted incidence ratio for new-onset psoriasis in the anti-TNF-alpha-treated patients through 2006 was increased, although not significantly, compared with DMARD-treated patients, he said.

When considered by agent, the increased rate ratio was significant for adalimumab (8.4), but not for etanercept and infliximab (2.7 and 3.7, respectively).

The median time to onset of psoriasis in these patients was 6 months, and in most of the patients, the psoriasis improved once anti-TNF treatment was stopped. Dr. Isenberg said in an interview. Although the exact mechanism for the paradoxical onset of psoriasis is unknown, it’s possible that TNF-alpha inhibitors might promote an inflammatory autoimmune process in a select group of genetically predisposed patients, he noted.

The BSRR has also been the source of good news about potential side effects, particularly the findings that anti-TNF-alpha therapy does not increase the risk of myocardial infarction in the short term, and that it may reduce the risk of cerebrovascular disease in the long term. Dr. Isenberg said, “Among patients who respond to TNF-alpha-blocking drugs, the frequency at which cardiovascular infarction occurs is falling. This is especially encouraging because patients with rheumatoid arthritis are at increased risk for myocardial infarction.”

The registry has yielded encouraging data: About 75% of patients respond to the first anti-TNF they take and half of those who fail one biologic agent respond to a second.

Vaccinations Are Key to Infection Control in TNF Blockers

BY PATRICE WENDLING

CHICAGO — Clinicians need to step up their use of vaccinations as part of an overall plan to reduce the risk of infection in patients with rheumatic disease who receive tumor necrosis factor inhibitors, Dr. John J. Cush said at a symposium sponsored by the American College of Rheumatology.

“We are not as good as we should be about vaccinating (patients), and they can really have a big impact by preventing serious infections, especially in our immunosuppressed patients,” he said.

Data from pivotal trials show that the risk of serious infectious events with the biologics is two times that with placebo. This trend has not reached statistical significance in many of the studies, but in the real world it becomes significant, said Dr. Cush, director of clinical rheumatology for the Baylor Research Institute and a professor of medicine and rheumatology at Baylor College of Medicine in Dallas.

He suggests that patients with rheumatoid arthritis (RA) should receive the yearly influenza vaccine, and that pneumococcal vaccinations should be given once, with a second dose 5 years later.

Vaccines for meningococcal disease, human papillomavirus, and hepatitis B are needed where exposure is likely, but it is important to avoid live attenuated vaccines.

The package inserts for several TNF inhibitors were also revised in 2007-2008, warning that tuberculosis has been observed with their use. Data from the British Society for Rheumatology Biologies Register on 10,403 patients taking anti-TNF agents need flu shots and other regular immunizations, attenuated vaccines should be avoided.

While patients need flu shots and other regular immunizations, attenuated vaccines should be avoided.

DR. CUSH

During the 2001-2002 season, the influenza vaccine was not recommended for patients receiving anti-TNF therapy, but the 2003-2004 season saw a change, with the Centers for Disease Control and Prevention recommending that they be vaccinated for infections such as pneumococcal pneumonia and meningococcal meningitis.

“Some of us have not been doing that,” Dr. Cush said. “The influenza vaccine is safe and effective and has minimal side effects. It is a good vaccine.”

Over the past five years, the rate of serious infections in patients receiving anti-TNF therapy has fallen. But while the risk is lower, the consequences of infection are more severe, Dr. Cush said.

For patients who have a history of TB or a positive purified protein derivative test, clinicians may want to consider using the QuantiFERON test, he said. There is no evidence to support waiting, he said, and in all cases of new-onset TB in patients, the symptoms or signs are suggestive of a mycobacterial infection. They need flu shots and other regular immunizations, attenuated vaccines should be avoided.

A study of 2,000 patients taking anti-TNF therapy who were initially anergic to conventional skin testing showed that 91% had positive responses to the QuantiFERON test, he said. Dr. Cush suggested that patients who had a positive skin test (5 mm or more) or a history of LTBI can be treated with TNF inhibitors immediately after TB therapy with isoniazid is initiated. Moreover, this practice is routine in some RA clinical trials.

Arguments for suspending anti-TNF therapy could include the belief that TB treatment confers protection, or that anti-TNF therapy may increase the potential for toxicity or may cause worsening of latent TB disease before treatment with isoniazid can start working. Dr. Cush contends that there are no data to support waiting, and although toxicity may be an issue, it can be identified early on by lab testing and physician observation. Reactivation of LTBI has not been shown to occur in anti-TNF-treated patients.

To drive home his point, Dr. Cush highlighted a study among Africans with HIV-associated TB in which eight doses of etanercept (25 mg) administered twice weekly beginning on day 4 of TB therapy actually improved TB killing and overall response, compared with control therapy (AIDS Res Hum Retroviruses 21:257-64).

Dr. Cush acknowledged that he would not use TNF inhibitors in RA patients who have invasive fungal disease or chronic hepatitis B, or in those infected with atypical mycobacteria. Clinicians should have safeguards and reminders in place to do PPD skin tests in all RA patients prior to TNF-inhibitor therapy and during year 2 (or when TNF-inhibitor therapy is changed), as this will occasionally pick up patients with latent TB who were initially anergic, he said.

There is no added yield to further annual testing, but the PPD skin test can be repeated if the patient has had a recent exposure, has traveled to a high-risk or endemic area, or has signs or symptoms of a mycobacterial infection.

PPD results are notoriously variable depending on who conducts the test, but results are good for 1-2 weeks, Dr. Cush said.

“It’s better to have a patient come back late rather than not at all,” he said. “The best PPD is the one done by you and read by you.”

As an alternative—or in addition—to conventional skin tests, clinicians may want to consider using the QuantiFERON TB test, which was approved by the Food and Drug Administration in 2001 and measures the release of interferon-gamma in whole blood in response to stimulation by a purified protein derivative. Roughly 10% of QuantiFERON testing is indeterminate, but in general, clinicians can “hang their hat on the results,” he said, noting that PPD tests may be positive in those with a history of bacille Calmette-Guérin (BCG) vaccination, whereas QuantiFERON is unaffected by BCG and more truly reflects the likelihood of latent TB infection.

There is no evidence to support the practice of suspending TNF-inhibitor use in the setting of nonserious infections, unless the symptoms or signs are suggestive of a mycobacterial infection, Dr. Cush said.

In a meta-analysis to be presented by colleague Dr. Kathryn Dao at the upcoming European League Against Rheumatism meeting in Copenhagen, the risk for nonserious infections was increased in patients with RA who received adalimumab (odds ratio, 1.39) or infliximab (OR, 1.53), but not etanercept (OR, 0.99).

“The magnitude is small, but we have to be mindful of these very common events and how they can be properly managed in patients receiving biologics,” he said.

Dr. Cush disclosed that he has been an advisor, consultant, or lecturer for Abbott Laboratories, Centocor Inc., Pfizer Inc., Roche, UCB SA, and Wyeth. He noted he has been a clinical investigator for or received research support from Celgene Corp., Genentech Inc., Pfizer, Roche, UCB, and the Consortium of Rheumatology Researchers of North America.