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 therapies for other rheumatoid diseases, but who had no known history of psoriasis—a particularly unexpected finding, given 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 rate 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 BSRBR 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 accident (CVA) in the short term, Dr. Isenberg said. "Among patients who respond to TNF-alpha–blocking drugs, the frequency at which myocardial infarction occurs is falling. This is especially encouraging because patients with rheumatoid arthritis are at increased risk for myocardial infarction," he explained.

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.

In analyses looking at the first 6 months of treatment with TNF-alpha blockers vs. DMARDs, the adjusted incidence rate ratios for MI and CVA, respectively, were 0.61 and 0.67. When the analysis was limited to patients with a EULAR good or moderate response, the rate ratio for MI was 0.28 (Arthritis Rheum. 2007;56:2905-12).

The register has provided some encouraging news about cancer risk as well, Dr. Isenberg noted. After adjustment for important cancer risk factors, data collected to date suggest that patients who take anti-TNF-alpha drugs have a comparable—or possibly lower—risk of developing cancers, relative to patients treated with DMARDS alone.

In analyses that focused on patients with a history of previous cancer, however, the risk for newly developing cancer, albeit rare, was increased among patients who received TNF inhibitors, he said.

As for what the future holds, "nobody knows what happens to patients who have been given TNF-alpha blockers for a long time, because they haven't been around that long," said Dr. Isenberg.

"With our plans to extend the follow-up to individual patients and linking it to cancer registers [in the United Kingdom], as well as continuing contact with the specialists looking after these patients, we will see what happens to these patients over much longer periods of time."

Dr. Isenberg reported having no financial relationships to disclose. ■

See related video at www.youtube.com/watch?v=QrETHuR0l4g.

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 vaccinations], and they can really have a big impact by preventing serious infections, especially in our immunosuppressed patients," he said.

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

DR. CUSH

Data from pivotal trials show that the risk of serious infectious events with the biologics is two times that with placebo. This trend did not reach 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 Biologics Register on 10,403 patients taking anti-TNF agents and 3,106 patients taking only disease-modifying antirheumatic drugs identified 35 cases of tuberculosis, all occurring in patients on anti-TNF agents. The TB rate was 110 per 100,000 patient-years in anti-TNF-treated patients, putting them above the rate for the general U.K. and U.S. populations (6 per 100,000 patient-years) and on par with alcoholics and patients with HIV, Dr. Cush said.

Manufacturers of anti-TNF agents advise clinicians to employ tuberculosis skin testing (purified protein derivative tuberculin) prior to initiating therapy; to monitor for signs and symptoms of TB, even if the initial PPD was negative; and to initiate latent tuberculosis infection (LTBI) treatment prior to TNF therapy.

Dr. Cush suggested that patients with 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 infection 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 responses, compared with control therapy (AIDS 2004;18:257-64).

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 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 more serious 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 adviser, 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. ■