TNF Blockers Tied to Hospitalization for Zoster

BY SHARON WORCESTER

FROM THE ANNALS OF RHEUMATIC DISEASES

Rheumatic disease patients who are exposed to tumor necrosis factor antagonists have a 10-fold increased risk of hospitalization for varicella zoster virus infections, compared with the general population, according to a secondary analysis of two large databases.

Nonetheless, the absolute incidence of varicella-related hospitalizations remains low at about three cases per 10,000 person-years of exposure, and the risks of using vaccination for prevention likely outweigh the benefits, Dr. Ignacio Garcia-Doval of Complexo Hospitalario de Pontevedra (Spain) and colleagues reported.

The estimated incidence rate of hospitalization for shingles in the rheumatic population was 32 cases per 100,000 patient-years, compared with an expected rate of 3.4 in the general population, and the estimated incidence of hospitalization for chickenpox in the rheumatic patients was 26 per 100,000, compared with 1.9 in the general population.

This finding is based on analysis of data from a national registry of rheumatic disease patients who were treated with TNF agents (BIOBADASER database) and from a database of all hospital admissions in public centers in Spain (Conjunto Minimo Basico de Datos al Alta Hospitalaria, or CMBD), which together represent more than 114 million patient-years.

The estimated age- and sex-standardized incidence rate per 100,000 person-years, and the estimated standardized incidence difference were 9 and 26, respectively, for shingles, and 19 and 33, respectively, for chickenpox, they said (Ann. Rheum. Dis. 2010;69:1751-5).

TNF antagonists are associated with an increased risk of tuberculosis in particular and of opportunistic infections in general. There is a biological basis for an increased risk of viral infections, the investigators said, noting that although some studies have shown an increased rate of viral infection in TNF antagonist–treated patients, the clinical relevance of the increase is uncertain. The current study does not allow differentiation of the causes for the increased risk, but it does show that the absolute rate is low.

The researchers said it is unlikely that the cohorts received systematic vaccination against varicella zoster virus because the general health mandate in Spain was given in 2005 and only for children aged 11-14 years. "Standard guidelines for chickenpox vaccination probably apply to the population included in our study," they wrote.

However, shingles vaccine (an attenuated vaccine with a higher dose of antigen) could potentially lead to more side effects in an immunosuppressed population, they said.

For example, in a randomized trial of adults older than age 60 years, shingles vaccine was associated with 7 cases of severe adverse events and 14 cases of vaccine-related adverse events per 10,000 vaccinations, they noted.

"These vaccination-associated risks are similar in rate and severity to the risks of hospitalized infections in our study. Hence, shingles vaccination before starting a TNF antagonist may not be warranted at present," they wrote.

The investigators concluded that although vaccination in healthy children is warranted, it is not warranted in adults with "immunosuppression secondary to the baseline inflammatory disease and its complications." ■

VITALS

Major Finding: The estimated incidence rate of hospitalization for shingles in the rheumatic population was 32 cases per 100,000 patient-years, compared with an expected rate of 3.4 in the general population. The estimated incidence of hospitalization for chickenpox in the rheumatic patients was 26 per 100,000, compared with 1.9 in the general population. The absolute incidence of varicella-related hospitalizations remains low, at about 3 cases per 10,000 person-years of exposure.

Data Source: A secondary analysis of data from two large databases.

Disclosures: Various authors on the study reported serving on the advisory board for and/or receiving lecture fees or honoraria from Wyeth, Abbott, Schering-Plough, Roche, and/or Bristol-Myers Squibb.

VIEW ON THE NEWS

Vaccinate Prior to Anti-TNF Therapy

The rationale for zoster vaccination goes beyond the goal of simply preventing hospitalized herpes zoster. Vaccination in RA patients who are at least 60 years of age should be the standard of care before initiation of anti-TNF or other long-term immunosuppressive therapy.

Prospective data on the efficacy of herpes zoster vaccination, particularly in patients with RA, are lacking. But there is strong evidence for the protective effects of vaccination in adults aged 60 years and older.

DR. FURST

Given that patients with rheumatoid arthritis are at increased risk for herpes zoster and that vaccination with live viruses is contraindicated while biological therapies are used, it would make sense to target this group for vaccination before anti-TNF therapy is initiated.

The purpose of vaccination is not only to lower the risk of rare, serious manifestations of herpes zoster, but also to lower the risk of uncomplicated herpes zoster, which causes considerable morbidity.

Future studies should look at the potential benefits of vaccinating those younger than age 60 and those receiving other types of immunosuppressive therapy.

The opinions above are excerpted from an editorial accompanying the research report (Ann. Rheum. Dis. 2010;69:1735-7). KEVIN L. WINTHROP, M.D., *is in the department of infectious diseases at the Oregon Health and Science University, Portland.* DANIEL E. FURST, M.D., *is Carl M. Pearson Professor of Rheumatology at the University of California, Los Angeles. Dr. Winthrop reported receiving funding from the Agency for Healthcare Research and Quality for work on the manuscript, and receiving a grant from UCB Pharmaceuticals, as well as consulting fees from Amgen, Wyeth, and Genentech. Dr. Furst reported receiving research support for studies of abatacept, adalimumab, certolizumab, etanercept, infliximab, rituximab, and tocilizumab, and consulting with Abbott, Amgen, Bristol-Myers Squibb, Centocor, Genentech, and UCB.*

Europeans Collaborate to Improve Outcomes in Joint Disease

Musculoskeletal conditions rank third in top-10 causes of years lived with disability.

BY BRUCE JANCIN

EXPERT ANALYSIS FROM THE ANNUAL EUROPEAN CONGRESS OF RHEUMATOLOGY

The European Commission and the European League Against Rheumatism have joined forces in an ambitious 3-year project that is designed to optimize the care of patients with musculoskeletal conditions all across Europe.

The new European Musculoskeletal Conditions Surveillance and Information Network (www.eumusc.net) will set and monitor standards of care; gather more comprehensive data than heretofore available on the incidence, prevalence, and health impact of rheumatologic disorders; and create a Web-based information system for patients and physicians, project coordinator Dr. Anthony D. Woolf explained as he unveiled the program.

The eumusc.net project is funded by a grant of nearly 1 million euros from the European Commission along with 300,000 euros from EULAR. After the project ends in 2013, EULAR will take it over, according to Dr. Woolf, professor of rheumatology at the Institute of Health Care Research of Peninsula College of Medicine and Dentistry, Plymouth, England.

"The goal is to improve quality of care [and] to harmonize care so there is more equity across countries and within countries," the rheumatologist said. "Wherever you're being treated, you should have the same chance of doing well or going into remission."

'If a woman breaks a hip, she has the same life expectancy as a metastasized breast cancer patient.'

DR. SMOLEN

"We're not going to come up with new guidelines because we already have excellent guidelines for the management of osteoarthritis and rheumatoid arthritis from EULAR. It's time to get them implemented," he continued.

The eumusc.net project was granted funding by the European Union Health Program in a competitive bidding process. EU health officials were persuaded to make improved care for musculoskeletal conditions a high priority, in part on the strength of data showing that osteoarthritis is tied with disorders related to alcohol abuse for fourth place on the top-10 list of causes of years lived with disability in high-income countries.

Only unipolar depression, dementias, and adult-onset hearing loss ranked higher. Osteoarthritis was rated higher than cerebrovascular disease, chronic obstructive pulmonary disease, diabetes, and other major chronic diseases. These are the sorts of data that grab the attention of social security and health department officials.

In the United Kingdom, "musculoskeletal conditions are the No. 3 reason for general practitioner consultations. One can put a price on that, and it's very impressive," Dr. Woolf said.

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Although mortality may not be the best indicator of the societal impact of musculoskeletal disorders, Dr. Josef S. Smolen said it's a factor that should not be underestimated.

"If a woman breaks a hip, she has the same life expectancy as a metastasized breast cancer patient, and that's not sufficiently appreciated," observed Dr. Smolen, professor and chairman of rheumatology at the Medical University of Vienna, 1 of 23 European medical centers and patient organizations serving as partners in eumusc.net.

Dr. Alan J. Silman sounded a note of skepticism regarding eumusc.net, saying that the project sounds like an effort to "harmonize toward the mediocre."

"We should be encouraging diversity and variability." Harmonization as a goal "won't work" and "is not something we should ascribe to," argued Dr. Silman, professor of rheumatic disease epidemiology at the University of Manchester (England).

He observed that virtually all discussion of the eumusc.net project has focused on developing and monitoring standards of care and process measurement. Yet what constitutes good outcomes for patients with many rheumatic diseases hasn't been well established.

"I'm concerned that we're going to get lost in terms of process, numbers of people on drugs, or waiting times for [dual-energy x-ray absorptiometry] scans, or how quickly people go onto [anti–tumor necrosis factor] drugs in the south of Sweden," he said. "I just wonder if we're deluding ourselves if we think that if we have so many patients on biologics, that's the end of the story."

In the United Kingdom, "we've got the British Society of Rheumatology Biologics Registry, and we know from that [that] there's a substantial proportion of patients being maintained on biologic agents who've not had a clinical response. We can say, 'Look how wonderful it is that the number of patients on biologics is increasing,' but surely we're failing those patients who aren't having a clinical response, and we're not doing anything further, Dr. Silman said." ■

Disclosures: Dr. Woolf, Dr. Smolen, and Dr. Silman had no financial conflicts of interest that were relevant to the report.

IMPORTANT SAFETY INFORMATION FOR SIMPONI® (GOLIMUMAB) (continued from previous page)

HEART FAILURE

Cases of worsening congestive heart failure (CHF) and new-onset CHF have been reported. Exercise caution and monitor patients with heart failure. Discontinue SIMPONI® if new or worsening symptoms of heart failure appear.

DEMYELINATING DISORDERS

TNF-blocking agents, of which SIMPONI® is a member, have been associated with cases of new-onset or exacerbation of demyelinating disorders, including multiple sclerosis (MS) and Guillain-Barré syndrome. In SIMPONI® clinical trials, cases of MS and peripheral demyelinating polyneuropathy were reported. Exercise caution in considering the use of SIMPONI® in patients with these disorders. Consider discontinuation if these disorders develop.

HEMATOLOGIC CYTOPENIAS

There have been reports of pancytopenia, leukopenia, neutropenia, and thrombocytopenia in patients receiving SIMPONI® in clinical trials. Additionally, aplastic anemia has been reported in patients receiving TNF-blocking agents, of which SIMPONI® is a member. Exercise caution when using SIMPONI® in patients who have or had significant cytopenias.

USE WITH OTHER DRUGS

The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections, therefore the use of SIMPONI® in combination with these products is not recommended. A higher rate of serious infections has also been observed in RA patients treated with rituximab who received subsequent treatment with a TNF blocker. People receiving SIMPONI® can receive vaccinations, except for live vaccines.

ADVERSE REACTIONS

The most serious adverse reactions were serious infections and malignancies.

Upper respiratory tract infection and nasopharyngitis were the most common adverse reactions reported in the combined Phase 3 trials through Week 16, occurring in 7% and 6% of patients treated with SIMPONI® as compared with 6% and 5% of patients in the control group, respectively. The rate of injection-site reactions was 6% with patients treated with SIMPONI® compared with 2% of patients in the control group.

Cases of new-onset psoriasis, including pustular and palmoplantar, or exacerbation of pre-existing psoriasis have been reported with the use of TNF blockers, including SIMPONI®. Some of these patients required hospitalization. Most patients had improvement following discontinuation of the TNF blocker. Discontinuation of SIMPONI® should be considered for severe cases and those that do not improve or that worsen despite topical treatments.

Please see Brief Summary of Prescribing Information for SIMPONI® on following pages.

References: 1. SIMPONI® (golimumab) Prescribing Information. Centocor Ortho Biotech Inc. **2.** Keystone E, Genovese MC, Klareskog L, et al. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the *GO-FORWARD* study. *Ann Rheum Dis.* 2010;69:1129-1135. **3.** Data on file. Centocor Ortho Biotech Inc.**4.** Keystone EC, Genovese MC, Klareskog L, et al. Golimumab, a human antibody to tumour necrosis factor α given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. *Ann Rheum Dis.* 2009;68:789-796.

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