Phase III Results for Tasocitinib Generate Buzz

BY AMY ROTHMAN SCHONFELD

FROM A COURSE SPONSORED BY NEW YORK UNIVERSITY

NEW YORK – Encouraging results from a phase III study of the oral Janus kinase 3 inhibitor tasocitinib used as monotherapy for rheumatoid arthritis have rheumatologists anticipating the possibility of a new oral disease-modifying antirheumatic drug, according to Dr. Yusuf Yazici.

Tasocitinib (CP-690550) is a small-molecule, oral JAK inhibitor that blocks cytokine signaling, cytokine-induced gene expression, and activation of cells involved in the immune and inflammatory responses.

Findings from the studies "look promising," remarked Dr. Yazici, director of the Seligman Center for Advanced Therapeutics and Behcet's Syndrome Evaluation, Treatment, and Research Center at New York University Hospital for Joint Diseases.

In this 6-month randomized, double-blind, placebo-controlled study, 243 RA patients who had failed at least one prior disease-modifying antirheumatic drug (DMARD) trial were treated for 3 months with 5 mg of tasocitinib b.i.d., 245 patients were given 10 mg of tasocitinib b.i.d., and 122 were given placebo. After 3 months, half of the placebo-treated patients were switched to 5 mg of tasocitinib and half were switched to 10 mg of tasocitinib.

At 3 months, the American College of Rheumatology (ACR) 20 response rates for 5 mg and 10 mg of tasocitinib were 60% and 66%, respectively, which were significantly higher than the 27% rate seen with placebo (*P* less than .0001). Just over 20% of patients on the 10-mg dose and 15% of those on the 5-mg pill achieved ACR 70, compared with 5% of those receiving placebo.

Significant differences for each tasocitinib dose compared with placebo were also found for another primary end point, the least squares mean change in the Health Assessment Questionnaire Disability Index (–0.31 and –0.38, respectively; *P* less than .0001).

The percentage of patients in disease remission (defined as a disease activity score [DAS] less than 2.6) was the third primary efficacy end point. No significant differences between treatment and placebo were found (6% for the 5-mg tasocitinib group vs. 4% for placebo, $P = .505$), although there was a trend toward significance for the 10-mg group (10%, $P = .056$). Significant differences were found on DAS improvement between each of the tasocitinib doses and placebo at 3 months (*P* less than .0001).

Meaningful differences were found as early as the second week on the ACR 20 for both tasocitinib doses, on the ACR 50 with the 10-mg dose, and on the ACR 70 for both doses.

In the first 3 months, 330 patients had 701 treatment-emergent adverse events (AEs), with a similar frequency in each of the tasocitinib and placebo groups. Thirteen patients discontinued treatment because of treatment-emergent AEs – there were no between-group differences. No deaths were reported. A total of 25 patients developed serious AEs (6 in the 5-mg tasocitinib group, 12 in the 10-mg tasocitinib group, 5 in the group that switched from placebo to 5-mg tasocitinib, and 2 in the group that switched from placebo to 10-mg tasocitinib).

Dr. Yazici serves as a consultant to Bristol-Myers Squibb, Celgene Corporation, Genentech, Roche, and UCB. ■

Evidence Called Insufficient For Comparing PsA Drugs

BY GREGORY TWACHTMAN

FROM THE AGENCY FOR HEALTHCARE RESEARCH AND QUALITY

A comparative effectiveness study on drug therapies used to treat psoriatic arthritis in adults determined that evidence is insufficient to draw any conclusions.

"Overall, the data are quite limited and the evidence is insufficient to draw firm conclusions on comparative efficacy, effectiveness, and harms of either oral or biologic DMARDs [disease-modifying antirheumatic drugs] in this condition," the draft report stated. AHRQ uploaded the draft report to the Effective Care portion of its Web site. The draft did not identify the lead investigators of the study.

AHRQ's findings come soon after the U.K.'s National Institute for Clinical Excellence rejected Simponi for the treatment of active and progressive psoriatic arthritis (PsA) in adults, claiming that evidence revealed that the Schering Plough/Johnson & Johnson product was not as effective as Pfizer's Enbrel.

The draft report noted that about 520,000 U.S. adults have PsA, with treatments aimed primarily at controlling pain and inflammation and, ultimately, at slowing or arresting the progression of joint destruction.

The study compared a variety of oral and biologic DMARDs, including Simponi (golimumab) and Enbrel (etanercept), as well as Sanofi-Synthelabo's Plaquenil (hydroxychloroquine), Sanofi-Aventis' Arava (leflunomide), methotrexate, sulfasalazine, Abbott's Humira (adalimumab), UCB's Cimzia (certolizumab) and J&J's Remicade (infliximab). Humira, Enbrel, Simponi, and Remicade are approved by FDA to be used in patients with PsA.

The comparative effectiveness study for PsA aimed to answer four key questions:

- ► Do drug therapies differ in their ability to reduce disease activity, to slow or limit progression of radiographic joint damage, or to maintain remission?
- ► Do drug therapies differ in their ability to improve patient-reported symptoms, functional capacity, or quality of life?
- ► Do drug therapies differ in harms, tolerability, adherence, or adverse effects?
- ► What are the comparative benefits and harms of drug therapies for PsA in subgroups of patients based on stage of disease, history of prior therapy, demographics, concomitant therapies, or comorbidities?

The limited evidence that surfaced during research addressed the first three questions but nothing could be found on the fourth.

The draft report noted that experts "have not arrived at consensus about the comparative effectiveness of corticosteroids, oral DMARDs, and biologic DMARDs for treating PsA. More importantly, it is unclear how the effectiveness and safety of different types of combination therapy compare. In addition, there is debate about how early in the disease process combination therapy should be initiated and whether patients will respond to a biologic agent if they have previously failed a different biologic agent."

The draft report added that questions remain about the risks of these agents. There is also limited understanding of the benefits and risks regarding subpopulations, including ethnic minorities, the elderly, pregnant women, and patients with other comorbidities. ■

Gregory Twachtman is a writer for "The Pink Sheet." This news organization and "The Pink Sheet" are owned by Elsevier.

Infection Risk Unchanged After TNF Inhibitor Switch

BY SHARON WORCESTER

FROM THE ANNUAL MEETING OF THE AMERICAN COLLEGE OF RHEUMATOLOGY

ATLANTA – Rheumatoid arthritis patients who switch from one tumor necrosis factor inhibitor to another during the course of their disease are not at increased risk for serious infections, according to an analysis of data from a large health claims database.

The unadjusted rates of first serious infection in 13,752 RA patients who received only one tumor necrosis factor (TNF) inhibitor between Jan. 1, 2001, and Dec. 21, 2007, and in 2,293 RA patients who switched at least once from one TNF inhibitor to another during that time period did not differ significantly in either a model that analyzed infection rates within 90 days of any health insurance claim for a TNF inhibitor (the index date), or in a model that analyzed infection rates at any time after the index date, reported Bao-Anh Nguyen-Khoa, D.Pharm.

Rates of first serious infection in the 90-day model were 6.31 and 6.78/100 patient-years in the nonswitchers and switchers; rates in the ever-treated model were 8.45 and. 9.10/100 patient-years in the nonswitchers and switchers.

Rates of first serious infection in both models declined significantly from the first year after the index date, to the second year after the index date and beyond. In the 90-day model, those rates declined from 8.59 to 2.66/100 patient-years in the nonswitchers, and from 8.72 to 2.64/100 patient-years in the switchers. In the ever-treated model, the rates declined from 10.15 to 4.18/100 patient-years in the nonswitchers, and from 10.11 to 4.44/100 patient-years in the switchers, said Dr. Nguyen-Khoa, a pharmacoepidemiology consultant in Arlington, Va.

After adjustment for age, sex, selected comorbidities, Charlson comorbidity score, hospitalizations, and other RA treatments, there still was no significant difference between the nonswitchers and switchers in the risk of serious infection for either attribution model (hazard ratio, 0.93 in the 90-day model, and 0.94 in the ever-treated model).

Patients in the health insurance claims database used for this study were included if they had not been treated with other biologic agents, and if baseline data were available for at least 365 days of enrollment prior to the index date. Serious infections were defined as infections requiring intravenous antibiotic treatment or hospitalization.

Prior studies have documented an increased risk of serious infections in patients using TNF inhibitors, with incident rates of 3.6-10.5 cases/100 patient-years, and with similar findings to the current study in regard to differences in infection rates in the first year compared with the second year. However, although switching anti-TNF agents is a common strategy in RA patients who experience adverse events or lack of efficacy, infection rates in patients who switch drugs have not been widely studied, Dr. Nguyen-Khoa said.

In the current study, he and his colleagues demonstrated that switching TNF inhibitors does not increase risk, and they also reported a reduced rate of serious infections in patients who survived into the second year – a finding that corresponded with the results of those earlier studies, he said.

This study was supported by Genentech and Biogen IDEC. Dr. Nguyen-Khoa said he had no conflicts of interest. ■