Biologic Gains FDA Panel Backing for RA Patients

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Silver Spring, Md. — Tocilizumab's many side effects prompted much discussion during a meeting of the Food and Drug Administration's Arthritis Advisory Committee but did not prevent the drug from winning its recommendation for approval.

The FDA advisory panel voted 10-1 to recommend approval of tocilizumab (Actemra), a humanized anti-IL-6 receptor monoclonal antibody that purports to offer a new line of attack against rheumatoid arthritis (RA). The lone dissenting vote was cast by Diane Aronson, the consumer representative to the Arthritis Advisory Committee, who said she was concerned about tocilizumab's long-term safety issues.

Neither the committee members nor the FDA reviewers took issue with tocilizumab's efficacy. The drug's developers, Chugai Pharmaceutical Co. and Hoffmann-La Roche, said they had already agreed to a postmarketing study that would follow patients for 5 years, and also presented a detailed plan for reducing the risks associated with tocilizumab.

Dr. Gary Hoffman, a panel member from the Cleveland Clinic, said that while safety was a concern, "I don't see a signal here that goes beyond what we've seen with anti–[tumor necrosis factor] agents."

The FDA usually follows its advisory panels' advice.

The Arthritis Advisory Committee considered data from five pivotal phase III studies and several ongoing open-label extension studies.

Roche was seeking approval for an 8-mg/kg dose, given every 4 weeks, to treat moderately to severely active RA. In several of the pivotal studies, a 4-mg/kg dose was effective, which led some panelists to question whether patients should be started on the higher dose.

Tocilizumab was studied as a monotherapy at 8 mg/kg, and in three studies in combination with methotrexate in patients who had an inadequate response to disease-modifying antirheumatic drugs (DMARDs); another study looked at tocilizumab's efficacy in patients who had an inadequate response to anti-TNF therapy. The primary end point in all five studies was the ACR 20 at 6 months.

Roche pooled the data for the three combination studies and in an analysis of the intent-to-treat population, found that among those who completed the study, 829 (59%) of those taking the 8-mg/kg dose had an ACR 20 response. Only 26% of those taking placebo had an ACR 20.

The patients taking DMARDs had an average 20-30 swollen joints, a mean C-reactive protein of 2.5 mg/dL, and a mean Health Assessment Questionnaire score of 1.5. They had RA for a mean of 9 years.

In patients who were inadequate responders to anti-TNF therapies, 85 (50%) of the 170 patients taking the 8-mg/kg dose had an ACR 20 response at 24 weeks. In the monotherapy study, 200 (70%) of patients taking 8 mg/kg had an ACR 20 at 6 months.

Roche presented safety data from the five pivotal trials and from open-label extension studies. Overall, there were 3,778 patients with exposure to tocilizumab, with the majority—3,242—exposed to 8 mg/kg. Across all the studies, 72% of treated patients had an adverse event. One or more serious adverse events occurred in 152 (6%). The FDA adjusted the incidence rates to account for the differences in exposure. The overall death rate was 0.4 per 100 patient-years on tocilizumab, compared with 0.9 for a DMARD and 0.8 for methotrexate, according to that exposure-adjusted analysis.

Five patients taking tocilizumab died of cardiac etiologies and four from infectious etiologies, said Dr. Sarah Okada, a reviewer from the FDA's Division of Anesthesia, Analgesia, and Rheumatology Products.

There were several adverse events that appeared to signal a possible association with tocilizumab: infections, decreased neutrophil count, gastrointestinal perforations, demyelination, malignancies, stroke and acute myocardial infarction, decreased platelet count, liver enzyme changes, and infusion reactions.

Roche proposed a variety of recommendations to minimize risk of these adverse events, including TB screening and close laboratory monitoring for neutrophils, platelets, cholesterol, and liver enzymes.

The panelists agreed with the need for close patient follow-up, particularly on lab values. ■

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