IL-6 Blocker Is First to Get Nod as RA Therapy

BY DIANA MAHONEY

The monoclonal antibody tocilizumab has received approval by the U.S. Food and Drug Administration for the treatment of moderate to severely active rheumatoid arthritis in adult patients who have failed one or more tumor necrosis factor blockers, according to an announcement made Jan. 11 by the drug's manufacturer, Roche Holding AG.

Tocilizumab (Actemra) is the first interleukin-6 (IL-6) receptor inhibitor to be approved for the treatment of RA, and it can be used alone or in combination with methotrexate or other disease-modifying antirheumatic drugs (DMARDs), according to the statement. The drug was codeveloped by Chugai Pharmaceutical Co. and its parent company, Roche.

The approval comes on the heels of an extensive clinical development program comprising five phase III trials, as well as a resubmission of documents, including a proposal for a risk evaluation and mitigation strategy. The pivotal clinical trials include RADIATE (Research on Actemra Determining Efficacy after Anti-TNF Failures), OPTION (Tocilizumab Pivotal Trial in Methotrexate Inadequate Responders), TOWARD (Tocilizumab in Combination With Traditional DMARD Therapy), AMBITION (Actemra vs. Methotrexate Double-Blind Investigative Trial in Monotherapy), and LITHE (Tocilizumab Safety and the Prevention of Structural Joint Damage).

In the RADIATE trial, 30% of patients who received tocilizumab in combination with methotrexate achieved disease remission, compared with 1.6% of patients receiving methotrexate alone. Lead investigator Dr. Paul Emery, professor of rheumatology at the University of Leeds (England), and colleagues wrote that the findings were especially promising for that subset of RA patients who have failed to achieve adequate symptom relief with anti-TNF agents (Ann. Rheum. Dis. 2008;67:1516-23).

The results from the OPTION trial showed that 59% of the patients with RA who had incomplete responses to methotrexate achieved an ACR 20 response following treatment with tocilizumab 8 mg/kg, compared with 26% of patients treated with placebo, and 27% of the patients on tocilizumab achieved remission, compared with 0.8% in the placebo group (Lancet 2008; 371:987-97).

Similarly, in the TOWARD trial, 61% of patients who received tocilizumab in a dose of 8 mg/kg achieved an ACR 20 response at 24 weeks, compared with 25% of patients treated with placebo plus DMARDs, and approximately 38% of tocilizumab-treated patients met ACR 50 criteria for symptom improvement, compared with 9% of patients receiving placebo (Arthritis Rheum. 2008;58:2968-80).

The AMBITION study, in which 70% of patients who received a dose of 8 mg/kg achieved an ACR 20 response at 24 weeks, was the first to show that treatment with a single biologic agent was superior to methotrexate alone for the treatment of RA at 6 months, according to a press release issued by Roche when the phase III results were released in 2008 at the annual Congress of the European League Against Rheumatism.

Findings from the LITHE study, which were presented by lead investigator Dr. Roy M. Fleischmann of the department of internal medicine at the University of Texas Southwestern Medical Center, Dallas, at the 2009 annual meeting of the American College of Rheumatology, showed that over a 2-year period, there was no radiographic progression or joint damage in 75% of RA patients taking tocilizumab 4 mg/kg plus methotrexate, or in 85% of those taking tocilizumab 8 mg/kg and methotrexate, compared with 66% of patients taking methotrexate alone.

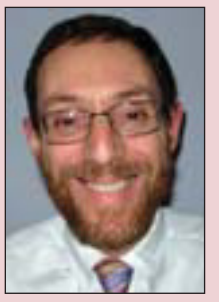
Among the serious tocilizumab-related adverse events that have been reported in the clinical trials are infections (including tuberculosis) that led to hospitalization or death, and bacterial, invasive fungal, viral, and other infections; gastrointestinal perforations; hypersensitivity reactions; and cellulitis.

Some of the common side effects included upper respiratory infections, including pneumonia; inflammation of the nose and throat; headache; high blood pressure; increased liver enzymes; increased cholesterol levels; neutrophil decreases; and platelet decreases, according to the press release.

Tocilizumab is expected to become available in the United States soon. ■

MY TAKE

Insurance Coverage May Be an Issue



Rheumatologists have been hearing a lot of preapproval hype about this agent from Roche.

Our interest is piqued by the novelty of the mechanism of action of tocilizumab. There are multiple anti-TNF medications currently, and their manufacturers are trying hard to convince clinicians to choose one medication over another, even though they are probably more similar than different. As an IL-6 blocker, tocilizumab is different.

The new-drug hype notwithstanding, there are still a number of questions to be answered before clinicians can consider the potential clinical impact of tocilizumab. The main questions for me are: Is this medication any safer or more dangerous than the current biologic drugs? Is this medication more or less affordable, or accessible, than the current biologics? Where does this medication belong in the treatment algorithm?

Undoubtedly, the company is going to try to convince doctors to use this medication immediately after methotrexate failure, but they will first have to convince doctors, and insurers, that this strategy is warranted.

LARRY GREENBAUM, M.D., *is a private practice rheumatologist in Indianapolis. He has no financial disclosures to make that are relevant to the approval of tocilizumab.*

Drop in Serum Uric Acid Seen Following Weight Loss

BY MITCHEL L. ZOLER

PHILADELPHIA — Weight loss was linked to significant drops in serum uric acid levels in a prospective study with more than 12,000 men with high cardiovascular risk.

"Weight loss could substantially help achieve a widely accepted therapeutic uric acid target level of 6 mg/dL among men with a high cardiovascular risk profile," Yanyan Zhu said at the annual meeting of the American College of Rheumatology.

Ms. Zhu and her associates used data from 12,510 men with a high cardiovascular risk profile enrolled in the MRFIT (Multiple Risk Factor Intervention Trial), a study begun in the early 1970s. MRFIT assessed the role of multiple risk-factor interventions, including a special diet, on mortality from coronary heart disease.

The men's mean age at baseline was 46 years. Their average body mass index was 28 kg/m^2. Hypertension (defined as blood pressure at or above 130/85 mmHg) was present in 86%, with 17% on a diuretic. Their average alcohol use was 13 drinks per week, and their average serum creatinine was 1.10 mg/dL. Their average serum level of uric acid at baseline was 6.8 mg/dL, with 73% identified with hyperuricemia based on a level of at least 6.0 mg/dL.

The study design had the men return annually for clinical assessments for 6 years. During follow-up, 39% had weight loss, 31% had no weight change, and 30% gained weight.

In an analysis that adjusted for baseline covariables of hypertension, diuretic use, alcohol use, and serum creatinine, men who lost weight during follow-up had a statistically significant reduction in their risk for having hyperuricemia, said Ms. Zhu, an epidemiologist at Boston University. The more weight they lost, the lower their risk for hyperuricemia. (See box.) A weight loss of at least 10 kg was associated with a 56% drop in the risk for hyperuricemia. In contrast, men who gained weight during follow-up had a significantly increased risk for hyperuricemia. Again, the risk rose with greater weight gain, with a weight gain of at least 10 kg associated with a 54% increased risk for hyperuricemia

A second analysis showed similar, significant relationships between changes in weight and changes in the serum level of uric acid. The more weight patients lost, the lower their uric acid levels fell, whereas the more weight they gained, the higher their levels rose. (See box.)

Ms. Zhu and her associates hypothesized that the impact of weight change on serum uric acid occurred through changes in uric acid production and renal excretion.

Ms. Zhu had no disclosures. ■

Weight Changes Linked to Uric Acid Changes

Weight change	Odds ratio for change in rate of hyperuricemia	Average change in serum uric acid level
Gain or loss of less than 1 kg (reference)	1.0	0
Loss of 1.0-4.9 kg	0.83	–0.12 mg/dL
Loss of 5.0-9.9 kg	0.68	–0.26 mg/dL
Loss of 10 kg or more	0.44	–0.58 mg/dL
Gain of 1.0-4.9 kg	1.09	+0.07 mg/dL
Gain of 5.0-9.9 kg	1.46	+0.23 mg/dL
Gain of 10 kg or more	1.54	+0.38 mg/dL

Note: Data from 12,510 men at high risk for cardiovascular disease followed for 6 years. All changes are statistically significant compared with reference group. All between-group differences are adjusted for baseline differences in hypertension, diuretic use, alcohol use, and serum creatinine.
Source: Ms. Zhu