# Pain Reduction of 50% in 3 Days

**Tanezumab** *from page 1*

monoclonal antibody against nerve growth factor (NGF). NGF, which is upregulated in locally inflamed tissue and pain states, stimulates the growth of sensory nerve cells peripherally and increases pain response.

Study participants had moderately severe osteoarthritic knee pain, with average baseline walking knee pain VAS scores of slightly more than 70 mm on a 0- to 100-mm scale. All patients were unresponsive to nonopiate pain medications or were candidates for total joint replacement or other surgical interventions.

After a washout, patients were randomized to intravenous placebo or tanezumab at 10, 25, 50, 100, or 200 mcg/kg. Two doses were administered 8 weeks apart.

Patients in the placebo arm averaged an 18-mm decrease in walking knee pain from baseline to week 16, as assessed by VAS. Those on 10-50 mcg/kg of tanezumab averaged 29- to 34-mm reductions. And those on 100 or 200 mcg/kg of the NGF inhibitor averaged 46- and 48-mm reductions, respectively, in VAS pain scores.

The most common adverse events related to tanezumab were transient episodes of hypoesthesia, which occurred in nearly 11% of patients at the two highest doses. These localized areas of numbness or reduced appreciation of pain are consistent with the inhibition of NGF, as NGF is a sensitizer to pain, Dr. Lane explained.

In the phase III trials to come, it's likely that weight-adjusted dosing will be replaced by three non–weight-dependent doses, perhaps 2.5 mg, 5 mg, and 10 mg. This dosing format allows for titration, which is attractive in treating chronic pain, the physician continued.

Whether some patients can go longer than 8 weeks between doses of tanezumab will be addressed in future studies.

There is a need for better pharmacologic therapies for OA pain. Many patients can't tolerate, or don't obtain, adequate pain relief with nonsteroidal anti-inflammatory drugs. In addition, cardiovascular issues limit the usefulness of NSAIDs in older patients. Narcotic analgesics entail problems with addiction and various toxicities. "For patients with moderately severe osteoarthritis of the knee who are not interested in getting a joint replacement or who want to put it off, a treatment that lasts for 2 months gives you a pain holiday," she added. "It allows a patient with chronic pain time to rest and restore their energy so they can better deal with their disease," Dr. Lane said. ■

# Tocilizumab Looks Promising For the Toughest Patients

BY NANCY WALSH
*New York Bureau*

PARIS — The anti–interleukin-6 monoclonal antibody tocilizumab may offer a new alternative for the most refractory patients with rheumatoid arthritis, including those who have failed antitumor necrosis factor drugs.

Both interleukin (IL)-6 and tumor necrosis factor (TNF)–α play major roles in the development and maintenance of rheumatoid arthritis (RA), explained Dr. Paul Emery, Arthritis Research Campaign Professor of Rheumatology and head of the academic section of musculoskeletal diseases at the University of Leeds (England). He gave his presentation at the annual European Congress of Rheumatology.

"While anti-TNF therapies have become established treatments for RA, significant proportions of patients do not achieve an adequate response or become refractory to them," Dr. Emery said. Inhibiting the ubiquitous cytokine IL-6, which drives the acute phase response among other effects, may offer an additional way of achieving disease control, he said.

In the Research on Actemra Determining Efficacy after Anti-TNF Failure (RADIATE) trial, 498 patients who had previously failed anti-TNF therapy were randomized to receive placebo or tocilizumab in doses of 4 mg/kg or 8 mg/kg administered intravenously every 4 weeks for 24 weeks. A total of 160 were randomized to placebo, 163 to 4 mg/kg, and 175 to 8 mg/kg.

Patients also were receiving stable doses of methotrexate, 10-25 mg/week, and corticosteroids, 10 mg or less/day.

Mean age of patients was 53 years and mean disease duration was 11 years. Most were seropositive, and disease activity scores (DAS) were high, at a mean of 6.8.

Approximately half the patients had failed one anti-TNF agent, another third had failed two, and 12%-18% had failed three prior agents, he said. The study design allowed for escape at 16 weeks. A total of 60% of the controls had withdrawn or were on 8-mg/kg rescue therapy by week 24, as had 34% of the 4-mg group and 25% of the 8-mg group.

ACR 20 responses were seen in 50% of patients receiving the 8-mg/kg dose, according to Dr. Emery, who was lead investigator of the trial, funded by Roche.

Significantly greater improvements were also seen in the 8-mg/kg group on other end points.

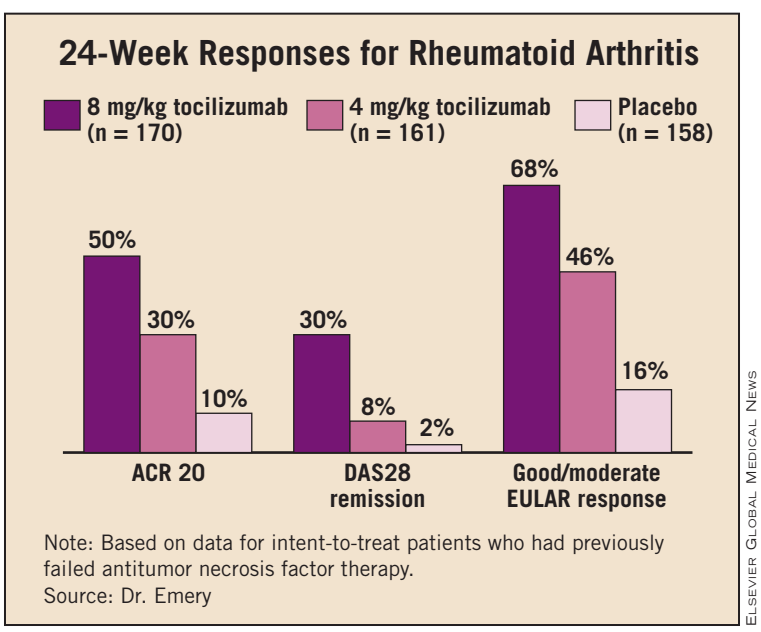
"Probably the most impressive finding was that one-third of patients who had previously failed the best we had to offer were able to get into remission, which is a much higher rate than previously has been seen in patients failing TNF," Dr. Emery said. Remission was defined as a DAS28 score below 2.6.

"This is our worst population, for whom we have no easy options, and the results were equal to or better than what we've seen before," he added.

Serious adverse events were seen in 11%, 7%, and 6% of the placebo, 4-mg/kg, and 8-mg/kg groups, respectively. Infections occurred in 41%, 47%, and 50% of the placebo, 4-mg, and 8-mg patients, while serious infections were seen in 3%, 2%, and 5%, respectively. There were no opportunistic infections or cases of tuberculosis.

Over the past 12 months, there have been research reports that tocilizumab improves quality of life in RA (RHEUMATOLOGY NEWS, May 2008, p. 6); lessens the articular and systemic manifestations of RA when used with disease-modifying antirheumatic drugs (RHEUMATOLOGY NEWS, January 2008, p. 1); and was beneficial in moderate to severe RA (RHEUMATOLOGY NEWS, October 2007, p. 20). The drug remains investigational both in the United States and Europe.

Dr. Emery has received consulting fees from Roche. ■




ELSEVIER GLOBAL MEDICAL NEWS

# *All RA Patients Need Heart Risk Screen, Says EULAR*

BY BRUCE JANCIN
*Denver Bureau*

PARIS — The European League Against Rheumatism Task Force on Cardiovascular Risk Management in Rheumatoid Arthritis has recommended annual cardiovascular risk screening for all patients with rheumatoid arthritis.

The task force also advised annual screening be considered for patients with ankylosing spondylitis or psoriatic arthritis as well, said task force member Dr. Mike J.L. Peters, in an interview.

These recommendations, to be published by year's end, were announced at the annual European Congress of Rheumatology. Included will be guidance on employing a multiplier or conversion factor in conjunction with the Systematic Coronary Risk Evaluation (SCORE)—the European equivalent of the Framingham Risk Score—in order to more accurately reflect the increased cardiovascular risk of patients with inflammatory arthritis.

In a separate presentation, Dr. Peters reported on his own data showing that the increased cardiovascular risk of RA patients is similar in magnitude to that associated with type 2 diabetes. This supports arguments for aggressive risk factor management in the RA population, especially given that type 2 diabetes is considered a coronary heart disease equivalent, meaning that diabetic individuals have roughly the same risk of future cardiovascular events as patients who've already had an acute MI, according to Dr. Peters of VU University Medical Center, Amsterdam.

Dr. Peters reported on 353 normoglycemic patients with RA of an average 7 years' duration and varied severity, 194 type 2 diabetic patients, and 258 healthy controls. All were aged 50-75. The prevalence of objective cardio- and/or cerebrovascular disease was 21.6% in patients with type 2 diabetes, 15.7% in those with RA, and 9.7% in controls.

After adjustment for differences in age, gender, and rates of the traditional cardiovascular risk factors, the prevalence of cardiovascular disease was found to be 85% greater in diabetic patients than controls, and 51% greater in the RA group than controls. The rates in diabetic and RA patients were not significantly different.

Audience member Dr. Daniel H. Solomon urged a cautious interpretation of the Dutch findings.

"When we think about diabetes as a risk factor for cardiovascular disease, we understand that some of the management techniques—aspirin, statins, other preventive measures—have been tested specifically in diabetic populations. But at this point, we have almost no data on the benefits of these sorts of preventive measures in a rheumatoid population," according to Dr. Solomon of Harvard Medical School, Boston.

"I'd be very careful about concluding that similar preventive measures would be beneficial in rheumatoids. We just don't have those data. I don't disagree that they might be, but I don't think we have enough data to make an evidence-based statement about that," he said. Dr. Peters said he agreed.

In a separate presentation, Dr. Peters reported that the rate of major cardiovascular events in 329 Dutch RA patients followed prospectively for nearly 3 years was 8.6%, compared with 4.3% in 1,852 controls drawn from the general population.

The RA patients had higher rates of smoking, hypertension, and some other traditional cardiovascular risk factors, as has been reported in other studies. But after adjusting for age, gender, and traditional risk factors, the cardiovascular event rate in the RA population remained twofold greater than in the general population, according to Dr. Peters. ■