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 tocilizumab at 10, 25, 50, 100, or 200 mg/kg. Two doses were administered 8 weeks apart. Patients in the placebo arm averaged a 18-mm decrease in walking average pain from baseline to week 16, as assessed by VAS. Those on 10–50 mg/kg of tocilizumab averaged 29% to 34-mm reductions. And those on 100 or 200 mg/kg of the NGF inhibitor averaged 46- and 48-mm reductions, respectively, in VAS pain scores.

The most common adverse events related to tocilizumab were transient episodes of hypothyroidism, 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 tocilizumab 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 oral or topical 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 Artremia Determining Ef- ficiency 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 non–weight-dependent, 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. 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 point factors. "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.