Fulranumab Shows Efficacy for Osteoarthritis Pain

BY MITCHEL L. ZOLER

FROM THE ANNUAL EUROPEAN CONGRESS OF RHEUMATOLOGY

LONDON – An investigational nerve growth factor inhibitor, fulranumab, showed promising efficacy and safety as a pain reliever for patients with hip or knee osteoarthritis in 12-week results from a phase II study of 466 patients.

Further study of fulranumab in osteoarthritis had been on hold. The Food and Drug Administration issued a moratorium last December that halted clinical testing of fulranumab and most other investigational agents in the anti–nerve growth factor class, following reports that some of these drugs appeared to trigger episodes of rapid progression of hip or knee osteoarthritis that led to joint replacement and possible osteonecrosis. The FDA lifted that moratorium on research with fulranumab in cancer pain this month. The moratorium on research involving OA pain remains in place, according to investigators.

Whether or not osteoarthritis progressed rapidly in any patient treated with fulranumab remains unknown. "Cases of joint replacement reported during the entire trial are under investigation, and will be reported in a future publication," Dr. John Thipphawong said.

The safety data Dr. Thipphawong presented for 12 weeks of treatment showed a well-tolerated profile compared with placebo. Specifically, serious adverse events occurred in 1% of patients treated with fulranumab, compared with 2% of those on placebo. Adverse events led to discontinuation of the assigned drug in 2% of fulranumab recipients and 1% of those on placebo. Adverse events that occurred more often in fulranumab-treated patients were paresthesia, with a 6%-10% rate in the higher fulranumab dosage subgroups, compared with a 3% rate for patients on placebo, and a hypoesthesia rate of 5%-6% in the higher dosage fulranumab subgroups, compared with a 1% rate with placebo. The fulranumab-treated patients also had no significant changes in laboratory values, ECG, or vital signs at 12 weeks after treatment began.

The study enrolled patients with documented hip or knee osteoarthritis who met the diagnostic criteria of the American College of Rheumatology and showed radiographic evidence of the disease, with a Kellgren-Lawrence grade of 2 or greater. All patients also reported moderate to severe pain, with a pain score of at least 5 on a 0-10 numerical rating scale despite treatment with an opioid, a nonsteroidal anti-inflammatory drug, or both.

The study randomized patients to receive fulranumab or placebo once every 4 or 8 weeks as a subcutaneous injection in addition to standard pain medications. The protocol tested five different fulranumab dosages: 1 mg every 4 weeks, 3 mg every 4 weeks, 3 mg every 8 weeks, 6 mg every 8 weeks, or 10 mg every 8 weeks. Fulranumab is a fully human, recombinant monoclonal antibody that neutralizes the biological actions of human nerve growth factor. About 78 patients entered each of the five active-treatment arms as well as a placebo arm. The study's primary efficacy end point was the change in average pain score from baseline to the end of week 12 of the study.

The patients' average age was 61 years, 58% were women, and two-thirds were white. Their average body mass index was 32 kg/m^2, and 60% weighed at least 85 kg. Knee OA predominated as the affected joint, in 77% of patients.

At 12 weeks after the start of treatment, average pain reduction with fulranumab significantly surpassed the placebo group in the 3–mg every 4 weeks, 6–mg every 8 weeks, and 10–mg every 8 weeks subgroups. In these three groups, pain scores fell by an average of 3.05, 2.64, and 2.65 points, respectively, compared with an average drop of 1.91 points in the placebo group, reported Dr. Thipphawong, who is senior director of clinical development, Johnson & Johnson Pharmaceutical Research & Development.

The study also included several secondary efficacy measures. The three highest-dosage subgroups, as well as the 3–mg every 8 weeks subgroup, showed statistically significant declines compared with placebo after 12 weeks in the average levels of the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) subscales for pain and global function. For the WOMAC subscales of physical function and stiffness, all five fulranumab dosage subgroups showed significant reductions compared with placebo.

On the Brief Pain Inventory-Short Form, patients in the 3–mg every 4 weeks and 10–mg every 8 weeks subgroups had significant average reductions compared with the placebo group for the subscales of pain intensity and pain interference with activities The three highest-dosage subgroups also produced average drops in patient global assessment of disease status that were statistically significant compared with the placebo group's average.

In a separate poster at the meeting, Dr. Thipphawong and his associates also reported that several of the fulranumab subgroups showed statistically significant average improvements compared with placebo in several subscale measures on the Short Form-36, specifically bodily pain, vitality, and physical component. The four highest-dosage subgroups also had significant average improvements in pain interference with sleep compared with placebo, and all five fulranumab dosage subgroups had significant average improvements in sleep adequacy compared with the placebo group. ■

VITALS

Major Finding: Treatment with several different dosages of fulranumab led to statistically significant improvements in a number of efficacy measures and was well tolerated. The primary efficacy end point of change in average pain intensity at 12 weeks from the start of treatment showed significant drops compared with the placebo group for the three largest dosages of fulranumab tested.

Data Source: Phase II randomized, placebo-controlled trial that assessed the efficacy and safety of five dosages of fulranumab after 12 weeks of treatment in patients with moderate to severely painful osteoarthritis of the hip or knee.

Disclosures: Dr. Thipphawong and several of his associates are employees of Johnson & Johnson, the company developing fulranumab.

Gut Perforation Risk Is Low in Treated RA Patients

BY SARA FREEMAN

FROM THE ANNUAL EUROPEAN CONGRESS OF RHEUMATOLOGY

LONDON – Although a potentially serious complication, perforation of the gastrointestinal tract is rare, judging from the findings of an analysis of more than 140,000 patients with rheumatoid arthritis.

Upper or lower GI tract perforation occurred in 696 (0.5%) of patients, with an overall, unadjusted incidence rate of 1.7 cases per 1,000 person-years, according to Dr. Jeffrey Curtis. "For [most of] the rheumatoid arthritis patients someone has in their practice, [GI perforation] is going to be very uncommon, I think that should be reassuring," he said during an interview.

"We also observed that there were cases [of GI perforation] for every biologic group," added Dr. Curtis, a rheumatologist, epidemiologist, and associate professor of medicine at the University of Alabama at Birmingham. This should help dispel any concerns that the adverse event might occur with certain biologic agents used to treat RA, he suggested.

In a retrospective study, Dr. Curtis and his associates analyzed records of 143,433 RA patients from a large U.S.-based administrative claims database for the years 2001-2009. The investigators used a validated algorithm to identify cases of upper and lower GI perforation and to determine predictive factors. The median follow-up was 2.5 years.

Older age was found to be a predictor of GI perforation, with adjusted relative risks of 1.6 and 2.1 for people aged 40-64 years and 65 years, respectively, compared with RA patients younger than 40 years. The mean age of the 142,737 patients who did not have a GI perforation was 57.6 years, and the mean age of the 696 patients who did was 62 years (*P* less than .01).

Diverticulitis and diverticulosis without diverticulitis were also significantly more common in patients who experienced a GI perforation than in those who did not, although the incidence was still low, with rates of 2.9% vs. 0.3% and 1.4% vs. 0.4%, respectively (both *P* less than .01). Diverticulitis but not diverticulosis was a significant risk factor for perforation.The main risk factors among the RA medication groups of most relevance were the use of oral glucocorticosteroids and nonsteroidal anti-inflammatory drugs, not biologics and not the disease-modifying antirheumatic drugs, he said. Indeed, the incidence of GI perforation was highest in patients who used glucocorticoids in combination with DMARDs other than methotrexate (3.03 per 1,000 patient years).

Steroid monotherapy carried an incidence of 2.86 per 1,000 patient-years. Steroids used in combination with methotrexate and biologics also increased the risk of the GI complications (2.24 and 1.87 per 1,000 patient-years, respectively).

The rates of GI perforations in patients treated with biologics, methotrexate, or other DMARDs without steroids were 1.02, 1.08, and 1.71 per 1,000 patient-years, respectively. NSAID use was associated with an incidence rate of 1.68 per 1,000 patient-years.

In the study, 80% of the perforations seen were in the lower GI tract, so the use of gastroprotective medications may not be that useful.

Although still important, upper GI bleeding and peptic ulcer disease are perhaps less critical than antecedent diverticulitis and its associated complications.

Minimization of NSAID and steroid use is probably warranted in higher-risk patients, Dr. Curtis advised. "In somebody with a history of diverticulitis, I would be very cautious." ■

VITALS

Major Finding: The incidence of GI perforation was highest in patients who used glucocorticoids in combination with DMARDs other than methotrexate (3.03 per 1,000 patient-years).

Data Source: Retrospective study of 143,433 patients with rheumatoid arthritis with at least two nondiagnostic claims in a U.S. administrative database filed between 2001 and 2009.

Disclosures: Dr. Curtis disclosed research and consulting relationships with Abbot, Amgen, BMS, Centocor, CORRONA, Crescendo, Pfizer, Roche, and UCB.