Risedronate Retains Impact on OA Biomarkers

It remains to be seen whether changes in biomarkers will translate into clinical joint preservation.

BY KERRI WACHTER
Senior Writer

Risedronate appears to be no better than placebo at improving symptoms and slowing structural changes associated with osteoarthritis, but the drug did significantly reduce markers of bone resorption and cartilage degradation, providing some measure of hope that the drug may still prove useful in treating this disorder.

"In the groups that were receiving placebo, there was worsening of their cartilage degradation marker [C-terminal crosslinking telopeptide of type II collagen, or CTX-II], whereas there was a dose-dependent reduction in all of the rise dronate treated patients. To date, CTX-II is the leading biomarker for osteoarthritis in terms of one that may be predictive of patients who are at risk for progression," Dr. Clifton O. Bingham III, the study's lead author and a rheumatologist at Johns Hopkins University, Baltimore, said.

Whether these changes in biomarkers will translate into a later clinically relevant change in joint preservation is unknown. "The fact that we are able to now show that certain treatments can affect this biomarker is really a very important piece for us in order to move forward in the development of therapeutics," said Dr. Bingham, who reported receiving consulting fees from Procter & Gamble Pharmaceuticals Inc., maker of risedronate (Actonel).

The study was conducted at 42 sites in North America and at 44 sites in the European Union (Arthritis Rheum. 2006; 54:3494-507). Patients were randomized to receive placebo or oral risedronate in dosages of 5 mg/day, 15 mg/day, 35 mg/week (Europe only), or 50 mg/week (North America only).

Patients aged 40-80 years were screened for inclusion if they had signal knee pain resulting from osteoarthritis (OA) most days during at least 1 month in a 3-month period, and had one of the following: morning knee stiffness lasting more than 30 minutes, or knee crepitus according to the American College of Rheumatology criteria for knee OA.

Patients were excluded if they had known inflammatory arthritis; body mass index (kg/m^2) greater than 40; cancer within 10 years; tetracycline use within 6 months; intra-articular injection of corticosteroids or hyaluron preparations within 3 months; calcitonin or fluoride use within 6 months; and prior use of bisphosphonates within 12 months or for more than 60 days ever.

All patients underwent radiography of the knee to confirm OA. For inclusion, patients had to have at least one osteophyte and minimal joint space width of 2-4 mm, inclusive, in the medial tibiofemoral compartment, and a medial compartment that was narrower than the lateral. Radiographic assessment was performed at baseline, 1 year, and 2 years.

Nonnarcotic analgesics, NSAIDs, or COX-2 inhibitors were allowed and monitored during the study. Patients underwent a stepped reduction and washout period for these medications prior to study visits, including the baseline visit. Patients were provided with 500 mg acetaminophen (North America) or paracetamol (Europe) and 50 mg diclofenac to be used as needed from 5 to 3 days prior to a visit. All pain medications were stopped 2 days prior to a visit.

The two primary end points were the effect of risedronate on structure and symptoms compared with placebo after 2 years. Patient symptoms were measured by the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index and by Patient Global Assessment (PGA) scores. Structure was assessed by measuring joint-space narrowing in the medial tibiofemoral compartment.

Joint-space narrowing of the target knee was evaluated at the narrowest point in the medial tibiofemoral compartment at baseline and at 1 and 2 years follow-up. Radiographs were performed using a semiflexed view of the knee (fluoroscopically assisted). Radiographs were obtained at 13 regional radiographic facilities in Europe and 12 in the United States. All radiographs were sent to a quality control center in Amsterdam for review and then to the central analysis facility in London, where films were digitized and semiautomated computer measurements of minimal medial joint-space width were performed. The test-retest standard deviation—the difference between radiographs obtained 2 days apart—for this technique was approximately 0.2 mm.

Urine samples were also collected at baseline and at 6 months, 12 months, and 24 months. Samples were analyzed for N-terminal crosslinking telopeptide of type I collagen (NTX-I) to assess bone resorption and for CTX-II.

In the North American cohort, 301 participants were randomized to placebo, 306 to 5 mg/day risedronate, 302 to 15 mg/day, and 314 to 50 mg/week. In the European cohort, 312 participants were randomized to placebo, 322 to 5 mg/day risedronate, 307 to 15 mg/day, and 310 to 35 mg/week.

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"In both the European and North American studies, no significant differences between treatment groups were noted in the mean change from baseline in total WOMAC score, scores for WOMAC components, or PGA scores," the researchers said. Notably, those patients treated with placebo had a mean reduction of about 20% from baseline in total WOMAC scores.

"In all treatment groups, including the placebo, there was a clinically detectable improvement in pain that occurred at the 6-month point and was maintained over 2 years," said Dr. Bingham. The results for the placebo patients highlight the importance of accounting for placebo benefit in osteoarthritis studies. Not only did placebo improvement occur, but it was maintained over time.

So either improvement is part of the natural course of the disease or there is a clinical benefit simply in entering a clinical trial. Regardless, this effect needs to be taken into consideration in designing future osteoarthritis trials, said Dr. Bingham, who is also with the division of allergy and immunology at Johns Hopkins University.

In terms of structure, 13% of participants had radiographic progression. There were no statistically significant differences in any treatment group in either cohort.

"When you looked at the people who were showing what was unequivocally progression … there was no drug effect that was demonstrated but interestingly that group of people was only a very small percentage of the entire study population," said Dr. Bingham.

The radiographic findings also have implications for future trial design: If only a small number of people are going to show substantial worsening in terms of joint structure, then—in order to study an OA drug by looking at structure as an outcome—greater numbers of patients are needed to be able to demonstrate a potential treatment effect, he said.

In both cohorts, a dose-dependent decrease in the level of NTX-I was observed within 6 months for those on risedronate, and it continued through 24 months. The mean percent change from baseline to 24 months for all dosages of risedronate was statistically different from the placebo group. In the North American group, those on placebo had a mean increase in NTX-I of 7.3%, whereas those on risedronate at dosages of 5 mg/day, 15 mg/day, and 50 mg/week had NTX-I level decreases of 21.6%, 39.2%, and 29.2%, respectively. In the European cohort, those on placebo had a mean increase in NTX-I of 3.0%, whereas those on risedronate at dosages of 5 mg/day, 15 mg/day, and 35 mg/week had NTX-I level decreases of 29.0%, 41.7%, and 28.2%, respectively.

The results for CTX-II levels were similar, with those on placebo having increases over 24 months, whereas those on risedronate had early decreases. At 15 mg/day risedronate, reductions of 17.9% and 19.6% from baseline were seen in North American and European patients respectively. In comparison, the North American and European placebo groups had increases of CTX-II levels of 26.3% and 10.1%, respectively.

The biomarker results suggest—from a pathobiologic perspective—that an agent that acts on subchondral bone, interrupts the turnover of bone, and improves bone structure can consequently improve cartilage stability. This suggests a fundamental interaction between bone and cartilage. This could be important because treatments already are available that interrupt bone turnover.

These study results indicate that "potentially the bone is an important therapeutic target in patients with osteoarthritis," said Dr. Bingham. ■

ADEPT: Adalimumab Improved Function in Psoriatic Arthritis

BY NANCY WALSH
New York Bureau

Treatment with adalimumab significantly improved quality of life and functioning among patients with moderate to severe psoriatic arthritis at 24 weeks, reported Dr. Dafna D. Gladman.

Previous analyses from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT), which is the largest randomized controlled trial of a tumor necrosis factor (TNF)–α inhibitor in psoriatic arthritis, have demonstrated that treatment with this drug significantly improves joint and skin manifestations and reduces radiographic disease progression.

But because psoriatic arthritis primarily afflicts patients in the productive years, 30-55 years, restoring function and reducing work-related disability also could help ease the economic burden of this disease, according to Dr. Gladman of the University of Toronto Rheumatic Disease Unit.

Among the 313 patients in ADEPT, those receiving adalimumab had a mean decrease of 0.4 points from a baseline score of 1.0 on the disease-specific Health Assessment Questionnaire Disability Index, which has a range of 0 to 3, while those receiving placebo had a decrease of 0.1 points, Dr. Gladman and colleagues reported (Ann. Rheum. Dis. [Epub doi: 10.1136/ard.2006.057901]).

By week 12, 33.8% of patients in the active treatment group had complete resolution of functional loss, compared with 14.3% of those in the placebo group, with similar results being seen at week 24, according to the investigators. Statistically significant and clinically important improvements also were seen at week 24 in seven of the eight domains of the Short Form 36 Health Survey among the adalimumab-treated patients, whereas patients receiving placebo did not experience clinically important improvements in any domain.

The investigators acknowledged that a limitation of their study was its short duration, but noted that data from the long-term, open-label extension of ADEPT are being assessed. ■