

## **Risedronate not an Effective Disease Modifier in Knee Osteoarthritis**

Despite its prevalence, no effective pharmacotherapies have been definitively proven to modify the course of radiographic knee osteoarthritis (OA). Risedronate, a bisphosphonate that reduces bone turnover, has been shown in animal models to inhibit cartilage degradation and progression of disease. Here, Bingham et al (*Arthritis Rheum* 2006; 54(11): 3494) report the results of the Knee OA Structural Arthritis (KOSTAR) study examining the effect of risedronate on symptoms, radiographic progression, and biomarkers of cartilage degradation in symptomatic medial compartment knee OA.

**Methods** The study was conducted at 42 centers in North America (NA) and 44 centers in Europe (EU). Men and women age 40 to 80 years with symptomatic knee OA in the medial compartment (at least 1 osteophyte and 2-4 mm of joint space width (JSW)) were randomized in a double-blind fashion to receive risedronate 5 mg/day, 15 mg/day, 35 mg/week (Europe), 50 mg/week (North America), or placebo for 2 years. The knee with the narrowest JSW was designated as the “signal” knee. Background analgesics and NSAIDs were allowed throughout, but washed out in a prespecified manner prior to follow-up visits occurring at 6, 12, and 24 months after enrollment. Outcome domains included symptoms (measured with the WOMAC questionnaire), radiographic progression, and biochemical markers of cartilage breakdown (urine N-terminal crosslinked telopeptide of type I collagen (NTX-I) and urine C-terminal crosslinked telopeptide of type II collagen (CTX-II)). Safety assessments were conducted every 3 months.

**Results** Of the 9,236 subjects screened, 2,483 were randomized with approximately equal proportions of subjects in the EU and NA cohorts. Three-quarters of the subjects completed the entire 2 years of the study, although an additional 11% of subjects who discontinued study drug before two years returned for the final 2 year follow-up radiographic assessment. Subjects tender to be older (around 60 vs. 63 years of age in the NA vs. EU cohorts, respectively) and female (61% vs. 79% in the NA vs. UE cohorts, respectively). WOMAC scores were slightly higher in the EU group compared to the NA group (45.8 vs 40.2, respectively). Compared to EU subjects, NA subjects had higher BMI, more use of estrogen/SERMs, and more use of analgesics and NSAIDs. However, subject characteristics were balanced within cohorts.

### *Symptom Outcomes*

All groups had a 20% or greater reduction in WOMAC total and subscores, including the placebo group. There were no significant differences in treatment effect between the placebo group and any dose of risedronate in either the NA or EU cohorts.

### *Radiographic Outcomes*

Overall, 13% of subjects had radiographic progression of JSW narrowing  $\geq$  6mm in the medial compartment at 2 years. There were no significant differences in the proportion of radiographic progressors between the placebo and any dose of risedronate groups. Similarly, the proportion of subjects with increases in osteophyte size did not differ between any of the treatment groups and placebo.

### *Biomarkers of Cartilage Degradation*

Increases in biomarkers of cartilage degradation (NTX-I and CTX-II) were noted in the placebo group in both cohorts, while dose dependent reductions in these markers were associated with risedronate treatment. These differences were significantly different from the placebo group and were noted as early as six months.

### *Safety*

No significant differences in safety were noted between placebo and any of the risedronate groups, including GI symptoms in patients with and without concomitant NSAID use.

**Conclusions** Risedronate therapy was not superior to placebo in altering the symptoms or delaying radiographic progression of symptomatic medial compartment knee OA, despite the observation of significant dose-dependent improvements in biochemical markers of cartilage degradation.

**Editorial Comment** This is an interesting study in that it is definitively negative for its primary clinical and radiographic endpoints. The findings with the biochemical markers of cartilage breakdown are interesting and, at best, suggest that further investigation into the mechanisms of risedronate on cartilage are warranted. However, they by themselves do not suggest a role for risedronate in treating or preventing knee OA in clinical practice.

The discrepancies with the animal studies are interesting, but not inconsistent with the discrepancies in studies of other agents in knee OA. A common theme in these studies is the power of the placebo response and the multifactorial nature of pain in this disease that makes detecting valid treatment effects particularly challenging. Considering a large, well designed, carefully executed study such as this one, we are reminded that underpowered, uncontrolled OA studies are more likely to mislead rather than enlighten.

The reasoning behind using a bone protective agent to prevent cartilage degradation is not intuitive. Recently, investigators have suggested that pain and the early pathology of OA occurs in the subchondral bone, with so-called “bone-edema”, rather than first in the articular cartilage. This concept has been insightfully argued (Link to [http://hopkins-arthritis.org/news-archive/2003/bone\\_edema\\_oa.html](http://hopkins-arthritis.org/news-archive/2003/bone_edema_oa.html)) but not definitively proven. For this reason, use of a bone protective agent makes sense. However, whether these agents can affect disease that is already established or whether subchondral bone is a location that is amenable to bone protection by bisphosphonates are two of many possible reasons to explain the lack of treatment effect observed in this study.