ARTHRITIS & RHEUMATISM
Vol. 54, No. 11, November 2006, pp 3494–3507
DOI 10.1002/art.22160

Risedronate Decreases Biochemical Markers of Cartilage Degradation but Does Not Decrease Symptoms or Slow Radiographic Progression in Patients With Medial Compartment Osteoarthritis of the Knee

Results of the Two-Year Multinational Knee Osteoarthritis Structural Arthritis Study

Clifton O. Bingham, III,[1] J. Chris Buckland-Wright,[2] Patrick Garnero,[3] Stanley B. Cohen,[4] Maxime Dougados,[5] Silvano Adami,[6] Daniel J. Clauw,[7] Timothy D. Spector,[8] Jean-Pierre Pelletier,[9] Jean-Pierre Raynauld,[9] Vibeke Strand,[10] Lee S. Simon,[11] Joan M. Meyer,[12] Gary A. Cline,[12] and John F. Beary[12]

Objective. **Bisphosphonates have slowed the progression of osteoarthritis (OA) in animal models and have decreased pain in states of high bone turnover. The Knee OA Structural Arthritis (KOSTAR) study, which is the largest study to date investigating a potential structure-modifying OA drug, tested the efficacy of risedronate in providing symptom relief and slowing disease progression in patients with knee OA.**

Methods. **The study group comprised 2,483 patients with medial compartment knee OA and 2–4 mm of joint space width (JSW), as determined using fluoroscopically positioned, semiflexed-view radiography. Patients were enrolled in 2 parallel 2-year studies in North America and the European Union. These studies evaluated the efficacy of risedronate at dosages of 5 mg/day, 15 mg/day, 35 mg/week (in Europe), and 50 mg/week (in North America) compared with placebo in reducing signs and symptoms, as measured by the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index and patient global assessment (PGA) scores, and in slowing radiographic progression.**

Results. **A reduction of ~20% in signs and symptoms, as measured by WOMAC subscales and PGA scores, was observed in all groups, with no treatment effect of risedronate demonstrated. Risedronate did not**

[1]Clifton O. Bingham, III, MD: Johns Hopkins University, Baltimore, Maryland; [2]J. Chris Buckland-Wright, PhD, DSc: King's College, London, UK; [3]Patrick Garnero, PhD: INSERM Research Unit 664, and Synarc, Lyon, France; [4]Stanley B. Cohen, MD: St. Paul Medical Center, Dallas, Texas; [5]Maxime Dougados, MD: Hôpital Cochin, Paris, France; [6]Silvano Adami, MD: University of Verona, Verona, Italy; [7]Daniel J. Clauw, MD: University of Michigan, Ann Arbor; [8]Timothy D. Spector, MD, MSc, FRCP: St. Thomas Hospital, London, UK; [9]Jean-Pierre Pelletier, MD, Jean-Pierre Raynauld, MD, FRCPC: Centre Hospitalier de l'Université de Montréal, Hôpital Notre-Dame, Montréal, Québec, Canada; [10]Vibeke Strand, MD: Stanford University School of Medicine, Palo Alto, California; [11]Lee S. Simon, MD: Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, Massachussetts; [12]Joan M. Meyer, PhD, Gary A. Cline, PhD, John F. Beary, MD: Procter & Gamble Pharmaceuticals, Mason, Ohio.

Dr. Bingham has received consulting fees (less than $10,000) from Procter & Gamble. Dr. Cohen has received consulting fees and/or honoraria (less than $10,000) from Procter & Gamble. Dr. Dougados has received consulting fees and/or honoraria (less than $10,000) from Procter & Gamble. Dr. Adami has received consulting fees and/or honoraria (less than $10,000) from Procter & Gamble. Dr. Spector has received consulting fees and/or honoraria (more than $10,000) from Procter & Gamble. Dr. Strand has served as a consultant to and/or has received honoraria (less than $10,000 each) from Abbott Immunology, Amgen, Biogen Idec, Can-Fite BioPharma Ltd., Celera, Centocor, Chelsea Therapeutics, Coley Pharmaceutical Group, Cypress Pharmaceutical, FibroGen, Genelabs Technologies, Genentech, Human Genome Sciences, Immunomedics, Incyte Pharmaceuticals, Millennium Pharmaceuticals, Novartis, Omeros, Pfizer, Procter & Gamble, Rigel Pharmaceuticals, Roche, Sanofi Aventis, Schering-Plough, Scios, Serono, Sanwa Kagaku Kenkyusho Ltd., Sumitomo, UCB Pharma, XDx, and Xencor. Additionally, Dr. Strand serves on advisory boards for Abbott Immunology, Alder Biopharmaceuticals, Amgen, BioSeek, CanFite BioPharma, Centocor, Chelsea Therapeutics, Jazz Pharmaceuticals, Novartis, Pfizer, Robert Wood Johnson Pharmaceutical Research Institute, Roche, Sanofi-Aventis, Savient Pharmaceuticals, UCB Pharma, and Wyeth, and serves on speaking bureaus for Abbott Immunology, Amgen, Centocor, Novartis, Pfizer, and Santofi-Adventis.

Address correspondence and reprint requests to Clifton O. Bingham, III, MD, Divisions of Rheumatology and Allergy and Clinical Immunology, Johns Hopkins University, 5200 Eastern Avenue, Mason F. Lord Building, Center Tower, Room 404, Baltimore, MD 21224. E-mail: Clifton.bingham@jhmi.edu.

Submitted for publication January 31, 2006; accepted in revised form July 11, 2006.

significantly reduce radiographic progression as measured by decreased JSW or using a dichotomous definition of progression (joint space loss of ≥0.6 mm). Thirteen percent of patients receiving placebo demonstrated significant disease progression over 2 years. A dose-dependent reduction in the level of C-terminal crosslinking telopeptide of type II collagen, a cartilage degradation marker associated with progressive OA, was seen in patients who received risedronate. No increase in the number of adverse events was demonstrated for risedronate compared with placebo.

***Conclusion*. Although risedronate (compared with placebo) did not improve signs or symptoms of OA, nor did it alter progression of OA, a reduction in the level of a marker of cartilage degradation was observed. A sustained clinically relevant improvement in signs and symptoms was observed in all treatment and placebo groups.**

Osteoarthritis (OA) is the most prevalent form of arthritis, affecting more than 10% of the population and an estimated 21 million adults in the US (1). The disease is associated with significant pain and disability and is a major factor necessitating hip or knee replacement. OA is characterized by focal cartilage loss, subchondral bony changes, osteophyte formation, and (in some cases) synovitis with involvement of periarticular structures. Most pharmacologic therapy for OA is directed toward symptom control, using analgesics, nonsteroidal antiinflammatory drugs (NSAIDs), and cyclooxygenase 2 (COX-2) inhibitors. Weight loss, physical therapy, and activity are also important components of treatment. To date, there has been limited evidence for therapies that slow the disease process. Although glucosamine has been advocated as a possible structure-modifying OA drug (SMOAD) (2), data are inconsistent, and questions remain as to its absorption and putative action (3,4). Recent data have suggested a possible benefit of doxycycline in slowing radiographic progression (but not altering symptoms) in obese women with knee OA (5). Treatment with diacerein slowed radiographic progression in patients with hip OA over 3 years but had no effect on signs and symptoms (6,7). Evaluating drugs as potential SMOADs presents significant challenges for developing appropriate study designs and outcomes.

Failure of the OA joint represents cartilage degradation but may also reflect changes in subchondral bone, with decreased numbers and thinning of tibial cancellous trabeculae and localized subchondral osteoporosis in knee OA (8–10), confirming earlier observations of periarticular osteoporosis in some patients (11). Subchondral bone lesions, which are seen by magnetic resonance imaging (MRI) in many patients with OA, may represent histologic microfractures (12–14). In the Duncan-Hartley guinea pig model of spontaneous OA, subchondral bony changes are a characteristic of the disease process (15), and risedronate inhibited histologic disease progression, with a 30–40% reduction in cartilage damage (16–18). Bisphosphonates have also been effective in slowing disease progression in other animal models of OA (19,20).

Agents that suppress bone turnover, including bisphosphonates, have been associated with fewer subchondral bony lesions (as visualized by MRI) in patients with OA (21); such lesions are independently correlated with levels of pain and disease progression (22). Levels of bone turnover markers are higher in patients with progressive OA and are similar to those in patients with postmenopausal osteoporosis (23). Data from trials of patients with Paget's disease indicated that short treatment courses of higher-dosage risedronate (30 mg/day) improved bone lesions, reduced biochemical indices of disease activity (24), and reduced bone pain (25–27). In a 1-year study, 285 patients with knee OA received risedronate at a dosage of 5 mg/day, risedronate at a dosage of 15 mg/day, or placebo (28). A consistent trend for pain reduction with the highest dosage of risedronate was observed at 6 months, and a consistent trend for statistically significantly different responses in patient global assessment of disease (PGA) scores was observed at 1 year. Although these differences suggested a possible benefit in retarding radiographic progression, with 1% of patients in the group receiving risedronate at a dosage of 15 mg/day showing disease progression (≥0.75-mm joint space loss) over 1 year compared with 8% of patients in the placebo group, the differences were not statistically significant. A dose-dependent reduction in the level of urinary C-terminal crosslinking telopeptide of type II collagen (CTX-II) was also observed in that study. Thus, there is rationale for suggesting that a bisphosphonate, potentially acting to inhibit bone turnover, may have a role in the treatment of OA.

Risedronate, a pyridinyl bisphosphonate that decreases bone resorption and turnover, is efficacious for postmenopausal and corticosteroid-induced osteoporosis and, in higher doses, for Paget's disease of bone (26,27,29,30). We explored the efficacy of risedronate, in a range of doses, in knee OA.

PATIENTS AND METHODS

Study design. Two parallel phase III studies were conducted in North American and European Union sites, respectively. These were 2-year, multicenter, randomized, double-blind, placebo-controlled studies of oral risedronate at dosages of 5 mg/day, 15 mg/day, and 35 mg/week (European sites) or 5 mg/day, 15 mg/day, and 50 mg/week (North American sites) in patients with medial compartment knee OA. The studies were conducted in 42 centers in North America (US and Canada) and in 44 European centers (11 countries). All patients provided written informed consent before entering the study, which was conducted in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines for Good Clinical Practice and was administered by local and central institutional review boards.

Male and female patients, ages 40–80 years (inclusive), were recruited. Patients who underwent screening had signal knee pain due to OA on most days during at least 1 month in a 3-month period prior to screening, plus at least 1 of the following: age >50 years, morning knee stiffness lasting <30 minutes, or knee crepitus according to the American College of Rheumatology (formerly, the American Rheumatism Association) criteria for knee OA (31). All patients then underwent radiography of the knee, to confirm the presence of OA. A specified minimum or maximum level of background pain was not required for inclusion in the study.

Major exclusions were the following: known inflammatory arthritis, body mass index (BMI) >40 kg/m^2, cancer within 10 years, tetracycline use within 6 months, intraarticular injection of corticosteroids or hyaluronan preparations within 3 months, calcitonin or fluoride use within 6 months, and prior use of bisphosphonates within 12 months or for >60 days ever.

To determine whether patients had a qualifying knee radiograph, standardized radiography with fluoroscopically positioned semiflexed anteroposterior (AP) views was used. The SD for this technique was ~0.2 mm for radiographs obtained 2 days apart, based on repeat measurements (32). At least 1 osteophyte and minimal joint space width (JSW) of 2–4 mm, inclusive, in the medial tibiofemoral compartment, and a medial compartment that was narrower than the lateral were required. If both knees qualified, the signal knee was defined as the knee with the smaller JSW. Radiographic assessments were conducted at baseline, 1 year, and 2 years. Patients who withdrew were asked to return for the 24-month assessment, which included radiography.

Treatment assignment. Equal proportions of North American patients were assigned to receive either placebo, risedronate 5 mg/day, risedronate 15 mg/day, or risedronate 50 mg/week. Equal proportions of European patients were assigned to receive either placebo, risedronate 5 mg/day, risedronate 15 mg/day, or risedronate 35 mg/week. At each center, patients were randomized to treatment groups and stratified according to current use of estrogens/selective estrogen receptor modulators (SERMs).

Patients were instructed to take the study drug with sufficient plain water, once daily while in an upright position, with an empty stomach in the morning at least 30 minutes before eating or drinking anything, or, at other times during the day, at least 2 hours before or after eating or drinking and not less than 30 minutes before bedtime.

The dosages of risedronate used in these studies were based on the dosage used for postmenopausal osteoporosis (5 mg/day) and a daily dose of 15 mg, which was believed to clearly separate from the 5 mg/day dosage with regard to serum concentrations. The weekly dosing groups (35 mg/week in Europeans and 50 mg/week in North Americans) were included to provide the opportunity to evaluate the efficacy of a more convenient weekly dosing regimen, with the 50 mg/week dosage chosen to provide information regarding an intermediate total weekly dose.

Background analgesics and stepped reduction. Nonnarcotic analgesics, NSAIDs, or COX-2 inhibitors were permitted and monitored, with changes according to physician preference and clinical course. All patients underwent a stepped analgesic reduction and washout period before study visits, including the baseline visit. Each patient was provided with acetaminophen (North America)/paracetamol (Europe) (500 mg) and diclofenac (50 mg), to be used as needed as the only pain medications from day −5 to day −3 preceding the baseline, 6-, 12-, 18-, and 24-month visits. All pain medications were discontinued on day −2 and day −1 prior to these visits and on the visit day. WOMAC and PGA questions referred to the preceding 48 hours.

Treatment outcomes. The coprimary efficacy objectives were to assess the effect of risedronate on structure and symptoms in patients with mild to moderate knee OA relative to placebo. OA symptoms were measured by the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index (33) and by PGA scores. WOMAC measurements were collected on a 100-mm visual analog scale. Questionnaires and assessment instruments in the local languages were provided to the investigative sites. Standardized training was provided at investigator meetings in North America and Europe and was monitored throughout the study.

The average values for each domain were calculated and reported at each time point. The total WOMAC score was calculated as the sum of individual measurements divided by the total number of questions. Structure was assessed by measuring the progression of joint space narrowing (JSN) in the medial tibiofemoral compartment in the pooled North American and European studies after 2 years.

Radiographic assessment. The JSW of the target knee was evaluated at baseline and after 1 and 2 years of followup, at the narrowest point in the medial tibiofemoral compartment (32,34,35). This protocol standardized radiographs with a semiflexed view of the knee, aided by fluoroscopy, and by attaching a metal sphere to the fibula head to correct magnification effects. Minimum medial compartment JSW was measured with a semiautomated computerized method.

To ensure proper quality, exposure, positioning of the knee joint, and reproducibility of the JSW measurements, radiographs were obtained at 13 regional radiographic facilities (RRFs) in Europe and 12 RRFs in the US, by specially trained personnel (32); quality, exposure, positioning, and acceptability were checked on an ongoing basis. A standing AP fluoroscopically assisted semiflexed view of the signal knee was obtained according to the procedure described by Buckland-Wright and was shown to be accurate and reproducible (34,35). Each knee was flexed until the tibial plateau was horizontal

relative to the floor, parallel to the central x-ray beam and perpendicular to the radiograph film. The center of the joint, defined by the joint space, was aligned with the center of the x-ray beam with the aid of the tube's positioning light.

The precise knee position was obtained visually with the aid of fluoroscopy. With the heel fixed, the foot was internally or externally rotated until the tibial spines appeared centrally placed relative to the femoral notch; then, the knee was flexed to achieve superimposition (±1 mm) of the anterior and posterior margins of the medial tibial plateau. All radiographs were sent to the Radiographic Quality Control Centre (RQCC) in Amsterdam, The Netherlands (European patients) or to the RQCC in Ann Arbor, Michigan (North American patients), where radiographs had to pass strict quality control measures, and then on to the Central Analysis Facility at King's College in London, where the films were digitized, and semiautomated computerized measurements of minimal medial JSW were performed. This is a highly reproducible image analysis technique. For this technique, the test–retest SD for the difference between radiographs obtained 2 days apart was ~0.2 mm. The coefficient of variation for the reproducibility of the software to measure medial compartment JSW had been determined previously as 1% for test–retest radiographs of the knee in the semiflexed position (34).

Osteophytes were assessed manually on temporally ordered films by 2 radiologists and scored (if present) on the medial tibial edge, the lateral tibial edge, or the tibial spine. Baseline and exit films were graded according to the Osteoarthritis Research Society International osteophyte grading conventions on a 0–3 scale, using a reference manual (36). The percent change in osteophyte size relative to baseline was also graded, as follows: 0 = no definite growth, 1 = <50% growth, 2 = growth >50% and <100%, 3 = >100% growth. In a small validation substudy of the percent change in osteophyte size parameter, the percent of exact matches of osteophyte scores ranged from 87–97% for intrareader agreement and 74–95% for interreader agreement.

Safety ssessments. Safety data, including physical examination, vital signs, laboratory evaluations, concomitant medications, and adverse events, were collected from all patients every 3 months. Adverse events were coded according to COSTART (Coding Symbols for a Thesaurus of Adverse Reaction Terms) definitions, with severity and attributability recorded.

Assessment of biochemical markers. Early-morning, fasting, second-void urine samples were collected at baseline and at the month 6, month 12, and month 24 (exit) visits, to measure bone and cartilage turnover. Samples were frozen and analyzed in bulk. Bone resorption was assessed by determining urine levels of N-terminal crosslinking telopeptide of type I collagen (NTX-I) (Osteomark; OrthoClinical Diagnostics, Rochester, NY), and cartilage degradation was assessed with urine levels of CTX-II (CartiLaps; Nordic Bioscience, Herlev, Denmark). The detection limits of the assays were as follows: for NTX-I, 4 nmoles of BCE/liter; for CTX-II, 0.25 μg/liter. The urinary CTX-II assay is based on a mouse monoclonal antibody raised against the EKGPDP sequence of human type II collagen C-telopeptide, a sequence observed exclusively in type II collagen and not in the other collagens, including type I, or other structural proteins. The antibody has no significant cross-reactivity with type I collagen C-telopeptide (37). Interassay variability and intraassay variability were lower than 10% for both assays. Levels of urinary creatinine were measured for marker normalization.

Sample size and data analysis plans. Each study was initially designed to assure 90% power to detect a 40% protective effect of risedronate versus placebo in reducing JSN, assuming a 0.2-mm/year rate of JSN in the placebo population, a SD of 0.45 mm, a 2-year dropout rate of 30%, and a Type I error rate of 5% with Dunnett's adjustment for multiple-dose 2-sided comparisons with placebo, with a sample size requirement of 302 patients per treatment group. The study was sized for 90% power to detect a mean 0.16-mm JSN difference between a placebo-treated and a risedronate-treated group.

Prior to unblinding, it was determined that the mean rate of radiographic progression among patients receiving placebo was expected to be ~0.085 mm per year, based on the results of a smaller study using the same radiographic techniques (28), rather than a rate of 0.20 mm per year, as originally expected. As a result, the protocols were modified to focus on a pooled JSW analysis from the combined North American and European studies as the primary structure end point to provide 90% power for a 50% relative risk reduction, with a placebo-associated progression rate of 14%. The statistical analysis plan specified that the primary JSW analysis was to compare the mean JSN that occurred with placebo, provided analysis of variance (ANOVA) assumptions were met. If ANOVA assumptions were not met, the primary structure was to be the proportion of patients in whom disease progressed (defined as JSW loss of ≥0.6 mm across treatment groups), representing 3 times the SD of the measurement (32), which was the case for the final analysis.

The first planned primary analysis was a comparison of the month 24 mean change from baseline in the total WOMAC score between patients receiving the highest dosage of risedronate (15 mg/day) and patients receiving placebo, within each study. If the total WOMAC score at month 24 was statistically significant for the group receiving risedronate at a dosage of 15 mg/day versus the placebo group, then the pooled study JSW and within-study PGA analyses would simultaneously be conducted to compare the group receiving 15 mg/day of risedronate with the placebo group, using a step-down approach. Sign and symptom end points were evaluated by study (North America or Europe); however, the analyses of structure examined patients in the different dose groups, pooled for the studies.

The primary analysis of mean JSW was adjusted at each time point by using the study (North America/European Union), baseline use of estrogen/SERMs, sex, age, BMI, and baseline JSW as covariates. The JSW progressor analysis used the Cochran-Mantel-Haenszel test, with the North American study and the European study as strata. Symptom analyses at each time point were adjusted by using the appropriate baseline total WOMAC score or PGA value, pooled centers, baseline use of estrogen/SERMs, sex, age, BMI, and baseline JSW as covariates. Mean changes from baseline in measures of signs and symptoms were evaluated using repeated-measures analysis adjusted for pooled centers, baseline PGA score, baseline use of estrogen/SERMs, sex, age, BMI, and baseline JSW. The ANOVA model was used for primary symptom

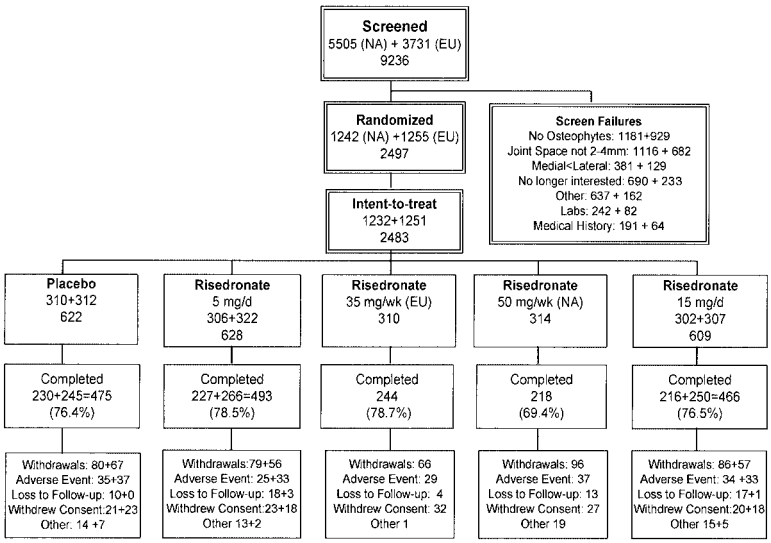

Figure 1. Flow chart of the study. Patients who continued to receive study medication through month 24 are indicated as completers. NA = North America; EU = European Union.

Table 1. Baseline characteristics of patients in the North American cohort*

Characteristic	Placebo (n = 310)	Risedronate, 5 mg/day (n = 306)	Risedronate, 15 mg/day (n = 302)	Risedronate, 50 mg/week (n = 314)	*P*	Total (n = 1,232)
Age, years	60.2 ± 0.51	60.6 ± 0.51	60.4 ± 0.51	60.7 ± 0.49	0.9125	60.5 ± 0.25
Female sex, no. (%)	178 (57)	189 (62)	196 (65)	194 (62)	0.2992	757 (61)
Race, no. (%)						
Asian	6 (2)	3 (1)	4 (1)	7 (2)		20 (2)
Black	27 (9)	28 (9)	33 (11)	21 (7)		109 (9)
Hispanic	11 (4)	10 (3)	11 (4)	11 (4)		43 (3)
Other	1 (<1)	7 (2)	6 (2)	5 (2)		19 (2)
White	265 (85)	258 (84)	248 (82)	270 (86)	0.6261	1,041 (84)
Height, cm	169.0 ± 0.59	168.5 ± 0.54	168.4 ± 0.58	167.7 ± 0.56	0.4677	168.4 ± 0.28
Weight, kg	87.0 ± 0.96	86.0 ± 0.90	85.0 ± 0.96	86.6 ± 0.93	0.4708	86.2 ± 0.47
Body mass index, kg/m^2	30.4 ± 0.28	30.2 ± 0.27	29.9 ± 0.27	30.7 ± 0.27	0.2018	30.3 ± 0.14
Postmenopausal, no. (%)†	130 (73)	148 (78)	141 (72)	150 (77)	0.4485	569 (75)
Estrogen/SERM use, no. (%)†	87 (49)	83 (44)	75 (38)	90 (46)	0.1903	335 (44)
WOMAC total score	39.7 ± 1.29	41.0 ± 1.27	39.6 ± 1.29	40.6 ± 1.31	0.8263	40.2 ± 0.65
WOMAC pain score	36.4 ± 1.24	37.8 ± 1.23	37.1 ± 1.27	37.6 ± 1.32	0.8546	37.2 ± 0.63
WOMAC function score	39.8 ± 1.36	41.3 ± 1.34	39.6 ± 1.36	40.9 ± 1.36	0.7733	40.4 ± 0.67
WOMAC stiffness score	45.9 ± 1.45	46.9 ± 1.48	45.4 ± 1.52	45.9 ± 1.52	0.9198	46.0 ± 0.75
Patient global assessment score	52.6 ± 1.38	52.8 ± 1.40	51.4 ± 1.39	54.2 ± 1.44	0.5627	52.8 ± 0.70
Joint space width, mm	2.947 ± 0.0335	2.970 ± 0.0346	2.979 ± 0.0341	2.997 ± 0.0335	0.7626	2.973 ± 0.0170
NSAID use, no. (%)	228 (74)	235 (77)	208 (69)	216 (69)	0.0742	887 (72)
Celecoxib use, no. (%)	53 (17)	48 (16)	54 (18)	52 (17)	0.9064	207 (17)
Rofecoxib use, no. (%)	42 (14)	53 (17)	33 (11)	40 (13)	0.1313	168 (14)
Acetaminophen use, no. (%)	138 (45)	140 (46)	145 (48)	136 (43)	0.6830	559 (45)
Glucosamine/chondroitin use, no. (%)	92 (30)	77 (25)	76 (25)	87 (28)	0.5227	332 (27)
NTX-I/Cr, nmole BCE/nmole Cr	37.48 ± 1.964	36.27 ± 1.001	38.80 ± 1.072	37.62 ± 1.009	0.6182	37.54 ± 0.662
CTX-II/Cr, ng/nmole Cr	296.47 ± 17.087	273.48 ± 10.682	297.16 ± 14.872	273.02 ± 9.637	0.3765	284.93 ± 6.690

* Except where indicated otherwise, values are the mean ± SEM. *P* values indicate differences across treatment groups. The chi-square test was used to compare categorical variables, and analysis of variance was used to compare continuous variables. SERM = selective estrogen receptor modulator; WOMAC = Western Ontario and McMaster Universities Osteoarthritis index; NSAID = nonsteroidal antiinflammatory drug; NTX-I = N-terminal crosslinking telopeptide of type I collagen; Cr = creatinine; CTX-II = urinary C-terminal crosslinking telopeptide of type II collagen.
† Female patients only.

Table 2. Baseline characteristics of patients in the European Union (EU) cohort*

Parameter	Placebo (n = 312)	Risedronate, 5 mg/day (n = 322)	Risedronate, 15 mg/day (n = 307)	Risedronate, 35 mg/week (n = 310)	*P*†	Total (n = 1,251)	*P*, NA vs. EU‡
Age, years	63.6 ± 0.48	63.7 ± 0.45	62.9 ± 0.47	64.1 ± 0.48	0.2901	63.6 ± 0.23	<0.0001
Female sex, no. (%)	259 (83)	254 (79)	235 (77)	243 (78)	0.2395	991 (79)	<0.0001
Race, no. (%)							
Asian	3 (1)	1 (<1)	1 (<1)	1 (<1)		6 (<1)	
Black	1 (<1)	3 (1)	2 (1)	0 (0)		6 (<1)	
Hispanic	0 (0)	0 (0)	0 (0)	1 (<1)		1 (<1)	
Other	10 (3)	10 (3)	9 (3)	14 (5)		43 (<3)	
White	298 (96)	308 (96)	295 (96)	294 (95)	0.6407	1,195 (96)	<0.0001
Height, cm	164.4 ± 0.45	164.6 ± 0.46	164.6 ± 0.49	164.6 ± 0.48	0.9799	164.5 ± 0.23	<0.0001
Weight, kg	79.8 ± 0.72	79.3 ± 0.66	79.6 ± 0.69	79.1 ± 0.72	0.9230	79.4 ± 0.35	<0.0001
Body mass index, kg/m^2	29.5 ± 0.24	29.3 ± 0.24	29.4 ± 0.23	29.2 ± 0.24	0.8494	29.4 ± 0.12	<0.0001
Postmenopausal, no. (%)§	244 (94)	240 (94)	213 (91)	222 (91)	0.4773	919 (93)	<0.0001
Estrogen/SERM use, no. (%)§	29 (11)	31 (12)	27 (11)	35 (14)	0.6979	122 (12)	<0.0001
WOMAC total score	47.0 ± 1.16	44.5 ± 1.16	47.1 ± 1.17	44.6 ± 1.21	0.2156	45.8 ± 0.59	<0.0001
WOMAC pain score	43.7 ± 1.20	40.8 ± 1.18	44.3 ± 1.19	41.0 ± 1.23	0.0766	42.4 ± 0.60	<0.0001
WOMAC function score	48.0 ± 1.23	45.5 ± 1.23	47.9 ± 1.24	45.7 ± 1.27	0.3108	46.8 ± 0.62	<0.0001
WOMAC stiffness score	47.4 ± 1.51	45.8 ± 1.40	47.1 ± 1.44	44.2 ± 1.53	0.4089	46.1 ± 0.74	0.9444
Patient global assessment score	56.9 ± 1.27	55.0 ± 1.29	56.2 ± 1.34	57.1 ± 1.30	0.6510	56.3 ± 0.65	0.0002
Joint space width, mm	2.976 ± 0.0345	2.991 ± 0.0346	2.955 ± 0.0309	2.963 ± 0.0337	0.8798	2.971 ± 0.0167	0.9405
NSAID use, no. (%)	175 (56)	193 (60)	180 (59)	170 (55)	0.5541	718 (57)	<0.0001
Celecoxib use, no. (%)	5 (2)	4 (1)	3 (1)	5 (2)	0.8840	17 (8)	<0.0001
Rofecoxib use, no. (%)	6 (2)	2 (1)	6 (2)	12 (4)	0.0399	26 (2)	<0.0001
Acetaminophen use, no. (%)	79 (25)	97 (30)	83 (27)	82 (26)	0.5654	341 (27)	<0.0001
Glucosamine/chondroitin use, no. (%)	25 (8)	26 (8)	24 (8)	25 (8)	0.9994	100 (8)	<0.0001
NTX-I/Cr, nmole BCE/nmole Cr	49.43 ± 1.364	46.79 ± 1.307	49.91 ± 2.097	46.20 ± 1.241	0.2238	48.07 ± 0.768	<0.0001
CTX-II/Cr, ng/nmole Cr	376.72 ± 13.724	367.17 ± 13.664	360.70 ± 12.059	361.71 ± 16.798	0.8498	366.58 ± 7.080	<0.0001

* Except where indicated otherwise, values are the mean ± SEM. The chi-square test was used to compare categorical variables, and analysis of variance was used to compare continuous variables. NA = North America (see Table 1 for other definitions).
† Differences across treatment groups.
‡ By Fisher's exact test for categorical variables and by analysis of variance for continuous variables.
§ Female patients only.

analyses. Unless noted otherwise, all statistical analyses were 2-sided, with a Type I error rate of 0.05.

The primary analyses were modified intent-to-treat (ITT) analyses conducted using data from all randomized patients who received at least 1 dose of study drug. In these ITT analyses, data for some patients may have been missing, due to missed visits, withdrawal, or other reasons. Missing data were not imputed for the primary efficacy end points. A per-protocol analysis for each efficacy end point was conducted for patients who met all protocol inclusion/exclusion criteria, who were compliant (taking at least 75% of the study drug), and who had no other major deviations.

RESULTS

A total of 9,236 patients at 42 sites in North America (US and Canada) and at 44 centers in Europe were screened for participation in the KOSTAR study. The most common factors involved in screening failure were radiographic criteria, including lack of qualifying osteophytes and JSW >4 mm or <2 mm. A total of 2,497 patients were randomized, and 2,483 were enrolled, constituting the ITT population, with 1,232 patients in the North American cohort and 1,251 patients in the European cohort (Figure 1). The overall screening-to-randomization ratio was ~4:1. Overall patient retention was very high, with 86.7% of patients completing the final visit at 2 years, and 76.4% completing the study without dropping out. The percentage of withdrawals in North America (27.7%) was greater than that in Europe (19.7%), largely because of loss to followup. The numbers of patients who withdrew due to adverse events were similar across groups. No differences in the number of withdrawals were noted in either study (North America or Europe), across treatment groups or in combined studies.

Several differences in the clinical characteristics of randomized patients in the North American and European studies were noted (Tables 1 and 2). The North American study population included more men, and the average age of North American patients was

Table 3. Changes in WOMAC and PGA scores from baseline to month 24 among patients in the North American and European cohorts*

		Risedronate			
	Placebo	5 mg/day	35 mg/week	50 mg/week	15 mg/day
North America					
WOMAC total	−9.5 ± 1.31	−7.9 ± 1.34	–	−10.8 ± 1.33	−8.2 ± 1.38
WOMAC pain	−8.4 ± 1.34	−8.2 ± 1.39	–	−9.9 ± 1.38	−7.9 ± 1.42
WOMAC function	−9.3 ± 1.33	−7.7 ± 1.37	–	−10.7 ± 1.36	−7.8 ± 1.41
WOMAC stiffness	−11.9 ± 1.59	−9.9 ± 1.65	–	−13.6 ± 1.63	−12.0 ± 1.69
PGA	−8.7 ± 1.71	−8.5 ± 1.77	–	−10.8 ± 1.75	−7.6 ± 1.82
European Union					
WOMAC total	−10.0 ± 1.63	−11.2 ± 1.58	−11.6 ± 1.60	–	−11.7 ± 1.62
WOMAC pain	−10.1 ± 1.71	−11.4 ± 1.66	−12.1 ± 1.67	–	−12.3 ± 1.70
WOMAC function	−9.9 ± 1.68	−11.0 ± 1.63	−11.6 ± 1.65	–	−11.5 ± 1.66
WOMAC stiffness	−10.5 ± 1.93	−13.9 ± 1.86	−12.3 ± 1.88	–	−12.8 ± 1.91
PGA	−15.6 ± 2.13	−15.2 ± 2.06	−17.0 ± 2.08	–	−17.2 ± 2.12

* Values are the adjusted mean ± SEM. The symptom analyses at each time point were adjusted using the appropriate baseline Western Ontario and McMaster Universities Osteoarthritis index (WOMAC) total score or patient global assessment (PGA) score, pooled centers, baseline use of estrogens or selective estrogen receptor modulators, sex, age, body mass index, and baseline joint space width as covariates.

younger (60.5 years versus 63.6 years in the European study). Although more European women were postmenopausal, more women in the North American group took estrogen or SERMs. Patients in North America were heavier, with a higher mean BMI (30.3 kg/m^2 versus 29.4 kg/m^2). The baseline total WOMAC scores, scores for all WOMAC domains, and PGA scores were higher in Europeans, although WOMAC scores for stiffness were not significantly different ($P = 0.944$). More patients in North America were taking NSAIDS and coxibs as analgesics. The baseline characteristics were, however, comparable across the different treatment groups within each study. The mean JSWs at baseline in the North American and European studies were not significantly different ($P = 0.9405$), reflecting standardized radiographic methods and the requirements for study entry.

Signs and symptoms. 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 (Table 3). In the placebo-treated group, a reduction of ~20% from baseline was seen in total WOMAC scores as well as in each subcomponent. No statistically significant differences or trends were noted for any dose of risedronate. Similarly, the reduction in PGA scores was of a similar magnitude across all 5 treatment groups. Although the baseline and final WOMAC scores, subscale scores, and PGA scores were higher in the European group than in the North American group, the reductions from baseline were similar. Reductions were seen at the first time point (6 months) and were maintained throughout 2 years in all groups (Figure 2). There was a reduction in the average number of days and number of pills of analgesic medi-

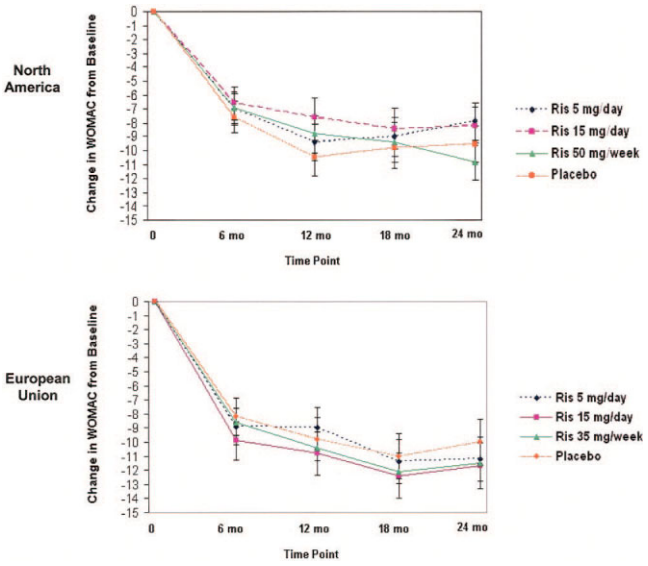

Figure 2. Adjusted mean ± SEM changes from baseline in total Western Ontario and McMaster Universities Osteoarthritis (WOMAC) and WOMAC pain subscale scores over 24 months. The symptom analyses at each time point were adjusted using the appropriate baseline WOMAC score, pooled centers, baseline use of estrogen or selective estrogen receptor modulators, sex, age, body mass index, and baseline joint space width as covariates. Ris = risedronate.

Table 4. Proportion of patients experiencing radiographic progression, defined as ≥0.6 mm of JSN over 24 months*

	Placebo	Risedronate, 5 mg/day	Risedronate, 35 mg/week	Risedronate, 50 mg/week	Risedronate, 15 mg/day	Total
North America						
No. of radiographs	269	268		268	260	1,065
No. (%) progressors	37 (14)	43 (16)		38 (14)	36 (14)	154 (14)
European Union						
No. of radiographs	280	305	280		283	1,148
No. (%) progressors	35 (13)	35 (11)	31 (11)		39 (14)	140 (12)
Combined total						
No. of radiographs	549	573	280	268	543	2,213
No. (%) progressors	72 (13)	78 (14)	31 (11)	38 (14)	75 (14)	294 (13)

* The narrowest medial compartment joint space width (JSW) was measured using standardized fluoroscopically positioned semiflexed-view knee radiographs obtained at baseline, 12 months, and 24 months, in the North American, European, or combined studies. A patient was defined as a progressor using a dichotomous definition of a ≥0.6 mm decrease in JSW from baseline at any postbaseline measurement. JSN = joint space narrowing.

cation taken per week in the placebo group and all treatment groups in North America and Europe, with no differences noted with any risedronate dose compared with placebo (data not shown).

Radiographic changes. Because in the combined symptomatic analysis of 15 mg/day of risedronate versus placebo, ANOVA assumptions were not met using the prespecified definitions, the primary analysis for structure modification was performed using JSW progression as the end point. The proportion of patients experiencing radiographic progression, defined as ≥0.6 mm of JSN over 24 months, was 13% overall, with no statistically significant differences noted in any treatment group or in the North American versus European cohorts (Table 4). Although the proportion of JSW progressors was small at 2 years, it was similar to that extrapolated based on progression among patients receiving placebo in the pilot study (31) on which this analysis was modeled.

Most patients had no radiographic worsening, defined as JSN of ≥0.6 mm. An approximate normal distribution within 3 SD of the measurement error was observed (Figure 3). Although a few patients could be classified as having joint space "improvement," this is most likely attributable to expected measurement error in joint space over 2 years. Far more patients were represented within the progression "tail," with many progressors demonstrating marked loss of joint space of >1 mm and sometimes >2 mm.

The observed mean ± SD reductions in JSW in the placebo groups over 24 months were 0.088 ± 0.040 mm in the European cohort and 0.130 ± 0.033 mm in the North American cohort. No statistically significant differences were noted for any dose of risedronate compared with placebo, for either study or for the combined data (data not shown). Although in this study, changes in grading according to the Kellgren/Lawrence scale (38) were not specifically evaluated, there was no difference between treatment groups in medial, lateral, or tibial spine osteophyte changes at 2 years. In the different treatment groups, 26–37% of patients had worsening of medial spine osteophytes, 10–22% had worsening of lateral spine osteophytes, and 3–19% had worsening of tibial spine osteophytes, with no group demonstrating trends or statistically significant differences compared with placebo (data not shown).

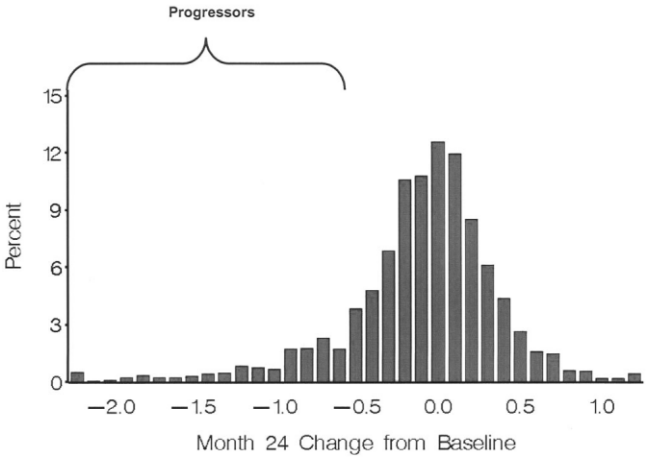

Figure 3. Histogram showing the percent change from baseline in joint space width (JSW) among patients defined as progressors, in the combined North American and European studies. The narrowest JSW in the medial compartment was measured using an automated method of digitized radiographs and was acquired using analog techniques, with highly standardized fluoroscopically positioned, semiflexed-view knee radiographs at baseline and 24 months. Patients were defined as progressors using a dichotomous definition of a ≥0.6 mm decrease in JSW from baseline.

Biochemical markers. In both the North American and European groups, an expected dose-dependent decrease in the level of NTX-I with risedronate was observed within 6 months and continued through 24 months, demonstrating effective drug delivery. The mean percent changes from baseline to 24 months for all doses of risedronate were statistically significantly different compared with placebo. In the North American placebo group, a 7.3% increase in the level of NTX-I was seen, with a decrease from baseline of 21.6% in patients receiving risedronate at a dosage of 5 mg/day, a decrease of 29.2% in those receiving risedronate at a dosage of 50 mg/week, and a decrease of 39.2% in the group receiving risedronate at a dosage of 15 mg/day. Similarly, in the European cohort, the level of NTX-I increased by 3.0% in the placebo group, while decreases were seen with all doses of risedronate (29.0% in the group receiving 5 mg/day, 28.2% in those receiving 35 mg/week, and 41.7% in those receiving 15 mg/day).

An early decrease in the level of CTX-II was seen in risedronate-treated patients, although placebo-treated patients had increases over the 24 months of the study. At the highest dosage of risedronate (15 mg/day), reductions of 17.9% and 19.6% from baseline to 24 months were seen in North American patients and European patients, respectively, compared with increases in the North American and European placebo groups of 26.3% and 10.1%, respectively. Even greater reductions in the levels of CTX-II (25–41%) were seen at earlier time points in patients receiving risedronate.

Safety. Risedronate was well tolerated over 2 years, using dosages that were up to 3-fold the currently approved dosage for osteoporosis. No clinically significant differences in any standard laboratory parameters (complete blood cell count, electrolytes, liver function, renal function) were evident in the risedronate-treated groups compared with those receiving placebo (data not shown), and there were no differences in the number of deaths. No significant difference was noted in the number of upper gastrointestinal (GI) adverse events between patients receiving risedronate and those receiving placebo. There were no significant differences between groups for prior GI disease and use of NSAIDs, aspirin, or proton pump inhibitors (data not shown). Upper GI adverse events were defined as abdominal pain, ulcers, esophagitis, gastritis, dyspepsia, dysphagia, hematemesis, and melena. The low rate of GI adverse events is especially notable in patients with OA, of whom >70% had taken an NSAID or aspirin. Furthermore, at the highest risedronate dosage (15 mg/day or a total dose of 105 mg/week), there were fewer adverse events associated with risedronate compared with placebo, although the difference was not statistically significant.

DISCUSSION

The Knee Osteoarthritis Structural Arthritis (KOSTAR) trial was designed to explore the effect of risedronate on JSN and symptoms in patients with mild to moderate knee OA. The risedronate OA research program consisted of 3 studies: a smaller, 285-patient study conducted in the UK (the British Study of Risedronate in Structure and Symptoms of Knee OA [BRISK]), which focused on symptom end points (28), and the 2 phase III studies summarized in this report, which explored changes in JSW and symptoms as primary end points. This is the largest interventional drug development study of knee OA reported to date, with >2,400 patients randomized, and >86.7% completing the month 24 visit. These studies demonstrate the feasibility of using centralized radiography facilities and fluoroscopically aided radiographs for a multinational study.

The previously reported BRISK study showed that risedronate at a dosage of 15 mg/day improved PGA scores over 1 year, with concomitant reductions in the level of a marker of cartilage degradation (CTX-II) (28). Fewer risedronate-treated patients had significant progression over 1 year compared with placebo-treated patients. In the current multinational study, the same techniques of measurement showed that even though risedronate was effective for reducing bone turnover and the level of cartilage degradation markers, no treatment effect was demonstrated for the primary study end points.

Signs and symptoms improved in all groups, including placebo-treated patients, representing a change of ~20% from baseline in symptom end points, including the total WOMAC score, WOMAC subscales, and PGA scores. The magnitude of this improvement has been accepted as clinically relevant at the level of the individual patient as well as in clinical trials (39,40). Furthermore, in patients with lower levels of pain, as seen in this study, previously reported clinically important improvements in both pain and PGA scores were similar to the reductions seen in the KOSTAR trial (40). This improvement was noted at the earliest time point and persisted through the 2 years of the study. There was, however, no demonstrable treatment difference in terms of signs and symptoms for risedronate compared with placebo. In the BRISK study, Spector et al reported an improvement in PGA scores (28); however, the

magnitude of the placebo-associated improvement was not as large as that in the current study, perhaps accounting for the significance of the treatment effect. It is unknown whether the placebo benefit we observed represents expectation bias on the part of patients or whether the WOMAC index is unable to discern a treatment effect at low background pain levels. In a recently completed study of doxycycline (5), patients had a similarly low level of background pain (WOMAC pain scores of 43.2 in the index knee and 36 in the contralateral knee), with no treatment effect on signs and symptoms in spite of an apparent treatment effect on structure in one knee but not the other. The doxycycline study also allowed use of background analgesics, to encourage participant retention over 30 months.

The KOSTAR trial enrolled patients who may have been taking analgesics to control pain at baseline, with >50% of patients in both the European and North American groups taking NSAIDs or coxibs at baseline. The KOSTAR study design was developed in conjunction with regulatory authorities to encourage patient retention over 2 years, recognizing that analgesic requirements are variable and may necessitate switches in medication. Given that traditional flare-design studies of knee OA using active comparators are associated with a withdrawal rate of up to 30% at 6 weeks (41–43) and even more in placebo groups, prohibiting patients from taking rescue medication would have likely resulted in a significant number of withdrawals over time. Other studies of structure-modifying therapies in OA have had dropout rates ranging from 29% to almost 50% over 2–3 years (2,7,44). Using the KOSTAR study design, an impressive 76% of patients completed 2 years without dropping out, and 86.7% completed the 24-month visit.

To account for differences in analgesic regimens, at 5 days preceding study visits, patients were provided with diclofenac and acetaminophen as the only allowable analgesics. These agents were eliminated during the 2 days preceding visits for symptom evaluation. In spite of analgesic washout, patients in the KOSTAR trial had lower levels of baseline pain than have been seen in most other studies of analgesics. Other OA studies in which background analgesic therapy was continued have enrolled only patients with higher levels of background pain, in order to demonstrate a treatment effect (45).

No treatment effect of risedronate was demonstrated for the primary structure end points. The proportions of patients in all treatment groups who demonstrated significant progression (≥0.6 mm of joint space loss) over 2 years were low (including 13% of placebo-treated patients). Most patients showed no change over time or changes were within the measurement error of the technique. In the similarly designed BRISK study, 8% of placebo-treated patients demonstrated progression at 1 year, using an even more stringent definition of progression (0.75 mm of joint space loss). In a study of glucosamine evaluating progression of knee OA using a fixed-extension x-ray and defining significant progression as >0.5 mm of joint space loss, only 14% of placebo-treated patients demonstrated progression over 3 years (2).

The changes in mean JSW in all groups were also smaller than originally anticipated. Although based on results of prior studies (46–50) mean radiographic progression was anticipated to occur at a rate of 0.20 mm per year, in the KOSTAR trial mean radiographic progression was 0.088 mm over 2 years in the European cohort and 0.13 mm in the North American cohort.

Many prior studies evaluating disease modification in OA have shown mean changes that were less than the measurement error of the technique of evaluation. Using the same fluoroscopically positioned flexed-knee view as that used in the KOSTAR trial, Brandt et al (5) found a decrease over 30 months of 0.45 mm in the index knee and 0.41 mm in the contralateral knee in placebo-treated patients; this decrease is more than 3-fold greater than that seen in the KOSTAR study. This may be attributable to enrichment of that study with patients with an identifiable risk factor for disease progression, namely obesity (the mean BMI was 36.7 kg/m^2, compared with 30.3 kg/m^2 in the North American cohort and 29.4 kg/m^2 in the European cohort of the KOSTAR study), or to the fact that patients enrolled in the doxycycline study (5) had more cartilage at baseline. Although the radiographic acquisition method used in the doxycycline study was the same (with the exception of use of digital radiographs), the analysis by Brandt et al used a manual method of determining JSW that, although reproducible, may be less accurate and reliable than the computer-assisted measurements used in the KOSTAR trial (34). In a study of glucosamine using fixed extension radiographs, the mean JSW change over 3 years was 0.19 mm in the placebo group, without enrichment for risks associated with progression (2).

Limb angulation and malalignment have been increasingly recognized as potentially important factors influencing the rates of radiographic progression in OA (51). In our study, however, neither a full-length radiograph nor a clinical assessment of varus and valgus alignment was performed. However, because our study was limited to an assessment of patients in whom medial compartment disease was greater than lateral compart-

ment disease, we would anticipate that malalignment in this population would be predominantly varus in nature. Thus, some of the effects of malalignment introduced in studies that combine medial and lateral compartment disease may have been somewhat mitigated. The ability to assess alignment using fluoroscopically positioned semiflexed-view radiographs, as were obtained in this study, is limited compared with other methods of evaluation (e.g., full-limb films).

Other studies have classified radiographic progression as a worsening of the Kellgren/Lawrence score, which is dependent predominantly on osteophytes, whereas progression in the KOSTAR trial was defined as a significant amount of JSN. Nevertheless, no treatment effect on osteophytes was observed. Although an effect of bisphosphonates on osteophytes has been demonstrated in animal models of OA (19), we did not observe a treatment effect of risedronate. The sensitive radiography technique used to detect changes in JSW may not be ideal for detecting changes in osteophytes over time, because osteophytes may not appear in profile, thus making assessment of their size difficult. It is also more difficult to detect changes in the categorical grading system used for osteophyte size compared with the linear changes derived from JSW measurement.

Many investigators have argued that a "hard" outcome should also be used in studies of SMOADs. Some have suggested that joint replacement represents ultimate joint failure and could be used as such an outcome (52). In this study, only ~3% of patients underwent joint replacement surgeries, some of which may have been planned prior to participation in the study, and there was no difference between treatment groups in the numbers of nontraumatic joint replacements (potentially of nonindex joints). The evaluation of joint failure may be a possible outcome measure in future studies but would likely require much longer periods of followup and even larger numbers of patients.

The retention of patients in the study indicated a high degree of compliance with the regimen. The adverse events recorded did not indicate any differences attributable to risedronate compared with placebo. The numbers of dropouts and withdrawals were similar across groups, and no clear relationship with the dosage of study medication was observed. The tolerability of dosages up to 3-fold the dosage used to treat osteoporosis over 2 years, especially in a population of patients with significant concomitant background use of NSAIDs, was impressive. In spite of concerns about potential GI toxicity with long-term administration of high doses, risedronate was well tolerated, with no increase in the incidence of GI adverse events, as previously observed (53).

Notwithstanding the lack of treatment effects on signs and symptoms or joint space, the demonstration of a dose-dependent reduction in a marker of cartilage degradation (e.g., urinary CTX-II) in response to risedronate was notable in both cohorts. Urinary CTX-II levels are thought to reflect the rate of cartilage degradation, and elevated levels of CTX-II have been seen in patients with imminent progression of OA and correlated with long-term progression (54,55). Similar results were previously reported in the smaller BRISK trial (28). Earlier studies of postmenopausal women and patients with Paget's disease also showed that bisphosphonates reduced the levels of markers of cartilage degradation (56,57). Whether a long-term reduction in the level of CTX-II would translate into a slower rate of progression could not be accurately determined from the current study, due to the limited time period.

The mechanism of action for a reduction in CTX-II levels with risedronate is unclear. This may represent a primary effect on subchondral bone turnover leading to improvement in cartilage stability. Given that in OA subchondral bone the size and number of trabecula are decreased (9), along with the known benefits of bisphosphonates on improving trabecular connectivity and bone strength (58), it is possible that local improvement in subchondral bone strength would better absorb load and translate into decreased levels of biomechanical stressors on cartilage. It is unknown whether a reduction in the level of cartilage degradation markers would correlate with visible joint structure changes using more sensitive imaging, but this remains an important question for future research. Indeed, reductions in the level of CTX-II have been recently reported to track with MR images of subchondral lesions in OA knees over 3 months (59).

This study demonstrates the challenges associated with evaluating a medication that may affect signs and symptoms along with a radiographic outcome and in developing a study design that will evaluate both outcomes. Although controlling pain is important for patient retention in a study, the measures used to control this pain may result in a high placebo response, as demonstrated here. Conversely, although patients with mild pain are potentially appropriate for enrollment in a longer-term study of structure modification, such patients may not be appropriate for studying an effect on signs and symptoms. Plain radiography, even over 2 years, will detect only a small number of progressors, as defined by stringent criteria that take into account the

measurement error of the radiographic technique. As is also the case in RA clinical studies, a small number of patients drive mean changes, with most patients experiencing no change during the course of the study. Defining clinical, biochemical, and genetic predictors of progression is important. Further analyses such as these may indicate a more appropriate group to study for future clinical trials (60,61). Although MRI may be more sensitive in detecting structural changes over time (59,62), additional correlation with plain radiography is still likely to be required by drug regulatory agencies and by the rheumatology community.

ACKNOWLEDGMENTS

We would like to acknowledge participation of the following investigators: in North America, W. Bensen, E. Keystone, H. Tannenbaum (Canada); R. D. Altman, H. S. Baraf, S. B. Herbert, J. M. Bathon, J. A. Block, D. G. Borenstein, A. Brodsky, B. Corser, T. Cupps, J. P. Donohue, R. D. Emkey, J. Fidelholtz, J. Z. Forstot, C. M. Franklin, K. H. Fye, N. Gaylis, J. Geohas, J. S. Gimbel, G. V. Gordon, R. Gordon, T. N. Hangartner, B. K. Harris, R. Katz, S. Kolasinski, J. A. Markenson, M. Neuwelt, C. Radis, W. Riskin, P. Rosenthal, T. Schnitzer, R. Severance, Y. Sherrer, J. Tesser, C. Thorne, N. Wei, M. A. Weitz (US); in Europe, J. Smolen, H. Bröll (Austria); Z. Chicy, K. Pavelka (Czech Republic); P. Bourgeois, A. Kahan, J.-M. LeParc, T. Bardin (France); H. Gaulrapp, V. Jaegermann, H. Rechl, M. Talke, H. Zippel, J. Zacher, A. Wagenitz (Germany); G. Balint (Hungary); B. Bresnihan, E. Casey, C. J. McCarthy, M. G. Molloy, P. O'Connell (Ireland); M. Cutolo, M. Bevilacqua, L. Sinigaglia (Italy); J. W. J. Bijlsma, J. D. Moolenburgh, V. Van de Walle (The Netherlands); E. Czerwinski, A. Filipowicz-Sosnowska, P. Gluszko, R. Lorenc, J. Przedlacki, A. Sawicki, L. Szczepanski, W. Tlustochowicz (Poland); B. Curkovic, A. Pahor, B. Rozman (Slovenia/Croatia).

We thank Curtis Hayes and Cornelius van Kuijk for radiography design and evaluations. We also thank the study coordinators and personnel at all investigative sites and radiography facilities. We gratefully acknowledge the participation of the almost 2,500 patients involved in these clinical trials. We would like to acknowledge the assistance of Ruby Xia and Chad Melson for programming support.

REFERENCES

1. Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum 1998;41:778–99.
2. Pavelka K, Gatterova J, Olejarova M, Machacek S, Giacovelli G, Rovati LC. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. Arch Intern Med 2002;162:2113–23.
3. Biggee BA, Blinn CM, McAlindon TE, Nuite M, Silbert JE. Low levels of human serum glucosamine after ingestion of glucosamine sulphate relative to capability for peripheral effectiveness. Ann Rheum Dis 2006;65:222–6.
4. Clegg DO, Reda DJ, Harris CL, Klein MA, O'Dell JR, Hooper MM, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med 2006; 354:795–808.
5. Brandt KD, Mazzuca SA, Katz BP, Lane KA, Buckwalter KA, Yocum DE, et al. Effects of doxycycline on progression of osteoarthritis: results of a randomized, placebo-controlled, double-blind trial. Arthritis Rheum 2005;52:2015–25.
6. Provvedini DM. The true results of the ECHODIAH study with diacerein [letter]. Osteoporos Int 2003;14:270.
7. Dougados M, Nguyen M, Berdah L, Mazieres B, Vignon E, Lequesne M, for the ECHODIAH Investigators Study Group. Evaluation of the structure-modifying effects of diacerein in hip osteoarthritis: ECHODIAH, a three-year, placebo-controlled trial. Arthritis Rheum 2001;44:2539–47.
8. Messent EA, Buckland-Wright JC, Blake GM. Fractal analysis of trabecular bone in knee osteoarthritis is a more sensitive marker of disease status than bone mineral density. Calcif Tissue Int 2005; 76:419–25.
9. Messent EA, Ward RJ, Tonkin CJ, Buckland-Wright C. Tibial cancellous bone changes in patients with knee osteoarthritis: a short-term longitudinal study using Fractal Signature Analysis. Osteoarthritis Cartilage 2005;13:463–70.
10. Messent EA, Ward RJ, Tonkin CJ, Buckland-Wright C. Cancellous bone differences between knees with early, definite and advanced joint space loss: a comparative quantitative macroradiographic study. Osteoarthritis Cartilage 2005;13:39–47.
11. Karvonen RL, Miller PR, Nelson DA, Granda JL, Fernandez-Madrid F. Periarticular osteoporosis in osteoarthritis of the knee. J Rheumatol 1998;25:2187–94.
12. Conaghan PG, Felson DT. Structural associations of osteoarthritis pain: lessons from magnetic resonance imaging [review]. Novartis Found Symp 2004;260:191–201; discussion 201–5, 277–9.
13. Bergman AG, Willen HK, Lindstrand AL, Pettersson HT. Osteoarthritis of the knee: correlation of subchondral MR signal abnormalities with histopathologic and radiographic features. Skeletal Radiol 1994;23:445–8.
14. Zanetti M, Bruder E, Romero J, Hodler J. Bone marrow edema pattern in osteoarthritic knees: correlation between MR imaging and histologic findings. Radiology 2000;215:835–40.
15. Anderson-MacKenzie JM, Quasnichka HL, Starr RL, Lewis EJ, Billingham ME, Bailey AJ. Fundamental subchondral bone changes in spontaneous knee osteoarthritis. Int J Biochem Cell Biol 2005;37:224–36.
16. Spector TD. Bisphosphonates: potential therapeutic agents for disease modification in osteoarthritis. Aging Clin Exp Res 2003; 15:413–8.
17. Meyer J, Farmer R, Prenger MC. Risedronate but not alendronate slows disease progression in the guinea pig model of primary osteoarthritis [abstract]. J Bone Miner Res 2001;16 Suppl 1:SA472.
18. Meyer JM, Dansereau SM, Farmer RW, Jeans GL, Prenger MC. Bisphosphonates structurally similar to risedronate (actonel) slow disease progression in the guinea pig model of primary osteoarthritis [abstract]. Arthritis Rheum 2001;44 Suppl 9:S307.
19. Hayami T, Pickarski M, Wesolowski GA, Mclane J, Bone A, Destefano J, et al. The role of subchondral bone remodeling in osteoarthritis: reduction of cartilage degeneration and prevention of osteophyte formation by alendronate in the rat anterior cruciate ligament transection model. Arthritis Rheum 2004;50:1193–206.
20. Muehleman C, Green J, Williams JM, Kuettner KE, Thonar EJ, Sumner DR. The effect of bone remodeling inhibition by zoledronic acid in an animal model of cartilage matrix damage. Osteoarthritis Cartilage 2002;10:226–33.
21. Carbone LD, Nevitt MC, Wildy K, Barrow KD, Harris F, Felson

D, et al, for the Health, Aging and Body Composition Study. The relationship of antiresorptive drug use to structural findings and symptoms of knee osteoarthritis. Arthritis Rheum 2004;50: 3516–25.
22. Felson DT, Chaisson CE, Hill CL, Totterman SM, Gale ME, Skinner KM, et al. The association of bone marrow lesions with pain in knee osteoarthritis. Ann Intern Med 2001;134:541–9.
23. Bettica P, Cline G, Hart DJ, Meyer J, Spector TD. Evidence for increased bone resorption in patients with progressive knee osteoarthritis: longitudinal results from the Chingford study. Arthritis Rheum 2002;46:3178–84.
24. Brown JP, Chines AA, Myers WR, Eusebio RA, Ritter-Hrncirik C, Hayes CW. Improvement of pagetic bone lesions with risedronate treatment: a radiologic study. Bone 2000;26:263–7.
25. Burger H, van Daele PL, Odding E, Valkenburg HA, Hofman A, Grobbee DE, et al. Association of radiographically evident osteoarthritis with higher bone mineral density and increased bone loss with age: the Rotterdam Study. Arthritis Rheum 1996;39:81–6.
26. Hosking DJ, Eusebio RA, Chines AA. Paget's disease of bone: reduction of disease activity with oral risedronate. Bone 1998;22: 51–5.
27. Miller PD, Brown JP, Siris ES, Hoseyni MS, Axelrod DW, Bekker PJ, for the Paget's Risedronate/Etidronate Study Group. A randomized, double-blind comparison of risedronate and etidronate in the treatment of Paget's disease of bone. Am J Med 1999;106: 513–20.
28. Spector TD, Conaghan PG, Buckland-Wright JC, Garnero P, Cline GA, Beary JF, et al. Effect of risedronate on joint structure and symptoms of knee osteoarthritis: results of the BRISK randomized, controlled trial [ISRCTN01928173]. Arthritis Res Ther 2005;7:R625–33.
29. Reid DM, Hughes RA, Laan RF, Sacco-Gibson NA, Wenderoth DH, Adami S, et al, for the European Corticosteroid-Induced Osteoporosis Treatment Study. Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized trial. J Bone Miner Res 2000;15: 1006–13.
30. Harris ST, Watts NB, Li Z, Chines AA, Hanley DA, Brown JP. Two-year efficacy and tolerability of risedronate once a week for the treatment of women with postmenopausal osteoporosis. Curr Med Res Opin 2004;20:757–64.
31. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al, for the Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. Arthritis Rheum 1986;29:1039–49.
32. Buckland-Wright JC, Bird CF, Ritter-Hrncirik CA, Cline GA, Tonkin C, Hangartner TN, et al. X-ray technologists' reproducibility from automated measurements of the medial tibiofemoral joint space width in knee osteoarthritis for a multicenter, multinational clinical trial. J Rheumatol 2003;30:329–38.
33. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833–40.
34. Buckland-Wright JC, Williams SA, Ward RJ. Accuracy and precision of joint space width measurements in standard and macroradiographs of osteoarthritic knees. Ann Rheum Dis 1995;54: 872–80.
35. Buckland-Wright JC, Wolfe F, Ward RJ, Flowers N, Hayne C. Substantial superiority of semiflexed (MTP) views in knee osteoarthritis: a comparative radiographic study, without fluoroscopy, of standing extended, semiflexed (MTP), and schuss views. J Rheumatol 1999;26:2664–74.
36. Altman RD, Hochberg M, Murphy WA Jr, Wolfe F, Lequesne M. Atlas of individual radiographic features in osteoarthritis. Osteoarthritis Cartilage 1995;3 Suppl A:3–70.
37. Christgau S, Garnero P, Fledelius C, Moniz C, Ensig M, Gineyts E, et al. Collagen type II C-telopeptide fragments as an index of cartilage degradation. Bone 2001;29:209–15.
38. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthrosis. Ann Rheum Dis 1957;16:494–501.
39. Angst F, Aeschlimann A, Stucki G. Smallest detectable and minimal clinically important differences of rehabilitation intervention with their implications for required sample sizes using WOMAC and SF-36 quality of life measurement instruments in patients with osteoarthritis of the lower extremities. Arthritis Rheum 2001;45:384–91.
40. Tubach F, Ravaud P, Baron G, Falissard B, Logeart I, Bellamy N, et al. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. Ann Rheum Dis 2005;64:29–-33.
41. Geba GP, Weaver AL, Polis AB, Dixon ME, Schnitzer TJ, for the VACT Group. Efficacy of rofecoxib, celecoxib, and acetaminophen in osteoarthritis of the knee: a randomized trial. JAMA 2002;287:64–71.
42. Pincus T, Koch G, Lei H, Mangal B, Sokka T, Moskowitz R, et al. Patient Preference for Placebo, Acetaminophen (paracetamol) or Celecoxib Efficacy Studies (PACES): two randomised, double blind, placebo controlled, crossover clinical trials in patients with knee or hip osteoarthritis. Ann Rheum Dis 2004;63:931–9.
43. Pincus T, Koch GG, Sokka T, Lefkowith J, Wolfe F, Jordan JM, et al. A randomized, double-blind, crossover clinical trial of diclofenac plus misoprostol versus acetaminophen in patients with osteoarthritis of the hip or knee. Arthritis Rheum 2001;44:1587–98.
44. Mazzuca SA, Brandt KD, Katz BP, Lane KA, Bradley JD, Heck LW, et al. Subject retention and adherence in a randomized placebo-controlled trial of a disease-modifying osteoarthritis drug. Arthritis Rheum 2004;51:933–40.
45. Emkey R, Rosenthal N, Wu SC, Jordan D, Kamin M. Efficacy and safety of tramadol/acetaminophen tablets (Ultracet) as add-on therapy for osteoarthritis pain in subjects receiving a COX-2 nonsteroidal antiinflammatory drug: a multicenter, randomized, double-blind, placebo-controlled trial. J Rheumatol 2004;31: 150–6.
46. Lequesne M. Quantitative measurements of joint space during progression of osteoarthritis: "chondrometry." In: Kuettner K, Goldberg V, editors. Osteoarthritic disorders. Rosemont (IL): American Academy of Orthopaedic Surgeons; 1995. p. 427–44.
47. Ravaud P, Giraudeau B, Auleley GR, Edouard-Noel R, Dougados M, Chastang C. Assessing smallest detectable change over time in continuous structural outcome measures: application to radiological change in knee osteoarthritis. J Clin Epidemiol 1999;52: 1225–30.
48. Buckland-Wright JC, Macfarlane DG, Jasani MK, Lynch JA. Quantitative microfocal radiographic assessment of osteoarthritis of the knee from weight bearing tunnel and semiflexed standing views. J Rheumatol 1994;21:1734–41.
49. Kirwan JR, Cushnaghan J, Dacre J, McAlindon T, Dieppe PA, Rogers J. Progression of joint space narrowing in knee osteoarthritis [abstract]. Arthritis Rheum 1992;35 Suppl 9:S134.
50. Buckland-Wright JC, Macfarlane DG, Lynch JA, Jasani MK. Quantitative microfocal radiography detects changes in OA knee joint space width in patients in placebo controlled trial of NSAID therapy. J Rheumatol 1995;22:937–43.
51. Sharma L, Song J, Felson DT, Cahue S, Shamiyeh E, Dunlop DD. The role of knee alignment in disease progression and functional decline in knee osteoarthritis. JAMA 2001;286:188–95.
52. Dougados M, Gueguen A, Nguyen M, Berdah L, Lequesne M, Mazieres B, et al. Requirement for total hip arthroplasty: an outcome measure of hip osteoarthritis? J Rheumatol 1999;26: 855–61.

53. Adami S, Pavelka K, Cline GA, Hosterman MA, Barton IP, Cohen SB, et al. Upper gastrointestinal tract safety of daily oral risedronate in patients taking NSAIDs: a randomized, double-blind, placebo-controlled trial. Mayo Clin Proc 2005;80:1278–85.
54. Garnero P, Landewe R, Boers M, Verhoeven A, van der Linden S, Christgau S, et al. Association of baseline levels of markers of bone and cartilage degradation with long-term progression of joint damage in patients with early rheumatoid arthritis: the COBRA study. Arthritis Rheum 2002;46:2847–56.
55. Reijman M, Hazes JM, Bierma-Zeinstra SM, Koes BW, Christgau S, Christiansen C, et al. A new marker for osteoarthritis: cross-sectional and longitudinal approach. Arthritis Rheum 2004;50: 2471–8.
56. Lehmann HJ, Mouritzen U, Christgau S, Cloos PA, Christiansen C. Effect of bisphosphonates on cartilage turnover assessed with a newly developed assay for collagen type II degradation products. Ann Rheum Dis 2002;61:530–3.
57. Garnero P, Christgau S, Delmas PD. The bisphosphonate zoledronate decreases type II collagen breakdown in patients with Paget's disease of bone. Bone 2001;28:461–4.
58. Borah B, Dufresne TE, Chmielewski PA, Johnson TD, Chines A, Manhart MD. Risedronate preserves bone architecture in postmenopausal women with osteoporosis as measured by three-dimensional microcomputed tomography. Bone 2004;34:736–46.
59. Garnero P, Peterfy C, Zaim S, Schoenharting M. Bone marrow abnormalities on magnetic resonance imaging are associated with type II collagen degradation in knee osteoarthritis: a three-month longitudinal study. Arthritis Rheum 2005;52:2822–9.
60. Bingham CO III, Cline G, Adami S, Buckland-Wright C, Cohen S, Conaghan P, et al. Predictors of structural progression in knee osteoarthritis over 24 months [abstract]. Osteoarthritis Cartilage 2004;12 Suppl B:S136.
61. Lohmander LS, Felson D. Can we identify a 'high risk' patient profile to determine who will experience rapid progression of osteoarthritis? Osteoarthritis Cartilage 2004;12 Suppl A: S49–52.
62. Raynauld JP, Martel-Pelletier J, Berthiaume MJ, Labonte F, Beaudoin G, de Guise JA, et al. Quantitative magnetic resonance imaging evaluation of knee osteoarthritis progression over two years and correlation with clinical symptoms and radiologic changes. Arthritis Rheum 2004;50:476–87.