A 2 yr longitudinal radiographic study examining the effect of a bisphosphonate (risedronate) upon subchondral bone loss in osteoarthritic knee patients

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Objectives. To determine whether risedronate (RIS) slows down trabecular bone loss in the medial compartment of the proximal tibia, a characteristic of patients with progressive knee osteoarthritis (OA).

Methods. Initially, 100 patients were randomly selected from each treatment group (each N~300) comprising placebo and RIS 5 mg/day, 15 mg/day and 50 mg/week from a double blind, multi-centre, placebo-controlled, 2 yr investigation of OA knee patients in North America. Using fluoroscopic semi-flexed standard radiography, baseline and exit knee radiographs were digitized by laser scanner. Following computerized measurement of minimum medial compartment joint space width, each group was subdivided into joint space narrowing (JSN) non-progressor or JSN-progressor (JSN ≥ 0.6 mm measured at any point post-baseline). Computerized method of fractal signature analysis (FSA) quantified longitudinal changes separately in horizontal and vertical trabeculae in region of interest (three-fourth width of tibial compartment x 6 mm height) in the medial compartment. Following the initial study, all JSN-progresor knees within the entire patient cohort (N = 1232) were similarly analysed.

Results. OA knees in JSN non-progressor group had a slight decrease in FSA for vertical and horizontal trabeculae and showed no drug effect. In JSN-progressor knees, bone loss was greater in both placebo and RIS 5 mg/day groups compared with those in RIS 15 mg/day group in which trabeculae were retained, and in the RIS 50 mg/week group in which the vertical trabecular number increased significantly (P < 0.05).

Conclusion. This preliminary study showed that patients with marked cartilage loss (JSN ≥ 0.6 mm) receiving RIS 15 mg/day retained vertical trabecular structure, and those receiving RIS 50 mg/week increased vertical trabecular number, thereby preserving the structural integrity of subchondral bone in knee OA.

KEY WORDS: Osteoarthritis, Knee, Radiography, Bisphosphonates, Bone structure, Trabeculae, Risedronate.

Osteoarthritis (OA) is a major public health problem as it is the most common form of arthritis, affecting over 20 million people in the US, and is ranked as among the top 10 causes of disability worldwide. Evidence for therapies that act upon the articular cartilage and slows down its loss in knee OA has been limited. While glucosamine has been proposed as a possible structure-modifying osteoarthritis drug (SMOAD) [1], questions remain as to its action at the joint itself [2], as well as to the methods used to assess radiographic progression [3]. Recent data have suggested a possible benefit of doxycycline in slowing radiographic progression in obese women with knee OA. However, the treatment effect was observed in one knee only but not in the contralateral, and there was no effect on symptoms [4].

The characteristic feature of cartilage degradation and loss in OA is accompanied by subchondral sclerosis. This thickening of the cortical plate and subjacent thickened horizontal trabecular bars [5–10] is an early radiographic feature [5, 6, 11] that precedes [12] and is linked to cartilage degeneration [13–17]. Quantification of cancellous bone changes in the subchondral and subarticular regions of the diseased compartment has shown that OA knees with progressive joint space narrowing (JSN) have a significant reduction in both vertical and horizontal trabeculae [18, 19] (Fig. 1), confirming the observations of periarticular osteoporosis in knee OA patients [20, 21] and in animals with experimentally induced OA [8, 22, 23]. It is hypothesized that increased subchondral sclerosis [5, 6, 10] leads to osteoporosis in the subchondral and subarticular regions [18–20] due to decreased load transmission [5, 21, 24].

Risedronate (RIS) is a nitrogen-containing bisphosphonate and an effective inhibitor of osteoclastic bone resorption as shown by the reduction in bone turnover detected in experimental animal models [9, 25–27], in studies of post-menopausal osteoporosis [28], steroid-induced osteoporosis [29] and Paget’s disease [30]. A recent cross-sectional study also suggested an association between anti-resorptive treatments (oestrogen or bisphosphonates) and decreased bone marrow abnormalities detected by magnetic resonance imaging (MRI) [31]. Increased evidence for the role of bone in both the initiation and progression of OA [15] has resulted in an interest in drugs that affect bone metabolism, and might slow down or even halt the process of joint degeneration [32].
Our study undertook to determine whether RIS slowed down the loss of trabecular bone in the medial diseased tibial compartment of patients with knee OA. The study radiographs were obtained from the North American multi-centre, placebo-controlled, 2yr study to investigate the effect of RIS upon the rate of JSN in patients with medial compartment OA of the knee [33].

Quantification of structural alterations in the proximal tibia was obtained from the computerized method of textural image analysis called fractal signature analysis (FSA). The sensitivity of fractal methods in detecting bone changes in short-term longitudinal studies has been previously demonstrated [34–36]. The fractal dimension (FD) of cancellous bone assesses the composite nature of the tissue, which is determined principally by trabecular number, spacing and cross connectivity [37]. Further, previous work has demonstrated that fractal dimension of trabecular bone projection images is related to three-dimensional microarchitecture [38–40]. FSA measures the fractal dimension separately for vertical and horizontal trabeculae over a range of scales corresponding to a range of trabecular widths, identified as the ‘fractal signature’ [41]. Here, we use fractal analysis to provide quantitative data detailing the change in subchondral cancellous bone structure at the proximal tibia in the medial, diseased compartment in patients administered either placebo or RIS 5 mg/day, 15 mg/day or 50 mg/week over 24 months.

Patients and methods

Study protocol and patient selection

The North American arm of the clinical trial examining RIS in structure and symptoms of knee OA, KOSTAR (Knee OA Structural ARthritis study), was a 2 yr, multi-centre, double blind, randomized, placebo-controlled study of 1232 patients in ~40 study centres in the US and Canada [33]. Male and female subjects aged between 40 and 80 yrs with mild-to-moderate medial compartment knee OA, diagnosed according to the clinical and radiological criteria of the American College of Rheumatology [42], were selected for the trial. All subjects provided written informed consent before entering the study, which was conducted in accordance with the International Conference on Harmonization (ICH) guidelines for Good Clinical Practice, and administered by local and central Institutional Review Boards (IRBs).

Study protocol required patients to have medial compartment joint space width (JSW) between 2 and 4 mm, a narrower JSW in the medial compared with the lateral compartment of the same knee, at least one osteophyte present in the signal knee and knee pain most days, at least 1 month out of the last 3 months prior to screening. If both knees qualified, the side with the smaller JSW was selected as the signal knee. Major exclusion criteria included other types of arthritis and secondary knee OA, non-OA causes of knee pain, trauma to the signal knee, previous surgical intervention, BMI > 40 kg/m², previous use of steroids, calcitonin, fluoride, bisphosphonates or injection with hyaluronic acid.

Treatment assignment

Patients were randomized to receive placebo (n = 313), RIS 5 mg/day (n = 310), RIS 15 mg/day (n = 305) or RIS 50 mg once a week (n = 314). The doses of RIS used in this study were based on doses used in the earlier British study of risedronate in structure and symptoms of knee OA (BRISK) study (5 and 15 mg/day) [43]. The weekly dosing group (50 mg/week) was included to provide the opportunity to evaluate the efficacy of a potentially more convenient weekly dosing regimen. The 50 mg/week dose was chosen to provide information for an intermediate total weekly dose that lay between the 5 mg/day (total weekly dose 35 mg) and the 15 mg/day regimen (total weekly dose 105 mg). To facilitate subject retention, analgesics and NSAIDS were permitted, with a standardized stepped reduction and washout prior to symptomatic assessment [33].

Radiographic and digitization procedure

Radiographs of the knee were taken at baseline, 12 and 24 months using a standardized radiographic method with fluoroscopic positioning of the joint in a standing, semi-flexed position [44]. The centre of the joint, defined by the joint space, was aligned with the centre of the X-ray beam with the aid of a cross-optic laser. Using fluoroscopy, each knee was flexed until the tibial articular surface was horizontal relative to the floor, parallel to the central X-ray beam and perpendicular to the X-ray film. Radiographic magnification was determined from automated measurement of the diameter of a metal ball, which was taped to the skin over...
the head of the fibula [44]. After ensuring that all radiographs met the quality control criteria [44], the films were digitized using the high resolution Lumysis 200HR laser film digitizer (Lumysis, Sunny Vale, CA, USA) at a pixel resolution of 60 μm (after correction for magnification), and the images were stored and analysed with a Sun Sparcstation, model 20/61 (Sun Microsystems Ltd). A program written in C++ called Mdisplay was used to view the digitized images and calculate the fractal signature of selected regions of interest. Minimum medial compartment JSW measurements were obtained using a highly reproducible automated image analysis technique [6, 44]. The test–retest standard deviation of the difference between radiographs taken 2 days apart for this technique was 0.2 mm [44].

**Patient grouping**

In order to provide a preliminary assessment of treatment effect compared with placebo, FSA was performed on 100 randomly selected patients from the placebo and each treatment group, giving 400 knees in total. The overall statistical analysis plan for the KOSTAR study specified that the analysis was to be based upon the proportion of patients who progress JSN, i.e. JSN ≥0.6 mm [33]. Thus, for our evaluation, knees in each group were divided into JSN non-progressors (JSN <0.6 mm) and JSN-progressors (JSN ≥0.6 mm) at any time post-baseline as measured from the change in minimum medial compartment JSW.

The results of our pilot analysis revealed two factors: (i) the proportion of knees that were in the JSN-progressor (JSN ≥0.6 mm) group was small (<20%) compared with the JSN non-progressor group (>80%), a result consistent with the overall study [33], and (ii) a difference in the bone’s response in the groups administered the higher dosages of RIS. Consequently, radiographs of all knees within the entire patient cohort (N=1232) that had JSN ≥0.6 mm (progressors) were selected. We report here the results for OA knees in the JSN non-progressor group and the total number of study knees in the JSN-progressor group which includes those in the pilot study. The number of patients’ knees together with demographic data and annual rate of JSN for each group are given in Table 1.

**Region of interest (ROI)**

The medial tibial subchondral region (Fig. 2) was selected for analysis based on previous work that established that substantial change in trabecular structure occurs in this region in patients with knee OA [17–19, 45]. To account for variation in tibial size between patients, the ROI width measured three-fourths of tibial compartment width measured from a vertical line projected down from the medial tibial spine to the outer tibial margin. The outer one-fourth of the width of the tibial compartment was not included for analysis due to the occurrence of periarticular osteopenia associated with marginal osteophyte formation in this area [46]. The height of the ROI measured 100 pixels (6 mm). The ROI commenced immediately beneath the inferior border of the medial cortical plate, drawn onto the image by an automated ridge-tracing function in Mdisplay (Fig. 2).
Measurement of subchondral cancellous bone

We used the computerized method of FSA [17–19, 41], which measures the FD separately for vertical and horizontal trabeculae over a range of scales corresponding to a range of trabecular widths, to identify changes in trabecular structure in short-term longitudinal radiographic studies [34, 36]. Fractal analysis is a robust method [37, 41] that is independent of a range of factors that may vary during routine radiographic procedure, such as the effect of radiographic magnification and projection geometry [41, 47] changes in object or patient positioning [37, 41, 47], and variations in the sensitometric properties of radiographs, such as film contrast and mean density [38, 41]. FSA of vertical and horizontal trabecular structures for each ROI quantified trabecular structures ranging from 0.12 to 1.14 mm in increments of one pixel (0.06 mm). This range of widths was chosen because trabecular thicknesses in the proximal tibia have been shown to fall within this range [48]. The coefficient of variation for test–re-test for FSA measurements is 2.1% [41].

Statistical analysis and presentation of data

Changes in the vertical and horizontal trabecular structures between baseline and 24 months in each treatment group were determined using 95% confidence intervals (CI) and paired t-tests.

To simplify graphical presentation, the fractal signature at exit was subtracted from the baseline fractal signature for each knee. Therefore, each line on the graph represents the mean change in fractal signature for each treatment group over the range of trabecular widths from 0.12 to 1.14 mm (Figs 3 and 4). Data points below the abscissa corresponded to a decrease in complexity of the image texture (reduction in the FD) associated with a decrease in trabecular number, whereas those above the abscissa corresponded to an increase in complexity (increase in the FD) associated with an increase in trabecular number resulting from the formation of new cancellous bone [34]. In the descriptive account, trabeculae are referred to as belonging to those which are small (width range: 0.12–0.42 mm), medium (width range: 0.48–0.78 mm) or large (width range: 0.84–1.14 mm).

Significant differences between the placebo and treatment groups were determined using the one-way analysis of variance, followed by the post hoc Dunnett test. Significant differences between treatment groups were determined using the one-way analysis of variance, followed by the post hoc Tukey test. Significant differences between patients administered placebo with JSN-progressor or JSN non-progressor groups were calculated using unpaired t-tests. The significance level for all statistical tests was set at \( P < 0.05 \), with \( P < 0.01 \) and \( P < 0.001 \) indicated where appropriate.

Results

Cancellous bone changes in the JSN non-progressor group

Vertical trabeculae. Compared with baseline values, loss of small vertical trabecular structures occurred in all groups except in RIS 15 mg/day group (Fig. 3a). In the placebo, RIS 5 mg/day and RIS 50 mg/week groups, a significant decrease in FD \(( P < 0.05 \) occurred at small vertical trabecular widths (0.12–0.36 mm).

Horizontal trabeculae. Compared with baseline values, all groups showed some trabecular loss (Fig. 3b). In RIS 15 mg/day and RIS 50 mg/week groups, significant decrease in FD \(( P < 0.05 \) occurred at most horizontal trabecular widths (0.12–1.14 mm). In RIS 5 mg/day and placebo groups, a significant decrease in FD \(( P < 0.05 \) occurred at a range of small to medium horizontal trabecular widths (0.12–0.54 mm).

Cancellous bone changes in the JSN progressor group

Vertical trabeculae. Compared with baseline values, the trabecular number increased mainly in RIS 5 mg/week group, demonstrated by a significant increase in FD \(( P < 0.05 \) at most vertical trabecular widths (0.12–0.48 mm) and at a single medium and large trabecular width (0.84 mm). Decrease in trabecular number occurred in RIS 5 mg/day and placebo groups, demonstrated by the significant decrease in FD \(( P < 0.05 \) at mostly small vertical trabecular widths in the former (0.12–0.48 mm) and at a single medium and large trabecular width in the latter group (0.72 and 0.84 mm, respectively) (Fig. 4a).

Horizontal trabeculae. Compared with baseline values, trabecular loss occurred in the placebo and RIS 5 mg/day groups only, demonstrated by the significant decrease in FD \(( P < 0.05 \) at a range of small and medium horizontal trabecular widths (0.12–0.84 mm). In RIS 15 mg/day, there was minimal, non-significant decrease in trabecular number. In RIS 50 mg/week group, trabecular number remained constant (Fig. 4b).

Between treatment group differences

For all groups in the JSN non-progressor group (Fig. 3a and b), there were no significant differences in FD between treatment groups at any trabecular width. A significant difference in FD between treatment groups occurred for vertical trabeculae within the JSN-progressor group only, as displayed in Table 2. Compared with the placebo group, the increase in vertical
showed that there is a marked loss of horizontal and vertical trabeculae [18, 19] from the subchondral region in the diseased compartment of the tibia. The current investigation also demonstrated the loss of subchondral tibial bone structure in the medial OA compartment in all knees in the JSN non-progressor group (Fig. 3) and in the JSN-progressor groups that were administered placebo and RIS 5 mg/day (Fig. 4). The removal or perforation of the structural elements in cancellous bone has been shown to decrease the strength of bone by a factor of 2-3 over simple thinning of trabeculae [49]. The long-term consequences of such changes would potentially lead to the weakening and loss of the vertical trabecular support and cross-brazing horizontal trabeculae under the subchondral cortical plate. Alteration in structure, when combined with the biomechanical weakening of the bone due to disease-related reduction in its mineral content, stiffness and its increased porosity [50], likely contributes to the collapse of the tibial compartment in late-stage OA [5].

RIS, a potent pyridinyl-bisphosphonate, has the effect of reducing bone turnover in post-menopausal osteoporosis by inhibiting the differentiation and recruitment of osteoclasts and in reducing the activity of the resorptive cells at the level of the remodelling unit [25, 51]. The effects of RIS on bone remodelling help to preserve the trabecular architecture and thus improve bone strength in humans [51]. The results of our study show that in OA knees with progressive disease (JSN ≥0.6mm, at any time post-baseline), patients who administered a high dose of RIS (15 mg/day) preserved their trabecular architecture, as there was no significant decrease in either vertical or horizontal trabecular number over the 2 yr period. Indeed, compared with the placebo group, a number of large vertical trabeculae, ranging in width from 0.84 to 0.90 mm, increased in number significantly by the end of the study (Table 2). Further, patients with progressive knee OA (JSN ≥0.6 mm) who received a single dose of RIS 50 mg once a week showed not only preservation of their subchondral horizontal trabeculae but also a significant increase in the number of medium and large vertical trabeculae (ranging in width from 0.66 to 0.90 mm) compared with those knees in the placebo group (Table 2). New bone formation in OA knees with marked JSN receiving RIS 50 mg/week may be due to the greater bioavailability of this pulsed dose of RIS that produced a greater effect upon osteoclast activity than a lower daily dose.

Although it is suggested that bisphosphonates are associated with decreased bone formation as an expected consequence of suppressing the coupled bone remodelling process [51], our results show that this does not appear to be the case. The findings of the current study tend to agree with the experimental work that shows that high doses of bisphosphonates as well as its repeated administration may contribute to enhanced bone accretion [52, 53], leading to increased bone formation [54]. Further, angiogenesis, which is linked to bone formation and thus a stimulus for bone remodelling, is not blocked by RIS [25]. The indications are that the effect of RIS 50 mg/week upon subchondral cancellous bone architecture results in an increase in medium and large vertical trabeculae [55], and an increase in bone mass [56, 57] as the remodelling spaces are filled in [57]. Bone formation in OA knees in this group reversed the disease-related bone loss, maintaining the structural integrity within the subchondral cancellous bone. The long-term outcome of such treatment is unknown. Studies in post-menopausal osteoporosis suggest that, subsequent to the initial increase in bone content, bone accretion slows down and eventually reaches a plateau [57].

Bone loss was unaltered in the JSN-progressor group that was administered RIS 5 mg/day. Although this dose is known to provide effective treatment in post-menopausal osteoporosis [56], the loss of trabeculae detected in this group suggests that the effectiveness of the dose may be below the threshold for preservation of trabeculae in knee OA with rapid JSN. Studies are required to determine whether the 5 mg/day dose reduces the rate of bone turnover and provides stronger bone in comparison

Differences between placebo patients in JSN non-progressor and JSN progressor groups

There were no statistically significant differences in either vertical or horizontal FD between patients with rapid JSN and those with non-rapid JSN. However, compared with patients with non-rapid JSN, patients with rapid JSN demonstrated a trend towards greater loss of medium to large vertical trabeculae (0.66-0.84 mm).

Discussion

The results of this preliminary study into the effect of the bisphosphonate RIS in patients with knee OA showed that those patients with progressive disease over 2 yrs (JSN ≥0.6 mm) who received higher doses of RIS (15 mg/day and 50 mg/week) had the inhibition of trabecular bone loss in the subchondral region of the diseased medial compartment of the tibia.

Previous longitudinal studies using FSA to quantify cancellous bone changes from radiographs of patients with knee OA have
with untreated patients [56]. Further, the lack of therapeutic effect in JSN non-progressor OA knees, as seen by the lack of any differences in trabecular architecture parameters between placebo and the RIS-treated arms, suggest that they may have a mild osteoporosis combined with a low rate of bone turnover.

The difference in responses to RIS between knees in the JSN non-progressor and JSN-progressor groups, described above, suggests that a wide spectrum of bone remodelling may exist [51], which has been described as bimodal [51,56]. The apparent bimodal pattern of therapeutic response in trabecular bone between OA knees in the JSN-progressor and JSN non-progressor groups bears a similarity to that detected in post-menopausal osteoporosis [51,56]. In addition, although the differences in vertical and horizontal trabecular loss between the placebo groups of OA knees with non-progressive and progressive JSN did not reach significance, a trend was seen towards greater loss of vertical trabecular width (mm) 15 mg placebo 50 mg 50 mg placebo

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*P < 0.05, †P < 0.01.

was not correlated with a concomitant treatment effect for signs and symptoms of knee osteoarthritis [33]. In both the North American study reported here as well as a similarly designed parallel study in the European Union of 1251 patients, there was a clinically detectable (~20% reduction from baseline) improvement in the signs and symptoms, as measured by the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) as well as by patient global assessments of the disease that was apparent as early as 6 months and maintained for the 2 yrs of the study. This improvement, however, was seen in all treatment groups, including placebo, with no indication of an effect for any dose of RIS [33].

In summary, analysis of the standard radiographs obtained from each treatment group comprising placebo, and RIS 5 mg/day, 15 mg/day and 50 mg/week from a double-blind, multi-centre, placebo-controlled 2yr investigation of patients with knee OA showed that in patients receiving placebo there is a progressive loss of vertical and horizontal trabeculae within the subchondral cancellous bone in the diseased medial compartment [19,21]. This, it is suggested, is due to progressive thickening and flattening of the subchondral cortical plate [6,58,59], which produces a 'stress shielding' effect [60], resulting in localized osteoporosis in the subchondral bone. Study knees were subdivided into those with minimal (JSN non-progressor, JSN<0.6 mm) or marked cartilage loss (JSN-progressor, JSN>0.6 mm measured at any point post-baseline). Cancellous bone in patients with OA knees in the latter group who received RIS 15 mg/day retained their vertical and horizontal trabecular structure, and those receiving RIS 50 mg/week increased vertical trabecular number significantly, thereby preserving structural integrity. However, trabecular bone in patients with minimal JSN showed no drug effect. We suggest that the difference in response to RIS between knees with minimal and marked cartilage loss may be due to differences in their rates of bone turnover. This proposition requires a further study into the role of biochemical markers and their relation to the differences in trabecular architecture between OA knees with minimal or marked cartilage loss.

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