JOURNAL OF BONE AND MINERAL RESEARCH
Volume 24, Number 7, 2009
Published online on February 16, 2009; doi: 10.1359/JBMR.090213

Risedronate in the Treatment of Mild Pediatric Osteogenesis Imperfecta: A Randomized Placebo-Controlled Study

Frank Rauch, Craig F. Munns, Christof Land, Moira Cheung, and Francis H. Glorieux

ABSTRACT: Intravenous pamidronate is the most widely used treatment for moderate to severe osteogenesis imperfecta (OI). Currently, there is no medical treatment for patients with mild OI. We conducted a single-center randomized double-blind placebo-controlled trial to examine the efficacy and safety of oral risedronate in the treatment of pediatric patients with mild OI. A total of 26 children and adolescents (age, 6.1–17.7 yr; 11 girls) with OI type I were randomized to either placebo ($N = 13$) or risedronate ($N = 13$) for 2 yr. Risedronate doses were 15 mg once per week in patients weighing <40 kg and 30 mg once per week in patients weighing >40 kg. After 2 yr of treatment, risedronate decreased serum levels of the bone resorption marker collagen type I N-telopeptide by 35% compared with a 6% reduction with placebo ($p = 0.003$). Risedronate increased lumbar spine areal BMD Z-scores by 0.65, whereas patients receiving placebo experienced a decrease of 0.15 ($p = 0.002$). In contrast, no significant treatment differences in bone mass and density were found at the radial metaphysis and diaphysis, the hip, and the total body. Histomorphometric analysis of transiliac bone biopsies at the end of the study period did not show a significant treatment difference in cortical width, trabecular bone volume, or parameters of bone turnover. Similarly, there was no detectable treatment effect on vertebral morphometry, second metacarpal cortical width, grip force, bone pain, or number of new fractures. Regarding safety, risedronate was generally well tolerated, and the incidence of clinical or laboratory adverse experiences was similar among treatment groups. These results suggest that the skeletal effects of oral risedronate are weaker than those that are commonly observed with intravenous pamidronate treatment but still lead to an increase in lumbar spine areal BMD. Future studies should investigate whether oral risedronate is effective in reducing fracture rates in children and adolescents with mild OI type I.
J Bone Miner Res 2009;24:1282–1289. Published online on February 16, 2009; doi: 10.1359/JBMR.090213

Key words: bisphosphonates, children, osteogenesis imperfecta, risedronate

Address correspondence to: *Frank Rauch, MD, Genetics Unit, Shriners Hospital for Children, 1529 Cedar Avenue, Montreal, Quebec, Canada H3G 1A6, E-mail: frauch@shriners.mcgill.ca*

INTRODUCTION

Osteogenesis imperfecta (OI) is a genetic disorder with increased bone fragility of varying severity. The mildest variant, OI type I, comprises patients who do not have major bone deformities.[1] Typical features include gray or bluish sclera, close to normal growth, and autosomal dominant inheritance. In the large majority of patients with OI type I, the disease is caused by mutations in one of the two genes encoding collagen type I α chains (*COL1A1* and *COL1A2*). Frequently, mutations associated with OI type I result in a null *COL1A1* allele, causing a 50% reduction in normal type I collagen synthesis.

The best therapeutic approach to patients with mild forms of OI is unclear at present, because available treatment studies have focused on more severely affected patients. In these, cyclical intravenous treatment with the bisphosphonate pamidronate is beneficial.[1] It has been reported that this treatment increases lumbar spine areal BMD and metacarpal cortical width, decreases fracture rates, leads to reshaping of vertebral bodies in growing patients, and improves mobility.[1,2] Histomorphometric studies have shown that iliac cortical width and trabecular bone volume increase with pamidronate treatment in such patients.[3] Randomized controlled trials have shown that neridronate, a bisphosphonate compound similar to pamidronate, has similarly beneficial effects in both adults and children with OI.[4,5]

As a result of these observations, pamidronate is now widely used worldwide to treat patients with moderate to severe forms of OI. However, treatment with pamidronate requires frequent intravenous infusions, which places a significant burden on the patients and their families. For many patients, it would be preferable to use oral medication instead. A cross-over study found that orally administered alendronate improved the quality of life in severely affected children with OI.[6] In a similar population, treatment with oral olpadronate decreased fracture rate.[7]

These previous studies mostly included children with moderate to severe forms of OI who had bone deformities and functional deficits. Whether bisphosphonate treatment

Dr. Glorieux has acted as a consultant for Novartis. All other authors state that they have no conflicts of interest.

Genetics Unit, Shriners Hospital for Children, Montreal, Quebec, Canada.

is useful for children and adolescents with mild OI who have occasional fractures but are otherwise fully functional is not known at present. Bone densitometric studies generally find that the majority of children and adolescents with mild OI have low areal BMD at the lumbar spine.[8,9] Some clinicians feel that these low areal BMD results by themselves provide sufficient arguments to treat young OI patients with bisphosphonates, regardless of clinical status.[10] We therefore conducted a single center randomized double-blind placebo-controlled trial to examine the efficacy and safety of oral risedronate in the treatment of pediatric patients with mild OI.

MATERIALS AND METHODS

Subjects

The participants of this study were recruited among patients who were seen at the outpatients department of the Shriners Hospitals for Children in Montreal, Canada, between October 2003 and October 2004. Patients of either sex were eligible for the study if they were between 4.0 and 18.0 yr old at entry into the study and had a diagnosis of OI type I.

The diagnosis of OI type I was made clinically. Patients were classified as having OI type I if they fulfilled one of the following criteria:

1) In the presence of a family history of OI: presence of blue sclera or dentinogenesis imperfecta.
2) In the absence of a positive family history: presence of at least one fracture and either blue sclerae or dentinogenesis imperfecta

Patients who fulfilled one of these two criteria, but in addition had long bone deformities, were classified as having other types of OI and therefore were not included in this study. Patients with a diagnosis of OI type I who had vertebral compression fractures also were not included in this study. Such patients were classified as suffering from OI of moderate severity and were offered intravenous pamidronate treatment.

Patients were ineligible if they were unable to comply fully with the dosing instructions (including the requirement to stand or sit upright for at least 30 min after dosing), had received prior treatment with a bisphosphonate, or were regularly using drugs that alter gastric acidity. Pregnancy at baseline or at any time during the study also was exclusionary. Of the 50 patients who were assessed for eligibility, 22 declined to participate and 2 did not meet entrance requirements for the study (Fig. 1). Thus, 26 patients were randomized.

The study was approved by the McGill University Institutional Review Board, and informed consent was obtained from the legal guardians and/or patients. Assent was obtained from children $\geq$7 yr of age.

Treatment protocol and follow-up

Patients were randomized in equal number to receive either risedronate or placebo. Patients were stratified according to their weight at baseline to receive either risedronate 15 mg once per week (in those who weighed <40 kg), risedronate 30 mg once per week (in those who weighed >40 kg), or matching placebo. Both risedronate and placebo pills were provided by the manufacturer (Procter & Gamble).

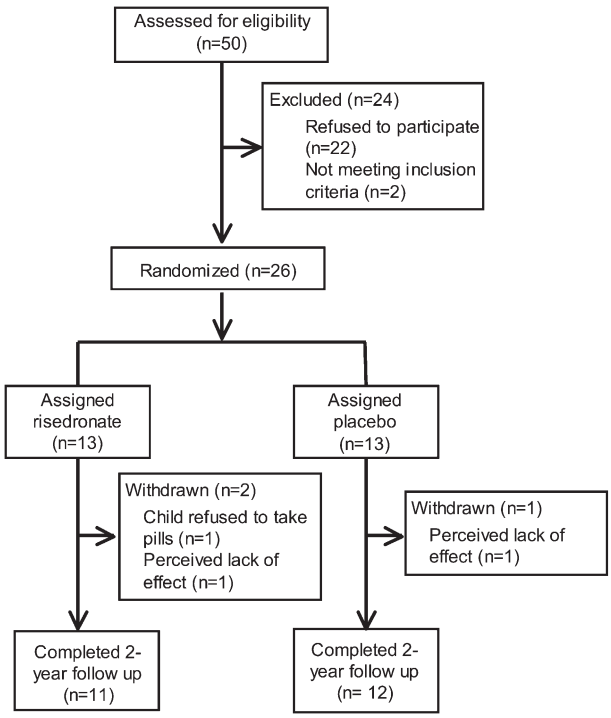

FIG. 1. Study population.

Study visits occurred every 3 mo. Compliance was assessed by tablet count at each study visit after randomization. A patient's compliance rate was defined as the ''number of weeks when study medication was taken'' divided by the ''number of weeks under observation.'' In females with child-bearing potential, a urine or serum pregnancy test was conducted at each study visit.

All patients received standard orthopedic care, regardless of treatment allocation.[11] Patients received supplemental calcium and vitamin D as part of standard care if daily intake was <800 mg or 400 IUs, respectively.

The primary efficacy variable was the change in lumbar spine (L_1–L_4) areal BMD Z-score. Secondary efficacy variables were cortical width at the midpoint of the second metacarpal, the change in cortical width of iliac bone, and the number of radiologically confirmed fractures.

Each visit included physical examination and anthropometric measures. Bone pain was assessed at each study visit as the maximum pain in the extremities or the back during the last 24 h, using a visual analog scale from 0 to 10. Height was measured with a Harpenden stadiometer. Height and weight measurements were converted to age- and sex-specific Z-scores on the basis of reference data published by the Centers for Disease Control and Prevention.[12] Maximal isometric grip force of the dominant hand was measured using a standard adjustable-handle Jamar dynamometer at baseline and yearly thereafter. Three

consecutive tests were conducted on each hand, and the best of these three measurements was used in the analysis.

Radiographs of the upper extremity long bones (humerus, radius, and ulna) and lower extremity long bones (femur, tibia, and fibula) were obtained at baseline and at the end of the study. These radiographs were evaluated for signs of fractures. Radiographs were also obtained from local hospitals whenever a patient sustained a fracture. Thus, all fractures that occurred during the study interval were radiologically confirmed.

Radiographs of the left hand and wrist in the postero-anterior view were obtained at baseline and at yearly intervals thereafter. These hand X-rays were evaluated by a radiologist to determine cortical width at the midpoint of the second metacarpal. Bone age was assessed according to the Greulich-Pyle method.[13]

Radiographs of the thoracic and lumbar spine in the lateral view were obtained at baseline and at yearly intervals thereafter. Vertebral morphometry was performed on lateral spine radiographs for the region from lumbar vertebra L_1 to L_4 as described.[14] Anterior, posterior, and midheight of each vertebra were expressed relative to lower vertebral length to account for magnification effects.

Bone densitometry was performed in the antero-posterior direction at the lumbar spine (L_1–L_4) by DXA at baseline and at yearly intervals thereafter (QDR Discovery; Hologic, Waltham, MA, USA). A quality-control program was conducted throughout the study. Areal BMD results were converted to age- and sex-specific Z-scores using data provided by the manufacturer. These are based on the studies of Glastre et al.[15] and Southard et al.,[16] which were comprised of a total of 353 children and adolescents.

pQCT was performed at the radius using the Stratec XCT2000 equipment (Stratec, Pforzheim, Germany). Measurements were preferably performed at the nondominant forearm, but the dominant forearm was analyzed when there was a recent fracture (<1 yr before the pQCT analysis) on the nondominant side. Two sites were assessed, representing metaphyseal (at the so-called 4% site) and diaphyseal bone (at the 65% site), respectively, as described.[17]

Blood and urine samples were collected at baseline and every 3 mo thereafter after an overnight fast. The samples were stored at −20°C until analysis. Serum total calcium, phosphate, and alkaline phosphatase activity were measured using colorimetric methods (Monarch; Instrumentation Laboratories, Lexington, MA, USA). Serum PTH concentrations (fragment 39–84) were determined by radioimmunoassay.[18] 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D were measured with radioimmunoassays (25-Hydroxyvitamin D and 1,25-Dihydroxyvitamin D Osteo SP; Incstar, Stillwater, MN, USA). Urinary calcium and creatinine were quantified colorimetrically. The bone resorption marker urinary cross-linked N-telopeptide of type I collagen (NTX) was quantified by ELISA (Osteomark; Ostex, Seattle, WA, USA) on the second void sample of the morning. Serum levels of NTX were quantified by ELISA (Osteomark NTX Serum; Wampole Laboratories, Princeton, NJ, USA). Serum activity of TRACP5b was determined by immunoassay (BoneTRACP Assay; Suomen Bioanalytiikka, Turku, Finland).

Full-thickness transiliac bone biopsy specimens were obtained at month 24 with a Bordier trephine (5 or 6 mm core diameter) under general anesthesia from a site located 2 cm behind the anterior superior iliac spine. Two patients, who otherwise completed the study, did not consent to have the biopsy procedure performed. Transiliac bone samples were collected on days 4 or 5 after dual labeling with demeclocycline (15–20 mg/kg body weight/d taken orally during two 2-day periods separated by a 10-day free interval). Biopsy preparation and histomorphometric analyses were performed with procedures that have been described in detail previously.[19] Measurements were carried out using a digitizing table with Osteomeasure software (Osteometrics, Atlanta, GA, USA). In some cases, the quality of the bone sample was not sufficient for complete analysis, which explains the differences in the number of observations between parameters. Nomenclature and abbreviations follow the recommendations of the American Society for Bone and Mineral Research.[20]

Statistical analysis

The required size of the study population was calculated on the hypothesis that lumbar spine areal BMD Z-score changes would differ by 1 (SD 1) between treatment groups. To be able to detect this treatment difference with an α error of 5% and a power of 80%, a sample size of 24 participants was required.

All comparisons between treatment groups were based on an intention-to-treat analysis. In case of missing data, the last observation was carried forward. For group comparison at baseline, we used two-sample *t*-tests and χ^2 tests. Non-normally distributed results were log-transformed before performing *t*-tests.

Changes from baseline for laboratory investigations were expressed as percentages of the baseline value. Univariate tests were performed on these percentages to assess for the significance of differences in treatment effect between groups. A 5% significance level was maintained throughout these analyses, and all tests were two sided. All calculations were performed using SPSS software version 11.5 for Windows (SPSS, Chicago, IL, USA).

RESULTS

Twenty-six patients were randomized (Fig. 1). Most baseline characteristics of the risedronate and placebo groups were similar (Tables 1 and 2). However, a higher proportion of patients in the placebo group complained of bone pain (Table 1). The median pain score was also higher in this group.

Compliance rates of 98.3% and 98.8% were observed in the risedronate and placebo groups, respectively. Two patients in the risedronate group and one patient in the placebo group discontinued the study prematurely, for the reasons indicated in Fig. 1. During the 24-mo study interval, the average changes in height and weight Z-scores were not significantly different between the risedronate and placebo groups even though the trend was for larger changes in the risedronate group (Table 3).

TABLE 1. Clinical Characteristics at Baseline

Variable	*Placebo (n = 13)*	*Risedronate (n = 13)*	*p*
Male/female	7/6	8/5	0.69
Pubertal stage (I/II/III/IV/V)	6/1/0/1/5	5/4/0/1/3	0.66
Age (yr)	11.9 (4.0)	11.7 (3.6)	0.89
Height (Z-score)	−0.95 (0.99)	−1.21 (1.14)	0.54
Weight (Z-score)	−0.50 (1.14)	−0.53 (1.06)	0.94
Lifetime number of fractures (*n*)	5.5 (3–17)	7.5 (2–16)	0.90
Patients with bone pain (*n*)	8	2	0.02
Severity of pain	2 (0–6)	0 (0–4)	0.01
Grip force of dominant hand (*n*)	167 [1.55]	144 [1.87]	0.49
Bone age (yr)	12.0 (4.6)	11.2 (4.1)	0.67

Results represent mean (SD) or geometric mean [geometric SD].

Biochemistry

Twenty-four months of treatment with risedronate was significantly more effective than treatment with placebo in decreasing serum NTX (Table 3; Fig. 2). In contrast, no significant treatment difference was observed with regard to changes in the other markers of bone and mineral metabolism (Table 3).

Radiology

DXA showed that risedronate treatment was associated with a larger increase in lumbar spine BMC, whereas changes in lumbar spine bone projection area did not differ between groups (Table 3). Consequently, patients receiving risedronate experienced a significantly larger increase in lumbar spine areal BMD during the study period (Fig. 3). Converted to age-specific Z-scores, these results corresponded to a significant mean treatment difference of 0.80 in favor of risedronate (Table 3).

No significant difference between the risedronate and placebo groups were detected for changes in DXA parameters for hip and total body, as well as for results of pQCT at the radial metaphysis and diaphysis (Table 3). Trabecular BMD at the distal radius tended to decrease in the risedronate group, whereas there was a trend toward increasing values in patients receiving placebo. However, because baseline results for trabecular BMD had been slightly (and nonsignificantly) higher in the risedronate group (Table 2), these changes led to similar average values at the end of the study (163 ± 75 [SD] mg/cm^3 in the risedronate group versus 152 ± 41 mg/cm^3 in the placebo group, $p = 0.65$).

There were also no detectable treatment differences regarding changes in the shape of lumbar vertebral bodies (data not shown) and cortical thickness of the second metacarpal bone (Table 3). Qualitative evaluation of radiographs did not show any signs of sclerosis in the metaphyses of long bones (data not shown).

Histomorphometry

Iliac bone biopsies were performed at the end of the study only. Histomorphometric analysis of these samples showed that bone formation and resorption parameters were similar between the risedronate and placebo groups (Table 4). Similarly, there was no difference in bone size, cortical width, or the amount of trabecular bone.

Clinical outcome measures

Treatment differences in the changes of grip force were not statistically significant (Table 3). Seven patients in the risedronate group and six patients in the placebo group sustained at least one fracture during the study interval. The total number of fractures was 11 in each group. The number of fractures per patient ranged from 0 to 2 in the risedronate group and from 0 to 4 in the placebo cohort. The number of patients suffering from bone pain at the end of the study was four in the risedronate group and four in the placebo group. None of these outcomes concerning fractures and bone pain were significantly different between groups.

Clinical adverse events and laboratory safety data

All patients had at least one adverse event. The number of patients who had adverse events affecting the gastrointestinal tract was similar in the risedronate and the placebo groups ($N = 7$ in the risedronate group, $N = 9$ in the placebo group; $p = 0.42$). No serious adverse events were noted apart from fractures.

No significant differences between the risedronate and placebo groups were observed for changes between baseline and month 24 in serum levels of phosphorus, creatinine, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, PTH, urinary calcium/creatinine ratio, alanine aminotransferase, aspartate aminotransferase, and complete blood count (data not shown). During the course of the study, serum calcium decreased by 0.09 ± 0.08 mM in the risedronate group and by 0.02 ± 0.04 mM in the placebo group ($p = 0.01$). However, serum calcium levels were similar between groups both at baseline (Table 2) and at the end of the study (2.33 ± 10 mM in the risedronate group, 2.36 ± 0.07 mM in the placebo group; $p = 0.34$). Regarding histomorphometric safety data, none of the patients had histomorphometric results indicative of a mineralization defect. Traces of unremodeled calcified growth plate cartilage were found in four patients receiving risedronate and in one patient on placebo ($p = 0.12$).

DISCUSSION

In this study, we found that oral risedronate given once per week to children and adolescents with mild OI type I was well tolerated and was more effective than placebo in increasing areal BMD at the lumbar spine. Because this trial was designed to show a treatment difference in the change of lumbar spine areal BMD Z-score during a 2-yr period, we can conclude that risedronate treatment successfully met the main study objective. Nevertheless, a few additional observations deserve comment.

Given the treatment effect on lumbar spine areal BMD, it is somewhat surprising that risedronate had only a mild and hardly detectable effect on bone metabolism. Four of

TABLE 2. Densitometry and Biochemical Results at Baseline

Variable	*Placebo (n = 13)*	*Risedronate (n = 13)*	*p*
Urine biochemistry			
Ca/creatinine (mmol/mmol)	0.27 [1.80]	0.19 [2.15]	0.19
NTX/creatinine (nmol/mmol)	252 [2.01]	350 [1.77]	0.20
Serum biochemistry			
CICP (μg/liter)	55 [1.84]	52 [1.74]	0.76
NTX (nM)	64 (28)	74 (26)	0.39
TRACP5b (U/liter)	11.1 (5.4)	11.8 (3.7)	0.69
Alkaline phosphatase (U/liter)	249 (123)	271 (127)	0.66
DXA lumbar spine			
BMC (g)	25.6 (13.1)	22.5 (13.4)	0.55
Projection area (cm^2)	43.5 (10.4)	41.3 (11.5)	0.61
Areal BMD (mg/cm^2)	558 (173)	511 (146)	0.46
Areal BMD (Z-score)	−2.66 (0.86)	−2.97 (0.97)	0.39
DXA hip			
Areal BMD (mg/cm^2)	672 (109)	633 (147)	0.47
Projection area (cm^2)	24.6 (7.8)	24.7 (6.8)	0.96
BMC (g)	17.2 (7.3)	16.4 (8.8)	0.82
DXA total body			
BMC (g)	676 [1.82]	573 [1.86]	0.51
Areal BMD (mg/cm^2)	713 (116)	691 (179)	0.72
Lean body mass (g)	23227 [1.47]	22060 [1.46]	0.74
Fat mass (g)	7576 [2.06]	7258 [2.00]	0.88
pQCT radial metaphysis			
BMC (mg/mm)	55 (21)	60 (35)	0.69
Total BMD (mg/cm^3)	254 (46)	270 (69)	0.49
Total cross-sectional area (mm^2)	219 (73)	212 (61)	0.78
Trabecular BMD (mg/cm^3)	140 (36)	173 (64)	0.12
pQCT radial diaphysis			
BMC (mg/mm)	58 (17)	54 (21)	0.61
Total cross-sectional area (mm^2)	64 (20)	59 (24)	0.56
BMD (mg/cm^3)	776 (135)	776 (114)	0.99
Cortical BMD (mg/cm^3)	1067 (80)	1058 (69)	0.76
Cortical width of second left metacarpal (mm)	1.84 (0.42)	1.75 (0.76)	0.72

Results represent mean (SD) or geometric mean [geometric SD].

the five biochemical markers of bone metabolism used in this study did not indicate a significant treatment difference (alkaline phosphatase, procollagen type I C-propeptide, TRACP5b, and urinary NTX), whereas the fifth (serum levels of NTX, a bone resorption marker) decreased by about 30% within the 2-yr study period. In comparison, a single 3-day course of intravenous pamidronate given to children with OI decreases urinary NTX levels by >60%.[21] Similarly, histomorphometry studies in pediatric OI patients have shown that 2 yr of pamidronate treatment is associated with a decrease of >70% in bone formation rate.[3] In contrast, at the end of this study, histomorphometric parameters of bone metabolism were similar between the placebo and the risedronate groups. Oral risedronate thus clearly had a lower antiresorptive activity than the pamidronate protocol that was used in our earlier studies.

A number of factors might contribute to these differences in effect between oral risedronate and intravenous pamidronate, including the variable bioavailability of bisphosphonates after oral administration and the difference between weekly exposure to relatively small doses with risedronate versus quarterly infusion of high doses of pamidronate. The cumulative dose of risedronate used in this study also may not have been ''equivalent'' to that of our pamidronate schedule. The patients of this study received an average annual risedronate dose of 27 mg/kg body weight, whereas our intravenous pamidronate protocol results in an annual dose of 9 mg/kg body weight. Assuming an average bioavailability for oral risedronate of 0.65%,[22] it can be estimated that our patients experienced a systemic risedronate exposure of 0.18 mg/kg body weight. Because in vivo rat studies suggest that risedronate is ~36 times more potent than pamidronate,[23] this dose of risedronate should have a similar effect as a systemic pamidronate exposure of 6.5 mg/kg body weight, which is 28% lower than the dose of pamidronate given in our earlier studies. Even though such dose comparisons between drugs have to be taken with a grain of salt, it is likely that higher doses of risedronate might have led to a stronger effect on bone metabolism. However, participants of this study who weighed >40 kg received risedronate at the same dose as has been used for adults suffering from osteoporosis.[24,25] Exceeding the ''adult dose'' in the treatment of children may be difficult to justify in clinical practice because of safety concerns.

The densitometric analyses did not show statistically significant effects of risedronate at sites other than the

TABLE 3. Changes During Study Period

Variable	*Placebo (n = 13)*	*Risedronate (n = 13)*	*p*
Height (Z-score)	−0.04 (0.28)	0.13 (0.52)	0.31
Weight (Z-score)	0.00 (0.50)	0.19 (0.33)	0.26
Serum biochemistry			
Alkaline phosphatase (%)	2.2 (42.8)	2.0 (36.5)	0.99
CICP (%)	−50.1 (33.1)	−51.9 (40.9)	0.90
TRACP5b (%)	0.9 (47.0)	−10.9 (33.1)	0.47
NTX (%)	−6.2 (39.0)	−34.6 (22.2)	0.03
Urine biochemistry			
Ca/creatinine (%)	57.2 (180.8)	74.9 (198.8)	0.81
NTX/creatinine (%)	−10.7 (43.7)	−27.7 (33.6)	0.28
DXA lumbar spine			
BMC (%)	18.5 (22.2)	45.2 (30.0)	0.02
Projection area (%)	10.2 (11.6)	16.4 (13.8)	0.23
Areal BMD (%)	6.8 (10.6)	23.8 (15.4)	0.003
Areal BMD (Z-score)	−0.15 (0.39)	0.65 (0.65)	0.002
DXA hip			
BMC (%)	24.9 (27.7)	34.5 (28.5)	0.40
Areal BMD (%)	6.5 (5.9)	12.4 (10.8)	0.11
Projection area (%)	16.6 (20.8)	18.7 (15.9)	0.77
DXA total body			
BMC (%)	30.9 (25.0)	45.2 (24.0)	0.16
Areal BMD (%)	6.5 (4.6)	10.7 (7.1)	0.09
Lean body mass (%)	22.1 (17.3)	28.3 (16.1)	0.37
Fat mass (%)	23.8 (33.3)	28.8 (21.0)	0.67
pQCT radial metaphysis			
BMC (%)	21.5 (15.7)	18.8 (21.2)	0.72
Total BMD (%)	9.3 (15.5)	2.2 (16.1)	0.26
Total cross-sectional area (%)	13.1 (20.8)	18.8 (27.6)	0.56
Trabecular BMD (%)	9.6 (24.1)	−7.5 (18.0)	0.05
pQCT radial diaphysis			
BMC (%)	9.9 (11.8)	16.8 (10.1)	0.13
Total BMD (%)	2.1 (11.0)	1.2 (8.8)	0.83
Total cross-sectional area (%)	8.8 (8.3)	13.4 (9.4)	0.21
Cortical BMD (%)	1.9 (3.9)	0.6 (3.9)	0.49
Cortical width of second left metacarpal (%)	12.8 (18.0)	17.4 (19.3)	0.53

Results represent the mean (SD) of changes compared with baseline.

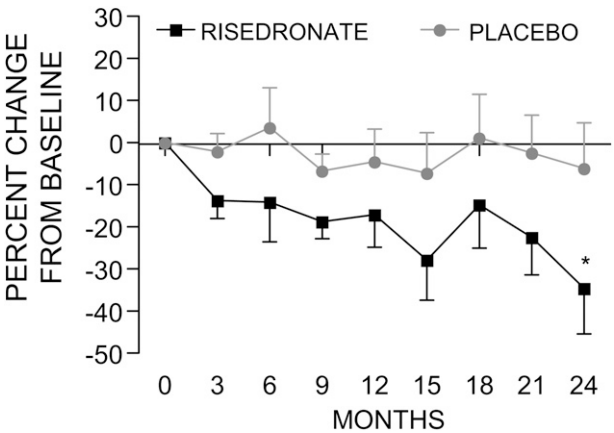

FIG. 2. Change in serum levels of collagen type I N-telopeptide.

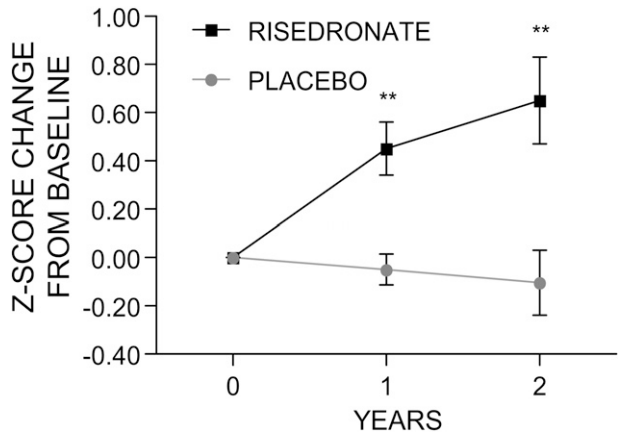

FIG. 3. Change in lumbar spine (L_1–L_4) areal BMD.

spine. Nevertheless, risedronate-treated patients tended to have a larger increase in BMC at sites with a significant contribution of cortical bone (total body, hip, radial diaphysis) and a larger increase in cortical thickness at the second metacarpal. These trends may reflect a drug effect on cortical bone that failed to reach statistical significance because of insufficient sample size. However, it is also possible that these trends simply reflect the fact that the

TABLE 4. Histomorphometric Results at the End of the Study

	N	*Placebo*	*N*	*Risedronate*	*p*
Structural parameters					
Core width (mm)	10	7.6 (1.5)	7	7.2 (2.4)	0.64
Cortical width (μm)	10	999 (467)	11	896 (204)	0.52
Bone volume per tissue volume (%)	10	24 (8)	6	25 (4)	0.85
Formation parameters					
Osteoid thickness (μm)	10	6.1 (2.0)	9	5.6 (1.3)	0.52
Osteoid surface per bone surface (%)	10	33 (12)	9	35 (19)	0.76
Osteoblast surface per bone surface (%)	10	14 (8)	9	10 (6)	0.32
Mineralizing surface per bone surface (%)	9	18 (9)	8	13 (9)	0.27
Mineral apposition rate (μm/d)	9	0.84 (0.25)	8	0.78 (0.11)	0.59
Bone formation rate per bone surface ($\mu m^3/\mu m^2/yr$)	9	58 (33)	8	41 (30)	0.29
Mineralization lag time (d)	9	13 (6)	8	19 (8)	0.13
Resorption parameters					
Osteoclast surface per bone surface (%)	10	0.9 (0.6)	9	0.9 (0.9)	0.99
Eroded surface per bone surface (%)	10	17 (7)	9	14 (3)	0.25

Results represent mean (SD).

risedronate-treated group tended to grow slightly faster than the control group.

In contrast to these ''cortical bone sites,'' there was no hint of a positive effect of risedronate treatment on trabecular bone, either at the ilium (as measured by histomorphometry) or at the distal radius (as quantified by pQCT). This lack of risedronate effect on metaphyseal trabecular bone at the distal radius is surprising. In both growing children and animal models, bisphosphonate effects are usually largest in the newly created metaphyseal bone close to the growth plates.[17,26] For example, intravenous pamidronate treatment of growing children leads to radiographically visible lines in metaphyseal bone and, correspondingly, to very high readings for trabecular volumetric BMD at this site.[17] In contrast, patients who received risedronate did not have radiographically detectable changes in the density of long-bone metaphyses and no change in trabecular volumetric BMD at the distal radial metaphysis. Thus, similar to the considerations on bone metabolism, these radiological observations in metaphyseal bone point to a much weaker effect of oral risedronate than intravenous pamidronate.

This study did not find any treatment differences on fracture rates and on bone pain. Nevertheless, it must be acknowledged that the study population was not large enough to detect anything but dramatic effects on these outcome measures. It also has to be stressed that this was a study on fully functional mildly affected OI patients. Therefore, mobility function or activities of daily living were not evaluated as outcome measures in this study.

Risedronate caused few adverse events. In particular gastrointestinal symptoms were not more common in patients receiving risedronate than in those receiving placebo. Bone histology did not show a mineralization defect in any of the patients and there was no sign of ''drug-induced osteopetrosis'' in any patient.[27] Serum calcium levels decreased more in the risedronate group than in patients receiving placebo. Even though the small difference was statistically significant, it is probably clinically irrelevant.

Thus, in this study we found that oral risedronate treatment of children and adolescents with mild OI type I led to an increase in lumbar spine areal BMD Z-scores. Further evidence suggests that the skeletal effects of oral risedronate were weaker than those that are commonly observed with intravenous pamidronate treatment. It is important to note that this study was designed to assess the effect of risedronate on lumbar spine areal BMD but was not powered to evaluate parameters indicating direct clinical benefit, such as fracture rates. Therefore, these results do not provide a rationale for treating mildly affected OI type I patients with oral risedronate. Rather, the data presented here can inform the design of future treatment studies that evaluate the clinical benefit of oral risedronate in mildly affected OI type I patients.

ACKNOWLEDGMENTS

We thank Sylvie Cornibert for support in study organization and Rose Travers, Mireille Dussault, and Guy Charette for performing biochemical and histomorphometric analyses. F.R. is a Chercheur-Boursier Clinicien of the Fonds de la Recherche en Santé du Québec. This study was supported by grants from Procter & Gamble and from the Shriners of North America.

REFERENCES

1. Rauch F, Glorieux FH 2004 Osteogenesis imperfecta. Lancet **363:**1377–1385.
2. Letocha AD, Cintas HL, Troendle JF, Reynolds JC, Cann CE, Chernoff EJ, Hill SC, Gerber LH, Marini JC 2005 Controlled trial of pamidronate in children with types III and IV osteogenesis imperfecta confirms vertebral gains but not short-term functional improvement. J Bone Miner Res **20:**977–986.
3. Rauch F, Travers R, Plotkin H, Glorieux FH 2002 The effects of intravenous pamidronate on the bone tissue of children and adolescents with osteogenesis imperfecta. J Clin Invest **110:** 1293–1299.
4. Adami S, Gatti D, Colapietro F, Fracassi E, Braga V, Rossini M, Tato L 2003 Intravenous neridronate in adults with osteogenesis imperfecta. J Bone Miner Res **18:**126–130.

5. Gatti D, Antoniazzi F, Prizzi R, Braga V, Rossini M, Tato L, Viapiana O, Adami S 2005 Intravenous neridronate in children with osteogenesis imperfecta: A randomized controlled study. J Bone Miner Res **20:**758–763.
6. Seikaly MG, Kopanati S, Salhab N, Waber P, Patterson D, Browne R, Herring JA 2005 Impact of alendronate on quality of life in children with osteogenesis imperfecta. J Pediatr Orthop **25:**786–791.
7. Sakkers R, Kok D, Engelbert R, van Dongen A, Jansen M, Pruijs H, Verbout A, Schweitzer D, Uiterwaal C 2004 Skeletal effects and functional outcome with olpadronate in children with osteogenesis imperfecta: A 2-year randomised placebo-controlled study. Lancet **363:**1427–1431.
8. Lund AM, Molgaard C, Muller J, Skovby F 1999 Bone mineral content and collagen defects in osteogenesis imperfecta. Acta Paediatr **88:**1083–1088.
9. Rauch F, Land C, Cornibert S, Schoenau E, Glorieux FH 2005 High and low density in the same bone: A study on children and adolescents with mild osteogenesis imperfecta. Bone **37:**634–641.
10. Batch J, Couper J, Rodda C, Cowell C, Zacharin M 2003 Use of bisphosphonate therapy for osteoporosis in childhood and adolescence. J Paediatr Child Health **39:**88–92.
11. Zeitlin L, Fassier F, Glorieux FH 2003 Modern approach to children with osteogenesis imperfecta. J Pediatr Orthop B **12:**77–87.
12. Ogden CL, Kuczmarski RJ, Flegal KM, Mei Z, Guo S, Wei R, Grummer-Strawn LM, Curtin LR, Roche AF, Johnson CL 2002 Centers for Disease Control and Prevention 2000 growth charts for the United States: Improvements to the 1977 National Center for Health Statistics version. Pediatrics **109:**45–60.
13. Greulich WW, Pyle SI 1959 Radiographic Atlas of Skeletal Development of the Hand and Wrist. Stanford University Press, Stanford, CA, USA.
14. Land C, Rauch F, Munns CF, Sahebjam S, Glorieux FH 2006 Vertebral morphometry in children and adolescents with osteogenesis imperfecta: Effect of intravenous pamidronate treatment. Bone **39:**901–906.
15. Glastre C, Braillon P, David L, Cochat P, Meunier PJ, Delmas PD 1990 Measurement of bone mineral content of the lumbar spine by dual energy x-ray absorptiometry in normal children: Correlations with growth parameters. J Clin Endocrinol Metab **70:**1330–1333.
16. Southard RN, Morris JD, Mahan JD, Hayes JR, Torch MA, Sommer A, Zipf WB 1991 Bone mass in healthy children: Measurement with quantitative DXA. Radiology **179:**735–738.
17. Rauch F, Cornibert S, Cheung M, Glorieux FH 2007 Long-bone changes after pamidronate discontinuation in children and adolescents with osteogenesis imperfecta. Bone **40:**821–827.
18. D'Amour P, Labelle F, Lecavalier L, Plourde V, Harvey D 1986 Influence of serum Ca concentration on circulating molecular forms of PTH in three species. Am J Physiol **251:**E680–E687.
19. Glorieux FH, Travers R, Taylor A, Bowen JR, Rauch F, Norman M, Parfitt AM 2000 Normative data for iliac bone histomorphometry in growing children. Bone **26:**103–109.
20. Parfitt AM, Drezner MK, Glorieux FH, Kanis JA, Malluche H, Meunier PJ, Ott SM, Recker RR 1987 Bone histomorphometry: Standardization of nomenclature, symbols, and units. Report of the ASBMR Histomorphometry Nomenclature Committee. J Bone Miner Res **2:**595–610.
21. Rauch F, Plotkin H, Travers R, Zeitlin L, Glorieux FH 2003 Osteogenesis imperfecta types I, III, and IV: Effect of pamidronate therapy on bone and mineral metabolism. J Clin Endocrinol Metab **88:**986–992.
22. Dunn CJ, Goa KL 2001 Risedronate: A review of its pharmacological properties and clinical use in resorptive bone disease. Drugs **61:**685–712.
23. Green JR, Muller K, Jaeggi KA 1994 Preclinical pharmacology of CGP 42′446, a new, potent, heterocyclic bisphosphonate compound. J Bone Miner Res **9:**745–751.
24. Brown JP, Kendler DL, McClung MR, Emkey RD, Adachi JD, Bolognese MA, Li Z, Balske A, Lindsay R 2002 The Efficacy and Tolerability of Risedronate Once a week for the Treatment of Postmenopausal Osteoporosis. Calcif Tissue Int **30:**103–111.
25. Reid DM, Hughes RA, Laan RF, Sacco-Gibson NA, Wenderoth DH, Adami S, Eusebio RA, Devogelaer JP 2000 Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: A randomized trial. European Corticosteroid-Induced Osteoporosis Treatment Study. J Bone Miner Res **15:**1006–1013.
26. Pataki A, Muller K, Green JR, Ma YF, Li QN, Jee WS 1997 Effects of short-term treatment with the bisphosphonates zoledronate and pamidronate on rat bone: A comparative histomorphometric study on the cancellous bone formed before, during, and after treatment. Anat Rec **249:**458–468.
27. Whyte MP, Wenkert D, Clements KL, McAlister WH, Mumm S 2003 Bisphosphonate-induced osteopetrosis. N Engl J Med **349:**457–463.

Received in original form August 13, 2008; revised form December 23, 2008; accepted February 11, 2009.