A Randomized, Double Blind, Placebo-Controlled Trial of Alendronate Treatment for Fibrous Dysplasia of Bone

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Context: Fibrous dysplasia (FD) is a rare skeletal disorder, resulting in deformity, fracture, functional impairment, and pain. Bisphosphonates have been advocated as a potential treatment.

Objective: To determine the efficacy of alendronate for treatment of FD.

Design: Two-year randomized, double-blind, placebo-controlled trial.

Setting: Clinical research center.

Patients: Forty subjects with polyostotic FD (24 adults, 16 children). Subjects were randomized and stratified by age.

Interventions: Study drug was administered over a 24 month period in 6 month cycles (6 months on, 6 months off). Alendronate dosing was stratified: 40 mg daily for subjects >50 kg, 20 mg for 30–50 kg, 10 mg for 20–30 kg.

Main Outcome Measures: Primary endpoints were bone turnover markers, including serum osteocalcin, and urinary NTX-telopeptides. Secondary endpoints included areal bone mineral density (aBMD), pain, skeletal disease burden score, and functional parameters including the 9-min walk test and manual muscle testing.

Results: Clinical data was collected on 35 subjects who completed the study. There was a decline in NTX-telopeptides in the alendronate group ($P = .006$), but no significant difference in osteocalcin between groups. The alendronate group had an increase in areal BMD in normal bone at the lumbar spine ($P = .006$), and in predetermined regions of FD ($P < .001$). There were no significant differences in pain scores, skeletal disease burden scores, or functional parameters between the groups.

Conclusions: Alendronate treatment led to a reduction in the bone resorption marker NTX-telopeptides, and improvement in aBMD, but no significant effect on serum osteocalcin, pain, or functional parameters. **(*J Clin Endocrinol Metab* 99: 4133–4140, 2014)**

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Abbreviations: aBMD, areal bone mineral density; ANOVA, analysis of variance; CBC, complete blood count; DXA, dual x-ray absorptiometry; FD, fibrous dysplasia; GI, gastrointestinal; MAS, McCune-Albright syndrome; MMT, manual muscle testing; ROI, region of interest.

Fibrous dysplasia (FD) is an uncommon skeletal disorder in which normal bone and bone marrow are replaced by fibro-osseous tissue (1–3). Clinical sequelae result from bone weakness and fragility, including fracture, functional impairment, deformity, and pain. FD arises from activating mutations in *GNAS*, which encodes the α-subunit of the G_s stimulatory protein ($G_s\alpha$) (4, 5). Mutations occur postzygotically, leading to mosaic disease with wide clinical variability between individuals (6). FD may occur in one bone (monostotic) or multiple bones (polyostotic), and may be associated with café-au-lait macules and hyperfunctioning endocrinopathies, termed McCune-Albright syndrome (MAS) (7, 8). The downstream cellular effects of constitutively activated $G_s\alpha$ result in increased adenylyl cyclase activity and inappropriate intracellular cyclic adenosine monophosphate (cAMP) production (4). In bone, this is associated with proliferation of undifferentiated bone marrow stromal cells resulting in marrow fibrosis, abnormal matrix production, and increased osteoclastogenesis (3, 9–11).

Currently there are no effective medical treatments for FD. Antiresorptive therapy with bisphosphonates has been advocated due to high levels of bone resorption frequently seen in FD tissue (10). Early studies showed encouraging results, including a report by Liens et al of 9 patients treated with pamidronate who demonstrated improvement in pain, a decrease in bone turnover markers, and improvement in the radiographic appearance of FD lesions (12). Longer-term studies of this regimen reported similar results (13, 14). Additional studies showed consistent benefit in pain and turnover markers, but were unable to replicate the previously reported radiographic improvement (15–17). Until now, determining the role of bisphosphonates in management of FD has been limited by a lack of controlled studies. Here we report the results of the first controlled trial of bisphosphonate treatment for FD in a 2-year randomized, double-blinded, placebo-controlled study of alendronate.

Subjects and Methods

Subjects

Subjects were recruited from an existing FD/MAS natural history study at the National Institutes of Health (NIH). Inclusion criteria included polyostotic FD with at least 2 skeletal lesions, and age > 12 years. When safety had been demonstrated in 5 children under age 18, the age requirement was lowered to 6 years. Exclusion criteria included antiresorptive (specifically bisphosphonate) treatment within one year of enrollment, severe esophageal motility problems, pregnancy, and history of skeletal sarcomas. The protocol was approved by the Institutional Review Board of the National Institute for Dental and Craniofacial Research, and all subjects and/or their guardians gave informed assent/consent.

Study design

Randomization to the alendronate and placebo groups was stratified by age, and subjects and investigators were blinded to intervention group. Alendronate and placebo were provided by Merck & Co under an Investigational New Drug Application. Alendronate or placebo was administered over a 24-month period in 6-month cycles (6 months on, 6 months off), with no crossover. A cyclical design was chosen due to the unavailability of robust safety data for long term, high dose, and continuous treatment with alendronate at the time of study initiation. Alendronate was chosen over an intravenous (IV) bisphosphonate due to its greater ease of administration. Alendronate dosing was chosen based upon available data in Paget's disease (18), and was approximately 4 times the typical dose used for osteoporosis (19). Dosing was stratified by weight, with 40 mg daily for adults > 50 kg, 20 mg for 30–50 kg, and 10 mg for subjects 20–30 kg. Subjects were instructed to take each dose in the morning prior to eating, with a full glass of water, and to remain upright for at least 30 minutes. Calcium and vitamin D intake was monitored with diet questionnaires and maintained in accordance with the recommended daily allowances. Subjects were evaluated at baseline at the NIH Clinical Center, with follow-up assessments at 6, 12, 18, and 24 months. Compliance was assessed at each visit through subject report and pill counts. Between visits, telephone interviews and outpatient laboratory tests were obtained for safety monitoring.

Outcome measures

The primary endpoint was effect of alendronate on biochemical markers of bone turnover, including urine NTX-telopeptides (reflecting bone resorption), and serum osteocalcin (reflecting bone formation). Secondary endpoints included effects on FD-related bone pain, areal BMD (aBMD) of FD lesions, and functional parameters including walking speed and muscle strength.

Biochemistry

Standard laboratory panels were assessed on all subjects at baseline and at each follow-up visit, including complete blood count (CBC), chemistry panel, and mineral panel (calcium, phosphorus, PTH, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, urinary calcium, phosphorus, and creatinine). Bone turnover markers were assessed at baseline and at each follow-up visit. All subjects were evaluated at baseline and treated for endocrine complications of MAS. Specifically, all subjects with FGF23-mediated hypophosphatemia were treated with phosphorus and calcitriol supplementation to maintain normal serum phosphorus levels for the duration of the study.

Radiographic imaging

^{99}Technetium (Tc-99) bone scintigraphy was used at baseline and 24 months to identify areas of the skeleton affected by FD, and to quantify skeletal FD burden using previously described methodology (20). Areas of the skeleton affected by FD were visualized by plain radiographs at baseline, 12 and 24 months. To quantify the effects of treatment on FD lesions radiographically, aBMD of FD lesions was measured by dual x-ray absorptiometry (DXA) (Hologic 4500A device, Hologic, Inc) at baseline, 12, and 24 months. As an internal control of the effect of

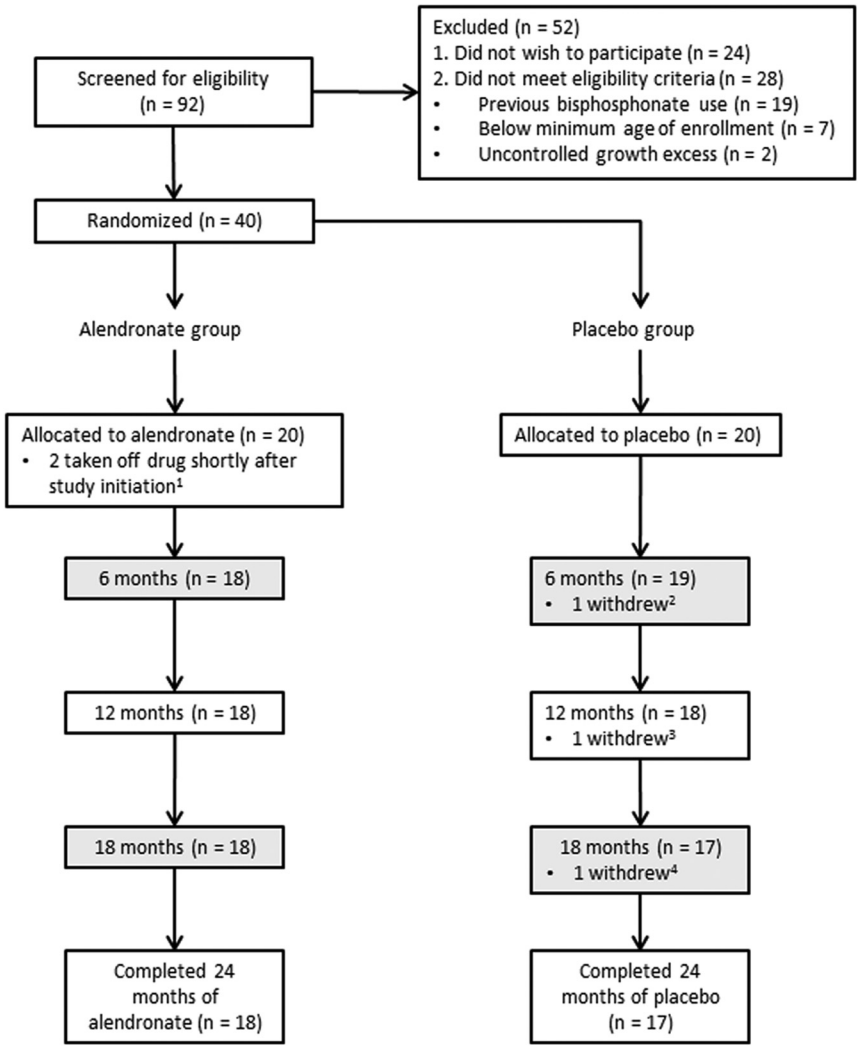

Figure 1. Study flow diagram. 1, Shortly after starting alendronate, an adult subject with an undisclosed history of reflux developed an esophageal stricture, and a pediatric subject developed nausea and vomiting. Both were taken off study drug. 2, An adult subject voluntarily withdrew. 3, An adult subject voluntarily withdrew and was placed on open-label bisphosphonates. 4, A pediatric subject was taken off study drug after developing diarrhea and a 10 pound weight loss.

drug on unaffected bone, bone density of the lumbar spine was assessed in all subjects who did not have FD in this location. To assess the effect of drug on FD, sentinel sites of FD were identified and aBMD measured by DXA. Using the whole body DXA image, the region of interest (ROI) software was used to create a ROI around an FD lesion that that had been identified on plain radiograph. A ROI was created around an FD lesion and the borders modified to include only the area of the bone that included FD. The ROI and the location of the sentinel lesion, as determined by adjacent anatomical landmarks, were noted and saved electronically. The same areas were analyzed on repeat scans at 12 and 24 months. On repeat scanning the difference in area of the ROI had to be $\leq 5\%$ of the baseline scans. Areas that included metallic devices were excluded from analysis, and if metallic devices were introduced into a site during the study, the site was excluded from repeat analysis. Analyses were performed after completion of the study by a single co-investigator (MHK), experienced at reading DXA scans and blinded to the treatment.

Pain

Bone pain was evaluated at baseline and at each follow-up visit using the Wisconsin Brief Pain Questionnaire, a validated pain assessment tool (21).

Functional testing

Subjects underwent functional assessment at baseline and each follow-up visit. Ambulation endurance and efficiency were evaluated using the 9-minute walk test (9 MW), a standardized, validated measure (22). Subjects were instructed to walk and/or run at the fastest comfortable pace that they would be capable of sustaining for 9 minutes. Endpoints for the analysis included walking velocity and distance covered.

Muscle strength was evaluated using manual muscle testing (MMT) of the lower limbs. This was performed using a standard technique scored on the Medical Research Council (MRC) ordinal scale of 0–5 (23). The median score for each muscle (gluteus maximus, gluteus medius, iliopsoas, quadriceps, hamstrings, and ankle plantar and dorsiflexors) was determined. Endpoints for analysis included overall strength of the right and left hips, and combined total median strength of all lower extremity muscle groups.

Statistical analysis

All analyses were based on an a priori approved analysis plan and performed using SAS (version 9.2). The primary statistical comparison was based on all treated subjects (ITT population of adults and pediatric cases combined) at 18 months. The primary endpoint was the percentage change from baseline in each of the two separate measures of bone turnover between treated and placebo. The *P*-value to establish statistical significance for the primary efficacy analysis was set at $\alpha = 0.025$ divided by 2, 1-sided. Bonferroni adjustments for all nonprimary analyses were not performed. All numerically continuous data are summarized using mean $\pm$ SD with differences between means compared using a repeated measures mixed model analysis of variance (ANOVA). Categorical data are presented using proportions with categorical comparisons between treatment groups tested using Fisher's exact test.

Results

Subjects

Fifty-two subjects were screened and 40 were enrolled, including 24 adults and 16 children (Figure 1). Screening and enrollment data are included in Table 1. There were

Table 1. Subject Demographics

	Drug	Placebo	*P*
Number of subjects	20	20	
Age (y):			
Mean/Median	24.5/19	30.3/33	.26
Range	8–52	6–54	
Male	11 (55%)	7 (35%)	.34
Female	9 (45%)	13 (65%)	
Skeletal Disease Burden (%)[a]			
Mean/Median	48/46	32/21	.07
Range	(3–100)	(1–91)	
Endocrinopathies			
None (FD only)	9 (45%)	5 (25%)	.99
Precocious Puberty	6 (30%)	11 (55%)	.20
Hyperthyroid	3 (15%)	5 (25%)	.69
Growth Hormone Excess	1 (5%)	0	.99
Phosphate Wasting	6 (30%)	7 (35%)	.99

Abbreviation: NS, non-significant.

[a] Percent of skeleton involved with FD.

no significant differences between the alendronate and placebo groups with respect to age, sex, or MAS-associated endocrinopathies. There was a trend toward higher skeletal disease burden in the alendronate group ($P = .07$) (Table 1).

Two alendronate-treated subjects withdrew shortly after study initiation due to gastrointestinal (GI) side effects. Two subjects in the placebo group voluntarily withdrew due to personal preference. At 18 months a subject in the placebo group was taken off study drug after developing diarrhea and weight loss. Data from these subjects were not included in the analyses.

Bone turnover markers

There was a significant decline in the bone resorption marker NTX-telopeptides in the alendronate group as compared to the placebo group at 18 months ($P = .006$) (Figure 2A). These differences were statistically significant when children were analyzed separately (observed $P = .03$, Bonferroni adjusted $P = .06$), with a trend toward significance for adults (observed $P = .07$, Bonferroni adjusted P value $= .14$). For osteocalcin, there were no significant effects of alendronate on any analysis (Figure 2B). Alkaline phosphatase levels were analyzed as a secondary endpoint with no Bonferroni adjustments, with no significant effect on any group (data not shown).

Radiographic imaging

To confirm the established effect of bisphosphonates on normal bone and indirectly assess compliance, aBMD was measured in the lumbar spine in subjects without spinal FD, as determined by examination of bone scintigraphy. Eleven subjects in the alendronate group (6 adults, 5 children) and 14 in the placebo group (8 adults, 6 children) did not have FD in the spine. At 24 months there was a significant difference in the change in aBMD from baseline in the subjects treated with alendronate ($P = .006$), that was not apparent at 12 months ($P = .26$). When adults and children were analyzed separately, there was a significant difference in aBMD at 24 months in treated children ($P = .01$), however the changes in adults did not reach statistical significance ($P = .13$) (Figure 3A). Analyses were also performed using a comparison to normative data (Z-scores for both children and adults), which showed similar findings (data not shown). To assess the effect of alendronate on FD, sentinel lesions (as defined in Methods) were selected in 6 adults and 5 children treated with alendronate and 8 adults and 6 children treated with placebo. There were 9 lesions in femora, 13 in humeri, and 8 in tibiae. When there was more than one lesion in an individual subject, the changes in aBMD in the lesions were averaged. At 24 months there was a significant change in the aBMD at the FD sites in subjects treated with alendronate ($P < .001$), that was not apparent at 12 months ($P = .81$) (Figure 3B). When children were analyzed separately the change in aBMD at 24 months was significant ($P = .001$), however there was no significant change detected in a subanalysis including only adults ($P = .25$).

Skeletal disease burden scores determined from Tc-99 bone scintigraphy were compared at baseline and 24 months to determine the effect of alendronate on the development of new, or expansion of existing FD lesions using previously described methodology (20). Previous investigation of our cohort has shown that most FD disease burden is determined by age 15 years (24), therefore a subanalysis was performed on subjects age 15 and younger. Four out of 6 children in the alendronate group and 3 out of 4 in the placebo group

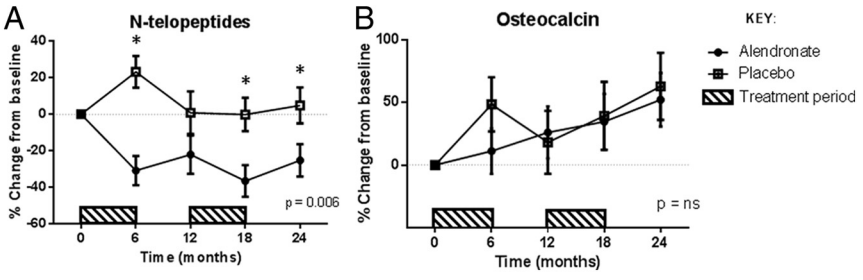

Figure 2. Effects of alendronate on bone turnover markers. A, Subjects in the alendronate group had a sustained decrease in the bone resorption marker urine NTX-telopeptides over the study period, which was significantly different from the placebo group. Time points that were statistically different are marked with an asterisk (*). B, There was no significant change in serum osteocalcin, a bone formation marker, in either group. Error bars represent 1 standard error and the hatched rectangles indicate the periods during which study drug or placebo were administered.

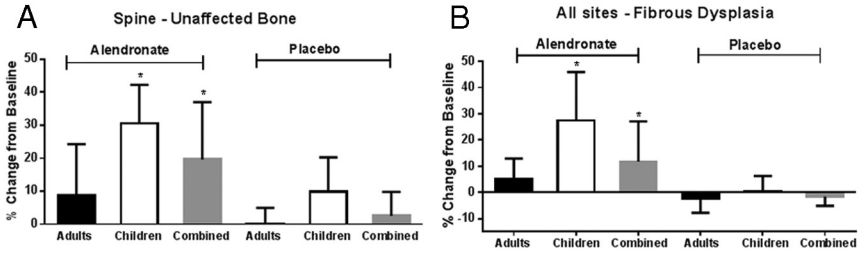

Figure 3. Effect of alendronate on areal BMD of normal and FD bone. A, aBMD was measured by dual-energy x-ray absorptiometry in the lumbar/sacral (L/S) spine of all subjects who did not have FD at the standard L/S sites as determined by bone scan. Differences between groups were measured as percent change from baseline for each individual. Adults are represented by black-filled bars (alendronate n = 6, placebo n = 12), children by open bars (alendronate n = 5, placebo n = 2), and combined adults and children by gray bars (alendronate = 11, placebo n = 14). There was a statistically significant effect of alendronate on bone density at 24 months on the combined group of adults and children ($P = .006$). When adults and children were analyzed separately, there was a significant difference in treated children ($P = .01$), however the changes in adults did not reach statistical significance ($P = .13$). B, Effect of alendronate on aBMD of FD lesions. Areal BMD was measured at sentinel sites of FD as defined in the Methods. Differences between groups were measured as percent change from baseline for each individual. Adults are represented by black-filled bars (alendronate n = 12, placebo n = 5), children by open bars (alendronate n = 9, placebo n = 3), and combined adults and children by gray bars (alendronate n = 19, placebo n = 8). There was a statistically significant effect of alendronate on the combined group of adults and children ($P = .0009$). When children were analyzed separately the change in aBMD was significant ($P = .001$), however there was no significant change detected in a subanalysis including only adults ($P = .25$).

had progression in bone scan score over the course of the treatment period. There were no significant differences in mean bone scan score at baseline or 24 months in either group of those subjects ≤ 15 or > 15 years (data not shown).

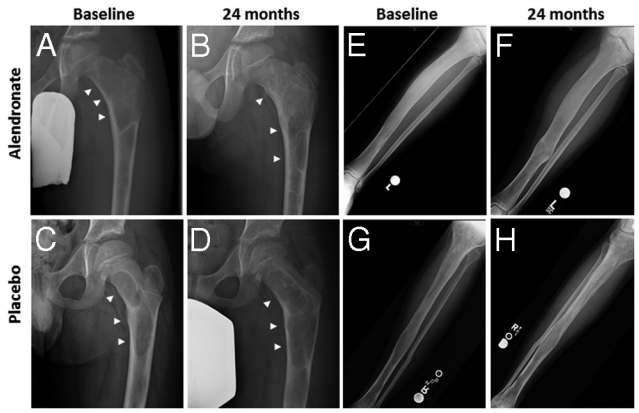

Figure 4. Representative radiographs. The left upper panels show images of the proximal femur from a 10-year-old boy in the alendronate group at baseline (A) and 24 months (B). Note lucent lesions consistent with fibrous dysplasia (FD) (arrowheads), which do not improve over the course of treatment. The radiographs in the left lower panels are from a 6-year-old boy in the placebo group at baseline (C) and after 24 months of treatment (D), which show mild progression of cortical thinning. The right upper panels show images from a 12-year-old girl in the alendronate treated group with diffuse tibial involvement at baseline (E) and 24 months (F). The images exhibit typical features of FD including radiolucency, cortical thinning, and deformity, with no evidence of improvement over the treatment course. The right lower panels (G and H) show similar views of the right tibia and fibula from a 17-year-old boy in the placebo group, which likewise did not change significantly over 24 months.

Skeletal radiographs were performed at baseline and 24 months to verify the presence of FD lesions seen on bone scintigraphy. Because of the inherent subjectivity in interpretation of radiographs (due in part to inconsistencies in exposure and positioning), changes in FD radiographic appearance were not quantified. A member of the study team reviewed the radiographs over the course of the study (M.T.C.). As expected there was variation in the progression of FD lesions between individuals, however there was no subjective improvement in FD appearance in alendronate-treated subjects, and no subjective differences between groups over the treatment period (Figure 4).

Pain

There was no difference in mean pain score between the two groups at baseline, and no significant differences in pain between groups at any point during the treatment period (Figure 5). Separate analyses of adults and children likewise failed to detect an effect of alendronate on bone pain.

Functional testing

There was no significant difference in 9 MW distance or walking speed between the alendronate and placebo groups at baseline, or at any point during the treatment period. Likewise there was no difference between the groups for MMT of the hips and lower extremities at any point.

Safety

Six fractures occurred over the treatment period; three in the alendronate group and three in the placebo group. Of note, the study was not powered to detect an effect of alendronate on fracture incidence. No subjects developed disturbances in biochemical safety measures, including markers of mineral metabolism, renal function, blood count, or liver function. Two adverse events were determined to be likely related to alendronate use. An esophageal stricture developed in an adult subject shortly after starting alendronate; the subject was subsequently found to have an undisclosed history of gastroesophageal reflux. A pediatric subject developed nausea and vomiting shortly after starting alendronate, which resolved after the drug was discontinued.

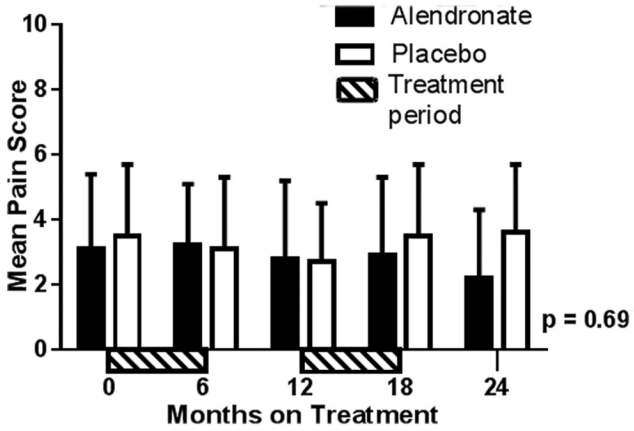

Figure 5. Effect of alendronate on bone pain. There was no significant change in mean bone pain score in either the alendronate or the placebo groups over the study period, as assessed by the Wisconsin Brief Pain Questionnaire (21). Error bars represent 1 standard deviation and the hatched rectangles indicate the periods during which study drug or placebo were administered.

Discussion

In this randomized, double-blind, placebo-controlled trial, alendronate treatment of subjects with FD at 4 times the typical osteoporosis dose resulted in a significant decrease in NTX-telopeptides, a biochemical marker of bone resorption, and a significant increase in aBMD of FD lesions at 24 months. There were no effects on the bone formation marker osteocalcin, or clinical parameters including bone pain, 9-minute walk time, or lower extremity muscle strength.

The decrease in the marker of bone resorption N-telopeptides is concordant with other studies in FD showing that bisphosphonates decrease markers of bone metabolism (13, 25–28). Because FD is a mosaic disorder, it is unknown to what degree the decrease in bone turnover markers is the result of a decline in metabolic activity of FD lesions vs that of the unaffected skeleton. It is possible that with prolonged antiresorptive treatment there is excessive suppression of the normal areas of the skeleton. Future studies including bone histomorphometry would allow more direct investigation of the effects of bisphosphonates on FD lesions vs unaffected bone. The lack of effect on osteocalcin is of interest. Osteocalcin is the product of mature cells of the osteoblastic lineage, and is considered a marker of bone formation. While the degree of osteocalcin elevation in FD is correlated with disease burden, it is the most weakly correlated bone metabolism marker (20, 29). Generally, treatment with bone resorption inhibitors such as bisphosphonates leads to a concurrent decline in both markers of bone formation and resorption (30, 31). This is believed to reflect a not well-described cross talk between osteoclasts and osteoblasts (32). A potential explanation for the lack of decrease in osteocalcin may be an absence of this cross talk in FD, and/or the fact that FD cells are less differentiated than the bone cells that typically secrete osteocalcin.

The lack of alendronate effect on bone pain contradicts previous uncontrolled studies in which bisphosphonates were consistently reported to have a beneficial effect on FD-related bone pain (13–17). There are several potential explanations for this disparity: (1) previous studies of bisphosphonates in FD were uncontrolled, and improvements in pain may have resulted from placebo effects; (2) previous studies did not consistently evaluate pain quantitatively, which may have led to an overestimation of pain relief effects; and (3) previous studies involved use of IV bisphosphonates, which may have more potent effects on bone pain than the oral formulations. The lack of an effect on pain of an oral bisphosphonate in a controlled vs uncontrolled study is similar to what was found in studies of bisphosphonates in osteogenesis imperfecta. While the IV bisphosphonates pamidronate and zoledronic acid were reported to improve bone pain in open label studies in osteogenesis imperfecta (33–35), the oral formulations alendronate and risedronate had no effect on bone pain in placebo-controlled trials (36, 37). Our findings and those in subsequent studies of osteogenesis imperfecta suggest that additional placebo-controlled trials with IV formulations are needed to determine the effect of bisphosphonates on bone pain.

As expected, aBMD increased at the spine by 24 months, confirming that treatment was sufficient to have an impact on non-FD bone (Figure 4A). The effect of alendronate on aBMD of FD lesions is less clear. DXA is a suboptimal tool for evaluating mosaic diseases such as FD due to its inability to distinguish between normal and affected bone. Although efforts were made to select ROIs that appeared to consist primarily of FD tissue, in all cases some amount of normal bone was included, confounding the aBMD measurements. DXA evaluation is also complicated by the heterogeneity of FD tissue, which may include areas of sclerosis adjacent to poorly mineralized bone. It is unknown whether DXA evaluation of FD offers any advantage over plain films, which allow assessment of clinically relevant features such as skeletal deformity and cortical thickness. While the radiographic appearance of FD varied between individuals over the course of the study, we were unable to determine a consistent effect of alendronate on the radiographs (Figure 3).

The clinical significance of these findings is uncertain. Despite the increase in areal BMD, the lack of change in the radiographic appearance of FD lesions calls into question whether alendronate had a significant impact on FD at the tissue level. FD lesions continued to expand in pediatric subjects treated with alendronate, suggesting it is not ef-

fective as a preventative therapy. Based on these data, the authors do not recommend alendronate treatment in patients with FD. Additional controlled studies are needed to determine if IV bisphosphonates are effective for treatment of FD. Another potential antiresorptive treatment is denosumab, a monoclonal antibody inhibitor of the osteoclast promoting receptor activator of nuclear-B kappa ligand, which has shown encouraging results in several case reports of patients with FD (38, 39).

Strengths of this study include a randomized, controlled, double-blinded design. It is the first controlled study reported in this disease. A primary limitation was the small number of subjects. Given the rarity of FD/MAS, recruiting enough subjects to demonstrate statistically significant changes in clinical endpoints is challenging. The failure to demonstrate a significant effect of alendronate on NTX and aBMD when adults were analyzed separately likely reflects an insufficient sample size to perform separate subanalyses of this group. Bisphosphonates are thought to have a relatively larger impact on aBMD in children (40), which may explain why the significance in this subgroup was preserved. A potential flaw in the design was studying subjects with a relatively low baseline pain levels (scores of 3.1 and 3.6 out of a possible 10 for the alendronate and placebo groups, respectively). This fact limited the potential for the intervention to affect large changes in pain.

In conclusion, alendronate does not appear to be effective for treatment of FD-related bone pain. Additional controlled studies are needed to determine if there is a role for IV bisphosphonates or denosumab in management of FD-related bone pain. Alendronate may improve bone density of FD lesions, but did not have any effect on FD radiographic appearance or bone scan score. Given the findings from this study and previous open label studies, bisphosphonates are not likely to be effective in altering the FD disease course, and alendronate is not indicated for treatment of FD.

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