

Alendronate for the Treatment of Pediatric Osteogenesis Imperfecta: A Randomized Placebo-Controlled Study

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Context: Information on the use of oral bisphosphonate agents to treat pediatric osteogenesis imperfecta (OI) is limited.

Objective: The objective of the investigation was to study the efficacy and safety of daily oral alendronate (ALN) in children with OI.

Design and Participants: We conducted a multicenter, double-blind, randomized, placebo-controlled study. One hundred thirty-nine children (aged 4–19 yr) with type I, III, or IV OI were randomized to either placebo ($n = 30$) or ALN ($n = 109$) for 2 yr. ALN doses were 5 mg/d in children less than 40 kg and 10 mg/d for those 40 kg and greater.

Main Outcome Measures: Spine areal bone mineral density (BMD) z-score, urinary N-telopeptide of collagen type I, extremity fracture incidence, vertebral area, iliac cortical width, bone pain, physical activity, and safety parameters were measured.

Results: ALN increased spine areal BMD by 51% vs. a 12% increase with placebo ($P < 0.001$); the mean spine areal BMD z-score increased significantly from -4.6 to -3.3 ($P < 0.001$) with ALN, whereas the change in the placebo group (from -4.6 to -4.5) was insignificant. Urinary N-telopeptide of collagen type I decreased by 62% in the ALN-treated group, compared with 32% with placebo ($P < 0.001$). Long-bone fracture incidence, average midline vertebral height, iliac cortical width, bone pain, and physical activity were similar between groups. The incidences of clinical and laboratory adverse experiences were also similar between the treatment and placebo groups.

Conclusions: Oral ALN for 2 yr in pediatric patients with OI significantly decreased bone turnover and increased spine areal BMD but was not associated with improved fracture outcomes. (*J Clin Endocrinol Metab* 96: 355–364, 2011)

Osteogenesis imperfecta (OI) is a heritable disorder featuring increased bone fragility and low bone mass. In most cases, OI is caused by a mutation affecting one of the two genes that encode collagen type I α chains, *COL1A1* and *COL1A2*. The traditional classification of OI distinguishes four clinical types (1). Type I comprises patients with absence of bone deformities. Type II is lethal in the perinatal period. Type III is the most severe form in children surviving the neonatal period; patients have extremely short stature and limb and spine deformities secondary to multiple fractures. Patients with less severe bone deformities and variable short stature are classified as having OI type IV. More recently additional types of OI have been described that share many features with OI types I-IV but can be distinguished on the basis of clinical and histological findings as well as by the presence of mutations affecting genes other than *COL1A1* and *COL1A2* (2–6).

Bisphosphonates are drugs widely used to treat adult osteoporosis (7). They are potent inhibitors of bone resorption that reduce the recruitment and activity of osteoclasts and osteoblasts and decrease bone turnover. Several observational studies suggested that iv therapy with the bisphosphonate pamidronate has a beneficial effect in children and adolescents with moderate to severe forms of OI (reviewed in Ref. 1). Reported benefits include improved bone mass and muscle force, reshaping of vertebral deformities, fewer long-bone fractures, and better mobility. A small randomized trial reported that oral therapy with the bisphosphonate olpadronate increased bone mineral density (BMD) and decreased the incidence of long-bone fractures (8). Similar conclusions appear in an observational report in which oral alendronate (ALN) was administered to children and adolescents with OI (9, 10).

The purpose of this study was to evaluate the efficacy and safety of daily oral ALN in the treatment of pediatric OI through a 2-yr, randomized, placebo-controlled, multicenter study. The main goals of the investigation were to study the changes in lumbar spine (LS) areal BMD, fracture rates, bone pain, self-care, transiliac histomorphometry, bone biochemistry, and safety in response to ALN therapy.

Patients and Methods

Patients

Children and adolescents with OI were recruited from May 1999 through April 2001 at 16 Shriners Hospitals for Children in North America for this prospective, randomized, double-blind, parallel-group, placebo-controlled, multicenter study. Boys and girls were eligible if they were between 4 and 18 yr of age and had a diagnosis of OI types III or IV or a diagnosis of OI type I associated with one or more of the following: chronic pain, more than three fractures (including vertebrae) per year with

minimal trauma for the previous 2 yr, or limb deformity requiring surgery. The diagnosis of OI was based on the presence of bone fragility associated with abnormal (blue or gray) scleral hue or dentinogenesis imperfecta. Patients with OI type I were specifically distinguished from those with OI type IV by the presence of blue sclerae and absence of dentinogenesis imperfecta. 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 previously received 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. Parents or guardians provided written informed consent; patients 8 yr and older provided written assent. The study was approved by an institutional review board at each center.

Treatment protocol and follow-up

Patients were randomized in a 3:1 ALN to placebo ratio and stratified according to their weight at baseline to receive either ALN 5 mg daily (those <40 kg) or ALN 10 mg daily (those \geq 40 kg), or matching placebo. The dose allocation for children of 40 kg or greater was based on the dose used in postmenopausal osteoporosis (70 mg/wk), which equals 10 mg/d. For younger children (<40 kg), the dosage was halved.

Study visits at the respective center occurred every 3 months. Compliance was assessed by tablet count at each study visit. Compliance rate was defined as the number of days when study medication was taken divided by the number of days under observation. In females of child-bearing potential, a pregnancy test was conducted whenever pregnancy was suspected and at each study visit. Patients were advised to meet the age-related dietary reference intake for calcium and vitamin D; supplemental calcium and vitamin D were added in quantities to meet the dietary reference intake if the dietary intake was inadequate. During the trial, patients in both groups received routine medical, occupational, and physiotherapy care through routine medical visits as per the usual on-site standards of care.

The primary efficacy variable was the change in LS (lumbar vertebrae 1 to 4) areal BMD z-score. Secondary efficacy variables were cortical width determined radiographically at the midpoint of the second metacarpal, the number of radiologically confirmed fractures, the number of investigator-reported fractures, and the change in cortical width of iliac bone determined by transiliac biopsy. Safety end points were the incidence of adverse events, incidence of upper gastrointestinal adverse events, change from baseline in body mass index z-score, and change from baseline in the relative amount of unmineralized osteoid in trabecular bone. In addition, a variety of clinical, radiological, and biochemical outcome variables were assessed.

Each visit included physical examination and anthropometric measures. Height was measured with a Harpenden stadiometer (Seritex Inc., East Rutherford, NJ). Height measurements were converted to age- and gender-specific z-scores using reference data published by the National Center for Health Statistics (11).

Radiological studies

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 yearly intervals thereafter in both anteroposterior and lateral views. These radiographs were evaluated for signs of fractures by an expert

panel of three radiologists who were blinded to treatment allocation. All decisions regarding the presence of fractures had to be unanimous. Fractures that were identified in this manner were classified as radiologically confirmed fractures.

In a second type of fracture analysis, fractures at all skeletal sites experienced since the last study visit, as reported by the patient or the guardian, but not necessarily radiologically confirmed, were recorded at each study visit by the investigator (investigator-reported fractures) along with their date of occurrence.

A *post hoc* analysis was conducted to assess the healing status at month 24 of radiologically confirmed long-bone fractures that occurred between baseline and month 12 (*i.e.* fractures that were seen on month 12 films but not on baseline films). The healing status of each of these fractures at month 24 was graded as healed, delayed union, or nonunion. The term delayed union was used to describe fractures in which there appeared to be radiographic evidence of partial but incomplete fracture healing, whereas nonunion was used to describe fractures in which there was no evidence of fracture healing.

Radiographs of the left hand and wrist in posteroanterior view were obtained at baseline and at yearly intervals thereafter. These films were evaluated by a central radiologist to determine cortical width at the midpoint of the second metacarpal (given the increase in metacarpal cortical width previously documented in OI during iv pamidronate therapy) (12) and bone age according to the Greulich-Pyle method (13).

Radiographs of the thoracic spine and LS in the lateral view were obtained at baseline and at yearly intervals thereafter. The midline height of each of 14 vertebral bodies (thoracic vertebra 4–12 and lumbar vertebra 1–5) was determined by a central radiologist. The midline height was chosen as an indicator of vertebral height because it would be less influenced by a wedge-shaped fracture than the posterior or anterior heights.

Bone densitometry was performed in the anteroposterior direction at the LS (L1–L4) by dual-energy x-ray absorptiometry at baseline and at 6-month intervals (Hologic Inc., Waltham, MA). All the scans were analyzed centrally and a quality-control program was conducted throughout the study that included machine cross-calibration. Areal BMD results were converted to age- and sex-specific z-scores using data provided by the manufacturer. These were based on the studies of Glastre *et al.* (14) and Southard *et al.* (15), which were comprised of a total of 353 children and adolescents.

Strength assessments

Maximal isometric grip force of the dominant hand was measured using a standard adjustable-handle Jamar dynamometer (Sammons Preston Rolyan, Bolingbrook, IL) at baseline and every 6 months thereafter. Three consecutive tests were conducted on each hand, and the mean of these three measurements was used in the analysis. Occupational therapists assessed patients at baseline and at each subsequent study visit. The Pediatric Evaluation of Disability Inventory (PEDI) was used to evaluate gross motor abilities (16). The PEDI includes 59 mobility and self-care items, which were reviewed with a questionnaire and observations for each subject. Results are presented as scaled scores. Scaled scores are not adjusted for age and therefore can be used to describe the functional status of children at all ages to document individual improvements over time.

Biochemical studies

Blood and urine samples were collected at baseline and every 3 months thereafter following an overnight fast. The samples were stored at -20°C and analyzed centrally. Biochemical tests were performed at the Shriners Hospital for Children (Montréal, Canada). Serum total calcium, phosphate, and alkaline phosphatase activity were measured using colorimetric methods (Monarch; Instrumentation Laboratories Inc., Lexington, MA). Serum PTH concentrations (fragment 39–84) were determined by RIA (17). 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D were measured with RIAs (25-hydroxyvitamin D and 1,25-dihydroxyvitamin D Osteo SP; Incstar Corp., Stillwater, MN). Urinary calcium and creatinine were quantified colorimetrically. The bone resorption marker urinary cross-linked N-telopeptide of type I collagen (uNTx) was quantified by ELISA (Osteomark; Ostex, Seattle, WA) using the second void sample of the morning. The interassay coefficient of variation at the midpoint of the standard curve for uNTx was 7%.

Transiliac histomorphometric studies

Full-thickness trans-iliac bone biopsy specimens were obtained at baseline and at Month 24 with a Bordier trephine (5 or 6 mm core diameter) under general anesthesia, from a site located 2 cm below and behind the anterior superior iliac spine. Samples were collected on days 4 or 5 after dual labeling with demeclocycline (15–20 mg/kg per day taken orally during two 2-day periods separated by a 10-day free interval). Specimen preparation and histomorphometric analyses were performed with procedures as detailed previously (18). Measurements were carried out by a single technician using a digitizing table with Osteomeasure software (Osteometrics Inc., Atlanta, GA). Nomenclature and abbreviations follow the recommendations of the American Society for Bone and Mineral Research (19).

Statistical analyses

The data and assessments collected in this study were compiled by Merck (Whitehouse Station, NJ), and statistical analyses were performed by Merck. The authors had access to the data and take responsibility for the veracity of the analyses. This study was coordinated and organized under the control of an independent steering committee, whose members were not involved in the study as investigators. Safety issues were monitored by a Data and Safety Monitoring Board, whose members were independent of the sponsor and of other committees.

To assess the primary efficacy variable, change from baseline in LS BMD z-score, a statistical comparison between the patient groups was done by an analysis of covariance model including factors for treatment, center and stratum (baseline weight <40 kg; ≥ 40 kg), and the baseline value as covariate. The primary analysis was based on a modified intention-to-treat approach. This included all patients who took at least one dose of study medication and had a baseline and at least one measurement during treatment. For missing data, the previous on-treatment observation was carried forward. This strategy explains differences in the final number of patients for the various clinical outcomes. Whereas the children in the treatment group received different doses of ALN, depending on body weight, analyses were conducted to compare the overall response to ALN in the treated group, regardless of ALN dose, compared with placebo.

Based on prior experience with pamidronate, it was expected that the treatment difference in LS areal BMD z-score would at

least be equal to 1.0 at 12 months (20). Therefore, 120 patients (90 receiving ALN and 30 receiving placebo) were needed to demonstrate the superiority of ALN or placebo at month 12 with an overall power of 99%, using a two-sided test with an overall type I error equal to 5% and accounting for the multiplicity adjustment for an interim analysis.

Fracture assessment was based on the analyses of both the radiologically confirmed and the investigator-reported fractures. The evaluation of radiologically confirmed fractures was based on the proportion of patients who experienced at least one fracture, using a Mantel-Haenszel test, adjusted for stratum, and on the rate of fractures, using a Poisson regression model, with terms for treatment, stratum, and center. The evaluation of investigator-reported fractures was based on the time to first fracture (using a log-rank test) and on the annual rate of fractures (using a Poisson regression model) with terms for treatment, stratum, and center.

The percent changes from baseline to 24 months were assessed by ANOVA models with factors for treatment, center, and stratum, for the following clinical parameters: LS areal BMD, LS bone mineral content (BMC), LS bone area, second metacarpal cortical thickness, and midline vertebral height.

Patient groups were compared with respect to the iliac bone cortical thickness and osteoid volume per bone volume using the Wilcoxon rank sum test.

Changes from baseline in the frequency of bone pain, PEDI scores, grip strength, bone age, weight z-score, height z-score, and body mass index z-score were analyzed similarly as the primary end point.

Because of the presence of large individual changes from baseline, analyses of biochemical markers and mineral homeostasis (with the exception of urine calcium/creatinine measurements) were performed using the log-transformed fraction of baseline measurements. Results were then backtransformed to produce statistics summarizing the percent change from baseline in each treatment group (geometric mean percent change from baseline). Groups were compared by means of an ANOVA model with terms for treatment, study center, and stratum. For descriptive purposes, uNTx was also expressed as the change in the percent of the healthy average (21).

The safety of ALN *vs.* placebo was assessed through the incidence rates of adverse experiences grouped under the specific subsets, including drug-related adverse experiences, discontinuations due to adverse experiences, serious adverse experiences, upper gastrointestinal adverse experiences, discontinuations due to upper GI adverse experiences, serious upper GI adverse experiences, and drug-related upper GI adverse experiences. The incidence rate of adverse experiences in each of these subsets was compared between the treatment groups using Fisher's exact test, and the rate difference was calculated along with a 95% confidence interval (CI) based on Wilson's score method.

Results

Study subjects

One hundred thirty-nine OI patients were randomized (Fig. 1). Baseline characteristics of the ALN and placebo groups are presented in Table 1. Twenty-six (24%) of the patients in the ALN group and four (13%) of the patients

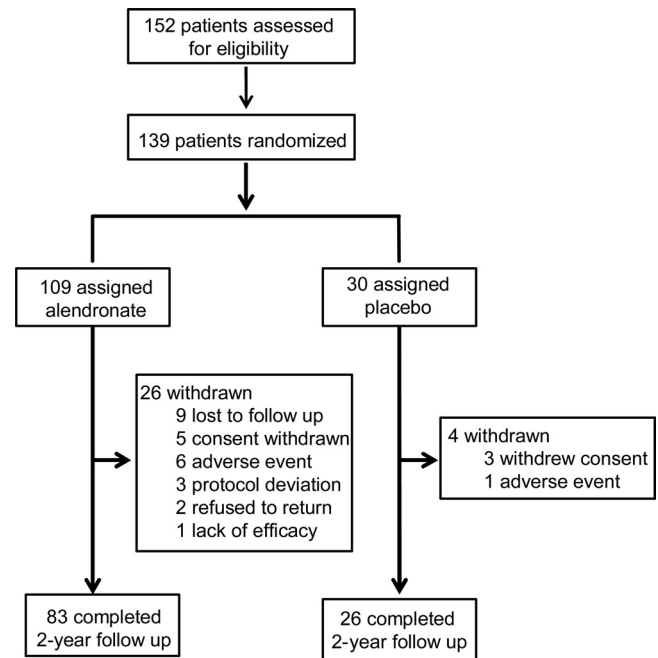


FIG. 1. Study population.

receiving placebo ($P = 0.316$) discontinued the study, for the reasons listed in Fig. 1.

Compliance, clinical adverse events, and laboratory safety data

Compliance rates of 91.7 and 94.3% were observed in the ALN and placebo groups, respectively. The rates of adverse events, serious adverse events, and withdrawal due to adverse events were similar in the two groups. For two (1.8%) ALN and one (3.3%) placebo patients, a serious adverse event resulted in discontinuation from the study; none of the serious adverse events were deemed to be drug-related by the study investigators. Six patients in the ALN-treated group withdrew from the study due to adverse events that occurred while participating in the trial, including abdominal pain, vomiting, extraskeletal ossification, leukopenia, agitation, and syringomyelia/platybasia. Only the abdominal pain and vomiting were attributed to the study drug. No patient died during the double-blind period of the study. The incidence of adverse experiences by system organ class was similar in the ALN and placebo groups. Gastrointestinal symptoms were the most commonly reported drug-related adverse experiences and occurred in 61 patients of the ALN group (56%) and in 18 patients of the placebo group (60%) ($P = 0.836$). The reported gastrointestinal symptoms in both groups included abdominal pain, dyspepsia, nausea, and vomiting. One patient in the ALN-treated group withdrew from the study because of a perceived lack of treatment efficacy. There were no episodes of gastrointestinal bleeding.

TABLE 1. Baseline characteristics by treatment allocation

	n	ALN (n = 109)	n	Placebo (n = 30)
Male sex, n (%)	109	62 (57)	30	16 (53)
Age (yr)	109	11.0 ± 3.6	30	11.1 ± 4.0
Prepubertal, n (%)	109	51 (47)	30	12 (40)
Type of OI, n (%)	109		30	
I		26 (24)		6 (20)
III		32 (29)		7 (23)
IV		37 (34)		17 (57)
Unknown		14 (13)		0 (0)
Clinical				
Weight (z-score)	108	−1.12 ± 1.49	30	−0.94 ± 1.78
Height (z-score)	106	−3.60 ± 3.36	25	−3.39 ± 3.09
Body mass index (z-score)	106	0.69 ± 1.94	25	0.66 ± 2.11
Lifetime number of reported fractures	107	51.6 ± 70.8	30	40.6 ± 53.6
Number of fractures reported during the year before the study	107	2.0 ± 3.0	30	2.6 ± 2.6
Patients with bone pain, n (%)	109	69 (63)	30	20 (67)
Frequency of bone pain (d/wk)	107	2.2 ± 2.6	30	3.0 ± 2.9
PEDI self-care (scaled score units)	105	89.4 ± 14.4	28	91.6 ± 13.8
PEDI mobility (scaled score units)	105	73.9 ± 21.6	28	73.9 ± 20.5
Grip force of dominant hand, newton	90	131 ± 93	26	121 ± 86
Current dietary calcium intake (mg/d)	59	707 ± 383	17	738 ± 339
Radiology				
LS areal BMD (z-score)	97	−4.50 ± 1.45	26	−4.56 ± 1.61
LS areal BMD (g/cm ²)	97	0.37 ± 0.16	26	0.36 ± 0.16
LS BMC (g)	97	13.8 ± 11.4	26	13.4 ± 10.8
LS area (mm ²)	97	32.8 ± 11.6	26	32.7 ± 12.1
Cortical width of second left metacarpal (mm)	83	2.70 ± 0.90	24	2.88 ± 0.68
Mean midline vertebral height (mm)	78	14.0 ± 6.4	27	13.6 ± 6.3
Bone age (yr)	82	10.7 ± 3.9	25	11.6 ± 3.2
Biochemistry				
Serum alkaline phosphatase (IU/liter)	104	290 ± 113	30	279 ± 118
uNTx to creatinine ratio [nmol/mmol (creatinine)]	99	588 ± 288	29	573 ± 235
PTH (pmol/liter)	104	7.4 ± 2.5	30	7.0 ± 1.6
25-dihydroxyvitamin D (nmol/liter)	104	48.0 ± 18.8	30	48.6 ± 17.2
Iliac bone histomorphometry				
Cortical thickness (μm)	92	570 ± 314	24	515 ± 227
Bone volume/tissue volume (%)	64	14.8 ± 6.3	18	17.9 ± 7.4

Values are mean ± sd, unless otherwise specified.

Transiliac histomorphometric safety data showed the ALN group had a significant reduction in osteoid volume per bone volume after treatment (Table 2). None of the patients had results to suggest a mineralization defect. Semiquantitative evaluation of iliac bone samples obtained at the end of the treatment period revealed the presence of at least one large osteoclast (>50 μm) in 42 of 58 patients who had received ALN (72%) but in none of the 17 patients who had received placebo. This difference between treatment groups was highly significant by χ^2 test. In contrast, there was no significant treatment difference in the presence of calcified cartilage, which was present in 30 patients who had received ALN (52%) and in seven patients who had received placebo (41%) ($P = 0.44$ by χ^2 test).

Measures of bone mass and density

LS areal BMD increased significantly from baseline to month 24 in both ALN and placebo patients, but the mean

percent increase from baseline was 38.8% greater in the ALN group (Table 2). Converted to age-specific z-scores, these results corresponded to a significant mean treatment difference value of 1.18 [95% CI 0.81 to 1.55] in favor of ALN (Fig. 2). No treatment-by-center, treatment-by-stratum, or treatment-by-baseline BMD z-score interactions were detected. The greater increase in LS areal BMD in the ALN group was entirely due to a larger increase in BMC because the projection area of the lumbar vertebrae increased to a similar extent in both groups of patients (in keeping with growing children) (Table 2).

Twenty-four months of ALN was not significantly more effective than placebo in increasing midline vertebral height, metacarpal cortical thickness, iliac bone cortical thickness, and bone volume per tissue volume (Table 2). Similarly, there were no differences in trabecular thickness and trabecular number between the two groups (data not shown).

TABLE 2. Changes after 2 yr of treatment with ALN or placebo

Parameter evaluated for 24-month change	n	ALN	n	Placebo	P
Radiology					
LS BMD (% increase) ^a	86	50.7 (38.0, 63.4)	26	11.9 (−6.4, 30.2)	<0.001
LS BMD z-score ^b	86	1.32 (1.08, 1.56)	26	0.14 (−0.21, 0.48)	<0.001
LS BMC (%) ^a	86	73.7 (56.8, 90.5)	26	27.6 (3.3, 51.9)	0.001
LS area (%) ^a	86	14.2 (10.4, 18.0)	26	12.2 (6.7, 17.6)	0.493
Cortical width of second left metacarpal (%) ^a	81	19.0 (9.2, 28.9)	23	8.9 (−6.2, 24.0)	0.209
Mean midline vertebral height ^a	76	29.9 (18.0, 41.8)	26	22.4 (4.9, 40.0)	0.444
Bone age (yr) ^b	80	2.13 (1.83, 2.42)	24	2.26 (1.80, 2.72)	0.578
Iliac bone histomorphometry^c					
Cortical thickness (μm) ^d	60	162 (76, 273)	16	58 (−31, 346)	0.287 ^e
Bone volume/tissue volume (%) ^d	32	0.2 (−2.6, 4.3)	8	−1.9 (−10.2, 8.1)	0.054 ^e
Osteoid volume/bone volume (%) ^d	43	−1.1 (−1.5, −0.7)	12	−0.2 (−1.5, 1.0)	0.039 ^e
Clinical					
Weight (z-score) ^b	101	0.18 (0.02, 0.34)	30	0.01 (−0.22, 0.25)	0.183
Height (z-score) ^b	98	−0.30 (−0.57, −0.04)	25	−0.17 (−0.60, 0.26)	0.544
Body mass index (z-score) ^b	98	0.46 (0.16, 0.77)	25	0.16 (−0.34, 0.65)	0.248
Patients with at least one new radiologically confirmed long-bone fracture at month 24, n (%)	95	71 (74.7)	29	21 (72.4)	0.757
Number of new long-bone radiologically confirmed fractures at month 24 (cumulative incidence of first fracture) ^a	95	1.96 (1.40, 2.75)	29	1.75 (1.10, 2.80)	0.614
Patients with bone pain at month 24, n (%)	102	38 (37.3)	30	17 (56.7)	0.065 ^f
Bone pain (d/wk) ^b	100	−0.88 (−1.53, −0.24)	30	−0.15 (−1.13, 0.84)	0.167
Self-care (scaled score units) ^b	94	5.05 (3.22, 6.88)	28	3.04 (0.27, 5.81)	0.160
Mobility (scaled score units) ^b	94	6.46 (3.12, 9.80)	28	4.96 (−0.08, 10.00)	0.568
Grip force, newton ^b	84	54 (38, 70)	26	57 (35, 79)	0.780
Biochemistry^g					
Serum alkaline phosphatase (%) ^h	39	−21.7 (−30.8, −11.6)	18	−13.8 (−27.9, 2.9)	0.320
uNTx to creatinine ratio (%) ^h	38	−62.2 (−67.4, −56.1)	16	−32.0 (−46.7, −13.3)	<0.001
PTH (%) ^h	39	24.2 (10.8, 39.2)	17	15.0 (−0.8, 33.3)	0.442
25-dihydroxyvitamin D (%) ^h	39	−4.5 (13.8, 5.8)	17	−12.7 (18.5, −6.5)	0.248

Analysis as per modified intention-to-treat approach, unless noted otherwise. Results are expressed as mean change with 95% CIs.

^a Adjusted for center and stratum; ^b adjusted for center, stratum, and baseline result; ^c data as observed; ^d median; ^e Wilcoxon rank-sum test; ^f stratified by the presence of baseline bone pain; ^g per-protocol analysis; ^h backtransformed from ln(fraction of baseline).

Fractures, fracture healing, bone pain, self-care, and mobility outcome measures

The relative risk (95% CI) of having at least one new radiographically confirmed long-bone fracture between baseline and month 24 was 1.04 (0.81, 1.34) for the ALN

group, which was not significantly different from 1.00 (Table 2). Similar results were found after exclusion of fractures that had occurred in bones containing hardware. Eighty-three percent of the ALN patients and 92% of placebo patients sustained at least one investigator-reported fracture (*P* = 0.070) (Fig. 3). The mean midline vertebral height was also similar between the two groups (*P* = 0.444).

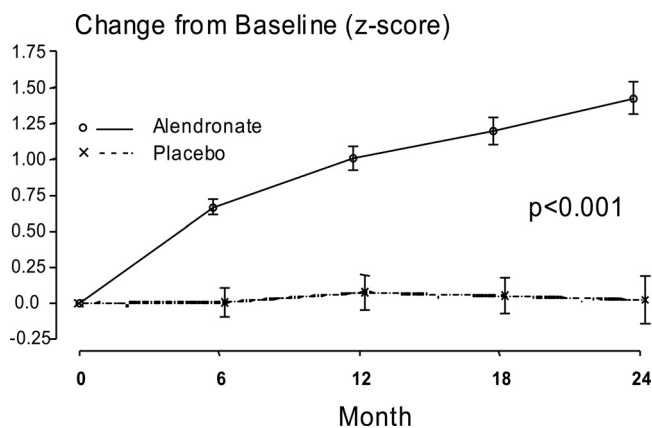


FIG. 2. Change in LS (L1-L4) areal BMD.

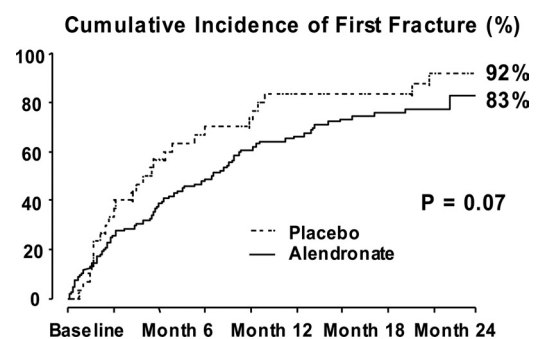


FIG. 3. Cumulative incidence of investigator-reported fractures.

Fracture healing was assessed at month 24 by evaluating the healing status of new fractures that had been noted on the month 12 radiographs. Forty-four ALN patients with 94 new fractures and 11 placebo patients with 23 new fractures comprised this analysis. In the ALN group, seven patients (15.9% of patients) had a total of eight fractures (8.5% of new fractures) that were classified as delayed union or nonunion, whereas for the placebo group, there was a single patient (9.1% of patients) with one such fracture (4.3% of new fractures), representing a nonsignificant difference between the two groups ($P = 0.669$).

Significantly fewer ALN patients experienced bone pain at month 24 than at baseline ($P < 0.001$). The difference between the ALN and placebo groups in the percentage of patients who experienced bone pain at month 24 was not statistically significant ($P = 0.065$) (Table 2), and there was no significant treatment effect on the number of days per week during which patients suffered bone pain (Table 2).

Differences in self-care or mobility functional skills scaled scores and in grip force were not statistically significant between the ALN and placebo groups (Table 2).

Anthropometry, bone age, and bone biochemistry outcome measures

No significant treatment effect was found for changes in bone age or z-scores for height, weight, or body mass index (Table 2). No significant differences between the ALN and placebo groups were observed for changes between baseline and month 24 in serum levels of calcium, phosphorus, creatinine, and urinary calcium to creatinine ratio (data not shown). Patients receiving ALN experienced a significant rise in PTH levels, but the difference compared with the placebo group was significant only early in the course of the study [at month 3 ($P = 0.049$)]. In the ALN group, serum 1,25-dihydroxyvitamin D levels also increased during the first 3 months and then remained constant through month 24, whereas in the placebo group, a decline in 1,25-dihydroxyvitamin D levels was observed. This difference in 1,25-dihydroxyvitamin D reached statistical significance at month 24 [mean percent change from baseline at month 24 (ALN group), 12.5 (95% CI $-3.0, 30.5$) compared with -15.6 ($-34.6, 9.0$) in the placebo group, $P = 0.048$]. In the ALN group, uNTx levels initially dropped sharply in the first 3 months and then decreased gradually throughout the remaining period (Fig. 4). In the placebo group, a slight decrease was seen. Twenty-four months of treatment with ALN was significantly more effective than placebo in decreasing uNTx levels ($P < 0.001$) (Table 2 and Fig. 4). uNTx decreased from 131% of the healthy average in the ALN group at baseline, to 63% of the healthy average after 2 yr ($P <$

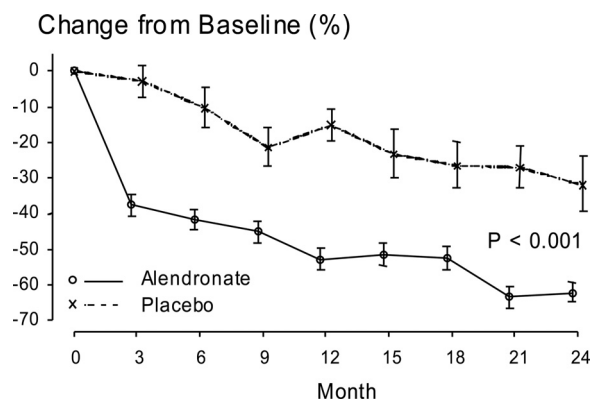


FIG. 4. uNTx to creatinine ratio.

0.001). In the placebo group, uNTx decreased from 128% of the healthy average at baseline to 112% 2 yr later (95% CI for the difference in change between the two groups was $-87, -15$; $P = 0.006$). In contrast, no significant treatment difference was observed with regard to changes in serum total alkaline phosphatase activity (Table 2).

Exploratory analyses were undertaken to determine whether there were significant differences between treated patients with 75% or greater compliance compared with the placebo group. Similarly, the data were also analyzed according to OI subgroup, as follows: children with treated OI type I were compared with those with OI type I who received placebo and children with treated OI type III and type IV were compared with children who received placebo with the same diagnosis. These exploratory subanalyses did not reveal any additional significant differences for the outcome parameters tested in this trial (data not shown).

Discussion

We found that for children and adolescents with OI, oral ALN over 24 months was more effective than placebo in increasing LS areal BMD z-score and was well tolerated. On the other hand, there was no significant effect of ALN on secondary efficacy parameters including fracture incidence, height of the vertebral bodies, cortical thickness, mobility, and bone pain. For the cumulative incidence of first investigator-reported fracture (shown in Fig. 3) and the percentage of patients with bone pain after 24 months, the P values for improvement in these secondary outcomes were 0.07 and 0.065, respectively. Because the study's sample size was established *a priori* to ensure adequate power for the primary outcome (spine BMD), it remains unknown whether a positive effect of ALN on these clinically relevant secondary outcomes would have been documented in a larger population of patients or with a higher dose and/or longer duration of ALN therapy.

Study participants weighing more than 40 kg received ALN 10 mg/d, a dose that has been shown to protect against fractures in adult men and women with osteoporosis (20, 22). In children weighing less than 40 kg, only 5 mg of ALN was given per day in an attempt to adapt the dose to body weight. As expected, the ALN dose was sufficient to significantly inhibit the activity of bone resorption, as indicated by a marked suppression of the urinary bone resorption marker uNTx. The treatment was also effective in increasing LS areal BMD to a similar extent reported for oral olpadronate in a comparable patient population (8). That ALN was successful in augmenting LS areal BMD but was not associated with improvement in other skeletal outcomes such as metacarpal and iliac cortical width may be due to the fact that a greater proportion of the vertebral body is comprised of primary and secondary spongiosa compared with other skeletal sites. In the growing child, more primary spongiosa survive to become secondary spongiosa during bisphosphonate treatment (23), a biological phenomenon that is readily apparent on spine radiographs as endplate sclerosis and also captured on dual-energy x-ray absorptiometry-based BMD testing (12). At the same time, the gain in LS areal BMD z-score was nevertheless attenuated in our ALN-treated patients (average increase 1.3 SD) compared with numerous observational studies using cyclical iv pamidronate (9 mg/kg · yr) in which the average gain ranged from 1.9 to 3.2 SD after 2 yr of therapy (10, 12, 24, 25).

The absence of significant effect on parameters such as metacarpal and iliac cortical width, iliac trabecular bone volume, and height of the vertebral bodies in our study despite improved LS BMD is consistent with other studies using oral bisphosphonate therapy (risedronate and olpadronate) (8, 26, 27). In contrast, iv bisphosphonate therapy among children with OI using pamidronate and neridronate has consistently shown improvement in the height of vertebral bodies and cortical width, both in observational and controlled studies (28–32). One study did show similar increases in the height of vertebral bodies with high-dose oral ALN (1 mg/kg · d) compared with iv pamidronate (10), suggesting the efficacy of oral ALN might be improved with much higher doses. This is a logical consideration, given the low bioavailability of oral ALN (less than 1%) previously documented in the pediatric OI setting (33).

Bone pain, fractures, and mobility, similar in this study between the two groups, are key clinical indices with direct impact to the quality of life of the child. A lack of change in mobility was also observed after 2 yr of oral olpadronate in pediatric OI (8), and an absence of improved bone pain was found in a dosing range study using oral risedronate (26). In contrast, improvements in all of these pa-

rameters have been reported in either controlled (32) or observational (12, 34, 35) trials with iv bisphosphonates. It might be argued that the observational studies in particular have overestimated the beneficial effects of iv therapy (pamidronate), but it is also possible that oral ALN at the studied dose and duration provides less benefit than iv therapy despite its convenient administration. In the absence of large and longer-term comparative studies measuring between group differences, it is difficult to prove which of these alternatives is best. In the placebo-controlled study of oral olpadronate, it was concluded that this agent decreased long-bone fracture risk (8). However, only 16 patients received olpadronate in this study, providing limited statistical power to judge olpadronate's antifracture effectiveness. The randomized, double-blind, placebo-controlled study of oral risedronate in mild pediatric OI by Rauch *et al.* (27) showed no difference in the number of new extremity fractures after 2 yr of study; similarly, the randomized, controlled dose-ranging study using the same oral agent by Bishop *et al.* (26) showed no difference for incident nonvertebral fractures for lower-, medium-, and higher-dose regimens. On the other hand, the only randomized controlled study of an iv bisphosphonate (neridronate) in OI, by Gatti *et al.* (32), showed a reduction in the total number of extremity fractures in the treated group compared with controls (relative risk 0.36; 95% CI 0.15–0.87) after 3 yr of therapy. Taken together, the currently available literature has not proven definitively that treatment with any bisphosphonate (oral or iv) improves mobility in children and adolescents with OI, whereas iv (compared with oral) therapy has been associated with improved extremity fracture rates and height of the vertebral bodies in the observational setting (12), findings that have been corroborated through controlled trial design (32).

Importantly, ALN was associated with few adverse events. In particular gastrointestinal symptoms were not more common in patients receiving ALN than in those receiving placebo, and ALN did not appear to interfere with fracture healing. Similarly, bone histology showed no evidence of a mineralization defect in any of the patients. Large osteoclasts were evident on transiliac bone biopsy in 72% of ALN-treated children compared with none in the placebo group, a finding also documented in pamidronate-treated children with OI (36). This observation is inherent to the mechanism of action of nitrogen-containing bisphosphonates (37), whereby osteoclast cytoskeletal organization is impaired and thereby associated with alterations in both osteoclast morphology and skeletal resorption.

Overall, despite its easier administration and favorable safety profile, the present study evaluating ALN 5 and 10

mg for 2 yr does not provide impetus for use of ALN over iv agents, the latter now used worldwide in the treatment of moderate to severe pediatric OI.

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