JOURNAL OF BONE AND MINERAL RESEARCH
Volume 20, Number 5, 2005
Published online on December 20, 2004; doi: 10.1359/JBMR.041232

Intravenous Neridronate in Children With Osteogenesis Imperfecta: A Randomized Controlled Study

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ABSTRACT: In a randomized controlled study, we investigated the effect of treatment with intravenous neridronate in prepubertal children with OI. Our study suggests that quarterly intravenous infusions of the bisphosphonate significantly raise the rate of increase in BMD at both the spine and hip, the projected area of the lumbar vertebrae, and height. These results are associated with a significant decrease in the risk of clinical fractures.

Introduction: Osteogenesis imperfecta (OI) is a heritable disease of connective tissue, characterized by increased bone fragility. Bisphosphonates currently seem to be the most promising therapy, but randomized, controlled studies are scarce and have never been carried out in prepubertal children.
Materials and Methods: This was a randomized, controlled 3-year clinical trial. The Italian Patients' Society of OI (AsItOI) sent their members affected by any type of OI to two centers at the University of Verona (Italy) to participate in the study. Sixty-four children, 6–11 years of age for boys and 6–9 years of age for girls, with no signs of puberty and who were never treated with bisphosphonates, were randomized to either intravenous neridronate (2 mg/kg infused IV in 30 minutes every 3 months) or no treatment, with a ratio of 2:1. Control patients were given the same bisphosphonate therapy at the end of the first year. BMD and projected bone areas, as measured by DXA, at spine and hip, height, and peripheral fracture incidence, both prospective and retrospective (2 years preceding randomization), were the main outcomes of the study.
Results: At the end of the first year, spine and hip BMD rose by 3.5–5.7% in control patients and by 18–25% ($p < 0.001$ versus controls) in the active group, respectively. During the following 2 years, the treatment in all patients was associated with BMD increases of 10–25% per year. Height and the DXA-derived projected area of lumbar spine rose during the first year of observation significantly more in the active group than in the control group (<0.01 and <0.05, respectively). Both height and spine projected area continued to rise in the treated patients toward levels found in healthy individuals. During the first year of treatment, 45% of the control patients and 27% of the active group had a nonvertebral fracture, but this difference was not statistically significant ($p = 0.2$). The total number of fractures was 18 in the 22 control patients and 13 in the active group (relative risk, 0.36; 95% CI, 0.15–0.87; $p < 0.05$).
Conclusion: Intravenous neridronate infusions, administered quarterly, significantly increase BMD and lower the risk of clinical fracture in prepubertal children with OI.
J Bone Miner Res 2005;20:758–763. Published online on December 20, 2004; doi: 10.1359/JBMR.041232

Key words: osteogenesis imperfecta, bisphosphonates, neridronate

INTRODUCTION

OSTEOGENESIS IMPERFECTA (OI) is a heritable disease of connective tissue caused by heterologous mutations in the genes encoding for type I collagen and characterized by increased bone fragility. Four types are commonly distinguished on the basis of clinical and genetic features, although overlap forms are often observed. In its mildest form (type I), fractures tend to occur mostly before puberty and again after menopause. Type II OI leads to perinatal death. Type III OI causes fractures that are very frequent, resulting in short stature, severe deformities, and shortened life expectancy. These fractures are also typical of type IV, but are less severe. The clinical expression of the disease is not always typical; this led to the identification of at least another three types of OI.[1]

New potentially ultimate therapies have been proposed for the treatment of OI,[2] but to date, bisphosphonates seem to be the most promising therapy both in adults[3] and in children.[4–12] The initial beneficial effect reported in a number of small studies has been recently supported in a larger cohort of children treated for up to 5 years with cyclical intravenous pamidronate.[6,8] This treatment resulted in clinically meaningful increases in BMD by DXA

The authors have no conflict of interest.

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at any studied skeletal site. More recently, in a 2-year randomized controlled trial, it was reported that oral daily olpadronate treatment results in a reduction of fracture risk of long bones in children with OI.[13] In 1995, in collaboration with the "Istituto Superiore di Sanità" (part of the Ministry of Health), the Italian Association of Patients with OI (AsItOI) initiated a large randomized, controlled therapeutical trial of intravenous neridronate in both children and adult patients with OI. We have recently reported the results obtained in men and in premenopausal women. Here, we report the results observed in prepubertal children. Neridronate is an amino-bisphosphonate structurally similar to alendronate and pamidronate, differing only in the number of methyl groups of the side-chain: five for neridronate, three for alendronate, and two for pamidronate.[14] It has been studied for the treatment of Paget's disease of bone[15–18] and recently registered in Italy for the treatment of OI on the basis of the clinical trials reported in the past and here.

MATERIALS AND METHODS

Patients

All subjects affected by any type of OI and registered with the AsItOI were informed by the association newsletter, either directly or through their parents, regarding the possibility to participate in a clinical trial of a new bisphosphonate.[3] Several other patients contacted our center after a public appeal on national radio.

After excluding the patients who had already received bisphosphonates or were <3 years of age, informed written consent was obtained from 219 patients (Fig. 1).

After the publication of the papers from the Montreal group,[6,8] one-half of the new patients refused their consent to be randomized into the trial. They were treated with the same dose of neridronate, and the observed results will be analyzed separately. The recruitment ended in January 2001. Interestingly, none of the patients who initially gave their consent withdrew from the study. Eligible OI patients were separated into four groups: infants, children, and peripubertal and adults. The interim analysis of adult patients has been reported elsewhere.[3] Here we report the results observed in the 64 prepubertal children with any type of OI, age ranging from 6 to 11 years of age in boys and 6–9 years of age in girls, with no signs of puberty.

The principal characteristics of the 64 patients are listed in Table 1. The history of prior clinical nonvertebral fracture during 2 years preceding recruitment was carefully collected from all patients.

Treatment

The patients were randomized according to OI type (type I or type III and IV) to either intravenous (active group) or no treatment (control group), with a ratio of 2:1. Neridronate (2 mg/kg body weight) diluted in 250 ml of saline solution was infused intravenously in 30 minutes every 3 months. All patients had their dietary calcium intake regularly evaluated and maintained, through diet or supplementation, above 600–800 and 1000 mg daily according to their age: <7, 7–10, >0 years of age, respectively. Vitamin D_2 supplements (50,000 units monthly) were given if the serum 25(OH)vitamin D levels fell below 20 ng/ml. Calcium and/or vitamin D_2 supplements were necessary throughout the study in only four patients. It is worth noting that all patients had adequate calcium and vitamin D intake for years because of the continuous educational program from AsItOI.

The control patients commenced the neridronate therapy after 12 months of follow-up with continued controlled calcium and vitamin D intake.

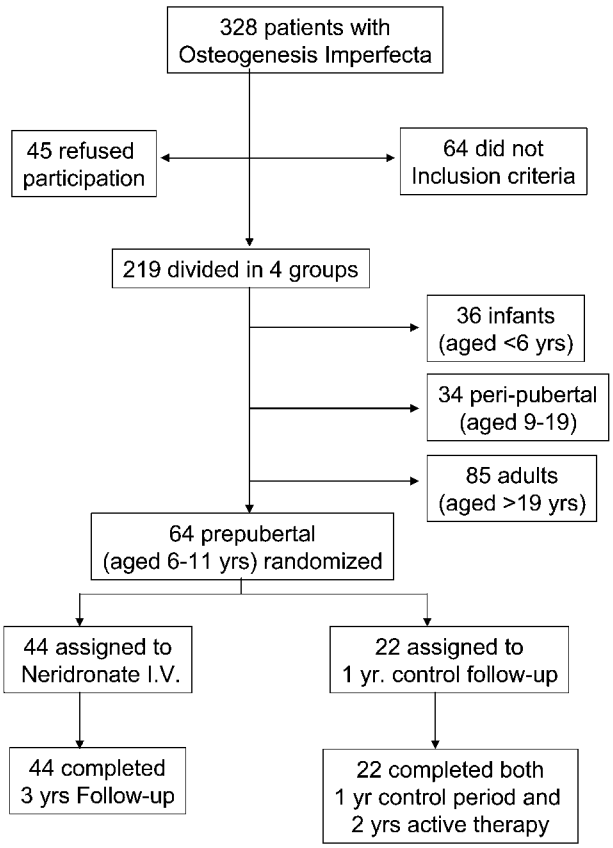

FIG. 1. Trial profile.

TABLE 1. PRINCIPAL CLINICAL AND ANAGRAPHIC CHARACTERISTICS (MEANS ± SD) OF STUDY POPULATION AT THE BEGINNING OF THE PROSPECTIVE OBSERVATION

	Control group	*Active group*
Patients (*N*)	22	42
Type of OI (I-III-IV)	14-2-6	28-2-12
Sex (Male-Female)	13-9	20-22
Age (years; mean ± SD)	8.6 ± 2.4	9.0 ± 2.3
Weight (kg, mean ± SD)	27.8 ± 14.6	29.2 ± 12.1
Height (cm, mean ± SD)	120.8 ± 23.7	123.0 ± 22.0
Lumbar spine BMD (mg/cm^2)	356 ± 165	407 ± 178
Femoral neck BMD (mg/cm^2)	422 ± 221	481 ± 162
Total hip BMD (mg/cm^2)	508 ± 216	519 ± 190
Total alkaline phosphatase (U/I)	281 ± 77	298 ± 66
Bone alkaline phosphatase (U/I)	122 ± 31	130 ± 27

Study protocol was approved and constantly monitored by the local ethical committee and the Istituto Superiore della Sanità (part of the Italian Ministry of Health).

Measurements

All patients were seen at 3-month intervals, but full clinical evaluation, including bone densitometry measurements by DXA and fasting serum and urinary (second morning voiding) biochemistry, was obtained per-protocol every 6 months before the infusion of neridronate. Routine biochemistry, including serum calcium, phosphate, creatinine, and total and bone alkaline phosphatase, were carried out on the same day of sample collection. Aliquots of both serum and urines were stored at –20°C for future evaluation of bone markers. The general practitioners of all patients were also asked to evaluate albumin-adjusted serum calcium at the appearance of symptoms even vaguely related to hypocalcemia. Routine biochemistry was measured by standard autoanalyzer procedures and serum bone alkaline phosphatase by a commercial kit (Bone AP: Alkphase–B; Metra-Biosystems, Mountain View, CA, USA) with an interassay CV of 9%.

Radiographs of the spine (antero-posterior and lateral views) were obtained at baseline and after 12 and 36 months, but the best approach for analyzing the changes in shape of the vertebrae is still under evaluation. Additional X-rays were obtained at any skeletal site whenever symptoms of fractures occurred. Changes in BMD and projected area at the lumbar spine and total hip were measured by DXA (QDR 4000; Hologic, Waltham, MA, USA). Appropriate DXA evaluations could not be obtained in 11% and 12% of the patients at the spine and hip, respectively, most often because it was impossible to obtain correct positioning. The precision error for BMD at different skeletal sites was assessed by double measurements at one of the time-points of the study in all participants. The CV is somewhat greater than that observed in adults, ranging from 1.4% to 2.9% at the spine and hip, respectively.

Height was obtained while patients were standing (Harpender stadiometer), or if wheelchair-bound, lying on the bed of the Hologic DXA instrument.

Statistical analysis

The within-subject changes in BMD were tested by two-sided paired *t*-test, and the between-group differences were tested by ANOVA and by Tukey test. These latter differences were also tested after adjustment for baseline BMD values, type of OI, and sex (covariance analysis). Intention-to-treat analysis was planned, but it was not applied because all patients completed the treatment follow-up. The change in the rate of fracture incidence was analyzed by the McNemar test (2 × 2; version 11; SPSS).

RESULTS

Before treatment, all subjects had normal serum calcium, phosphate, 25(OH)vitamin D (>12 ng/ml), and PTH levels (Allegro intact PTH, normal values < 60 pg/ml), and there was no evidence of other relevant diseases. The two groups

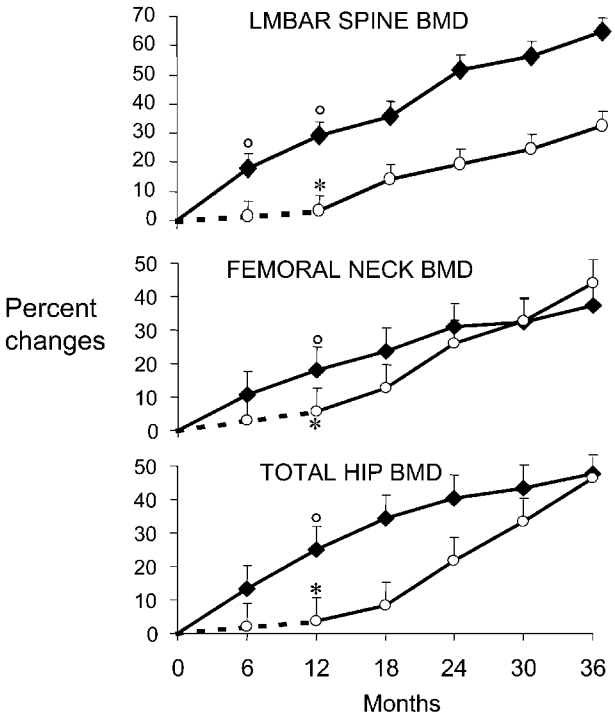

FIG. 2. BMD changes during treatment with intravenous neridronate (solid line) and no-treatment periods (dashed line) in the active (diamonds) and control (open circle) group. (°$p < 0.05$ between groups; *$p < 0.05$ vs. baseline in the control group; at all the other time-points, the changes were significantly different from zero at $p < 0.001$).

of patients were somewhat different for age, sex distribution, weight, height, and baseline BMD values, but none of these differences was statistically significant (Table 1). All patients completed the planned period of observation and treatment. None of the children developed signs of puberty during the first year of observation. Four patients in the control group and seven in the active group showed signs of puberty (stages 2 and 3) at the end of the third year of observation.

The mean changes in BMD in the two groups are shown in Fig. 2. In the control group, spine and hip BMDs rose significantly ($p < 0.01$) by 3.5–5.7% (Fig. 1) during the first year without active treatment. The treatment in both groups was associated with BMD changes at the spine of ~30% during the first year, 20% during the second year, and 15% during the third year of treatment. The corresponding changes at the femoral neck and total hip were 18–25%, 13–15%, and 7–8%, respectively (all highly significant versus both baseline and the previous year). Spine Z score did not change in the control group during the first year, but it rose gradually from –3.39 to –2.01 ($p < 0.001$) in the active group over 3 years.

During the first year, the projected area of lumbar spine rose by 2.0% in the control group, which is significantly lower than the 6.7% increase observed in treated patients (Table 2). In the subsequent 2 years, the projected spine area rose by 14%.

The mean individual height rose by 0.9% and 2.6% dur-

TABLE 2. PERCENT CHANGES (MEANS ± SD) IN HEIGHT AND DXA-DERIVED ANTERO-POSTERIOR PROJECTED AREA OF LUMBAR SPINE AND NUMBER OF PATIENTS IN WHOM PUBERTAL STAGE ROSE FROM INITIAL 1 TO EITHER 2 OR 3 DURING YEARS 1 AND 2–3

Time (months)		*Control group (n = 22)*	*Active group (n = 42)*	*Between-group p*†
0–12	Height	0.92 ± 1.08%*	2.64 ± 2.50%*	<0.01
	Spine area	1.97 ± 3.25%	6.68 ± 8.05%*	<0.05
	Tanner >1	0	0	
12–36	Height	4.12 ± 4.11%*	3.88 ± 3.51%*	
	Spine area	14.18 ± 4.24%*	12.87 ± 5.99%*	
	Tanner >1	4	7	

* $p < 0.01$ vs. zero.
† For values adjusted for baseline BMD, sex, and OI type.

ing the first year in the control and active groups, respectively ($p < 0.01$). The rate of height increase was maintained during the second and third year, with an apparent catch-up to the values found in healthy subjects of the same age (data not shown). There were no differences in the BMD, projected area, and height increments between boys and girls or among OI types, and the increments were not related to initial age or pubertal stage at the end of the study. The densitometric and height values and their changes during follow-up remained substantially identical after adjustment for baseline BMD values, sex, and OI type.

Both total and bone alkaline phosphatase progressively declined during treatment (Fig. 3). A significant decrease was observed also during the control year.

Over the 5 years of evaluation (2 retrospective and 3 prospective years), all patients had at least one fracture at the lower and/or upper limbs. Nine patients had fractures at the ribs, scapula, and clavicle.

The numbers of nonvertebral fractures during the entire period of evaluation are listed in Table 3. During the first year of observation, 45% of the patients of control group and 27% of the active group had at least one fracture (adjusted relative risk [RR] = 0.60; 95% CI, 0.21–1.59). The treated patients who fractured experienced most often a single fracture (Table 4), and the overall number of fractures was significantly lower in the active than in the control group: 13 in 44 patients and 18 in 22 patients, respectively (RR = 0.36; 95% CI, 0.15–0.87; $p < 0.05$). A slight further decrease in the RR of fracture was observed for values adjusted for initial BMD, OI type, and sex (RR = 0.33; 95% CI, 0.15–0.82; $p < 0.02$).

During the >150 patient-years during a pooled no-treatment period (prerecruitment and control time), 88 (59%) had 285 fractures (mostly multiple during the same traumatic event), whereas the incidence during treatment was 20% (34 of the 170 patient-years had 71 fractures; RR for number of fractured patients 0.34; 95% CI, 0.22–0.54; $p > 0.001$; RR for global number of fractures 0.18; 95% CI, 0.13–0.29; $p < 0.001$; Tables 3 and 4).

Ten of the patients complained of flu-like symptoms, resembling a typical acute phase reaction,[19] 24–36 h after the first intravenous infusion, which lasted <36 h. An attenuated response was also noted by all of them after the second infusion. None of the patients complained of other typical side effects associated with intravenous aminobisphosphonate administration.[20] Serum calcium and phosphate were within the normal range at all time-points before the neridronate infusions. Symptomatic hypocalcemia was never reported. Serum calcium was measured 3–7 days after the infusion, 19 times in 16 patients, with values ranging from 8.1 to 9.2 mg/dl (normal range, 8.5–10.2 mg/dl).

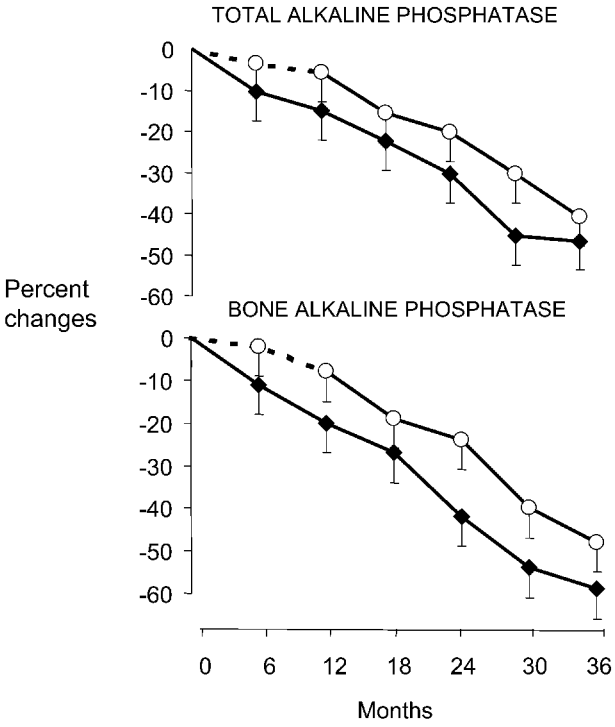

FIG. 3. Changes in total and bone alkaline phosphatase during treatment with intravenous neridronate (solid line) and no-treatment periods (dashed line) in the active (diamonds) and control (open circle) group. With the exception of the 6-month time-point in the control group, the changes at all time-points were significantly different from zero at $p < 0.01$.

DISCUSSION

Bone fragility in OI results from quantitative and qualitative alterations in type I collagen that are not expected to benefit directly from a treatment with antiresorbing agents, such as bisphosphonates. However, there is histomorpho-

Table 3. Fracture Incidence During the Observation Time: Number of Patients or Number of Events per Patient-Year

	Control group (22 patients)			*Active group (42 patients)*		
Year	*Treatment*	*Fractured patients [number (%)]*	*No. of fractures*	*Treatment*	*Fractured patients [number (%)]*	*No. of fractures*
–2/–1	No	12 (54%)	22	No	24 (57%)	82
–1/0	No	18 (82%)	91	No	24 (57%)	72
0/1	No	10 (45%)	18	Yes	12 (27%)	13*
1/2	Yes	4 (18%)	11	Yes	5 (12%)	13
2/3	Yes	4 (18%)	9	Yes	9 (21%)	25

* Relative risk reduction 0.36 (CI, 0.15–0.87; $p < 0.02$).

Table 4. Number of Fractures Occurred per Patient-Year (PYR) During the Prospective Study and During the Overall Observation Period

	Neridronate therapy			
	Prospective controlled observation (1 year)		*Prospective + retrospective observation (5 years)*	
Fractures/ patient-year	*No (PYR n = 22)*	*Yes (PYR n = 42)*	*No (PYR n = 150)*	*Yes (PYR n = 170)*
0	54.5%	71.4%	41.3%	80.0%
1	22.7%	26.2%	11.3%	8.8%
2	13.6%	2.4%	25.3%	4.7%
≥3	9.1%	0%	22.0%	6.5%

metric and biochemical evidence of increased bone resorption in OI.[21–23] The high bone turnover might be caused by recurrent fractures or be directly related to the abnormal bone structure, but it might also contribute to further bone loss and fragility. This provides a reasonable rationale for the use of antiresorptive agents for the treatment of OI. In fact, bisphosphonates are now the most frequently reported therapeutic regimens for OI. The majority of the studies with bisphosphonates were uncontrolled, but recently, two randomized clinical trials have been reported, one, as part of this study, in adults with intravenous intermittent neridronate,[3] and another in children with oral daily olpadronate.[13]

In all these studies, it seems that the beneficial effects in terms of DXA outcomes are associated with some evidence of reduction in fracture risk.

Our original choice for intravenous infusion was influenced by the fact that some children with the most severe type of OI are either intolerant or incapable of following recommendations for taking oral amino-bisphosphonates. The dose of neridronate we adopted (2 mg/kg/3 months) is somewhat comparable in terms of antiresorptive activity to the widely used dose of intravenous pamidronate (9 mg/kg/year).

Our results confirm the beneficial effects on BMD reported in uncontrolled studies. However, the significant BMD increases at all sites observed over 1 year in the control group emphasizes the need of controlled studies in growing subjects for rare diseases such as OI. The correct interpretation of the observed changes during neridronate therapy in both total and bone alkaline phosphatase (Fig. 3) remains partially uncertain. For example, the continuous decrease in bone and total alkaline phosphatase is somewhat surprising given that, in postmenopausal osteoporosis bone formation, parameters fall over 3–6 months and stabilize with continuous treatment. In growing children, the wide variation of changes related, in addition to treatment, to pubertal development, should be taken into account. We will hopefully be able to soon provide a clearer picture by measuring a series of bone markers in a large number of treated and untreated children with OI at the completion of the trial.

The 64% reduction in fracture risk during the first year of controlled observation is comparable with that observed in the study with olpadronate in children. The controlled period of our study is 1 year as opposed to the 2 years of the oral olpadronate controlled study, but the overall length of our study is greater (3 versus 2 years), and the number of patients completing the study is double. At variance with the olpadronate study, we decided to separately study prepubertal and peripubertal children to avoid the effect of puberty on both BMD changes and the clinical expression of the disease itself. For this careful selection, we have been able to show for the first time in a randomized, controlled trial that bisphosphonate therapy may significantly increase the rate of growth in height and in the projected area of lumbar spine. The latter increase is likely to be caused, at least in part, by increased mineralization of the outer profile of the vertebral bodies over the density threshold for the definition of the region of interest by DXA technology.

The good safety profile for intravenous therapy found in adults[3] is confirmed in this study in children. None of the patients complained of symptoms related to hypocalcemia, although this would be more likely to occur in children than in adults because of the higher bone turnover in children. However, the long-term bone safety of bisphosphonate therapy in growing subjects is still debated[24] for the potential risk of osteomalacia[25] or even osteopetrosis.[26] The correct degree of suppression of bone turnover is still unclear, and further studies are needed to establish if the dose and the duration of treatment should be tailored individually. It also remains to be assessed to what extent bisphosphonate therapy changes the natural course of OI for final height and skeletal deformities. We share these cautions, but we are also aware that, for a rare and serious

disease such as OI, the commitment for additional studies should be accompanied by a less conservative approach in using drugs with some evidence of efficacy. For this reason, the AsItOI, on the basis of the results of our studies both in children and adults, promoted and obtained the registration of neridronate for the treatment of OI by the Italian health authorities.

ACKNOWLEDGMENTS

The authors thank AsItOI and all children and parents who took part in the study, Abiogen (Pisa, Italy) for providing the study medication, and the University of Verona for funding the study. We also thank Istituto Superiore di Sanità (Ministero della Salute) for continuous legal support.

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Received in original form July 26, 2004; revised form December 16, 2004; accepted December 17, 2004.