

EARLY BISPHOSPHONATE TREATMENT IN INFANTS WITH SEVERE OSTEOGENESIS IMPERFECTA

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Objective To evaluate prospectively the efficacy of bisphosphonate treatment in infants with severe forms of osteogenesis imperfecta (OI).

Study design Of 10 children (6 females) with OI type III, 5 (group A) started treatment (2 mg/kg neridronate administered intravenously for 2 consecutive days, every 3 months) just after diagnosis at birth and 5 (group B) after 6 months. Ten untreated children, matched for sex, age, and clinical severity of OI, constituted a historical control group (group C). We measured weight, length, and number of fractures every 3 months and serum and urinary levels of calcium, phosphorus, creatinine, serum alkaline phosphatase, 25-hydroxyvitamin D, insulin-like growth factor I, parathyroid hormone, and osteocalcin, urinary type I collagen N-terminal telopeptide, and lateral radiography of vertebral column every 6 months.

Results Group A had better growth and a lower incidence of fractures than groups B and C in the first 6 months of treatment. In the second 6 months, both groups A and B had lower fracture rates than group C. After 12 months of therapy, osteocalcin and insulin-like growth factor I levels significantly increased only in group A. The urinary Ca/Cr ratio and N-terminal telopeptide/Cr ratio significantly declined only in treated patients. Vertebral body area and the structure of vertebral bodies improved in all treated patients, but especially in group A.

Conclusions Cyclical neridronate treatment, started just after diagnosis at birth, had positive effects on growth and fracture rate. (*J Pediatr* 2006;149:174-9)

Osteogenesis imperfecta (OI) is an inherited connective tissue disorder characterized by bone fragility, low bone mass, and other connective tissue malfunctions.¹ Severity varies widely, ranging from intrauterine fractures and perinatal lethality to very mild forms without fractures. OI type III is characterized by high frequency of fractures from birth, severe bone deformities, and extreme short stature. Physiotherapy, rehabilitation, and orthopedic surgery are the mainstay of treatment for these patients.² Other approaches have been proposed for this type of OI: gene-based or stem cell therapy, which presently remain in the early stage of research,³ and bisphosphonates.

Bisphosphonates, potent inhibitors of bone resorption with some effects on bone formation,⁴ demonstrated beneficial effects in children affected by severe types of OI.⁵⁻¹⁰ However, limited data are available on the efficacy of this therapy in children under the age of 3 years,^{11,12} and no controlled studies at present have been conducted in infants from the neonatal period. The aim of this prospective clinical trial was to evaluate the efficacy of bisphosphonate treatment during the first months of life in infants affected by severe forms of OI in the hopes of establishing the best age for the start of the therapy and to positively modify the natural history of the disease.

METHODS

Patient Selection

We studied 10 children (6 females) diagnosed as affected by OI type III in the neonatal period by means of clinical and radiologic evaluation. They were recruited and randomized consecutively as they were referred to our medical center between 2001 and 2003. After diagnosis, at the mean age of 33 days (range 18-44 days, age 0.09 ± 0.01 years), the patients were divided into 2 groups comparable for sex and clinical severity of OI for an unblinded prospective study.

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ALP	Alkaline phosphatase	PTH	Parathyroid hormone
IGF-I	Insulin-like growth factor I	uNTX	Urinary type I collagen N-terminal telopeptide
Oc	Osteocalcin		
OI	Osteogenesis imperfecta		

Five patients (3 females [group A]) started treatment at a mean age of 37 days (range 25–46 days, age 0.10 ± 0.02 years), just after diagnosis. The other 5 patients (3 females [group B]) were followed up for 6 months and started treatment at a mean age of 220 days (range 203–238 days) (age 0.6 ± 0.04 years). All patients were checked every 3 months until the age of 18 months (age 1.6 ± 0.05 years).

Ten children, matched for sex, age, and clinical severity of OI, whose charts were reviewed and collated, constituted an historical control group (group C). They were first examined at our institution between 1995 and 2000, before this study was started, therefore they received the same multidisciplinary care of the treated patients, including physiotherapy, but not bisphosphonate treatment in the first 2 years of life. Informed consent was obtained from parents, and the study protocol was approved and constantly monitored by the local Medical Ethical Committee, under the condition that infants were hospitalized during the first treatment cycle.

Treatment

Neridronate (6-amino-1-idrossiesilidene-1,1-bisphosphonate) (Nerixia, Abiogen Pharma, Italy) was administered at the dose of 2 mg/kg body weight every 3 months. In particular, the drug was administered by intravenous infusion at the dose of 1 mg/kg body weight diluted in normal saline solution to a final concentration of 0.1 mg/mL over a 4-hour period, repeated in the subsequent day. All infusions were given into a peripheral vein.

All families received counseling from a nutritionist to ensure that all patients had a daily intake of vitamin D of at least 400 IU/d, and of calcium of at least 600 mg/d. All subjects underwent specific and individualized physiotherapy.

Study Design

At the start of the study and every 3 months, weight, length, and number of fractures were measured. Routine blood cell count, blood and urinary levels of calcium, phosphate, creatinine, blood alkaline phosphatase (ALP), 25-hydroxyvitamin D, parathyroid hormone (PTH), osteocalcin (Oc), and insulin-like growth factor I (IGF-I), urinalysis and urinary excretion of the bone resorption marker type I collagen N-terminal telopeptide (uNTX) were measured at the beginning and thereafter every 6 months, before infusion of neridronate. Blood was collected between 10:00 and 12:00 AM. Urine specimens were collected between 10 and 12 hours. Lateral X-ray films of vertebral column were obtained at baseline and every 6 months.

Clinical Studies

Lengths were obtained with a recumbent length board. Weights were obtained by use of a calibrated scale. Anthropometric measurements were normalized for age and sex and expressed in standard deviation score (SDs) calculated as (measured value – mean)/standard deviation with Sempé and Pedron tables.¹³

Fracture incidence was assessed by parental recall and diary and from any available interim radiographs. Fractures were confirmed by radiologists blinded to the treatment status of the subjects. Spine compression fractures were not included in the analysis, because of the impossibility of accurately defining vertebral fractures. Pain was evaluated considering crying during handling and immobilization of a limb.

Laboratory Methods

Blood cell count, standard urinalysis, serum and urinary levels of calcium, phosphate, creatinine and calcium/creatinine ratio (uCa/uCr), serum ALP were measured by routine methods. Plasma 25-OH D was measured by high-pressure liquid chromatography (Eureka srl; Chiaravalle, Ancona, Italy). The intraassay and interassay coefficients of variations (CVs) were below 5.2% and 7.8%, respectively. The sensitivity was 5 nmol/L. Serum IGF-I was measured by immunoradiometric assay after acid-alcohol extraction (Diagnostic Systems Laboratories, Webster, TX). The intraassay and interassay CVs were less than 3.4% and 8.2%, respectively. The sensitivity was 0.1 nmol/L. Serum intact 1-84 PTH levels were determined by immunometric chemoluminescence assay (Nichols Institute Diagnostics, San Clemente, CA). The intraassay and interassay CVs were less than 6.7% and 9.2%, respectively. The sensitivity was 0.1 pmol/L. Serum OC was measured by immunometric chemoluminescence assay (Diagnostic Products Corporation, Los Angeles, CA). The intraassay and interassay CVs were less than 4.5% and 7.1%, respectively. The sensitivity was 0.02 nmol/L. Urinary excretion of uNTX was measured by an enzyme immunosorbent assay (Osteomark; Ostex, Seattle, WA). Assay values were expressed in nanomoles bone collagen equivalents per liter (nmol BCE/L), normalized for urine dilution by urine creatinine analysis and reported as nanomoles BCE per mmole creatinine (uNTX/uCr). The intraassay and interassay CVs were less than 9%. The sensitivity was 20 nmol BCE/L.

Radiologic Studies

Standard lateral radiographs of the spine were examined at a magnification of 100% for the measurement of anterior, posterior, and middle heights of each lumbar vertebral body (L1–L4) to evaluate projected area (cm², mean L2–L4), shape abnormalities of lumbar vertebral bodies and to estimate the effects of treatment on the spine.¹⁴

We were unable to perform in all subjects dual-energy x-ray absorptiometry because the ability to complete measurements was limited at times by the young children being cast or unable to stay still for the study. Thus, because of ethical reasons (necessity of conscious sedation in such young babies), technical difficulties in the evaluation of bone mineral density measurements and therefore the poor statistical significance of our data, we decided not to continue to perform dual-energy x-ray absorptiometry.

Because of the spontaneous decrease in fracture rate after birth in patients with type III OI in this age group, the

Table I. Auxological data (weight and supine length), vertebral projected area and number of fractures in infants affected by severe OI treated with neridronate

	Groups	T 0	T 1	T 2	T 3
Weight (SDs)	A	-3.2 ± 0.9	-3.0 ± 0.7*†	-2.8 ± 1.0†	-2.5 ± 1.2‡
	B	-3.1 ± 0.7	-3.6 ± 0.8	-3.2 ± 0.9	-2.8 ± 1.1†
	C	-3.2 ± 0.6	-3.7 ± 1.0	-3.8 ± 1.1	-3.7 ± 1.3
Length (SDs)	A	-4.3 ± 1.4	-3.8 ± 1.2*†	-3.5 ± 1.3‡	-3.4 ± 1.1‡
	B	-4.2 ± 1.3	-4.5 ± 1.4	-3.9 ± 1.5	-3.7 ± 1.4†
	C	-4.5 ± 1.5	-4.8 ± 1.4	-4.9 ± 1.5	-5.1 ± 1.7
Projected Area (cm ²)	A	1.8 ± 0.5	4.0 ± 0.8*†	5.1 ± 1.0†	5.8 ± 1.1†
	B	2.0 ± 0.6	3.2 ± 0.7	4.5 ± 0.9	5.2 ± 1.2
	C	1.9 ± 0.5	3.1 ± 0.8	3.8 ± 0.9	4.3 ± 1.0

Projected Area (cm²) mean of L2-L4.

Group A: Infants treated just after diagnosis; group B: infants treated after 6 months of follow-up; group C: untreated infants.

T0: age: 0.1 ± 0.02 yrs; first evaluation: group A at the start of treatment;

T1: age: 0.6 ± 0.04 yrs; group A after 6 months of treatment: group B at the start of treatment;

T2: age: 1.1 ± 0.06 yrs; group A after 12 months of treatment: group B after 6 months of treatment;

T3: age: 1.6 ± 0.05 yrs; group A after 18 months of treatment: group B after 12 months of treatment.

*= *P* < .05 vs Group B.

†= *P* < .05 vs Group C.

‡= *P* < .01 vs Group C.

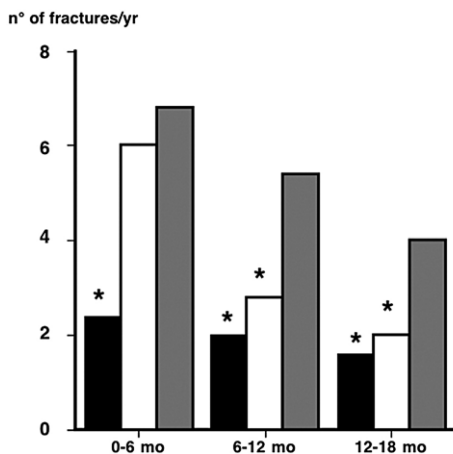


Figure 1. Number of fractures (expressed in no/yr) during different time intervals: 0-6 months, 6-12 months, 12-18 months. Group A (black bars): infants treated just after diagnosis; group B (white bars): infants treated after 6 months of follow-up; group C (gray bars): untreated infants. **P* < .05.

fracture rates before and after treatment were not comparable. Instead, we compared the fracture rates during the 6-month period in which group A was treated and group B was not, and observation for treated patients and control subjects, considering that age and severity were not significantly different in the 2 groups.

Statistical Analysis

Descriptive analyses are expressed as mean ± standard deviation (SD). Statistical analyses were performed with unpaired *t* test and repeated measures analysis of variance. All statistical analyses were performed with a data analysis system (StatView 4.5; Abacus Concepts, Berkeley, CA) run on an

Apple PowerMac Computer (Apple Computer, Cupertino, Calif). Statistical significance was set at *P* < .05.

RESULTS

Clinical Data

Infants with severe OI were small-for-age at baseline (Table I); the group as a whole showed both a length-for-age and weight-for-age below -2 SD. In untreated patients (group C) there was a significant decrease in mean SD of both weight and height, confirming the delay in physical development typically associated with severe OI.¹⁵ In the first 6 months, patients in group A, treated from the age of 1 month, grew significantly better in weight and length than those of group B and group C (*P* < .05); and patients in group B grew better than those in group C after the start of treatment, reaching a statistically significant difference versus the control group at 1.6 years of age (*P* < .05).

Concerning the fracture rate, the incidence of radiologically confirmed fractures significantly decreased in group A in comparison to groups B and C (2.4 vs 6.0 and 6.8 fractures/yr; *P* < .05) during the first 6 months of treatment. In the second 6 months, both groups A and B had a significantly lower fracture rate in comparison to group C (2.0 and 2.8 vs 5.4 fractures/yr; *P* < .05) (Figure 1).

Signs of bone pain, present in all children before therapy, tended to disappear in treated infants. The treatment did not alter the rate of fracture healing. No fractures sustained on treatment had clinical or radiographic impairment of healing as assessed by routine radiologic study. No one child required intramedullary rod placement during the study period.

Laboratory Data

Baseline Oc and IGF-I levels were significantly lower than our normal levels for age, whereas calcium, phosphate,

Table II. Biochemical data in infants affected by severe OI treated with neridronate

	Groups	T 0	T 1	T 2	T 3	Normal values for age*
<i>Blood</i>						
Calcium (mmol/L)	A	2.4 ± 0.1	2.5 ± 0.2	2.5 ± 0.2	2.4 ± 0.1	2.1–2.65
	B	2.5 ± 0.2	2.4 ± 0.1	2.3 ± 0.1	2.3 ± 0.2	
	C	2.4 ± 0.2	2.3 ± 0.2	2.4 ± 0.1	2.3 ± 0.2	
Phosphate (mmol/L)	A	2.1 ± 0.2	2.2 ± 0.3	2.2 ± 0.2	2.3 ± 0.3	1.6–2.6
	B	2.2 ± 0.1	2.1 ± 0.2	2.2 ± 0.3	2.2 ± 0.2	
	C	2.0 ± 0.2	2.1 ± 0.2	2.2 ± 0.2	2.1 ± 0.3	
ALP (IU/L)	A	318 ± 58	366 ± 46	418 ± 85	406 ± 89	200–600
	B	332 ± 53	352 ± 57	396 ± 88	397 ± 78	
	C	320 ± 47	348 ± 54	368 ± 75	355 ± 82	
25-hydroxyvitamin D (nmol/L)	A	39 ± 10	44 ± 12	51 ± 13	52 ± 12	24–120
	B	37 ± 11	48 ± 13	54 ± 14	49 ± 12	
	C	40 ± 11	46 ± 14	48 ± 13	50 ± 13	
Intact PTH (pmol/L)	A	2.6 ± 1.1	3.0 ± 1.3	3.2 ± 1.1	3.2 ± 1.0	1.1–5.8
	B	2.9 ± 1.2	3.1 ± 1.2	3.3 ± 1.4	3.3 ± 1.3	
	C	3.0 ± 1.3	3.1 ± 1.3	3.2 ± 1.3	3.1 ± 1.2	
Osteocalcin (nmol/L)	A	2.5 ± 1.0	4.1 ± 1.3	5.4 ± 1.1 ^b	5.2 ± 1.8	4.2–10.3
	B	2.3 ± 1.1	3.8 ± 1.2	4.9 ± 1.3	6.1 ± 1.9	
	C	2.6 ± 1.0	3.6 ± 1.1	4.0 ± 1.2	4.2 ± 1.4	
IGF-I (nmol/L)	A	2.9 ± 0.9	4.8 ± 1.4 ^{ab}	5.2 ± 1.8 ^b	5.4 ± 1.6 ^b	3.7–20.4
	B	2.6 ± 0.8	3.2 ± 1.5	4.9 ± 2.1	5.1 ± 2.2	
	C	2.7 ± 0.7	3.1 ± 1.3	3.7 ± 1.6	3.8 ± 1.5	
<i>Urine</i>						
uCa/uCr (μmol/mmol)	A	800 ± 220	635 ± 235	580 ± 216	650 ± 148	<1 year 90–2,200; 1–2 yrs 70–1,500
	B	750 ± 215	800 ± 255	600 ± 264	640 ± 206	
	C	770 ± 232	790 ± 280	730 ± 295	710 ± 212	
uNTX/uCr (nmol BCE/mmol)	A	1900 ± 350	1350 ± 334 ^{ab}	1200 ± 388 ^b	1170 ± 337	<1 year 1,400–2,200; 1–2 yrs 800–1,500
	B	1880 ± 310	1950 ± 410	1380 ± 355 ^b	1295 ± 328	
	C	1850 ± 335	1910 ± 390	1870 ± 340	1650 ± 440	

Group A: infants treated just after diagnosis; group B: infants treated after 6 months of follow-up; group C: untreated infants.

T0: age: 0.1 ± 0.02 yrs; first evaluation: group A at the start of treatment;

T1: age: 0.6 ± 0.04 yrs; group A after 6 months of treatment: group B at the start of treatment;

T2: age: 1.1 ± 0.06 yrs; group A after 12 months of treatment: group B after 6 months of treatment;

T3: age: 1.6 ± 0.05 yrs; group A after 18 months of treatment: group B after 12 months of treatment.

*Normal values for age in our laboratory.

^a= $P < .05$ vs Group B.

^b= $P < .05$ vs Group C.

ALP, 25-OH D and PTH were in the normal range for age (Table II). Urinary uCa/uCr ratio and uNTX/uCr ratio were significantly higher than normal values for age.

During neridronate therapy there were no significant changes in serum calcium, phosphate, and 25-OH D, and a slight rise in ALP and PTH levels. Osteocalcin levels increased in group A from 2.5 ± 1.0 at the beginning to 5.4 ± 1.1 nmol/L after 12 months ($P < .05$ vs group C), but they remained in the lower range of normal values. IGF-I levels increased in groups A and B after the start of treatment, but the increment was statistically significant only in group A ($P < .05$ vs group C). Urine uCa/uCr ratio and uNTX/uCr ratio showed a significant decline over time, and uNTX/uCr ratio levels were significantly lower in treated compared with untreated patients ($P < .05$ vs group C).

Radiologic Studies

Before treatment, lateral X-ray films of vertebral column showed severe vertebral body deformities, such as flattened or wedged vertebrae, in all patients. An increase in vertebral size on the lateral view of the spine and in projected vertebral body area was found in all treated patients, but the difference became statistically significant only in group A with respect to the untreated group ($P < .05$ vs group C), suggesting that more new bone formed (Table I).

Figure 2 shows lateral X-ray films of the column in the same infant treated with neridronate from the age of 1 month, at the beginning and after 6 and 12 months of treatment. The progressive improvement in the structure of vertebral bodies and a correction of deformities is evident. Other radiologic changes included decreased deformities of long bones in all

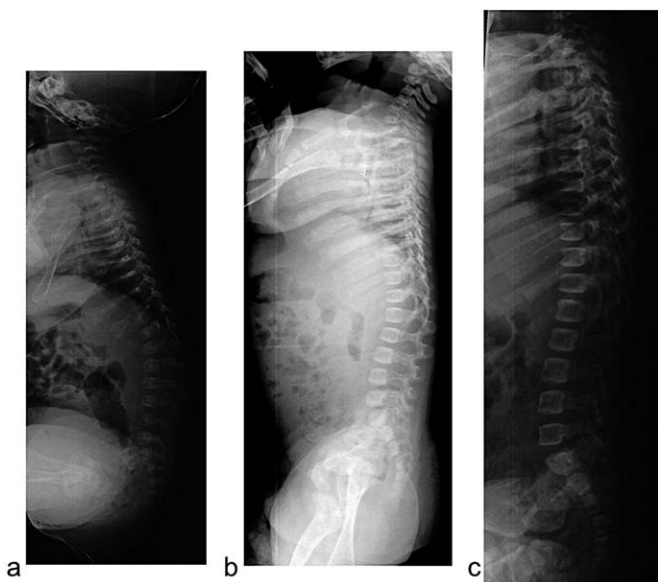


Figure 2. Lateral X-ray films of column in infant treated with neridronate from age 1 month; (a) at beginning, (b) after 6 months, and (c) after 12 months of treatment. It is evident progressive improvement of vertebral bodies.

patients. Radiographs showed discrete dense parametaphyseal lines corresponding to the time of each treatment cycle in all patients, confirming that linear growth continued.

Side Effects

Considering the possible adverse side effects of treatment, we only noted the well-known acute phase reaction after the first infusion cycle in 9 patients,¹⁶ with short-term fever up to 38.5° C responsive to acetaminophen. During treatment, none of our patients showed urinary protein excretion, white blood cell count reduction, or respiratory distress syndrome.¹⁷ No infant missed a scheduled infusion because of difficulty with the protocol.

DISCUSSION

Bisphosphonates represent a class of drugs that are potent inhibitors of bone resorption⁴ and are widely used to treat children⁵⁻¹⁰ and adults¹⁸ with osteogenesis imperfecta. Little experience is available on the effect of these drugs in the youngest infants^{11,12} and the optimal age to start bisphosphonate treatment is unknown. We compared 2 groups, one that started treatment just after diagnosis at birth, and the other 6 months later. We judged it unethical to perform placebo infusions at this age and incorporate an untreated control group, because some data suggest that bisphosphonate therapy is beneficial and that there is no other established pharmacologic treatment. Therefore we chose an open study design and compared the results of the 2 treated groups with those of a historical control group of patients previously seen in our unit. This is, to our knowledge, the first controlled study conducted of infants with OI from the neonatal period.

In our patients with OI, baseline height and weight

were low for age. Neridronate did not have a detrimental effect on growth; in fact, we found an increase in SD score of growth parameters in all treated children in comparison to the decrease in SD score in the control group. These results confirm previous studies that reported a significant height gain in moderately to severely affected patients with OI.¹⁹

In our patients, the response to treatment appeared more pronounced than in older children. This better gain is probably due to the younger age of patients; in fact, during first and second year height velocity is very high and also a small percentage in height velocity gain results in a great positive difference.

At the age of our patients, it is difficult to interpret the significance of change in fracture rate. Because many infants sustain fractures either prenatally or perinatally and fracture rate may relate to the degree of birth trauma, we excluded fractures present at birth. Moreover, some fractures may not be diagnosed radiographically or clinically or may be influenced by external factors (mode of handling, mobility), and fracture rates may also decrease spontaneously with increasing age.¹⁵ For these reasons, a change in fracture rates in very young children as a result of intravenous bisphosphonate is not easy to demonstrate. Thus we compared treated with untreated patients, even though patients from group C did not use the same protocol for nonpharmacologic therapy. A decrease in fracture rate has been described previously in older children with severe OI treated with long-term intravenous pamidronate,^{7,11,12} neridronate,¹⁰ or olpadronate.^{9,20} In our experience, though, during the study period, the treated patients had increased mobility and therefore presented a higher risk of injury and became more susceptible to fractures, we noted that intravenous neridronate significantly reduced fracture rates, suggesting a direct effect of the therapy.

Our results confirm that infants with severe OI have a high bone turnover rate before therapy, as previously reported.^{8,12} This may be a primary or secondary effect of the disease, related to immobilization from fractures as suggested by the hypercalcemia and mild hypercalciuria.²¹

With treatment, however, markers of bone turnover decreased as a direct consequence of intravenous bisphosphonate therapy.¹² We measured bone metabolic markers only before infusion of bisphosphonate, and thus we cannot document their variations after the drug administration, with the postulated drop in serum calcium with transitory increase in PTH levels and the possible effect of these bursts of PTH secretion on the reported increase in BMD in older patients.²² In the first months of treatment, we found a significant increase in IGF-I levels in patients of group A, correlated to higher growth velocity and probably related also to the increase in osteocalcin levels. We cannot say if this is due to the increase of physical activity, which is not easy to quantify at this age, or to a direct variation of catabolic pattern in a more anabolic one, as just elegantly postulated.²³ The mechanisms of action of bisphosphonates, in fact, seem to involve both inhibition of osteoclastic resorption and stimulation of PTH-mediated anabolic effects on osteoblastic processes. The evi-

dence of a shift from catabolic to anabolic pattern of bone may be confirmed also by the increase in vertebral size and apparent reshaping of both vertebrae and long bones in treated patients. In this bone anabolic process, the amount of physical exercise is also probably involved, because of the increase of the maximal isometric grip force reported after bisphosphonate treatment in children with severe forms of OI.²⁴

Although there is no consensus on optimal dosing or age of start of treatment, our data show that treatment with intravenous neridronate from ages as young as 1 month is an ineffective treatment for reducing fractures. Although bisphosphonate treatment is a symptomatic not curative treatment that does not alter the genetic defect underlying OI, it is an adjunct to physiotherapy, rehabilitation, and orthopedic care that must be continued carefully. The optimal treatment schedule and the length and the long-term outcomes of bisphosphonate therapy are unclear at present²⁵; however, cyclical neridronate treatment, started as soon as possible, just after diagnosis at birth, seems to have the best positive effect on growth, fracture rate, and skeletal improvement at an age very important for psychological and motor development.²⁶

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