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Long-Term Effects of Intravenous Pamidronate in Fibrous Dysplasia of Bone

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ABSTRACT

Fibrous dysplasia of bone (FD) is a rare disorder characterized by proliferation of fibrous tissue in bone marrow leading to osteolytic lesions. It causes bone pain and fractures. To date the only treatment is orthopedic. Histological and biochemical similarities between FD and Paget's bone disease related to increased osteoclastic resorption led us to propose treatment with the bisphosphonate pamidronate. The aim of the study was to assess the long-term effects of intravenous pamidronate in FD. In this open label phase III study, 20 patients with FD (11 males and 9 females; mean age 31 years) received courses of 180 mg of intravenous pamidronate every 6 months (60 mg/day during 3 days by infusion). The mean duration of follow-up was 39 months (range 18–64). Severity of bone pain, number of painful skeletal sites per patient, X-rays of all involved areas, serum alkaline phosphatase, fasting urinary hydroxyproline, and urinary type I collagen C-telopeptide were assessed every 6 months. The severity of bone pain and the number of painful sites appeared to be significantly reduced. All biochemical markers of bone remodeling were substantially lowered. We observed a radiographic response in nine patients with refilling of osteolytic lesions. A mineralization defect proven by bone biopsy was observed in one case. Four patients sustained bone stress lines, but no fracture occurred. We suggest that intravenous pamidronate alleviates bone pain, reduces the rate of bone turnover assessed by biochemical markers, and improves radiological lesions of FD. Few side effects were observed. (J Bone Miner Res 1997;12:1746–1752)

INTRODUCTION

Fibrous dysplasia of bone (FD) is a skeletal disorder characterized by extensive proliferation of fibrous tissue in bone marrow, leading to osteolytic lesions, fractures, and deformations.[1] It represents about 2.5% of bone disorders and 7% of benign bone tumors.[2] Initial symptoms most often present during childhood or adolescence as bone pain and repeated fractures. The other usual clinical findings are bone deformity and neurologic compression, especially when the facial bones or the skull are involved.[3,4] FD may be limited to a single bone (monostotic form) or may involve several bones (polyostotic form). Monostotic forms are often asymptomatic.[5] The McCune-Albright syndrome is a polyostotic form of FD associated with melanotic cutaneous macules and endocrine abnormalities, including precocious puberty.[6] Recurrent fractures can cause severe disability. Sarcomatous transformation of FD is rare and often occurs after radiation therapy.[7]

Radiological signs of FD consist mainly of lytic and cystic lesions, with reduction of cortical thickness, and sometimes widening of the diaphysis. Radioisotope bone scans usually disclose increased uptake of isotope in affected areas. This feature is useful for defining the skeletal distribution of lesions.[8] Computed tomography (CT) and magnetic resonance imaging (MRI) can be used for differential diagnosis with malignancies.[9,10]

FD is a congenital disease, due to a somatic activating mutation of the gene of the α subunit of the G-protein resulting in a mosaic population of normal and mutant tissues,[11] with an increase in cyclic adenosine monophosphate (cAMP) formation. This activating mutation can be found in bone cells[12,13] and in the endocrine tumors of the McCune-Albright syndrome.[11,14] There is also an in-

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creased expression of the proto-oncogene c-*fos*, presumably a consequence of raised adenylate cyclase activity in abnormal cells.[12] This increased expression of c-*fos* appears to be specific to FD.[12]

Pregnancy has been implicated in exacerbation of FD perhaps because of estrogen receptors in the fibrous tissue.[15] Bone lesions include collagen fibers randomly distributed, synthetized by fibroblasts that can originate by metaplasia of osteogenic cells.[16] These incompletely differentiated osteoblasts produce within connective tissue irregular islands of woven bone with no evidence for later replacement by mature lamellar bone. Osteocalcin has been discovered in several types of FD cells, confirming their osteogenic lineage.[17] Increased rates of bone resorption can be noted and may be due to elevated secretion of interleukin-6 (IL-6) by bone cells.[18]

To date, orthopedic surgery has been the only treatment of FD and consists of preventive measures (curettage, bone grafting, internal fixation of long bones) and management of fractures.[19] Calcitonin, mithramycin, and etidronate have been tried in a few cases of FD with poor results.[20,21] Use of antiresorptive drugs has been proposed because of the evidence for increased osteoclastic bone resorption, mediated by the presence of numerous and large osteoclasts at the interface between marrow fibrous areas and bone surfaces (with similarities with Paget's disease of bone) and by the increase of fasting urinary hydroxyproline.[1,4,6]

We have assessed the long-term effects of intravenous pamidronate, a second generation bisphosphonate which is a potent inhibitor of bone resorption, in 20 patients with FD. We have reported preliminary findings on the short-term effects of pamidronate in nine patients in 1994.[22]

MATERIALS AND METHODS

Patients

Twenty patients have been followed up in an open label study design, 9 females and 11 males, for a mean duration of 39 months (range 18–64, SD = 16.72, 65 years follow-up) after the first course of treatment. The mean age at diagnosis was 18 (range 1.5–46). The mean age at onset of treatment was 31 (range 13–69); 18 patients were mature adults, and 2 were 13 years old at the beginning of treatment. We chose to perform a study without a control group because FD is a very uncommon and heterogeneous disease. No improvement of FD has been experienced by our patients before treatment, and for 12 of them the period before diagnostic and treatment was over 4 years.

Two patients had monostotic form. The distribution of FD lesions in our patients is presented in Table 1. One woman had McCune-Albright syndrome, with precocious puberty at age 8 and characteristic melanotic skin macules. Thirteen patients had sustained one or several fractures before treatment with pamidronate. Pathological confirmation of FD was available for eight patients. For the other 12 patients, FD was diagnosed with radiographs, because of characteristic lesions. X-rays were taken for each localization in all patients, and bone scans were performed in 14 patients at baseline. These bone scans were used to determine the sites of the disease but not to assess the efficacy of the treatment. There was a total number of 145 sites of FD in our 20 patients, with a mean of 7.25 per patient (range 1–25). There were 65 lesions involving limbs, with 14 patients having one or more sites in the lower limbs (40 lesions). Before treatment, 13 patients were suffering from bone pain. Painful sites were sites of FD.

Table 1. Distribution of Bone Lesions of FD

Bone	*Number of patients*	*%*
Femur	13	65
Skull	10	50
Tibia	9	45
Iliac bone	7	35
Humerus	6	30
Radius	5	25
Ribs	4	20
Lumbar spine	3	15
Fibula	3	15
Face	3	15
Thoracic spine	2	10
Cervical spine	2	10
Metatarsus	2	10
Sacrum	1	5
Tarsus	1	5
Scapula	1	5

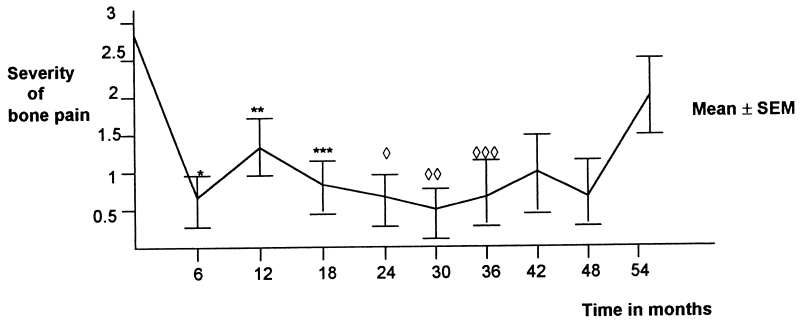
Treatment

Pamidronate was given by intravenous infusion over 3 days with a total dose of 180 mg/course (60 mg/day), i.e., one course consists of a complete 3-day package. The drug was administered in normal saline or glucose solution (1 l/day), as a 4-h infusion on 3 consecutive days. During the study period, patients received supplements of calcium (1000 mg/day) and vitamin D_2 (800–1200 IU) or D_3 (600–900 IU) to prevent potential vitamin D deficiency and secondary hyperparathyroidism induced by the bisphosphonate. For the two patients who were 13 years old at the beginning of treatment, the dose of pamidronate was adapted to their weight (1 mg/kg/day). Patients received a course of treatment every 6 months, during the first 18 months, and subsequently every 12 months.

Measurement and follow-up

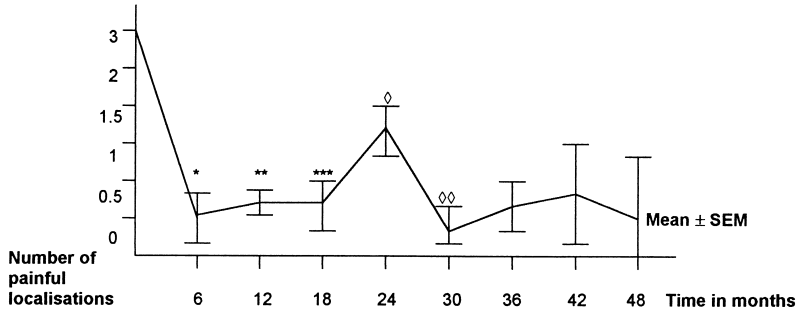
Each patient was examined every 6 months. Biochemical measurements were performed, and X-rays of involved sites were taken at each visit.

We used a pain scale to assess the severity of bone pain: 0 for no painful site, 1 for low, 2 for moderate, 3 for medium, and 4 for severe. When patients had several painful sites, the most painful was chosen to evaluate the effect of treatment. We also assessed the number of painful sites per patient before and after each course of treatment. We defined the clinical response as follows: complete response if the pain intensity dropped from 4, 3, 2, or 1 to 0, with a



* p = 0.0091; ** p = 0.0111; *** p = 0.0277; ◊ p = 0.0105; ◊◊ p = 0.0072; ◊◊◊ p = 0.0412.

FIG. 1. Evolution of severity of bone pain with treatment. Comparison of pain scores at each visit with baseline values (Wilcoxon match pairs test).



* p = 0.0099; ** p = 0.006; *** p = 0.0204; ◊ p = 0.0165; ◊◊ p = 0.0106

FIG. 2. Evolution of the number of painful localizations with treatment. Comparison of pain scores at each visit with baseline values (Wilcoxon match pairs test).

number of painful localizations which fell to 0; and partial response if there is a decrease of the intensity of pain or of the number of painful localizations. We defined radiographic response as a decrease in the area of one (or several) lytic lesion(s) and/or as a thickening of bone cortex.

Laboratory tests were performed before treatment and during the follow-up period (every 6 months) for each patient, including serum calcium, phosphate, total alkaline phosphatase (ALP), and fasting urinary excretion of hydroxyproline and calcium, by standard laboratory methods in our department (colorimetric assays). We also measured, in a subgroup of patients, serum intact parathyroid hormone (PTH) by immunochemoluminometric assay (N: 28.5 ± 11.2 ng/ml), serum 25-hydroxyvitamin D (25(OH)D) (D_2 and D_3 isomers together) by competitive binding-protein assay (N: 28.1 ± 11 ng/ml). Urinary peptides of cross-linking domains of collagen I, also called CTX (CrossLaps Osteometer, Copenhagen, Denmark), a sensitive and specific marker of bone resorption,[23] were measured after a pamidronate course in 10 patients (12 courses). Urine pyridinoline was also measured in seven patients, with an immunoassay (Pyrilinks, Metra Biosystems, Mountain View, CA, U.S.A.). We defined the biological response as follows: partial response if serum ALP and/or fasting urinary hydroxyproline decreased at least 30%, and complete response if serum ALP and/or fasting urinary hydroxyproline returned to within normal values. We defined the relapse as clinical and/or radiological and/or biological worsening without any new treatment, among patients who present a response.

Statistical analysis

Biochemical data at each visit were compared with baseline values, expressed in percentage of variation, using the Wilcoxon matched pairs test. Pain was assessed by comparing the data at each visit with the baseline values (for the severity using the pain scale and for the number of painful sites) with the Wilcoxon matched pairs test.

RESULTS

Clinical effects

Before the first treatment, 13 patients complained of bone pain. The mean severity at baseline was 2.8 on our pain scale. Pain severity was significantly reduced (using the Wilcoxon test) after 6, 12, 18, 24, 30, and 36 months (Fig. 1).

The mean number of painful sites per patient at baseline was 2.9 (range 0–4; SD 1.67), corresponding to a total number of painful localizations of 41 in our 20 patients. The number of painful localizations was significantly reduced (Wilcoxon test) after 6, 12, 18, 24, and 30 months (Fig. 2). The clinical response in these 13 patients was complete in 8 of them and partial in 5 of them.

There was a relapse in 8 patients out of 13, but we

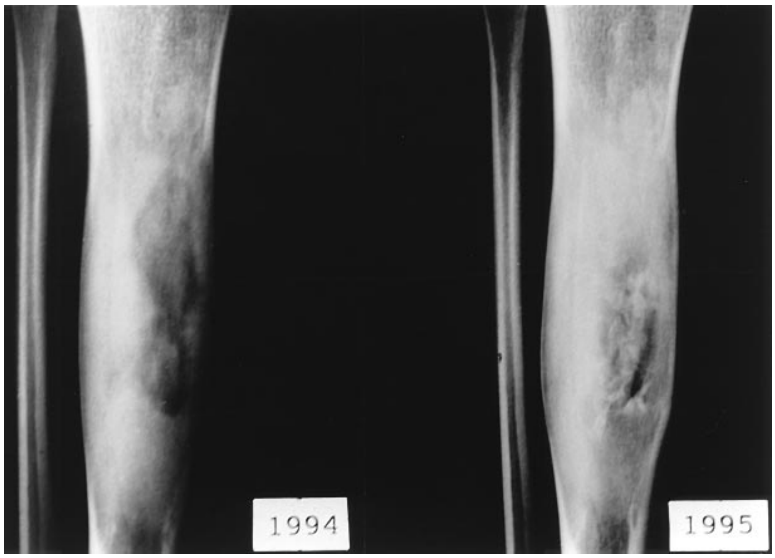


FIG. 3. (A) Before treatment, 1994. (B) After treatment, 1995. Radiographic aspect (A) before and (B) after three courses of pamidronate: filling of a lytic area.

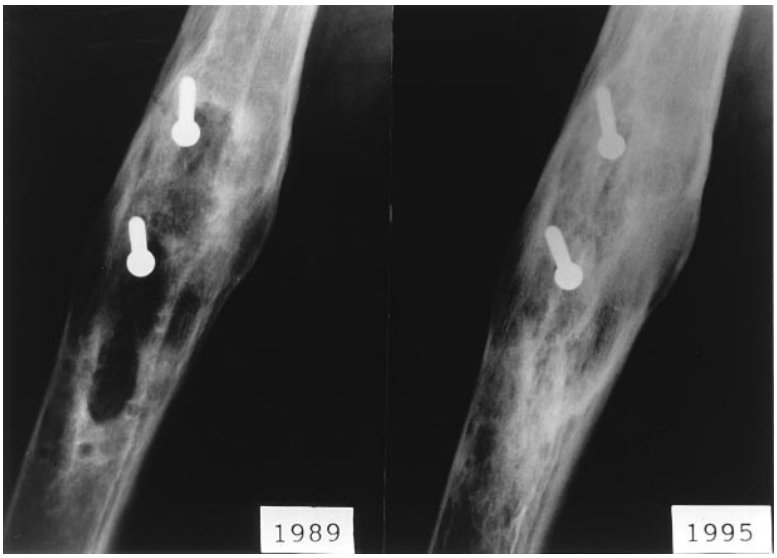


FIG. 4. (A) Before treatment, 1989. (B) After treatment, 1995. Radiographic aspect (A) before and (B) after 10 courses of pamidronate: filling of a lytic area and thickening of a cortice.

obtained a response to a new course of pamidronate in all of them. Children, the two monostotic patients, and the McCune-Albright patient did not respond differently.

Radiological changes

Radiological changes were evident in nine patients, consisting in a progressive filling of osteolytic areas and in cortical thickening. No obvious changes were observed in the other 11 patients. There was neither spreading of previous lesions nor appearance of new bone lesions during the period of therapy in all patients. Among these nine patients, two had monostotic FD. A mean of 15 months (range 6–25) was necessary to achieve a clear improvement in the radiographic aspect. The mean age of these patients was 32 years (range 19–59 years). There were four females and five males. These characteristics were similar to those of the total sample. Examples of radiological changes are shown on Figs. 3A, 3B, 4A, and 4B. Seven out of the nine patients who had a radiographic response had painful sites, and all of them presented a clinical response.

No patient sustained a complete fracture. Four patients developed a stress line during the period of treatment. These stress lines appeared in a dysplasic area of femur. Complete healing was achieved for three patients within 6 weeks of ceased weight bearing. For one of these patients (age 13 at the beginning of treatment), the line has occurred after 7 months of treatment, on a great trochanter, and has increased with time, resulting in a varus of the femoral neck. It was necessary to undertake a surgical correction.

Biochemical changes

During the treatment period, repeated infusions of pamidronate led to a marked decrease of serum ALP and of urinary

Table 2. Baseline Values of Biochemical Markers

	Calcium (mmol/l)	*Phosphorus (mmol/l)*	*SAP (IU/l)*	*25OH D (ng/ml)*	*PTH (pg/ml)*
Serum	2.33 ± 0.1	1.1 ± 0.12	176 ± 176	44 ± 15	26.3 ± 13
	Calcium (mg/g Cr)	*Hydroxyproline (mg/g Cr)*	*Pyridinoline (nmol/mmol Cr)*		*CTX (μg/mmol Cr)*
Urine	105.8 ± 60.1	85.3 ± 83.3	38.3 ± 24.2		282.4 ± 146.2

Data shown are means ± SD.

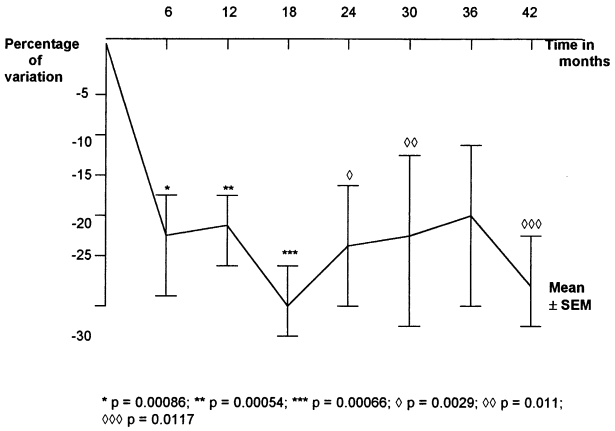


FIG. 5. Evolution of serum alkaline phosphatase (SAP) as a function of time, expressed as a percentage of variation. Comparison of SAP at each visit with baseline values (Wilcoxon match pairs test).

type I collagen C-telopeptide (CTX). Baseline values of all biochemical markers measured are shown in Table 2.

Serum ALP was significantly lower than baseline values after 6, 12, 18, 24, 30, 42, and 48 months of treatment (Fig. 5). Urinary CTX levels were reduced after treatment by 71%, $p = 0.002$, in 10 patients (12 courses).

Fasting urinary excretion of hydroxyproline was also decreased, but this was significant only after 12 and 18 months. It was also reduced after 1, 2, and 4 courses of treatment. For the 11 patients in whom it was measured, we observed a trend for a decrease of urinary pyridinoline (not significant: $p = 0.4$).

Serum calcium, phosphate, 25 hydroxyvitamin D, and fasting urinary excretion of calcium remained unchanged. PTH had a tendency to increase, but this was significant only after 6 months of treatment (mean = 74%; $p = 0.038$).

Side effects

We observed some of the side effects usually described with intravenous pamidronate.[24] Transient fever occurred in eight patients after the first infusion (maximum 38.5°C), but this effect did not reappear with subsequent infusions of pamidronate. Hypocalcemia (minimum: 2.05 mmol/l) was regularly noted after the infusions, but was seldom symptomatic (four times) and was quickly corrected by oral intake of calcium. Four patients complained of transient stiffness and bone pain located on the dysplasic areas, which occurred once or twice for each of them.

After three courses of pamidronate (540 mg), our younger patient (age 13 at the beginning of treatment) suffered from unusual changes of the right knee. The thickness of the growth plate on the medial side of both the femur and the tibia expanded over 18 months, reminiscent of rickets. Complete healing of these lesions was observed on X-rays 12 months after cessation of treatment. A transiliac bone biopsy in a bone involved by fibrous dysplasia showed clear evidence of osteomalacia (Fig. 6). A bone biopsy was also taken in two other adult patients. Focal mineralization defects were seen in these two adult patients, but without increase in the mean osteoid seam width nor decrease in mean calcification rate measured by bone histomorphometry after tetracycline double labelling.

DISCUSSION

We provide evidence that in FD treated with intravenous pamidronate, bone pain could be alleviated, bone turnover could be reduced, and radiological lesions could be improved. Few reports have studied the nonsurgical treatment of FD. The existence of increased bone resorption and remodeling activity, at least in agressive forms of FD, encouraged some open therapeutic trials with calcitonin in order to inhibit osteoclastic resorption. Bell reported a decrease in elevated urinary excretion of hydroxyproline in one patient treated with calcitonin for 16 days.[20] The same effect was obtained in a 12-year-old girl treated with elcatonin for 20 weeks.[17] Morii showed a decrease of serum ALP after administration of porcine calcitonin to a patient with polyostotic fibrous dysplasia.[24] But Helmstedt[25] and Yamamoto[17] did not find any change of serum ALP levels in their patients treated with calcitonin. No report mentioned the effects of calcitonin on clinical symptoms or X-ray abnormalities. One study reported the effects of a treatment with disodium etidronate[26] in an 18-year-old boy suffering from a polyostotic fibrous dysplasia, who had an unsuccessful attempt with calcitonin for 3 months. He has been treated with etidronate 400 mg/day during a 2-week period. This treatment did not induce any change in ALP and fasting urinary excretion of hydroxyproline. Besides, these parameters were reduced after administration of mithramycin, but this effect lasted only 1 week after the improvement, and this treatment was poorly tolerated.

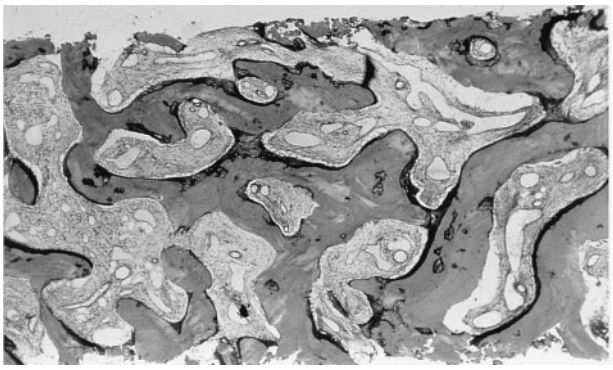


FIG. 6. Bone biopsy from the only patient with FD having developed a mineralization defect after treatment. Transiliac bone biopsy taken in an iliac crest with FD. Osteomalacia proved by the existence of extended and thick osteoid seams (in black). Typical fibrosis of marrow spaces also containing many vascular luminae. Undecalcified bone. Goldner method staining. Magnification 50×.

Our current study is the continuation of the communication about short-term effects of pamidronate in nine patients with FD.[22] Pamidronate is a potent inhibitor of bone resorption and has, like other bisphosphonates, a lasting effect on bone turnover.[27] It has been successfully and extensively used in Paget's disease of bone,[28,29] malignant hypercalcemia,[30] lytic bone metastases,[31,32] multiple myeloma,[33] and osteoporosis.[34,35] Intravenous administration is preferred to oral intake because of the poor digestive tolerance (gastralgia, esophagitis) of the compound when it is given orally[36] and of the low intestinal absorption of bisphosphonates in general.[37] The intravenous administration allows a rapid and prolonged intake of pamidronate in bone matrix. We chose a dose used in our department and by several authors for patients with Paget's disease of bone.[29]

In our present study, pamidronate has led to a marked decrease in pain severity, and in the number of painful sites per patient, as far as an open study permits us to conclude. Usually two courses of pamidronate were necessary to achieve the improvement. Bone pain was always alleviated when pamidronate was given after a relapse of bone pain. There was no difference concerning the quality of clinical response according to the location of the involved sites.

The radiological survey has shown that in about half of patients lytic lesions could be filled, at least in part, and that a thickening of cortices could be obtained. This result is in agreement with our previous report.[22] Therefore, pamidronate may induce an increase of bone strength in sites affected by FD, thus reducing the fracture risk. It must be noted that there are more radiological responses in long bones of lower limbs than in upper limbs or in skull, but the interpretation of skull X-rays is far more difficult than for lower limbs. Furthermore, it is difficult to conclude about the difference of response between lower and upper extremities because we had fewer patients presenting upper limb involvement. The absence of radiological changes in some patients (or in some sites in patients who show radiological response) can be explained by the histologic heterogeneity of FD. Thus, in the lesions of FD, which would contain too many osteoclasts, fibrous tissue, and/or metaplasic cartilage in comparison with the amount of osteoblasts, bone resorption could not be sufficiently inhibited, and the subsequent period of enhanced bone formation would be inadequate.

The biochemical changes induced by pamidronate in FD are consistent with a marked reduction of bone remodeling, as shown by the decrease of fasting urinary excretion of hydroxyproline, and above all of serum ALP and urinary CTX. Despite the intake of adjuvant calcium and vitamin D, we observed a tendency toward a rise in serum PTH. This point allows us to emphasize the importance of the adjuvant calcium and vitamin D.

To improve our knowledge of the disease, biochemical markers of bone remodeling should be measured on a monthly basis, at least at the beginning of the follow-up. This would allow the studying of the kinetics of markers after a course of pamidronate on the one hand and of whether these kinetics are different among several patients on the other hand. We therefore would be able to decide more precisely when a new course of treatment is necessary for one given patient. This moment may be different among different patients because the disease is perhaps more active in some patients and thus more likely to relapse.

A transient mineralization defect visible in dysplasic bone has occurred in one patient, a 13-year-old boy. In two adults, focal and limited mineralization defects were seen by biopsy in noninvolved iliac bone. The growth rate of the adolescent was not affected. The abnormal findings in the adolescent may be explained by the increased uptake of pamidronate by his growth plates and by the iliac bone involved with FD. This has very likely increased the focal concentration of the compound and enhanced the inhibiting effects of pamidronate on bone mineralization. Similar and also reversible changes on growth plates have been induced by high daily doses of tiludronate, another bisphosphonate, in baboons.[38] This fact suggests a cautious use of high doses of bisphosphonates in children and the preventive use of calcium and vitamin D. For these three patients, it has been possible to resume courses of pamidronate without any problem.

In conclusion, intravenous pamidronate appears to have potential as a nonsurgical treatment of FD, because it can induce radiological and biochemical improvement in some patients and may alleviate bone pain in most affected individuals. This treatment was well tolerated, but the possibility of a mineralization defect must be monitored in young patients. Further double-blind study is required to establish fully the efficacy of pamidronate for FD.

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