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Case Series

Long-Term Pamidronate Treatment of Polyostotic Fibrous Dysplasia of Bone: A Case Series in Young Adults

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ABSTRACT

BACKGROUND: Limited information is available about long-term pamidronate treatment in adults with fibrous dysplasia (FD) of bone.

OBJECTIVE: The aim of this case series was to report the clinical outcomes and the biochemical and densitometric findings in a group of young adult patients with polyostotic FD treated for ≥3 years with IV pamidronate.

METHODS: Pamidronate was administered every 6 months (60 mg/d for 3 days) for 2 years. Thereafter, treatment was individualized. Pamidronate was administered at shorter or longer intervals based on response. Bone pain, radiography, serum bone alkaline phosphatase (BALP) activity, and urinary C-terminal cross-linking telopeptide of type I collagen (CTX-I) concentration were assessed for a mean of 7 years. Bone mineral density (BMD) of FD areas (FDas) and contralateral areas (CLas) were measured at baseline and at 12 and 24 months. Data were collected prospectively.

RESULTS: Seven patients (5 women, 2 men; mean [SD] age, 31.0 [7.2] years [range, 22–43 years]) were included in the study. Patients received IV pamidronate for a mean of 6.9 years (median, 7.1 years [range, 3.7–10.9 years]). Pamidronate was associated with a reduction in bone pain and a significant reduction in BALP in all patients at the end of follow-up ($P < 0.02$). The mean reduction from baseline in CTX-I concentration (measured in 3 patients) was 56%; this difference was not significant. Mean BMD values of FDas were significantly increased at 12 months (by 5.9%; $P < 0.05$) compared with baseline; but was not significantly increased at 24 months (7.3%), probably reflecting a higher dispersion of values due to individual responses to treatment. No significant changes were observed in CLa BMDs. Mean BMD of FDa had a numerically lower decrease of 15.3% compared with CLa at baseline; these decreases with pamidronate were 10.8% at 12 months (P = NS) and 9.3% at 24 months ($P < 0.05$). Refilling of osteolytic lesions was not observed.

CONCLUSIONS: These patients with FD of bone treated with IV pamidronate long term had improvement in bone pain and BMD. The effectiveness of individualized pamidronate administration in the long-term treatment of FD in adult patients should be investigated in blinded controlled trials. (*Curr Ther Res Clin Exp*. 2009;70: 161–172) © 2009 Excerpta Medica Inc.

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KEY WORDS: pamidronate, fibrous dysplasia, bone mineral density, bone pain, bone markers, bone alkaline phosphatase.

INTRODUCTION

Over the past 10 years and since the first report in 1994 by Liens et al[1] suggesting that pamidronate might be associated with improvement in the clinical features of fibrous dysplasia (FD), several patient series and case reports, including both adults[1–9] and children,[10–17] have been published. IV pamidronate treatment in patients with FD of bone has been reported to reduce bone pain and markers of bone turnover, improve the radiographic appearance of lesions, and increase bone mineral density (BMD) of affected areas.[1–17] Radiographic evidence of improvement was reported in 50% of the patients in some of these studies,[1,2,4,7,8,12,17] but the percentage of patients showing such improvement was not as high in other studies.[3,5,6,9–11,13–16]

Information regarding tolerability and effectiveness after long-term (≥3-year) pamidronate treatment in adults is limited.[9] According to Chapurlat,[9] treatment with pamidronate has been found to be well tolerated, reduce increased osteoclastic activity in FD, and probably improve bone pain, but further randomized controlled trials are needed.

The aim of this case series was to report the clinical outcomes and the biochemical and densitometric findings in a group of young adult patients with polyostotic FD treated for ≥3 years with IV pamidronate.

MATERIALS AND METHODS

Patients

Data from patients aged 15 to 38 years, with a confirmed diagnosis of FD and hospitalized between 1996 and 2007 at the Bone Metabolic Disease Unit of Buenos Aires University Hospital (Buenos Aires, Argentina), a referral center for patients with rare bone diseases, were included. During this extended period, pamidronate therapy was administered to those patients with concentrations of bone turnover markers above the upper limit of normal (normal values, serum bone alkaline phosphatase [BALP] = 31–95 IU/L and urinary C-terminal cross-linking telopeptide of type I collagen [CTX-I] = 10–400 µg/mmol creatinine) and with bone pain related to the disease. A total of 16 patients were treated. Treatment was stopped when concentrations of bone turnover markers remained in the normal range and no bone pain was reported.

To evaluate the long-term response to pamidronate therapy in young adult patients with FD, registered data from the 7 patients who were treated for ≥3 years with pamidronate were reported. Data were collected prospectively.

The results from patients 1, 4, 6, and 7 at 1 year of pamidronate treatment were previously published in a 2-year prospective study[7] of the effect of pamidronate (180 mg every 6 months) on bone turnover markers and local BMD.

After concluding this initial study, all patients with FD at our referral center signed an informed consent form before starting treatment with IV pamidronate.

Data were recorded in keeping with a protocol approved by the ethics committee of Buenos Aires University Hospital. This protocol standardized the long-term follow-up of FD patients treated with pamidronate, as described.

Pamidronate Treatment

Based on previous reports,[1,2,18] pamidronate 180 mg (60 mg/d for 3 consecutive days) was administered intravenously every 6 months for the first 2 years of treatment. All patients received calcium and vitamin D supplementation.

Due to variability among patients in their responses to pamidronate treatment (reduction in bone pain and decrease in values of bone turnover markers), the interval between pamidronate cycles was lengthened or shortened after 2 years of therapy. The interval between pamidronate cycles was shortened to 3 months if the following occurred: *relapse*, defined as no reduction or increase in bone pain severity according to bone pain severity criteria (severe, moderate, mild, or asymptomatic); and/or an increase in bone turnover marker concentrations (higher levels or levels above the normal range in ≥1 bone turnover marker) was observed compared with the most recent previous evaluation. Conversely, the next pamidronate cycle was postponed 3 months only if both no bone pain was reported and previously high bone marker values were found to have reached normal values.

Clinical Follow-Up

All patients were evaluated every 3 months. Severity of bone pain was assessed using the following criteria[7]: severe = unbearable or continuous bone pain with or without impaired mobility; moderate = bearable bone pain and/or impaired mobility; mild = intermittent episodes of bone pain without impaired mobility; and asymptomatic = no bone pain or altered mobility. Adverse events were recorded at each clinical visit.

Biochemical Determinations

Serum and 24-hour urine samples were collected at baseline and at regular intervals (every 3 months). Serum calcium, 25-hydroxyvitamin D, phosphate, and creatinine; total alkaline phosphatase; and urinary calcium, phosphorus, and creatinine values were determined using standard techniques. Serum 25-hydroxyvitamin D concentrations were determined using radioimmunoassay (DiaSorin, Inc., Stillwater, Minnesota). Inter-assay and intra-assay %CVs were 19.0% and 7.6%, respectively. Serum parathyroid hormone concentration was measured by radioimmunoassay using an antiserum that recognizes the mid- to carboxy-terminal portions of the molecule. BALP activity was measured using selective wheat germ lectin precipitation.[19] Urinary CTX-I was measured using a competitive enzyme immunoassay method (Crosslaps Osteometer A/S, Rodrove, Denmark). Urinary excretion was corrected for creatinine values. To evaluate the presence of phosphate wasting, fractional excretion of phosphorus was calculated.[20]

Bone Mineral Density

Total skeleton BMD was assessed using dual-energy x-ray absorptiometry (DEXA). We reported the BMD results from the 5 patients (patients 1, 4, 5, 6, and 7) for whom

the same DEXA equipment was used to make all measurements. Due to fiscal constraints, however, the DEXA equipment was no longer available at the institution, resulting in the availability of data from the first 2 years of treatment only for comparison. Using baseline radiographs and bone scintigraphy, the BMD of long bones affected with areas of FD (FDas) was determined using a region-of-interest program. This method has been previously described by Parisi et al[7] and others.[21–23] To minimize interobserver variation, all analyses were made by the same technical expert. BMDs of FDas were compared with the contralateral areas (CLas). The difference in BMD between FDas and CLas was calculated as a percentage; the CLa value was considered to be 100%.

RADIOGRAPHY

Radiographs of affected areas were obtained before treatment commencement and annually thereafter.

STATISTICAL ANALYSIS

Statistical analysis was performed using the SPSS version 13.0 (SPSS Inc., Chicago, Illinois). BMD and biochemical data obtained at each follow-up visit were compared with baseline values using the Wilcoxon signed rank test and were expressed as a percentage of variation. The difference between FDa and CLa was expressed as a percentage and compared using the Wilcoxon signed rank test. A value of $P < 0.05$ was considered significant.

RESULTS

Seven patients (5 women, 2 men; mean [SD] age at the end of follow-up, 31.0 [7.2] years [range, 22–43 years]) were included in the study. Patients were treated with IV pamidronate for a mean of 6.9 years (median, 7.1 years [range, 3.7–10.9 years]). All patients had a diagnosis of polyostotic FD confirmed on bone biopsy. The characteristics of the patients are listed in the **table**.

All patients reported bone pain associated with FD lesions at baseline. Irrespective of disease severity, pamidronate treatment reduced bone pain criteria from baseline in all patients (**Table**), and none of the patients reported a new fracture throughout the follow-up period. All patients reported a decrease in bone pain after pamidronate administration (**Table**); however most (6/7) patients reported relapses before a new cycle of the drug was administered.

At baseline, the bone mineral metabolism parameters (serum calcium, 25-hydroxyvitamin D, phosphate, and creatinine; total alkaline phosphatase; and urinary calcium, phosphorus, and creatinine) were within the reference range, except for bone turnover markers (BALP and urinary CTX-I) (**Table**). Tubular phosphate wasting was not observed in any patient. Fractional excretion of phosphorus was calculated based on the assumption that in FDa renal phosphate, wasting might occur even though the serum phosphate concentration is in the low normal range. As described for bone pain, the concentrations of bone turnover markers also varied with the pamidronate cycles and were often found to be higher closer to the next administration (**Figure** 1).

Table. Clinical characteristics of patients with fibrous dysplasia treated with IV pamidronate.

Characteristic	P1	P2	P3	P4	P5	P6	P7
Sex	F	M	F	F	F	M	F
Age at the end of follow-up, y	22	27	27	32	43	28	24
Diagnosis	MCA	MCA	MCA	PFD	MCA	PFD	MCA
Location	Skull, humerus, ulna, radius, femur, tibia	Pelvis femur, fibula, skull, ribs	Skull, scapula, humerus, radius, ribs, vertebrae, clavicle, hands	Humerus, radius	Skull, humerus, radius, ulna, femur, pelvis, tibia, hands	Skull, ribs, tibia, pelvis, humerus, feet	Tibia, femur, pelvis, sternum
Previous fractures	Yes	No	Yes	Yes	Yes	No	Yes
Bone pain at baseline*	Moderate	Mild	Moderate	Moderate	Severe	Moderate	Severe
Bone pain at the end of follow-up*	Asymptomatic	Asymptomatic	Mild	Mild	Mild	Mild	Asymptomatic
Café au lait spots	No	Yes	No	No	Yes	No	No
Associated endocrinopathy	Precocious puberty	Acromegaly	Precocious puberty	None	Precocious puberty	None	Precocious puberty
Cumulative dose of pamidronate, mg	1140	1080	1080	1100	3060	2520	1980
Duration of treatment, y	6.83	4.67	3.70	8.10	7.00	7.25	10.92
BALP, IU/L†							
Baseline	160	172	255	417	3546	512	183
Final	64	59	110	226	995	385	92
CTX-I, µg/mmo creatinine‡							
Baseline	1270	NA	NA	662	1450	1057	197
Final	510	NA	NA	106	995	NA	NA

P = patient; F = female; M = male; MCA = McCune-Albright syndrome; PFD = polyostotic fibrous dysplasia; BALP = serum bone alkaline phosphatase; CTX-I = urinary C-terminal cross-linking telopeptide of type I collagen; NA = not available.

*Bone pain scale: severe = unbearable or continuous bone pain with or without impaired mobility; moderate = bearable bone pain and/or impaired mobility; mild = intermittent episodes of bone pain without impaired mobility; and asymptomatic = no bone pain or altered mobility.

† Normal range = 31 to 95 IU/L.

‡ Normal range = 10 to 400 µg/mmol creatinine.

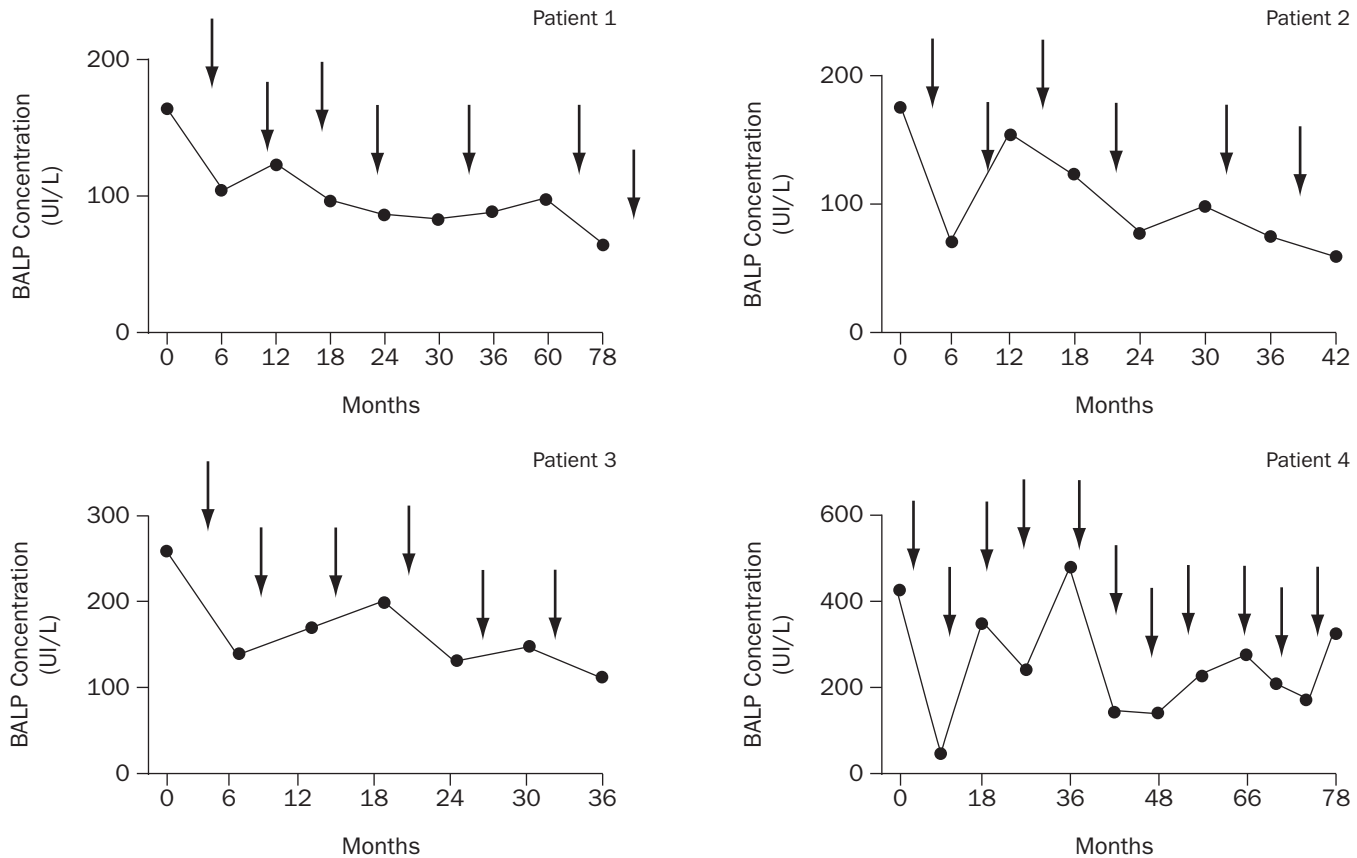

Figure 1. Individual values of serum bone alkaline phosphatase (BALP) activity in 7 patients with polyostotic fibrous dysplasia treated with IV pamidronate. Arrows indicate a cycle of 180 mg of pamidronate.

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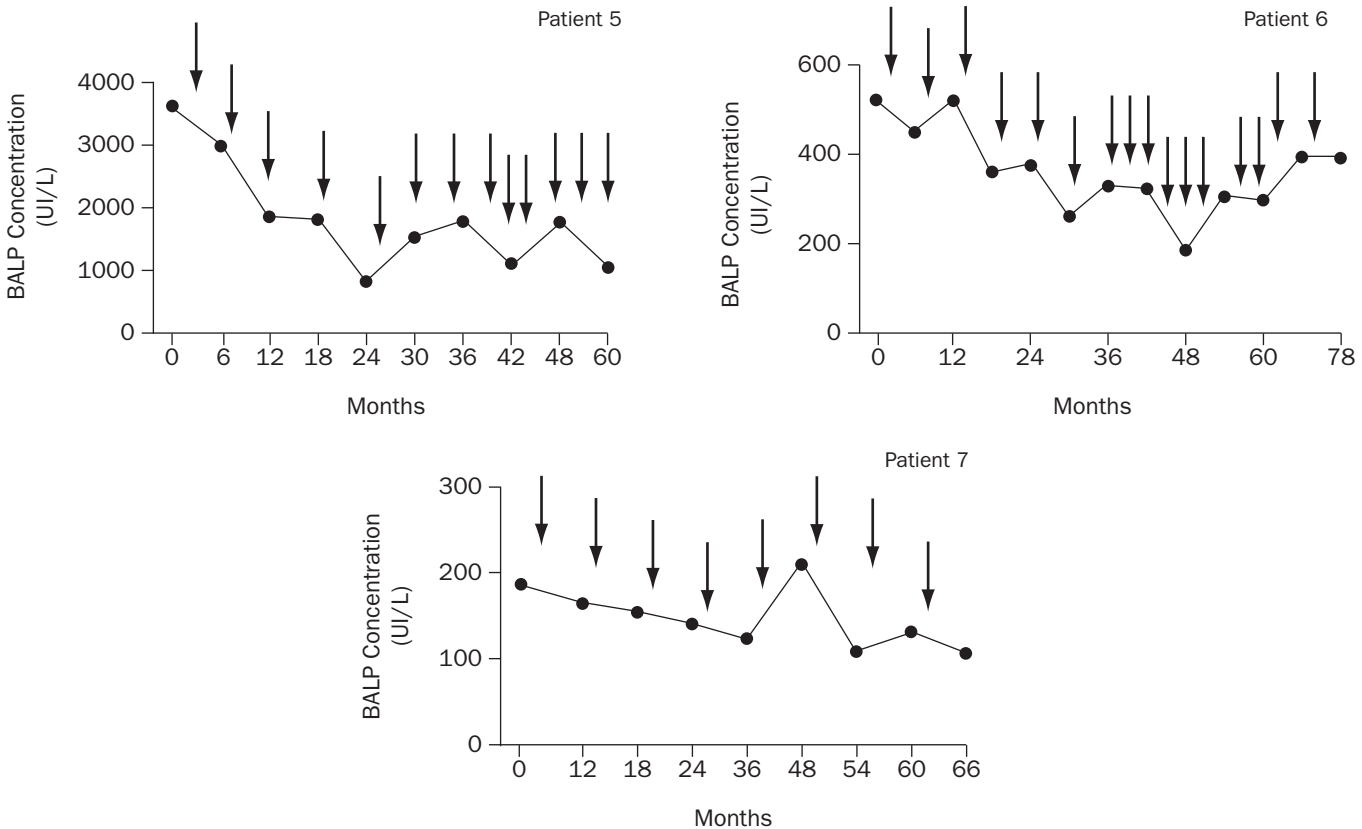

Figure 1 (continued). Individual values of serum bone alkaline phosphatase (BALP) activity in 7 patients with polyostotic fibrous dysplasia treated with IV pamidronate. Arrows indicate a cycle of 180 mg of pamidronate.

These observations served as the rationale for adjusting the interval between pamidronate cycles for each patient individually. These intervals ranged from 2 to 20 months. The mean (SD) final cumulative dose of pamidronate was 1709 (821) mg.

Figure 1 shows BALP concentration and pamidronate treatment cycles in each patient. BALP concentration decreased after the first pamidronate cycle in all patients (from 160 to 102 IU/L, from 172 to 70 IU/L, from 255 to 137 IU/L, from 417 to 39 IU/L, from 3546 to 2920 IU/L, from 512 to 432 IU/L, and from 183 to 160 IU/L for patients 1 to 7, respectively). Although BALP concentrations increased between cycles in some cases, continuous pamidronate treatment was associated with numerically decreased BALP concentration in all patients. Moreover, mean (SD) BALP concentrations were significantly lower at the end of follow-up compared with baseline in all patients (**Table**) (749 [1240] vs 276 [338] IU/L; $P < 0.02$). BALP concentrations decreased to normal values (31–95 IU/L) in 3 patients.

Baseline and final urinary CTX-I concentrations were determined in 3 patients, but the decrease (56%) was not statistically significant. At the end of follow-up, the urine CTX-I concentration was within the normal range (10–400 µg/mmol creatinine) in 1 patient (**Table**).

Thirteen FDas were analyzed—2 in patients 6, 7, and 4; 3 in patient 5; and 4 in patient 1. After the first 2 years of pamidronate treatment, the absolute BMD value increased in 9 of the 13 evaluated FDas. Individual values are shown in **Figure 2**. The mean (SD) BMD of the FDas was 5.9% higher at 12 months (0.929 [0.240] vs 0.981 [0.249] g/cm^2; $P < 0.05$) and 7.3% higher at 24 months (0.929 [0.240] vs 0.995 [0.277] g/cm^2; P = NS) compared with baseline. It is possible that statistically significant differences were not observed at 24 months due to a higher dispersion of values resulting from individual responses to treatment. The BMD of the CLas showed no significant changes from baseline values (1.104 [0.211] g/cm^2), a change of 0.20% at 12 months (1.106 [0.234] g/cm^2), and a change of –0.02% at 24 months (1.099 [0.209] g/cm^2). FDa BMD had a mean of 15.3% lower than the corresponding CLa values at baseline. Pamidronate treatment was associated with changes from baseline in the difference in BMD between FDa and CLa of 10.8% after 12 months (P = NS) and 9.3% after 24 months ($P < 0.05$). BMD analysis found that the response to treatment was not uniform among patients (**Figure 2**) or when comparing different affected areas in a single patient (eg, patients 1 and 5).

In these patients, evidence of refilling of osteolytic areas was not found. Two patients reported transient flulike symptoms after the first pamidronate cycle. No other adverse events were reported.

DISCUSSION

FD of bone is a rare disease for which definitive treatment has not been found.[9] Since initial evidence reporting beneficial effects of IV pamidronate treatment in patients with FD,[1] several authors have described the clinical outcome and radiographic, biochemical, and densitometric findings in these patients.[2–18] Based on a literature search using the PubMed and Current Contents databases, only the large series of patients studied by Chapurlat et al[2,8,9] described >3 years of follow-up in adult patients with

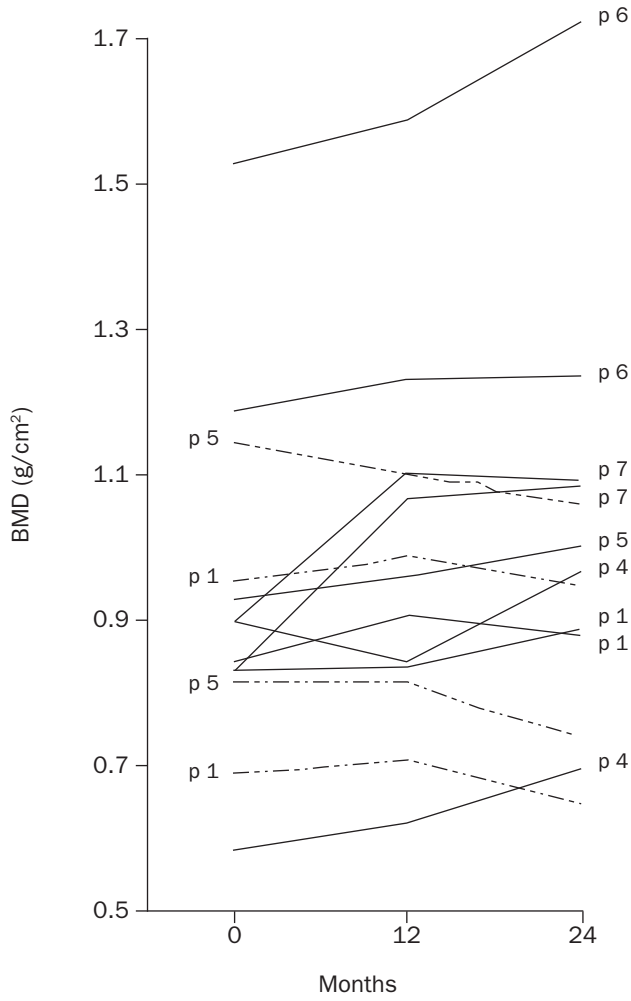

Figure 2. Bone mineral density (BMD) values of fibrous dysplasia areas in 5 patients (p) (p 1, 4, 5, 6, and 7) treated with IV pamidronate. Each line corresponds to 1 measured fibrous dysplasia area. Solid lines depict BMD increases (9 of 13 evaluated areas) and dashed lines depict BMD reductions.

FD who were treated with pamidronate. As described by Chapurlat,[9] treatment with pamidronate has been found to be well tolerated, reduce increased osteoclastic activity in FD, and probably improve bone pain, but further randomized controlled trials are needed.

The present case series summarized clinical outcome and bone turnover throughout ~7 years of treatment with IV pamidronate in young adults with polyostotic FD. Pamidronate treatment was associated with different outcomes in different patients. Biochemical findings served as rationale for lengthening or shortening the interval

between pamidronate cycles. Long-term individualized pamidronate treatment was found to reduce bone pain and bone turnover.

Unlike some patients with other bone diseases, such as Paget's disease, this group of patients with FD showed no apparent resistance to pamidronate treatment.[24]

Our long-term clinical and biochemical observations are in agreement with those recently reported by Chapurlat et al.[8,9] In contrast, however, we did not find conclusive radiographic evidence of improvement. It was not the purpose of this study to analyze the pathophysiologic mechanism that would account for these different findings.

In an analysis in 199 patients who did not receive pamidronate treatment, Hart et al[25] postulated that a plateau in FD lesions occurs between the ages of 20 and 30 years, as the natural history of the disease. This analysis was based on bone scintigraphy determinations; unfortunately, it did not include biochemical determination of bone turnover markers. It is possible that even though progression of the disease may reach a plateau in the third decade of life, already existing lesions would still be active, as evidenced by the increase in bone turnover marker concentrations and bone pain observed in the patients in the present analysis and by their decrease after each course of pamidronate treatment.

An increase in BMD of the FDas was seen after pamidronate treatment. However, BMD analysis also found that the response to treatment was not uniform among patients or when comparing different affected areas in a single patient (eg, patients 1 and 5).

LIMITATIONS

This study had several limitations, including the small case series, absence of a comparison group of patients with untreated FD, subjectivity of bone pain assessment, variable duration of follow-up, and incompleteness of BMD and CTX-I assessments. In addition, adherence to calcium and vitamin D was not monitored and adverse events were not detailed. However, we observed clinical improvement after long-term IV pamidronate treatment.

CONCLUSIONS

In this small group of patients with FD receiving long-term treatment with IV pamidronate, improvements in bone pain and BMD were observed. However, blinded controlled trials are needed to confirm the effectiveness of individualized pamidronate administration in the long-term treatment of adult patients with FD.

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