Fibrous dysplasia

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Chapter 10

Outcome of long-term bisphosphonate therapy in McCune-Albright syndrome and polyostotic fibrous dysplasia

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ABSTRACT

Introduction: McCune-Albright syndrome (MAS) is a rare bone disorder characterized by fibrous dysplasia (FD), endocrinopathies, and café-au-lait patches. FD patients have been shown to respond favorably to treatment with bisphosphonates, but data are scarce in the more severe polyostotic form (PFD), including MAS, and factors determining treatment outcome are not known, particularly in the long-term.

Methods: We evaluated the biochemical (bone turnover markers [BTMs]) and clinical (pain reduction) outcome of bisphosphonate therapy in 11 patients with MAS and 30 patients with PFD: median duration of treatment 6 years (range, 2 to 25 years). Prognostic factors for treatment outcome were identified in both groups.

Results: Patients with MAS were younger at diagnosis ($p < 0.001$), all had precocious puberty, and four (36%) had additional growth hormone (GH) excess associated with severe craniofacial FD. Extent of skeletal disease was more severe in MAS compared to PFD. MAS patients had higher serum alkaline phosphatase (ALP) concentrations ($p = 0.005$), higher skeletal burden scores ($p < 0.001$), and more fractures ($p = 0.021$). MAS patients had also higher levels of FGF-23 ($p = 0.008$) and higher prevalence of hypophosphatemia ($p = 0.013$). Twenty-four of 30 PFD patients (80%) demonstrated a complete clinical and biochemical response within a year of starting treatment ($p = 0.015$), compared to only four of 11 MAS patients (36%). There were no nonresponders. In the whole group, FGF-23, total ALP, P1NP, and CTX positively correlated with skeletal burden scores (all $p < 0.001$), which was the only significant risk factor for an incomplete response to bisphosphonate therapy ($p < 0.01$).

Conclusion: Our data suggest a beneficial and safe outcome of long-term bisphosphonate therapy in the majority of patients with PFD, although response to therapy was limited by the higher skeletal disease burden in MAS patients. In the PFD/MAS population studied, the only identified prognostic factor that influenced the outcome of bisphosphonate therapy was a high skeletal burden score.

BACKGROUND

Fibrous dysplasia (FD) is a rare genetic, non-inheritable bone disorder in which a single bone (monostotic form [MFD]; 70% of patients) or several bones (polyostotic form [PFD]; 30% of patients) may be affected by replacement of normal bone by fibrous tissue of poor structure and quality.[1] In McCune-Albright Syndrome (MAS), PFD is associated with endocrinopathies, primarily precocious puberty, and with cutaneous café-au-lait patches.[2,3] The various forms of FD are caused by a missense mutation of the GNAS1-gene in chromosome 20q13, leading to activation of the stimulatory a-subunit of the G-protein Gs, resulting in the activation of cAMP in mutated cells.[4,5] The mutation occurs postzygotically, resulting in a somatic mosaic state, and thus in a wide spectrum of clinical expression of the disease.[4] Because of the highly variable number of FD lesions and therefore of disease severity, clinical manifestations range from the completely asymptomatic patient with an incidentally discovered radiological lesion, to the patient with extensive skeletal disease who is crippled by severe bone pain, deformities, and fractures. Diagnosis of MAS is primarily clinical and radiological, and although bone histology and genetic analysis do confirm the diagnosis, these are seldom required to establish it. Patients with PFD often display a less severe disease pattern than those with MAS, with less extensive skeletal disease and generally less marked increases in bone turnover. However, the natural history of the various forms of FD remains elusive, and prognostic factors for outcome of therapeutic interventions remain to be identified, particularly in the more severe forms of the disorder.[6]

Therapeutic options for FD have so far been mainly surgical, aiming at reducing fractures, stabilizing impending fractures, and correcting deformities. Medical options consist primarily of treatment with bisphosphonates. The rationale for using these antiresorptive agents in FD is based on the increased bone resorption observed in and around FD lesions.[7] A positive outcome of treatment with bisphosphonates in the form of reduction in bone pain and arrest of expansion of fibrous lesions, was first reported by Liens and colleagues in 1994.[8] A number of reports on the potential beneficial effect of bisphosphonates on bone pain in FD have been published since.[9-14] However, all these publications reported on results of open studies, and the only recently conducted randomized, double-blind, placebo-controlled study of oral alendronate administered in adults and children at doses of 10 to 40 mg daily in cycles of 6 months on/off for 2 years failed to demonstrate a beneficial effect of alendronate over placebo, although a reduction of the bone resorption marker urinary NTx and an increase in areal BMD was observed in the actively treated group.[9]

Several factors such as high skeletal burden, increased serum concentrations of FGF-23, and the presence of endocrinopathies, particularly growth hormone (GH) excess, have been shown to predict poor prognosis in FD patients.[15] However, there are no published data on the long-term outcome of treatment with bisphosphonates or on prognostic factors influencing treatment outcome, particularly in patients with PFD, with or without endocrinopathies in the context of MAS. We speculated that because of their high skeletal disease burden, presence of endocrinopathies, and the often documented FGF-23–induced renal phosphate wasting, MAS patients may respond less well to bisphosphonate therapy than patients with PFD without endocrinopathies.

PATIENTS AND METHODS

We searched our hospital records for all patients with PFD and MAS from our cohort of 255 patients with FD, who were evaluated and followed at our Outpatient Clinic between 1990 and 2014. The diagnosis of PFD was established on the basis of clinical and radiological features, with occasional histological and genetic confirmation where required. The extent of bone involvement was determined by imaging using 99mTechnetium skeletal scintigraphy, and skeletal burden scores (SBSs) were calculated as described by Collins and colleagues.[6] Scoring was undertaken by two independent observers (BCJM and NMA-D), and differences between scores were resolved by consensus.

The diagnosis of MAS was established on the basis of PFD associated with endocrinopathies in the form of precocious puberty, with occasional additional endocrinopathies such as growth hormone or prolactin excess or hyperthyroidism. The presence of cafe-au-lait patches was recorded, but not considered essential for the diagnosis of MAS. Sixty-two patients with PFD, 13 of whom had endocrinopathies in the context of MAS, were identified from hospital records (Fig. 10.1). Twenty patients with PFD and one with MAS were excluded from analysis, as they did not require treatment with bisphosphonates because of absence of pain symptoms and/or in the presence of normal bone turnover (n.18), refusal of therapy (n.1), long-term treatment with bisphosphonates for osteoporosis (n.1), and inclusion in the on-going Profidys Eurocores study (http://clinicaltrials.gov/show/NCT00445575;n.1). Compared to bisphosphonate-treated patients, the 21 untreated patients (13 male and 8 female; 20 PFD and 1 MAS) were older at the time of diagnosis with a mean age 48 years ± 19.5 SD compared to 18.6 ± 16 years in treated patients. Analysis of the long-term effect of bisphosphonate treatment was thus conducted in 11 patients with MAS and 30

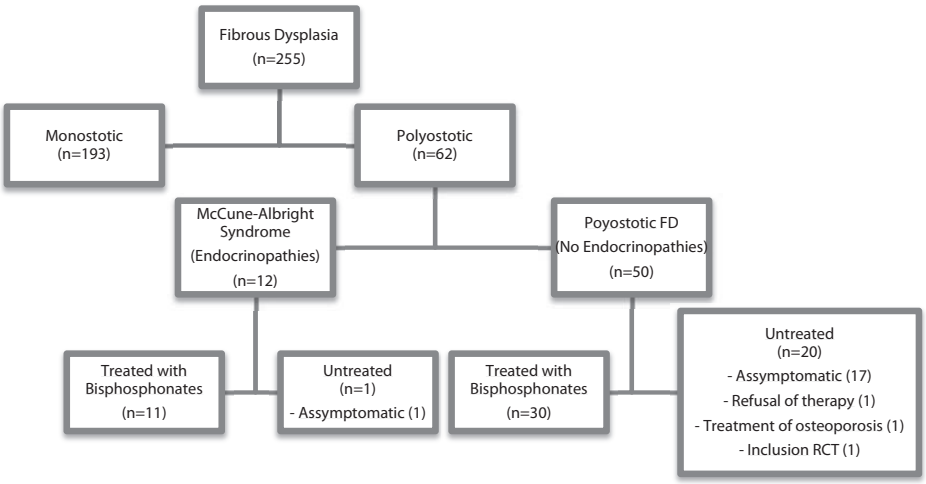

Fig. 10.1 Patient study flowchart.

patients with PFD without endocrinopathies. The study was approved by the Medical Ethical Committee of the Leiden University Medical Centre.

Data collection

Data of identified patients with PFD/MAS were retrieved from their hospital records about age, gender, and clinical and laboratory features in all patients studied. Data had been collected during outpatient visits at baseline (after an overnight fast) and at each subsequent outpatient visit at 3-month to 6-month intervals after start of treatment with bisphosphonates. These included data on pain (using verbal assessment that consisted of the same questions at each visit: Did the patient have pain or not? Was it mild, moderate, or severe? Was it better, worse, or unchanged since the previous visit?), presence of deformities, fractures, cafe-au-lait-patches, a history of precocious puberty, and confirmed additional endocrinopathies including GH excess, prolactin excess, hyperthyroidism, and FGF-23–induced renal phosphate wasting. Data were also retrieved about other laboratory parameters, including serum concentrations of creatinine, calcium, phosphate, albumin, 25-OH vitamin-D (RIA Incstar; DiaSorin, Stillwater, MN, USA), and intact PTH. Data on serum total alkaline phosphatase (ALP) (colorimetric method on the Roche Modular P800 analyzer; Roche Diagnostics, Almere, The Netherlands) were available in all patients. From 2006 onward, data on procollagen 1 aminoterminal propeptide (P1NP) and beta crosslaps (CTX) were also available as measured using an electrochemiluminescent immunoassay with a Modular Analytics

E-170 system (Roche Diagnostics, Almere, The Netherlands), but by then, treatment with bisphosphonates had been initiated in a number of patients so that baseline values before start of treatment were not available in all patients. The C-terminal FGF-23 (Immutopics, San Clemente, CA, USA) was randomly collected during medical care, off phosphate supplementation in ethylenediamine-tetraacetic acid (EDTA) plasma, and measured after short storage at –20°C prior to analysis using the BioTek ELx50 Washer (BioTek, Bad Friedrichshall, Germany).[16] All analyses were performed according to the manufacturer's protocol. Renal phosphate wasting was defined by the presence of two documented consecutive measurements of serum phosphate below the lower limit of normal (0.90 mmol/L) combined with a low tubular reabsorption of phosphate (TRP) (< 80%) as determined by the fractional TRP as measured by serum and urine concentrations of phosphate and creatinine in samples obtained after an overnight fast.[17] Data from the endocrinologic screening were collected in all MAS patients, including GH, IGF-1, prolactin, thyroid-stimulating hormone (TSH), and cortisol, with all blood samples collected after an overnight fast. Values for bone turnover markers (BTMs) and GH and IGF-1 were adjusted for age in all pediatric patients.[18,19]

Treatment protocol

In the early 1990s our center chose to treat FD patients requiring bisphosphonate therapy with the then newly developed nitrogen-containing bisphosphonate olpadronate, obtained by the dimethylation of the nitrogen molecule of the backbone structure of pamidronate. This dimethylation process was shown in our laboratory to increase the specificity of olpadronate toward bone resorption in vitro and vivo and to reduce its cellular toxicity.[20] The fivefold to 10-fold increase in potency of olpadronate compared to pamidronate was confirmed in a dosefinding study in patients with Paget's disease of bone, and its efficacy in achieving long-term remission and decrease in pain in > 89% of patients was further established in a long-term study in a cohort of 157 patients with this disease.[21,22] An advantage of olpadronate was that it could be used both orally and intravenously, and that its oral use provided more flexibility than the then-available bisphosphonate preparations by the availability of a 5-mg tablet for pediatric use for children 6 years or older, and of a 50-mg tablet for adult use. The maximumoral adult daily dose of 200 mg, and pediatric daily dose of 20 mg were very well tolerated, with only occasionally reported mild gastrointestinal side effects, which did not require discontinuation of the drug in most cases. The intravenous preparation of olpadronate was administered in doses of 4 or 8 mg as loading dose before starting oral olpadronate or as daily doses for 3 to 5 consecutive days at 3-month to 6-month intervals in the most severe cases with very high bone

turnover. The tablet and intravenous formulations of olpadronate were prepared and supplied by our hospital pharmacy for the whole period covered by this study. Treatment was administered in all forms of FD on the basis of increased bone turnover regardless of presence or absence of pain, but all patients with PFD and MAS analyzed in this study had pain of variable severity at one or more FD sites. Treatment was exceptionally administered in the presence of normal bone turnover in two patients who demonstrated rapid postoperative resorption of a recent fibula strut graft, and in one who was using high-dose inhalation corticosteroids for asthma, but all three did have bone pain. Olpadronate was administered orally at a starting dose of 200 mg/day, tapering to 50 mg/day and stopping 3 to 6 months after normalization of BTMs. The drug was administered intravenously as loading dose before starting oral treatment in case of very high bone turnover, in the rare case when oral medication was not well tolerated, or when oral use of maximum doses failed to normalize bone turnover after 12 months of treatment.

Ten of the 11 MAS patients and 28 of the 30 PFD patients were primarily treated with olpadronate in different doses and schedules orally and/or intravenously. Two patients with PFD were treated exclusively with oral risedronate or alendronate and one child with MAS did not tolerate oral olpadronate and was treated exclusively with i.v. pamidronate. Another eight patients temporarily received, at the discretion of their treating physician, oral or intravenous nitrogen-containing bisphosphonates other than olpadronate. These were in the form of daily 30 mg oral risedronate or daily 10 mg, or weekly 70 mg oral alendronate; 3 monthly cycles of intravenous pamidronate at doses of 15 mg daily for 3 consecutive days in adults, and 1 mg/kg body weight for 3 consecutive days in children older than 6 years, as recommended by Glorieux in osteogenesis imperfecta; or 6 to 12 monthly single infusions of 4 mg intravenous zoledronate.[23] The bisphosphonate preparations used, and cumulative doses of each preparation, are shown for MAS and PFD patients, in Tables 10.1 and 10.2, respectively. Relative potencies of all bisphosphonates used in this study have been reported.[24]

The aim of treatment with bisphosphonates, regardless of type of preparation, dosage, or schedule of administration, was to normalize bone turnover, hoping to achieve a consequent reduction in pain symptoms and to prevent the progression of FD lesions, thereby potentially decreasing the risk of complications such as deformities and fractures. Treatment was discontinued 3 to 6 months after normalization of bone turnover, and restarted as required when this was documented to increase again. The choice of high bone turnover to start and restart of therapy with bisphosphonates was based on the known FD temporal sequence of flare and remission, suggested

Table 10.1 Characteristics of patients with McCune-Albright Syndrome and cumulative dose of various nitrogen-containing bisphosphonates used

Patient ID	Gender/age at diagnosis (years)	Symptoms	Average FGF-23 (N < 125 U/ml)	Skeletal burden score	Age at start of therapy	Cumulative dose of Bisphosphonates**
1	F/3	Café-au-lait spots, precocious puberty and hypophosphatemia	NA*	59.66%	7	Olp 100 mg iv + 27375 mg oral, Zol 20 mg iv and Ris 5475 mg oral
2	F/4	Precocious puberty, hypophosphatemia and ovarian cysts	200 U/ml	26.08%	22	Olp 32 mg iv and 300000 mg oral, APD 1680 mg, Zol 20 mg iv
3	F/15	Café-au-lait spots, precocious puberty and hypophosphatemia	174 U/ml	25.28%	45	Olp 240 mg iv and 109500 mg oral
4	F/1	Café-au-lait spots, precocious puberty, hypophosphatemia, hyperthyroidism and GH-excess	274 U/ml	64.69%	45	Olp 720 mg iv and 365000 mg oral
5	F/0	Café-au-lait spots, precocious puberty and hypophosphatemia	161 U/ml	44.02%	19	Olp 764 mg iv and 144000 mg oral
6	F/3	Precocious puberty, hypophosphatemia and ovarian cysts	168 U/ml	9.77%	46	Olp 16 mg iv and 63250 mg oral
7	F/1	Café-au-lait spots, precocious puberty, hypophosphatemia, hyperthyroidism, GH-excess, hyperprolactemia and ovarian cysts	277 U/ml	42.63%	7	APD 360 mg iv
8	F/2	Café-au-lait spots, precocious puberty and hyperthyroidism	131 U/ml	56.46%	46	Olp 20 mg iv and 730000 mg oral, APD 900 mg iv
9	M/5	Café-au-lait spots, precocious puberty, hypophosphatemia, GH-excess, hyperprolactemia and autonomous testosteron production	180 U/ml	31.27%	13	Olp 20 mg iv and 328500 mg oral
10	M/10	Café-au-lait spots, precocious puberty, hypophosphatemia and hyperprolactemia	316 U/ml	64.26%	16	Olp 73000 mg oral
11	F/12	Café-au-lait spots, precocious puberty and hypophosphatemia	162 U/ml	38.70%	28	Olp 116 mg iv and 621975 mg oral, Ale 10500 mg, Ris 4200 mg, Zol 4 mg

* NA = not available.
** Olp = Olpadronate; Zol = Zolendronate; Ris = Risedronate; Ale = Alendronate.

to be associated with phases of expansion and consumption of mutated skeletal progenitor cells as mechanisms underlying the development, maintenance, and burning out of individual lesions.[25-27] It has been suggested that during skeletal growth the development and maintenance of a lesion would be associated with high bone turnover, and periods of remission would be associated with normal bone turnover, during which normal remodeling of FD bone may take place. However, the concept of the association between clinical flares and the level of BTMs has never been formally addressed. There are thus no direct studies examining the mechanism(s) that drive skeletal pain in FD. A number of observational studies, but not all, have shown the ability of antiresorptive therapy to relieve FD pain, suggesting that increased bone turnover may contribute to the mechanism of pain in FD.[8,9,11,13,14,28] However, other studies including ours here reported, fail to demonstrate a correlation between FD pain and disease burden.[29] The ultimate objective of the use of bisphosphonate therapy would thus be to normalize bone turnover with a view to prevent the development and/or expansion of FD lesions as well as to allow for normal remodeling to take place in FD lesions, theoretically aiming at improving bone quality and strength, although this is as yet to be formally demonstrated. All patients were prescribed calcium and vitamin D supplements concomitant to starting treatment with bisphosphonates, and serum 25-hydroxy-vitamin D level was controlled 3 months after start of therapy and supplementation adjusted accordingly. Active metabolites of vitamin D and phosphate supplements were additionally prescribed as required, predominantly in children, prior to start treatment with bisphosphonates, to correct moderate to severe hypophosphatemia associated with FGF-23–induced renal phosphate wasting. The decision not to treat FGF-23–induced mild hypophosphatemia in the absence of overt osteomalacia was based on published histomorphometry data in FD (albeit in children and adolescents), suggesting that although low serum phosphate may be associated with a mild systemic mineralization defect in PFD, it was debatable whether this warranted treatment in the absence of signs of rickets, as the more severe mineralization defect observed in dysplastic lesions was independent of serum phosphate levels.[30] Clinical and biochemical response to treatment in the form of verbal assessment of pain and biochemical markers of bone turnover and recurrence of FD activity after discontinuation of treatment were evaluated during outpatient clinic visits at start of treatment and at 3-month to 6-month intervals thereafter. Adverse effects were carefully documented at each outpatient visit.

Outcome of treatment with bisphosphonates was determined primarily by biochemical outcome as judged by normalization of serum values of the BTM (total) ALP (complete

Table 10.2 Characteristics of patients with polyostotic fibrous dysplasia and cumulative dose of various nitrogen-containing bisphosphonates used

Patient ID	Gender/age at diagnosis (years)	Extraskeletal symptoms	Average FGF-23 (N < 125 U/ml)	Skeletal burden score	Age at start of therapy	Cumulative dose of bisphosphonates**
12	F/5	Hypophosphatemia	133 U/ml	16.70%	35	Olp 68 mg iv and 146000 mg oral
13	F/9	-	160 U/ml	24.89%	22	Olp 124 mg iv and 219000 mg oral
14	F/5	-	134 U/ml	16.68%	39	Olp 91250 mg oral
15	F/45	-	100 U/ml	4.04%	51	Olp 60833 mg oral
16	M/9	Café-au-lait spots, hypophosphatemia	152 U/ml	17.10%	19	Olp 282875 mg oral
17	M/11	-	126 U/ml	24.78%	20	Olp 12 mg iv and 109500 mg oral
18	F/16	Café-au-lait spots	132 U/ml	15.30%	38	Olp 40 mg iv and 282875 mg oral
19	F/11	-	115 U/ml	15.75%	50	Olp 12 mg iv and 30417 mg oral
20	F/24	Hypophosphatemia	139 U/ml	15.80%	30	Olp 109500 mg oral
21	F/20	-	91 U/ml	7.13%	20	Olp 12mg iv and 27375 mg oral
22	F/8	-	166 U/ml	7.92%	19	Olp 20 mg iv and 27375 mg oral + Zol 8 mg iv
23	M/60	Hypophosphatemia	114 U/ml	13.74%	60	Olp 82125 mg oral
24	M/27	Hypophosphatemia	79 U/ml	7.65%	42	Olp 118692 mg oral
25	M/39	Café-au-lait spots	133 U/ml	24.96%	44	Olp 24 mg iv, Ale 900 mg, Ris 900 mg, Zol 48 mg iv
26	M/4	-	134 U/ml	23.90%	48	Ris 1800 mg
27	M/27	-	103 U/ml	2.05%	50	Olp 436 mg iv and 261583 mg oral, APD 360 mg iv, Zol 19 mg iv

Table 10.2 *Continued*

Patient ID	Gender/age at diagnosis (years)	Extraskeletal symptoms	Average FGF-23 (N < 125 U/ml)	Skeletal burden score	Age at start of therapy	Cumulative dose of bisphosphonates**
28	M/14	-	101 U/ml	16.42%	36	Olp 96 mg iv and 6083 mg oral
29	M/16	-	116 U/ml	NA	22	Olp 42583 mg oral
30	M/25	-	NA	15.80%	35	Olp 56 mg iv and 155125 mg oral
31	M/31	Hypophosphatemia	NA	7.07%	31	Olp 48 mg iv and 73000 mg oral
32	M/25	-	81 U/ml	7.93%	40	Olp 73000 mg oral
33	F/32	-	NA	16.26%	50	Olp 12 mg iv and 146000 mg oral
34	F/44	Café-au-lait spots, hypophosphatemia	112 U/ml	NA	51	Olp 100375 mg oral
35	F/24	-	107 U/ml	10.65%	55	Ale 3640 mg
36	M/8	Hypophosphatemia	195 U/ml	18.53%	12	Olp 28 mg iv and 360974 mg oral, Zol 12 mg
37	F/58	-	82 U/ml	16.12%	58	Olp 205313 mg oral
38	M/3	-	432 U/ml	15.75%	7	Olp 140 mg iv
39	F/35	-	131 U/ml	7.13%	37	Olp 4563 mg oral, Zol 8 mg iv
40	F/19	-	NA	15.75%	43	Olp 20 mg iv and 104938 mg oral
41	F/24	Hypophosphatemia	198 U/ml	17.87%	41	Olp 16 mg iv and 705667 mg oral, Ale 89180 mg, Zol 6 mg, Ale 114975 mg

* NA = not available.
** Olp = Olpadronate; Zol = Zolendronate; Ris = Risedronate; Ale = Alendronate.

response), decrease but no normalization of its value (incomplete response), or no change in its value (nonresponder). Clinical outcome was judged to be complete in case of disappearance or significant reduction in the severity of bone pain (complete response) and judged to be incomplete in the event of insufficient reduction in pain symptoms (incomplete response), usually coupled with non-normalization of ALP. In this study, time to normalization of bone turnover was evaluated using serum concentrations of ALP because this is a marker of bone formation, the prime defect in FD, and data on this marker were available at baseline and at each 3-month to 6-month outpatient clinic visit thereafter. Data were also retrieved for serum P1NP and CTX measurements but these were only available from 2006 onward, when they became available for use in the clinic, by which time a number of patients had already started treatment with bisphosphonates, so that these measurements are reported but not included in the analysis of primary outcome of treatment.

Statistical analysis

Statistical analysis was performed using SPSS for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA). Unless otherwise stated, results are presented as mean ± SD, or as a percentage in case of categorical data. We identified prognostic factors influencing the response of bone turnover to bisphosphonate treatment by incorporating gender, age at start of treatment, GH excess, phosphate level, and FGF-23 in a logistic regression model. We used Spearman's rank correlation coefficient to correlate serum levels of FGF-23 and ALP with SBS values.

RESULTS

Patients' characteristics

MAS patients

Data on MAS patients are shown in Table 10.1. Eleven patients had MAS (9 female and 2 male) with a median age at diagnosis of 3.0 years (range, 0 to 15 years). All MAS patients had precocious puberty, 5 (45%) had at least one or more additional endocrinopathies including growth hormone excess (n = 4; all associated with extensive craniofacial disease), prolactin excess (n = 3), and hyperthyroidism (n = 3). Not all patients had the characteristic cafe-au-lait patches (n = 9; 82%). Ten of the 11 MAS patients in whom it was measured (91%) had increased FGF-23 levels, with a median of 174 U/mL (range, 131 to 316 U/mL; normal range < 125 U/mL), and FGF-23 levels were significantly higher in MAS patients with GH excess, with a median serum concentration of 277

U/mL (range, 274 to 316 U/mL) compared to MAS-patients without GH excess: 165 U/mL (range, 131 to 200 U/mL), $p < 0.0001$. Despite the documented increased FGF-23 levels in all MAS patients, only eight (73%) developed age- and gender-adjusted low serum phosphate levels, and four of those required phosphate supplementation at some stage during childhood and adolescence. At the time of starting bisphosphonate therapy, only one of these four patients, an adolescent of 16 years with extensive skeletal involvement including craniofacial localization, treated excess prolactin and GH, corrected severe vitamin D deficiency, and inappropriately low serum phosphate due to FGF-23-induced renal phosphate wasting still required maximum doses of active metabolites of vitamin D and phosphate supplementation, which he had been using for 18 months prior to starting treatment to maintain his serum phosphate at 0.85 mmol/L (normal, 0.90 to 1.5 mmol/L). The mean lifetime number of fractures sustained by MAS patients was 3.6 (range, 0 to 13) and they required a mean of 2.4 surgical interventions per patient (range, 0 to 7). The lesions were bilaterally distributed in all MAS patients and all but one had craniofacial disease, particularly severe in the presence of GH excess. The mean ± SD SBS was 42.1% ± 18.0%. Scores were particularly high in patients with craniofacial disease and GH excess, with maximal scores of 75% in the craniofacial region in all patients with GH excess, compared with a mean score of 37.5% ± 30.6% in patients without GH excess ($p < 0.040$). The two patients with MAS but no cafe-au-lait patches had significantly lower SBS values (17.92% ± 11.54%) than those with cafe-au-lait patches (47.44% ± 14.47%), $p = 0.026$. Histological confirmation of the disease was available from specimens obtained at surgery for fractures and/or correction of deformities in six MAS patients, two of whom had genetic confirmation of the pathognomonic GNAS mutation.

PFD patients

Data on PFD patients are shown in Table 10.2. Thirty patients with PFD (15 female and 15 male), with a mean ± SD age at diagnosis of 23.5 ± 15.8 years were studied. None had laboratory evidence for endocrinopathies on endocrinology screening, but five (16%) had cafe-au-lait patches. The five patients with PFD and cafe-au-lait patches had higher SBS values (19.12% ± 5.13%) than the ones without pigmented skin lesions (13.29% ± 5.63%), although the difference was not statistically significant, $p = 0.115$. Fifteen of the 26 patients in whom it was measured (58%) had increased serum FGF-23 levels with an overall median of 128 U/mL (range, 79 to 432 U/mL), only two of whom had FGF-23–induced mild hypophosphatemia, which did not require treatment with active metabolites of vitamin D or phosphate supplementation prior to starting bisphosphonate therapy. Lateralization of the FD lesions was present in

18 patients (60%). The mean lifetime number of fractures sustained by PFD patients was 1.3 (range, 0 to 11) fractures and it was necessary to undertake a mean of 2.0 (range, 0 to 10) surgical interventions per patient. The mean SBS was 14.3% ± 6.5%. Twenty PFD patients had histological confirmation of the disease and in none was the disease genetically confirmed.

MAS versus PDF patients

Data on MAS versus PFD patients are shown in Table 10.3. There was no significant difference in gender distribution between PFD and MAS patients. Diagnosis was made at a significantly younger age in MAS compared to PFD (5.1 versus 23.5 years; p = 0.001), and disease was bilateral in all MAS patients compared to 67% of patients in the PFD group. MAS patients had more extensive skeletal disease compared to PFD patients with significantly higher ALP concentrations (a median of 257 U/L [range, 102 to 1782 U/L] versus 115 U/L [range, 72 to 604 U/L]; p = 0.002), significantly higher SBS values (42.1% versus 14.3%; p < 0.001), and they had sustained significantly more fractures (p = 0.024; 95% CI 0.37 to 4.26). MAS patients had also higher FGF-23 levels (a median of 174 U/mL [range, 131 to 316 U/mL] versus 128 U/mL [range, 79 to 432 U/mL]; 95% CI 19.7 to 123.7 U/mL; p = 0.008), and more frequent episodes of FGF-23–induced hypophosphatemia (81% versus 36%; p = 0.013), but did not significantly require more surgery than PFD patients (2.36 ± 2.6 versus 2.0 ± 2.5; 95% CI –2.15 to 1.42; p = 0.68).

Table 10.3 Comparative clinical, laboratory and disease burden characteristics between MAS and PFD

	McCune-Albright syndrome		Polyostotic fibrous dysplasia			
Factor	Mean	Standard deviation	Mean	Standard deviation	Mean difference	p-value
Alkaline phosphatase	499.6	± 619.0	144.1	± 116.3	355.5	0.005
Average FGF-23	207.1	± 64.9	135.4	± 66.9	71.7	0.008
Skeletal burden score	42.1%	± 18.0	14.3%	± 6.5	28.0	0.000
Age at diagnosis	5.1	± 5.0	23.5	± 15.8	18.4	0.001
Number of fractures	3.64	± 3.9	1.32	± 2.3	2.3	0.021
Number of surgeries	2.36	± 2.6	2.0	± 2.5	0.4	0.682
Hypophosphatemia	81.8%	-	35.5%	-	46.3	0.013

Correlates of SBS values

FGF-23 levels positively correlated with the extent of the skeletal lesions as measured by SBS values in the whole PFD/MAS group studied (Fig. 10.2A), as did serum ALP, P1NP, and CTX concentrations prior to starting bisphosphonate therapy (Fig. 10.2B for ALP) ($p < 0.001$ for all three BTMs). Spearman's rank correlation coefficient (SRCC) of SBS values and average serum FGF-23 levels was 0.620 ($p < 0.001$), and SRCC of SBS and serum ALP levels was 0.562 ($p < 0.001$). Serum FGF-23 also inversely correlated with serum phosphate levels, SRCC –0.426 ($p < 0.014$), but increased FGF-23 levels were not necessarily associated with hypophosphatemia in regression analysis.

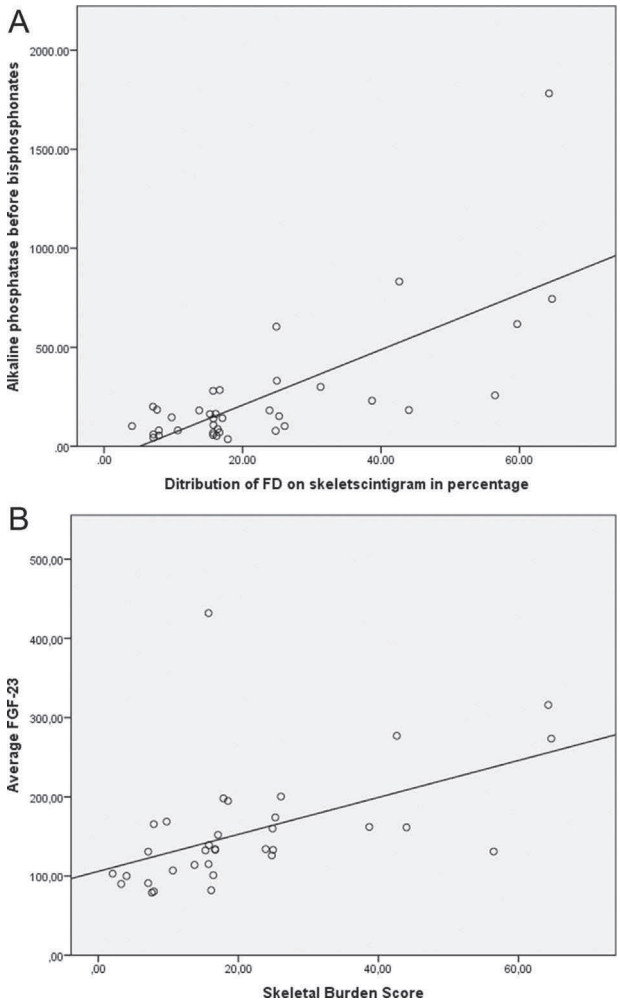

Fig. 10.2 (A) Positive relationship between skeletal burden scores and bone turnover as judged by total ALP concentrations prior to treatment with bisphosphonates. (B) Positive relationship between skeletal burden scores and average FGF-23 levels.

Outcome of bisphosphonate therapy

Mean age at start of bisphosphonate therapy was 27 ± 16.1 years in MAS patients compared to 37 ± 14.0 years in PFD patients ($p = 0.057$). There were six children who started therapy at age 16 years or less: two in the PFD group, both male, aged 7 and 12 years (Table 10.2), and four in the MAS group, three females and one male, aged 7, 7, 13, and 16 years (Table 10.1). Mean duration of follow-up after start of therapy was 12.3 ± 7.6 years in MAS patients, and 5.8 ± 6.4 years in PFD, with periods of discontinuation of treatment lasting between 6 and 12 months in the majority of PFD patients but not the majority of MAS patients. Bone turnover was significantly higher at start of treatment in MAS patients with a median serum ALP of 257 U/L (range, 102 to 1782 U/L) compared to 115 U/L (range, 72 to 604 U/L) in PFD patients (95% CI 139.1 to 541.3 U/L; $p = 0.002$). In the subgroup of patients in whom serum levels of P1NP and CTX were available at start of treatment with bisphosphonates and during follow-up (3 MAS and 22 PFD patients), median P1NP values were 960 ng/mL in MAS compared to 73.5 in PFD ($p < 0.0001$) and median CTX was 1.550 ng/mL in MAS compared to 0.360 ng/mL in PFD ($p = 0.001$). In both groups, serum ALP, P1NP, and CTX concentrations before starting bisphosphonate therapy were positively correlated with SBS (respectively, SRCC 0.72, $p < 0.001$; SRCC 0.87, $p < 0.001$; SRCC 0.71, $p < 0.001$) and with average FGF-23 levels (respectively, SRCC 0.588, $p = 0.001$; SRCC 0.671, $p = 0.001$; SRCC 0.663, $p = 0.001$).

Twenty-four of the 30 patients with PFD (80%) demonstrated a complete clinical and biochemical response to bisphosphonate therapy, with relief of pain symptoms and normalization of serum ALP concentrations, compared to only four of the 11 MAS patients (36%), of whom only one (of four) with GH excess demonstrated a similar complete response despite adequate suppression of GH excess in all patients ($p = 0.019$; Fig. 10.3). Patients with MAS required significantly higher cumulative doses of bisphosphonates to demonstrate a biochemical effect on ALP and to maintain it than patients with PFD (2696 mg versus 1470 mg, respectively; $p = 0.019$). In the subset of patients in whom data on P1NP and CTX were available before starting bisphosphonate therapy and sequentially thereafter, normalization of these markers was observed, in keeping with changes in ALP, within a year of starting treatment in 83% of PFD patients and in one of the three MAS patients. In patients in whom these markers did not normalize, maximum decrease in serum values was also observed, in keeping with changes in ALP, within the first year of treatment and stabilized thereafter. In complete responders, biochemical response in the form of normalization of ALP was observed within the first year of treatment in the majority of PFD and MAS patients except for one PFD patient in whom ALP normalized after 42 months of treatment, and one MAS

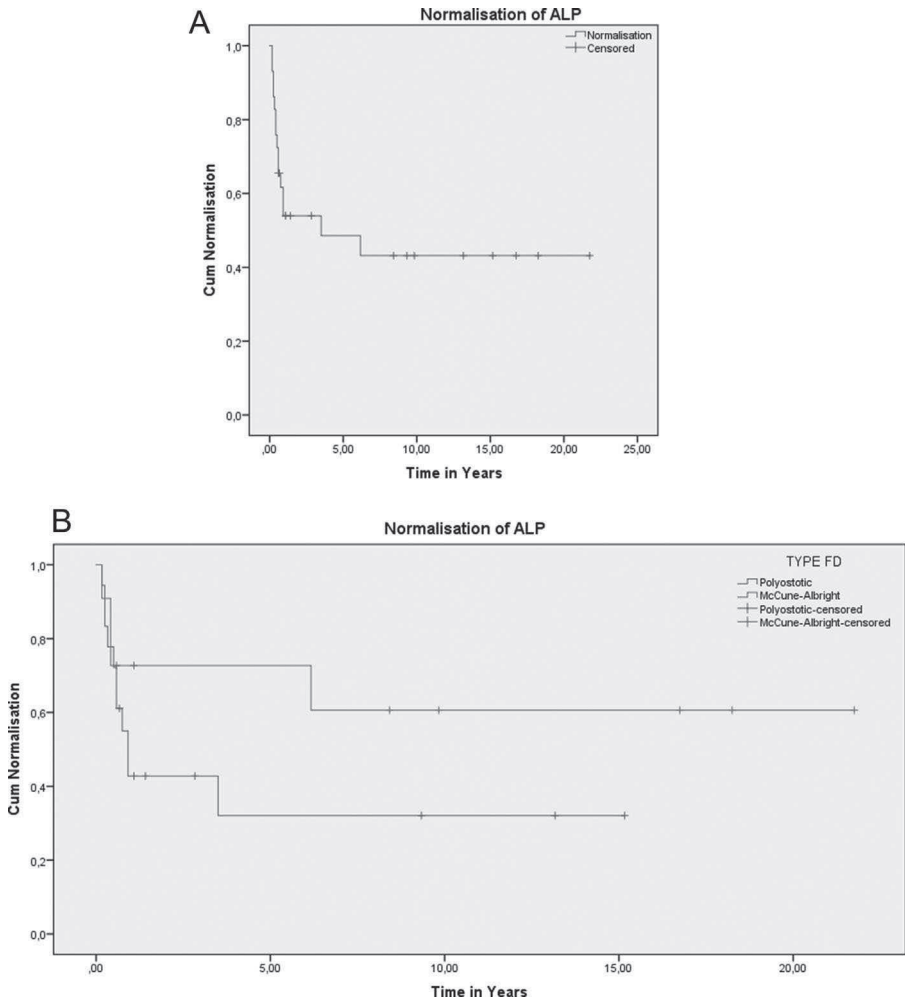

Fig. 10.3 Kaplan-Meier survival curves showing normalization of total ALP concentrations within the first year after starting treatment with bisphosphonates in the majority of complete responders with PFD or MAS (A), and similar course to normalization of ALP concentrations in patients with PFD or MAS with high ALP concentrations prior to starting bisphosphonate therapy (B).

patient in whom ALP normalized after 74 months of treatment (Fig. 10.3). Interestingly, the late normalizing PFD patient had a higher SBS than the mean for the PFD group (18.5% versus 14.3%), and the late and only MAS patient in whom ALP normalized had a lower SBS than the mean of the generally poorly-responding group of MAS patients (31.3% versus 42.1%). There were no absolute nonresponders, and all patients not showing a complete response (6/30 PFD and 7/11 MAS) demonstrated some decrease in severity of pain and a decrease in serum levels of ALP with a median decrease of

41% ranging from a minimum of 14% to a maximum of 78%. Treatment could not be discontinued in the long term, particularly in patients with MAS but also in patients with PFD with high SBS values, who required long-term bisphosphonate therapy to maintain the complete or incomplete suppression of increased bone turnover.

Factors affecting outcome of bisphosphonate therapy in PFD and MAS

In our series of patients, the only factor identified as affecting outcome of treatment with bisphosphonates in PFD after correction for age and gender was a high SBS ($p = 0.015$) independently of the presence or absence of endocrinopathies. A more limited response was consequently observed in patients with MAS who exhibited the highest SBS values because of more extensive skeletal disease. Neither serum concentrations of FGF-23 nor hypophosphatemia correlated with outcome of treatment with bisphosphonates either in PFD or in MAS patients. GH excess did not appear to influence outcome of treatment, although analysis was precluded by the limited number of patients with this endocrinopathy.

Safety issues with the long-term use of bisphosphonates in PFD and MAS

Ten of the 41 patients with PFD or MAS (24%) reported minor adverse effects, in the form of mild gastrointestinal complaints, headaches, and/or nausea with the use of oral medication. Only in one child with MAS did treatment need to be discontinued. In 38 patients who received one or more courses of olpadronate intravenously, only two had a severe acute phase reaction after the first course of treatment. Despite the high mean cumulative dose and long-term use of bisphosphonates, there was maintenance

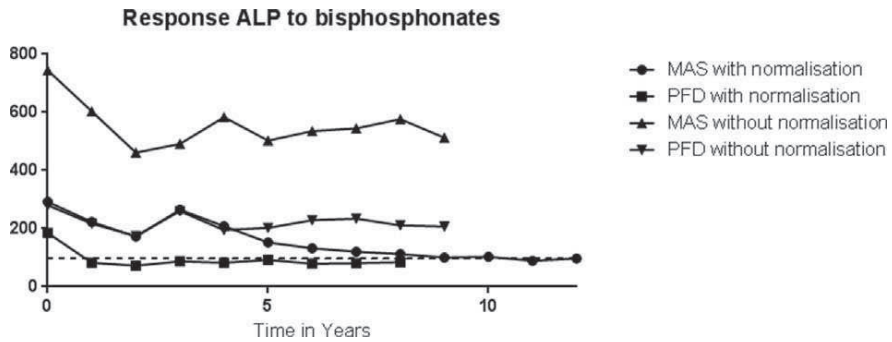

Fig. 10.4 Changes in serum total ALP concentrations in four individual patients illustrating similarities in complete and incomplete response to bisphosphonate therapy in PFD and MAS. The graphs also illustrate the maintenance of ALP activity with repeated treatment as required in complete responders, and no further suppression of the decreased bone turnover attained beyond 2 years of treatment, despite longer-term use of these agents in incomplete responders.

of normal BTMs with repeated treatment as required in complete responders, and no further suppression of the decreased bone turnover attained beyond 2 years of treatment despite longer-term use of these agents in incomplete responders (Fig. 10.4). There were no reports of osteonecrosis of the jaw or of atypical femoral fractures in any of the patients in our series. In children between the ages of 7 and 16 years treated long term for up to 9 years, there was no disturbance in linear growth.

DISCUSSION

In this study, we retrospectively evaluated the outcome and safety of long-term treatment with nitrogen-containing bisphosphonates in a case series of patients with the more severe polyostotic forms of FD, including those with endocrinopathies in MAS. Our findings demonstrate a beneficial effect of bisphosphonate therapy primarily on bone turnover and secondarily on pain symptoms in the majority of patients with PFD (80%), with a more limited response observed in patients with MAS (36%), likely due to their more extensive skeletal disease. In keeping with this premise, we further identify SBS as the only prognostic factor influencing the outcome of bisphosphonate therapy.

Over the past 25 years it has been the policy of our center to treat all patients with FD who demonstrated increased bone turnover, which with a few exceptions was associated with pain in all patients with PFD or MAS, with nitrogen-containing bisphosphonates, aiming at normalizing bone turnover, and hoping in the process for an associated reduction in pain symptoms, arrest of expansion of individual FD lesions, and prevention of debilitating complications such as deformities and fractures encountered in progressive disease, particularly of the growing skeleton. The lack of correlation between skeletal pain and disease burden in FD, is analogous to the highly variable frequency and severity of skeletal pain observed within and between individual patients suffering from the same metastatic tumor burden.[31] This analogy has led to the hypothesis that it is not just bone remodeling, but also a neuropathic component, possibly related to abnormal remodeling of the sensory innervation of bone, that may drive bone pain in FD.[32] This has been shown in animal models of skeletal cancer pain that effectively mirror the clinical picture observed in humans with bone cancer pain.[33] Whereas a neuropathic component to FD pain could not be excluded in our patients, our data based on long-term follow-up of a relatively large cohort of PFD and MAS patients with moderate to severe FD, support the association of clinical flares with increased BTMs, and the abatement of pain with normalization of these markers in the majority of patients, thus providing justification for the use

of antiresorptive agents in FD in the presence of high bone turnover. The hypothesis is further supported by the persistence of pain, albeit of lesser severity, in patients in whom these agents fail to normalize BTMs.

We chose to primarily use the nitrogen-containing bisphosphonate olpadronate in the medical management of these patients, because of its proven efficacy in Paget's disease of bone and its excellent track record for gastrointestinal tolerance, allowing the safe administration of high oral doses for longer periods of time in adult and pediatric patients with severe disease.[22] Its dosage flexibility in the pediatric population also represented a clear advantage. However, other bisphosphonates, albeit all nitrogen-containing, were also mostly temporarily prescribed during the course of the disease at the treating physician's discretion.

Our primary outcome measure was the effect of bisphosphonate therapy on parameters of bone turnover, regardless of preparation, mode of administration, or schedule of treatment. In this study, we used serum ALP as marker of bone turnover because this is a marker of bone formation and mineralization, and it was the marker with the most complete set of available data before treatment and at regular intervals thereafter for the duration of follow-up across the 25-year span of our study. We also chose ALP as bone turnover marker because of its significant correlation with SBS values, a specific marker of skeletal disease severity in FD, and because cells in the endosteal fibrosis of FD lesions have been shown to exhibit strong ALP activity.[6,7] We did not use the markers of bone turnover P1NP and CTX in our analysis because data on these were only available from 2006 onward when the measurements were first made available for use in the clinic, and a number of patients had by then already started treatment with bisphosphonates, so that a number of baseline values for these markers were consequently missing.

Our secondary outcome measure related to the effect of bisphosphonate therapy on bone pain, a vexing and often debilitating clinical feature of FD, particularly in the presence of extensive skeletal disease. A caveat about the data regarding this measure in our study is that although data on bone pain were documented in all patients at nearly all outpatient visits, which were at short intervals of 3 to 6 months, these consisted of recording the presence or absence of pain, its severity, and changes in the pattern of pain rather than the data being systematically obtained with the use of validated pain questionnaires such as a visual analogue score (VAS), which does represent a limitation of our study. Notwithstanding, there was a clear trend for reduction or disappearance of pain symptoms on bisphosphonate therapy, which

paralleled the normalization of bone turnover, and interestingly a beneficial effect on reducing pain symptoms was also observed in MAS patients with extensive skeletal disease even when bisphosphonate therapy was not able to sufficiently decrease bone turnover. FD is a disorder of bone growth, with excessive and abnormal bone of poor quality being formed instead of normal bone at one or more skeletal sites. In these sites, mutated cells of the osteogenic lineage at various stages of maturation are exposed to the effects of excess endogenous cAMP production, which is due to the inappropriate stimulation of adenylate cyclase by the mutated Gsa, leading to a spectrum of dysfunctional and architecturally imperfect bone growth, particularly in the growing skeleton.[34-38] As a result of the abnormal chemical composition and mineral content of the deposited matrix, the abnormal bone is mechanically unsound and fragile and at the same time more compliant than normal bone, leading to increased risk for deformities and insufficiency fractures with debilitating consequences particularly in the presence of high skeletal burden. The problem is further compounded by the increased production of FGF-23, leading to renal phosphate wasting, which has been documented in variable degrees in some 50% of patients with PFD/MAS, and may result in severe cases in further demineralization, osteomalacia, and further increased risk for deformities and fractures.[39] Increased expression of IL-6 from mutated mesenchymal precursor cells stimulates local osteoclast recruitment and activity, leading to increased bone resorption in and around FD lesions, associated with a local increase in bone remodeling.[7,40] However, increased bone resorption is not the prime pathophysiologic mechanism for an FD lesion so that it seems counterintuitive to use bisphosphonates, the most widely used antiresorptive agents, to treat a disorder of primarily disturbed bone formation. On the other hand, the use of bisphosphonates in such a disorder is supported by their successful use in osteogenesis imperfecta, in which they have been shown to significantly decrease skeletal morbidity.[23,41,42] Notwithstanding, the local increase in bone remodeling may contribute to the expansion of an FD lesion, particularly in the growing skeleton. The question arises whether a bisphosphonate-induced decrease in bone remodeling in an FD lesion may be beneficial on the natural history of the disorder by potentially halting the expansion or resulting in the regression of an FD lesion. There is some evidence for this from open studies, but because the natural history of the disorder remains elusive, more evidence from randomized, placebo-controlled trials is required to identify which patients respond best and should thus be targeted for therapy.

Available evidence for a beneficial effect of bisphosphonates in FD

Surgical interventions, successful in reducing pain, correcting deformities, and treating and preventing fractures have been the mainstay of treatment of FD since the disease was first described in the late 1930s.[43] Several publications, particularly using intravenous pamidronate in open studies, have shown the ability of this nitrogen-containing bisphosphonate to improve bone turnover and to decrease bone pain in adults and children with FD.[8,11,44-47] Some studies have also shown beneficial radiological changes potentially associated with improved bone quality and decreased risk of complications.[10,14,48] However, the only randomized controlled trial (RCT) using the nitrogen-containing bisphosphonate alendronate in daily oral doses ranging from 10 to 40 mg daily in 6-month cycles for 2 years failed to demonstrate any significant beneficial effect in FD patients compared to placebo. Notwithstanding, the lack of decrease in ALP in this study suggests that the dose and schedule of alendronate used may not have been adequate to efficiently decrease bone turnover in the severely affected treated patients. Longer-term treatment and higher cumulative doses may have been needed to significantly decrease bone turnover, although this would have been precluded by the use of the oral formulation of alendronate. Results of an ongoing RCT using risedronate 30 mg daily for 2 months every 6 months – the Profidys study – are eagerly awaited, but children, who probably represent the most important target group for bisphosphonates, have unfortunately not been included in this study. Moreover, it has also been suggested that the disease continues to progress with lesions expanding under bisphosphonate treatment,[49] and a direct beneficial effect of bisphosphonates on the characteristic abnormal structure of bone of an FD lesion has so far not been demonstrated.[13] Opinion is thus divided on the beneficial effect of bisphosphonates in FD, and their use in the management of patients with this disorder remains, therefore, a topic of debate.

Potential mechanism underlying the beneficial effect of bisphosphonates in FD

Bisphosphonates so far used in the management of FD have all been nitrogen-containing bisphosphonates, the antiresorptive effect of which is mediated by the inhibition of protein prenylation resulting in inactivation of osteoclasts.[50] Protein prenylation is a type of posttranslational modification critical to a variety of GTP binding proteins, including Gsg. A potential mechanism of action of bisphosphonates in FD besides its antiosteoclastic effect is a possible additional effect of the inhibition of prenylation of Gsg on Gsa mutated cells of the osteogenic lineage, which may potentially decrease the endogenous overexpression of cAMP and thus the potential development and expansion of an FD lesion.[51]

Concerns with long-term use of bisphosphonates in FD

A general concern with the use of bisphosphonates in any skeletal disorder is the potential consequences of continuing suppression of bone remodeling by the longer-term use of these agents. In patients with FD, the spectrum of clinical expression of the disease is wide and the skeletal burden variable. We have addressed this concern by individually tailoring treatment to bone turnover status, an approach which has allowed the possibility of "drug holidays" for a maximum duration of a year in most PFD patients, but not MAS patients. A second concern in the management of these patients is the use of bisphosphonates in MAS patients with untreated GH excess, in which case, the stimulatory effects of GH excess on bone turnover will compete or negate the inhibitory effects of bisphosphonates, calling for higher doses of bisphosphonates, and longer-term usage, with potential development of associated complications. A third concern is the use of these agents in the presence of FGF-23–induced renal phosphate wasting, a relatively common finding, although in variable degrees, in the more severe cases of PFD and MAS, because of the potentially associated disturbance in mineralization.[39,52] A last concern is the potential lack or curtailed skeletal uptake in predominantly sclerotic lesions such as those observed in craniofacial FD, but beneficial effects of these agents have also been reported particularly in isolated craniofacial (CF) FD.[53-55]

In our study, treatment with bisphosphonates was well tolerated in adults as well as in children except for one young MAS patient, and only mild side effects were documented despite the high cumulative dose required to achieve an effect in the more severely affected cases of FD described here. We believe our specific individually tailored treatment protocol, based on maintaining a normal bone turnover status, was probably instrumental in the prevention of potential complications such as atypical fractures and osteonecrosis of the jaw. Attention to correction of metabolic abnormalities such as vitamin D deficiency and hypophosphatemia, which could have worsened mineralization of FD lesions, has also helped in the prevention of further complications such as insufficiency fractures and associated increased pain symptoms. In our cohort, long-term bisphosphonate therapy was not associated with deleterious effects on linear growth in treated children, as also previously demonstrated by our group in bisphosphonate-treated children with severe osteoporosis.[56]

Factors influencing outcome of bisphosphonate therapy in FD

High SBS, GH excess, and high FGF-23 levels have been previously found to predict poor prognosis in FD.[6] However, in our cohort, we identified high skeletal burden as

the only prognostic factor influencing outcome of bisphosphonate therapy. Although GH excess has been shown to be associated with higher skeletal burden, and three of our four patients with GH excess did have an incomplete clinical and biochemical response to treatment, we could not demonstrate a significant impact of GH excess on outcome of treatment, probably because of the small number of patients with this endocrinopathy in our MAS series. FGF-23 has been shown to be expressed throughout the osteogenic lineage in osteoblasts, osteocytes, and stromal cells, as well as in the vascular walls in FD lesions.[57] The positive correlation of FGF-23 with SBS, as shown by Collins and colleagues and confirmed in our study, is thus not surprising.[39] However, neither FGF-23 levels nor phosphate levels predicted treatment outcome. This finding is in line with recent reports suggesting that the FGF-23 secreted by the FD lesions is not active FGF-23 but consists largely of the inactive form of the peptide.[57]

Strengths and limitations of the study

Our study has strengths as well as limitations. Its main strength is the inclusion of a relatively large number of patients with the more severe forms of FD, its novel treatment protocol choosing high bone turnover rather than bone pain to determine start and restart of therapy, and aiming at normalizing bone turnover thus permitting drug holidays as required and precluding unnecessary long-term treatment with bisphosphonates. A further strength is the close monitoring and long-term follow-up of these patients for the duration of treatment. The study has also limitations. Its main limitations are the limitations inherent to a retrospective study as well as the limitations resulting from the use of verbal assessment data rather than data derived from formally validated tools such as VAS for evaluation of the clinical outcome of pain. However, all patients had pain symptoms and data on pain were not randomly obtained in our study, but were consistently enquired about at each outpatient visit that took place at short intervals of 3 to 6 months for the duration of treatment. A last potential limitation of our study is the possibility that the progressive improvement in bone pain may not have been due to the use of bisphosphonates, but were at least in part due to the natural course of FD. In conclusion, our data from this retrospective study suggest a beneficial and safe outcome of long-term bisphosphonate therapy in the majority of patients with PFD, although response to therapy was limited in MAS patients by their higher skeletal disease burden. In our patients with high skeletal burden, who do demonstrate a complete response to treatment, maximum response is observed with few exceptions after 1 year of treatment. In the population studied, the only identified prognostic factor that influenced outcome of bisphosphonate therapy was a high SBS.

We believe our findings carry significant clinical implications, because they justify an attempt to treat patients with the more severe forms of FD with bisphosphonates, particularly in view of the demonstrated safety of the strictly monitored long-term administration of these agents and the as-yet-scarce evidence for the efficacy and safety of alternative therapeutic options such as denosumab or oral tocilizumab. Which bisphosphonate should be used, at which dose, at which dosing interval, and for which duration of treatment remains to be established. Whether bisphosphonates have also an antinociceptive effect independently of their antiresorptive effect in FD certainly warrants further investigation. Consensus over these issues should be reached in the design of future large-enough multicenter studies, conducted for long enough, in order to definitively establish the position of bisphosphonates in the armamentarium of therapeutic options used in the treatment of the ubiquitous skeletal disorder of FD.

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