Fibrous dysplasia

Majoor, B.C.J.

Chapter 11

Denosumab in bisphosphonate-refractory fibrous dysplasia: a case series

B.C.J. Majoor, S.E. Papapoulos, M. Fiocco, P.D.S. Dijkstra,
N.A.T. Hamdy, N.M. Appelman-Dijkstra

Submitted

ABSTRACT

Fibrous dysplasia (FD) is a rare bone disorder due to an activating mutation of the *GNAS*-gene. The effectiveness of denosumab, a monoclonal antibody to RANKL has been recently reported in case studies of FD. We present a case series of 12 patients (9 female), with FD treated with denosumab for at least a year at the Leiden Center for Bone Quality between May 2013 and May 2016. All patients had been previously treated with bisphosphonates at high cumulative doses for a mean of 8.8 years. One patient had monostotic craniofacial FD, 7 polyostotic FD and 4 McCune-Albright syndrome, 2 with growth hormone excess. Median Skeletal Burden Score was 20.8 (range 0.3–64.7). Denosumab was administered at a dose of 60 mg 3–6 monthly for a median of 14.5months (range 13–29M) on the basis of increased bone turnover markers (BTM) and pain. At baseline, mean±SD serum ALP was 226 ± 152 U/L, P1NP 369 ± 385 ng/mL and CTX 393 ± 257 ng/mL. Patients receiving denosumab at 3-monthly intervals demonstrated more significant decreases in BTM at 6 months in the 3 monthly compared to 6 monthly schedules of denosumab: ALP ($p = 0.007$) and P1NP ($p = 0.025$) but not CTX (NS). BTM normalized in 8 of the 12 treated patients after a median time of 4.7 months (range 2.1–24.0), 5 of whom had not reached normalisation of BTM after long-term treatment with bisphosphonates. Denosumab was well tolerated and no side effects were reported, particularly no hypocalcaemia, for the duration of treatment. Our data show that denosumab at a dose of 60 mg three-monthly is effective in significantly decreasing BTM and pain and is well-tolerated and safe in patients with severe FD, representing a promising therapeutic option in those refractory to treatment with bisphosphonates. Longer-term studies in larger number of patients are warranted to confirm these findings.

INTRODUCTION

Fibrous dysplasia is a rare bone disorder characterized by replacement of bone by highly vascularized fibrous tissue in one (monostotic) or more bones (polyostotic) that may be associated with significant skeletal morbidity.[1,2] The disorder is due to activating mutations of the *GNAS*-gene leading to overproduction of cyclic AMP and abnormal cellular responses, such as increased production of the bone resorbing factors IL-6 and RANKL.[3-5] Broader distribution of the *GNAS*-mutation may be associated with extraskeletal manifestations, particularly endocrine glands, such as endocrinopathies in the McCune-Albright Syndrome (MAS) and intramuscular myxomas in Mazabraud's syndrome.[6]

Although there is as yet no approved medical treatment for fibrous dysplasia, several studies have reported clinical and biochemical improvement in patients treated with variable bisphosphonate regimens.[7-14] However, response to bisphosphonates may be incomplete and inadequate in decreasing pain symptoms, particularly in patients with polyostotic disease and high skeletal burden.[12,13] Recent case reports suggest successful treatment of patients with fibrous dysplasia with the RANKL inhibitor, denosumab.[15-18] We have treated bisphosphonate-refractory patients with denosumab and here we describe the clinical and biochemical outcomes of 12 consecutively treated patients with this agent.

PATIENTS AND METHODS

Patients

Included in this retrospective study were adult patients with fibrous dysplasia attending the Outpatient Clinic of the Center for Bone Quality of the Leiden University Medical Center (LUMC) who fulfilled the following criteria: a. Previous treatment with bisphosphonates with incomplete biochemical and/or clinical responses defined as failure to achieve normal values of total serum alkaline phosphatase (ALP) activity, in the absence of liver disease, and/or of serum amino-terminal propeptide of type 1 procollagen (P1NP) levels and persistence of skeletal pain; b. To have received 3 or 6 monthly treatment with denosumab, with at least 4 administrations with this agent.

In our center, management of patients with fibrous dysplasia is conducted following a standard care trajectory that includes collection of data about type and extent of disease, extent of skeletal involvement as calculated by the skeletal burden score on

technetium-99 bone scans, screening for endocrinopathies, history of previous medical or surgical treatment and evaluation of laboratory and clinical parameters of disease activity (particularly pain) at predefined time intervals. Retrospective analysis of the collected data were approved by the Medical Ethics Committee of the LUMC and informed consent was obtained from all patients for the off label use of denosumab.

Treatment protocol

Treatment with denosumab was initially initiated at 6-monthly intervals in 6 patients, according to the regimen used in osteoporosis. As it became apparent that the biochemical response with this interval failed to sustain the initial decrease in bone turnover markers, the interval was reduced to 3 monthly administration of denosumab. All selected patients received subcutaneous injections of denosumab 60 mg every 3 or 6 months and daily calcium and vitamin D supplements. The primary outcomes of treatment were normalization of biochemical markers of bone turnover and reduction in skeletal pain. Patients were seen in the clinic every 3 months during which blood samples were collected for evaluation of bone and mineral metabolism and data on change in pain and potential adverse effects of treatment were obtained.

Radiological and biochemical investigations

The extent of bone involvement was determined by skeletal scintigraphy using the validated skeletal burden score (SBS).[19] Non-fasting blood samples were collected from all patients and measured for calcium, albumin, phosphate, creatinine and γ-GT by semiautomated techniques. Alkaline phosphatase was measured by a fully automated P800 modulator system (Roche BV, Woerden, The Netherlands). Parathyroid hormone (PTH) and 25-OH vitamin D (25-OHD) were measured using the Immulite 2500 assay (Siemens Diagnostics, Breda, The Netherlands) and the LIAISON® 25-OH Vitamin D TOTAL assay (DiaSorin S.A./N.V., Brussels, Belgium), respectively. P1NP and β C-terminal telopeptide of type 1 collagen (CTX) were determined by the E-170 system (Roche BV, Woerden, Holland). The C-terminal of Fibroblast Growth Factor 23 (FGF-23) (Immutopics, San Clemente, CA, USA) was measured after short storage at -20°C prior to analysis using the BioTek ELx50 Washer (BioTek, Bad Friedrichshall, Germany). All analyses were performed according to the manufacturer's protocol.

Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 23.0 (SPSS, Inc., Chicago, IL, USA). Unless otherwise stated, results are presented as median (range or

IQ), or as a percentage in case of categorical data. A linear mixed model was used to assess the subtypes of FD and dose intervals as attributive factors for the response to treatment with denosumab over time. A paired sample t-test was used to compare bone markers before and after treatment.

RESULTS

Twelve patients (9 women) who received at least 4 injections of denosumab (range 4 to 9) with a median follow-up of 18 months (range 14–30) were studied (Table 11.1). Seven patients had polyostotic fibrous dysplasia, 4 had MAS and one had severe monostotic craniofacial disease. All were previously treated with bisphosphonates predominantly olpadronate for a median period of 8.7 years (range 0.7–22.1) and their median SBS was 20.8 (0.3–64.7). Previous treatment with bisphosphonates had led to temporary normalisation of ALP in 3 patients (33%), temporary normalisation of P1NP in 3 patients (33%) and temporary normalisation of CTX in all patients. Serum values of biochemical markers of bone turnover (BTM) varied markedly among patients (see Table 11.1). At time of first denosumab initiation serum ALP activity was increased in 11/12 patients (median 191 U/L, range 75–538 U/L), serum P1NP in 12/12 patients (median 241 ng/ml, range 73–1235 ng/ml) and serum CTX in 3/12 patients (median 375 ng/ml, range 114–999 ng/ml). CTX values should be interpreted with caution because blood was obtained in the non-fasting state that can affect measured values of CTX, however, blood samples were always taken in the morning and therefore comparable to one another. Median time between the last bisphosphonate treatment and first denosumab injection was 4.0 months (range 0–103 months).

Serum calcium, adjusted for albumin, phosphate, creatinine and 25-OHD vitamin D concentrations and plasma PTH levels were within their respective reference ranges in all studied patients and despite absence of hypophosphatemia, plasma FGF-23 levels were elevated in 9/12 patients and correlated with the Skeletal Burden Score

Biochemical response to treatment

Treatment with denosumab was initially administered at 6 monthly intervals in six patients, which was not sufficient to retain serum levels of BTM below baseline values. For example, in 6 patients with 6 monthly intervals serum ALP activity, although significantly decreased at 3 months after a singe denosumab injection, was only 13% lower compared to the basal values after 6 months, while this was 50.8% lower in 6

Table 11.1 Patient characteristics

Patient ID	Gender/ age at start denosumab	Type of fibrous dysplasia	Skeletal Burden Score	Average FGF-23	Duration & cumulative dose of bisphosphonates	Follow-up (months)	Denosumab scheme	Bone turnover markers prior to denosumab treatment
1	F/36	PFD	16.70	133.00	1.7 yrs/ 1528 mg	14	60 mg sc/3 mo	ALP 183; P1NP 290; CTX 347
2	F/33	PFD	24.89	160.00	11.84 yrs/ 2314 mg	26	60 mg sc/3 mo	ALP 183; P1NP 290; CTX 347
3	M/52	PFD	24.96	133.00	9.52 yrs/ 24 mg	12	60 mg sc/3 mo	ALP 330; P1NP 354; CTX 548
4	F/50	MAS	64.69	273.50	8.9 yrs/ 4370 mg	20	60 mg sc/3 mo	ALP 503; P1NP 812; CTX 999
5	F41	MAS	44.02	161.40	22.1 yrs/ 2204 mg	11	60 mg sc/6 mo	ALP 161; P1NP 198; CTX 333
6	M/33	MAS	31.27	173	11.8 yrs/ 3305 mg	12	60 mg sc/3 mo	ALP 144; P1NP 124; CTX 604
7	F/46	MAS	38.70	162.00	18.5 yrs/ 6336 mg	9	60 mg sc/6 mo	ALP 203; P1NP 208; CTX 148
8	F/41	PFD	0.26	116	2.47 yrs/ 316 0mg	19	60 mg sc/6 mo	ALP 75; P1NP 73; CTX 241
9	F/35	PFD	0.58	71	4.7 yrs/ 570 mg	14	60 mg sc/6 mo	ALP 94; P1NP 80; CTX 114
10	F/68	PFD	5.60	159	0.7 yrs/ 600 mg	11	60 mg sc/3 mo	ALP 198; P1NP 864; CTX 403
11	F/28	MFD	13.80	202	8.6 yrs/ 4740 mg	15	60 mg sc/3 mo	ALP 135; P1NP 109; CTX 166
12	M/28	PFD	7.77	115	5.0 yrs/840 mg	11	60 mg sc/6 mo	ALP 275; P1NP 273; CTX 443

patients who received injections of denosumab at 3 monthly intervals. Changes in serum P1NP levels were very similar (Fig. 11.1). Linear mixed model analysis (Table 11.2 and Fig. 11.1) revealed a significant difference over time between patients who received denosumab at 3-monthly intervals compared to those who received the agent a 6-monthly intervals for ALP ($p = 0.007$) and P1NP ($p = 0.025$), but not for CTX ($p = 0.162$). There was no significant difference in biochemical response between subtypes of fibrous dysplasia. These results suggest that the denosumab regimen used in the treatment of osteoporosis is inadequate for the treatment of fibrous dysplasia and all patients were subsequently treated with a 3 monthly schedule of 60 mg denosumab. A single patient with a still modest biochemical response after 4 denosumab injections of 60 mg was further treated with 120 mg every 3 months.

Outcomes of denosumab treatment

Compared to pretreatment ALP levels, mean serum ALP levels after 12 months were significantly reduced from 237 ± 150 IU/L to 104 ± 59 IU/L ($p < 0.01$), reflecting a 51.5 ± 16.2% decrease in this bone turnover marker. P1NP also decreased, albeit not statistically significant, from 385.0 ± 76 ng/ml to 233.8 ± 505.4 ng/ml ($p = 0.146$). CTX decreased 23.5%, from 412 ± 251 to 315 ± 318 pg/ml, which was not significant ($p = 0.403$). At the end of the study at a mean of 18 ± 5 months after the start of treatment, serum ALP values were significantly decreased by 48% to 98 ± 50.3 IU/l ($p < 0.01$). P1NP levels similarly remained lower with a 48% decrease at 213.7 ± 35.7 ng/ml, albeit not significant ($p = 0.07$).

Of the 11 patients with increased serum ALP activity at baseline, values normalized in 9 (82%) whereas serum P1NP levels which were increased in all patients, reached the normal range in 9/12 (75%) at the end of follow up.

Biochemical response to treatment generally stabilized after the second injection of denosumab, with no further decrease observed at subsequent injections at (Fig. 11.1). This is illustrated in the patient shown in Fig. 11.2 in whom serum ALP activity decreased from 538 IU/l reaching a plateau of still inadequately high ALP at 321 IU/l after 18 months of treatment with denosumab given at 6-monthly and later 3-monthly intervals. Continuation of treatment at a dose of 120 mg denosumab 3-monthly resulted in a further decrease of serum ALP activity within the normal lab range to 100 IU/l.

A number of factors known to affect response to bisphosphonates did not appear to affect response to denosumab. Serum P1NP levels decreased by 66.5% in patients

Table 11.2A Results linear mixed model: polyostotic vs McCune-Albright

BTM	Subtype	Time	Mean	95% confidence interval	Sig.
ALP	Polyostotic	T1	228.5	130–327	0.083
		T2	172.6	73–272	
		T3	138.0	40–236	
	McCune-Albright	T1	252.8	113–392	
		T2	95.7	-48–237	
		T3	167.8	28–307	
P1NP	Polyostotic	T1	409.8	138–682	0.110
		T2	380.0	103–657	
		T3	230.6	-46–507	
	McCune-Albright	T1	335.5	-50–721	
		T2	42.0	-343–427	
		T3	223.0	-162–608	
CTX	Polyostotic	T1	357	143–572	0.010
		T2	511	287–736	
		T3	292	67–516	
	McCune-Albright	T1	521	217–825	
		T2	129	-206–464	
		T3	603	300–907	

Table 11.2B Results linear mixed model: 3-monthly vs 6-monthly doses

BTM	Dosis	Time	Mean	95% confidence interval	Sig.
ALP	3-monthly	T1	270.7	163–378	0.007
		T2	173.5	66–281	
		T3	118.5	11–226	
	6-monthly	T1	202.5	95–310	
		T2	116.7	6–228	
		T3	177.3	70–285	
P1NP	3-monthly	T1	450.3	144–757	0.025
		T2	319.7	13–626	
		T3	91.4	-222–404	
	6-monthly	T1	319.7	13–626	
		T2	175.1	-149–499	
		T3	342.7	36–649	
CTX	3-monthly	T1	484	238–731	0.162
		T2	555	308–801	
		T3	375	106–643	
	6-monthly	T1	339	93–586	
		T2	129	-170–428	
		T3	431	185–678	

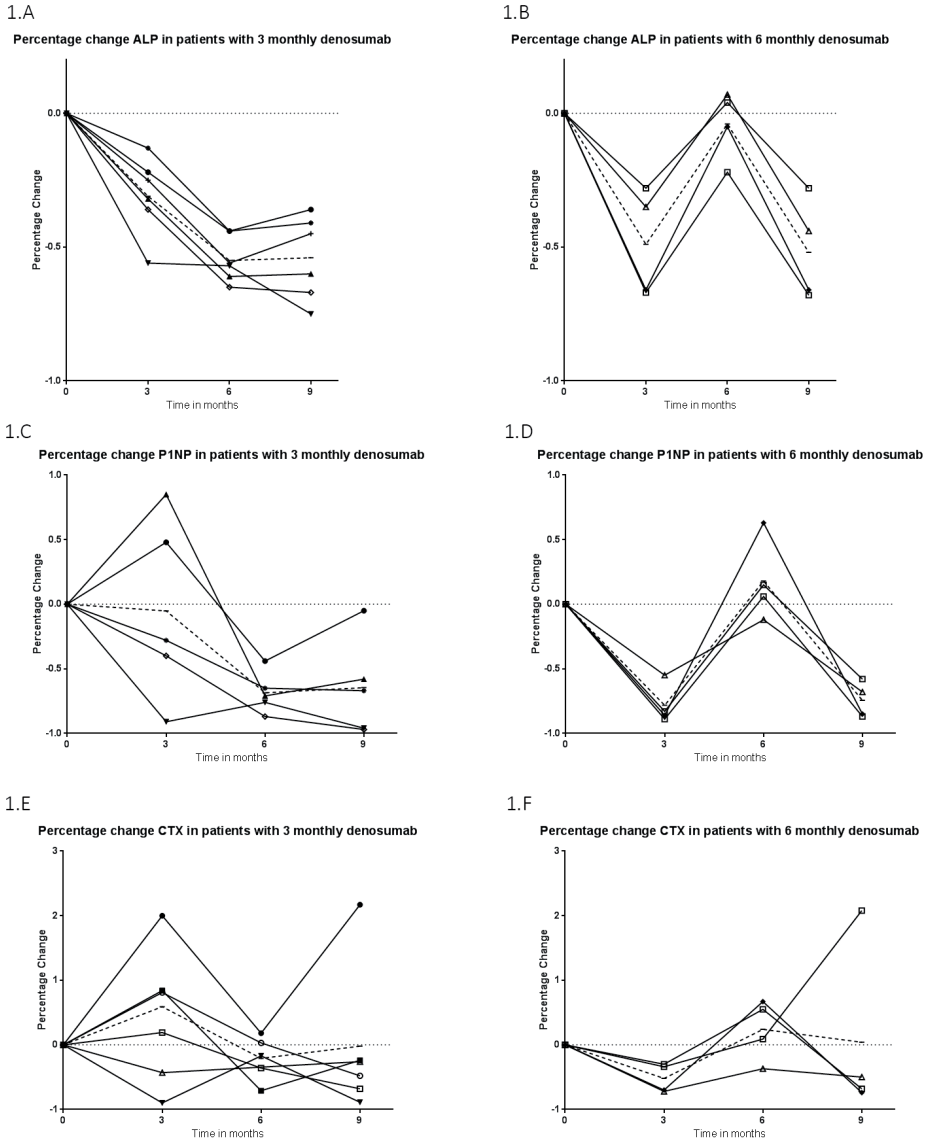
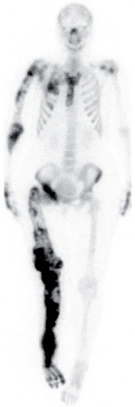
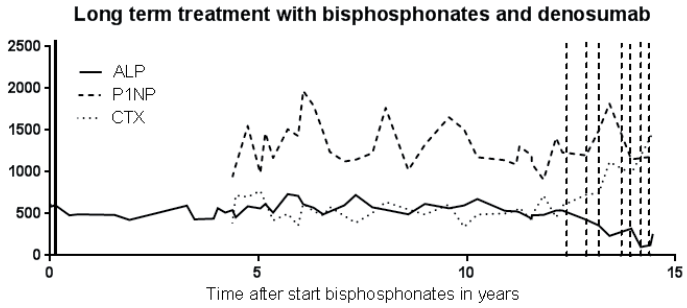


Fig. 11.1 Graphs showing the percentage change of ALP, P1NP and CTX after 9 months of treatment with 3-monthly or 6-mothly doses of denosumab. The dotted line indicates mean percentage change. The graphs clearly show an increase in ALP and P1NP levels after 3 months in the group with 6-monthly treatment with bone turnover returning to pre-treatment levels (ALP) or even higher (P1NP). The graphs regarding the group with 3-monthly doses however, show an increase decline in ALP and P1NP levels with stabilization after 6 months. Graphs on CTX do not show a clear pattern, which might be due to the fact that blood samples in our patients were taken in a non-fasting state, which might decrease the reliability of the samples. Another explanation for this unclear pattern of CTX levels might be based on the hypothesis that responses on CTX are generally more acute compared to those of P1NP and ALP, however, this remains to be shown.





2A 2B

Fig. 11.2 One of our patients (nr. 2, Fig. 11.2), diagnosed with polyostotic FD after a pathologic fracture of the right femur at the age of 3 years, has had denosumab injections for almost 3 years after she had previously been treated with bisphosphonates for over 12 years, mainly with olpadronate, orally (cumulative dose 146,000 mg) and IV (cumulative dose 68 mg) and twice with alendronate IV 5mg. Her femur was severely affected resulting in reduced mobility and pain, not only form her femur but due to the FD changes in the right side of the body with involvement of the complete upper and lower right extremity, several ribs, the sternum, the pelvis and in a lesser form the left upper extremity (2A). Although bisphosphonate treatment initially decreased ALP serum levels (2B) and subsequently resulted in a decrease in pain; bone turnover remained high during the treatment with bisphosphonates. Due to consistent high bone turnover in combination with increasing pain levels, she was started on 60mg denosumab injections 6-monthly. After 6 months but she had a notable decrease in pain, an increase in mobility and P1NP and ALP had both decreased, although CTX levels had increased, probably as a result of a rebound effect, and after 13 months P1NP levels had also increased. Due to an additional increase in pain, she was switched to 60 mg denosumab 3-monthly and later to 120 mg denosumab 3-monthly doses. P1NP levels dropped to baseline levels prior to denosumab and ALP even normalised two years after start of denosumab treatment. The decrease in bone turnover went hand in hand with a decrease in pain symptoms and increased mobility. During treatment she had muscle pains of the lower legs, possibly as a side effect of denosumab. Phosphate, calcium and PTH levels remained normal during treatment.

with skeletal bone score above the median value and by 46.5% in those with skeletal bone score below the median value. Similarly, serum P1NP levels decreased by 60.8% in patients with serum FGF23 levels above the median value and by 51.2% in those with levels below the median value.

Clinical response to treatment

Ten patients of the 12 patients reported significant improvement of pain. In some patients the response was remarkable, occurring early after the first injection with denosumab and two patients remained pain-free for the duration of the follow up period. In one patient with severe disease of the right lower limb, in addition to the

reported reduction in pain, local tenderness and skin temperature over the affected femur were also reduced. One patient reported no change in pain complaints while another experienced a transient increase in pain after initiation of treatment.

Safety aspects of treatment with denosumab

In two patients with MAS, treatment was associated with a mild decrease in serum phosphate concentrations to nadir values of 0.63 mmol/l (normal range: 0.8–1.5) while no decrease in serum calcium concentrations was observed but intact plasma PTH levels did increase to 11.2 and 20.7 pmol/l, respectively. Increases in the dose of vitamin D supplementation corrected these biochemical abnormalities. Except for the transient increase in bone pain in the patient described above, no other adverse events were observed in any of the patients and there was no incidence of symptomatic or asymptomatic hypocalcaemia.

DISCUSSION

Our findings from this retrospective study in 12 patients with mostly severe polyostotic fibrous dysplasia suggest that treatment with denosumab is effective, safe and well tolerated, and may provide an attractive option in patients who demonstrate resistance to treatment with bisphosphonates. Six-monthly intervals of 60 mg denosumab were not sufficient to sustain the initial effect on bone turnover markers, whereas bone turnover makers remained low in 3-monthly intervals of denosumab injections.

While there is currently no approved treatment of the disease, various regimens of different bisphosphonates are commonly used in the management of patients with fibrous dysplasia with skeletal complaints and/or high rates of bone turnover. Several open studies, mostly with pamidronate and olpadronate, have demonstrated reduction of bone turnover and bone pain in adults and children with fibrous dysplasia.[7,9-12,14,20] Some studies also reported beneficial radiological changes.[21-23] The only RCT study with daily oral alendronate in 6 monthly cycles for 2 years failed to demonstrate a significant beneficial effect compared to placebo.[13] However, in this study ALP failed to decrease, perhaps suggesting that higher doses or shorter interval schedules may have been required.[12] Despite success of bisphosphonate treatment, in some patients symptoms persist and bone turnover remains high necessitating alternative treatment options. The finding of upregulation of RANKL in skeletal lesions of patients with fibrous dysplasia provided the rationale for exploring the use of the

Table 11.3 Previous studies into denosumab treatment in fibrous dysplasia

Study	Number	Duration & cumulative dose of bisphosphonates	Mean follow-up (months)	Dose denosumab	Markers	Clinical outcome
Ganda and Seibel (2013)	2	8 years/45 mg zoledronic acid	8	60 mg	P1NP; uDPD; Ca; PO4; PTH	BTM's normalized in 1 month (P1NP 164* -> 15; uDPD 11.2 -> 3.5). Hip pain from 7/10 to 4/10.
		2.5 years/20 mg zoledronic acid	20	60 mg		Adverse event: asymptomatic hypocalcaemia and increased again after +- 3 months after injections.
Boyce et al. (2012)	1	1 year/unknown pamidronate	7	Start 1 mg/kg monthly; 0.25 mg/kg 3-monthly	P1NP; CTX; Ca; Phos;	BTM's normalized in 5 weeks (b-ALP 452->65; uDPD 15.3 -> 6.1). Pain not described. Adverse event: asymptomatic hypocalcaemia.
Eller-Vainicher et al. (2016)	1	> 9 years/81 mg pamidronate	20	60 mg	Osteocalcin, ALP (start 75), CTX	Dramatic reduction in BTM's (CTX 2000 dropped till 250; P1NP 1300 dropped till 100), pain -> no painkillers) and arrest tumor growth. Adverse event: hypophosphatemia and secondary hyperparathyroidism. Dramatic rebound in BTM's and severe hypercalcaemia.
Benhamou et al. (2014)	1	> 10 years/3600 mg pamidronate	35	60 mg	CTX	Pain response after a few hours and after 4 weeks normalization of BTM's (osteocalcin 55 to 10; ALP 75 to 42; BTX 1190 to 100). After 3 months accumulation of pain until next administration.

RANKL inhibitor denosumab in the management of severely affected patients with inadequate responses to bisphosphonates.[4]

Reports of 5 patients described early clinical improvements and dramatic reductions in biochemical markers of bone turnover with denosumab.[15-18] Different treatment schedules were used ranging from 120 mg once every 6 months to 60 mg one-monthly (Table 11.3).

We addressed the issue of denosumab dosing in our study and we showed that the dose of denosumab as used in the treatment of osteoporosis (60 mg once every 6 months) is insufficient for the treatment of patients with fibrous dysplasia. In contrast, 60 mg 3-monthly led to a significant decrease in the levels of bone turnover markers by more than 50% of baseline values leading to their normalization in a substantial number of patients, in contrast to failure of bisphosphonates to do so in these patients, some even after long term use and high cumulative doses. The relationship between baseline and final values of serum ALP activity indicated further that some patients, particularly those with extensive disease, may require higher doses in order to normalize bone turnover as illustrated in the patient who required 120 mg once every 3 months to achieve normalisation of bone turnover markers. It should be mentioned that in this patient 12 years of bisphosphonate treatment failed not only to normalize bone turnover markers but the lowest level ever achieved was still 4.5 times the upper limit of the reference range. Important for clinical practice is the observation that the decrease in biochemical markers of bone turnover reached usually their nadir values within the first 6 months of treatment with denosumab and, thus, a decision about changing the dose regimen can be made early in the course of treatment. Patients with high SBS scores responded to the 60 mg 3 monthly as well therefore we would suggest this as a starting regiment, which can be tailored to the individual patient.

Remarkable was the clinical response with reduction of bone pain very early after the start of treatment in all but one of our patients, as also reported in 4/5 previously described patients.[15-18] With the 3-monthly treatment regimen, the effect on pain persisted for the whole observation period up to 24 months. Our protocol with blood sampling every 3 months does not allow any conclusion about an association between the decrease of bone resorption and the improvement of bone symptoms. Earlier, pharmacodynamic studies of denosumab have shown dramatic reductions of serum CTX within days after a subcutaneous injection and there is no reason to believe that the response would be different in patients with fibrous dysplasia.[24,25] This remains, however, to be shown.

The clinical profile of our patients is similar to that described in the literature as most the likely to show an inadequate response to bisphosphonates because of severity of disease; 11 patients had polyostotic disease, 4 of whom had MAS, FGF23 was increased in 7/12 patients and the majority had a high skeletal burden score.[19,26] The latter has been recently identified by our group as the only prognostic factor influencing the outcome of bisphosphonate therapy.[12] Our results from this study demonstrated however that none of these factors influenced the response of the patients to denosumab, including the skeletal burden score.

We believe that the data presented in this case-series together with those of previous case reports provide sufficient rationale for the design of a controlled study on the efficacy and tolerability of denosumab in patients with severe fibrous dysplasia and inadequate response to bisphosphonates for whom no alternative treatment is currently available. Treatment was well tolerated and except for the non-symptomatic changes in phosphate and PTH which could be easily addressed with increasing vitamin D supplements.

An important question that this study does not address is the duration of the therapy and the management of patients once a clinical and biochemical remission is achieved. It is well known that the action of denosumab, in contrast to that of the bisphosphonates, is quickly reversible following discontinuation of treatment with transient increases in BTM above pretreatment levels, described also as "rebound phenomenon" that is thought to be due to a rapid, synchronous upregulation of osteoclastogenesis as also reported in the treatment of a child with fibrous dysplasia.[15,27] This response is intriguing because it was recently reported that patients treated with bisphosphonates followed by denosumab do not show a rebound of BTM following discontinuation of the latter.[28] Before additional data from a controlled study become available, physicians using denosumab to treat patients with fibrous dysplasia should be aware of this potential reaction to stopping denosumab treatment and emphasize treatment adherence. However the results of this study show that in certain patient groups denosumab may provide a well-tolerated alternative in patients resistant to treatment with bisphosphonates.

REFERENCES

1. Riminucci M, Fisher LW, Shenker A, Spiegel AM, Bianco P, Gehron Robey P. Fibrous dysplasia of bone in the McCune-Albright syndrome: abnormalities in bone formation. *The American journal of pathology.* Dec 1997;151(6):1587-1600.
2. Michael T. Collins MR, and Paolo Bianco. Fibrous Dysplasia. In: Rosen CJ, ed. *Primer on the metabolic bone diseases and disorders of mineral metabolism.* . Vol Eight: John Wiley & Sons, Inc; 2013.
3. Yamamoto T, Ozono K, Kasayama S, et al. Increased IL-6-production by cells isolated from the fibrous bone dysplasia tissues in patients with McCune-Albright syndrome. *The Journal of clinical investigation.* Jul 1 1996;98(1):30-35.
4. Piersanti S, Remoli C, Saggio I, et al. Transfer, analysis, and reversion of the fibrous dysplasia cellular phenotype in human skeletal progenitors. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* May 2010;25(5):1103-1116.
5. Weinstein LS, Shenker A, Gejman PV, Merino MJ, Friedman E, Spiegel AM. Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. *The New England journal of medicine.* Dec 12 1991;325(24):1688-1695.
6. Collins MT, Singer FR, Eugster E. McCune-Albright syndrome and the extraskeletal manifestations of fibrous dysplasia. *Orphanet journal of rare diseases.* May 24 2012;7 Suppl 1:S4.
7. Chapurlat RD, Delmas PD, Liens D, Meunier PJ. Long-term effects of intravenous pamidronate in fibrous dysplasia of bone. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* Oct 1997;12(10):1746-1752.
8. Lane JM, Khan SN, O'Connor WJ, et al. Bisphosphonate therapy in fibrous dysplasia. *Clinical orthopaedics and related research.* Jan 2001(382):6-12.
9. Lala R, Matarazzo P, Andreo M, et al. Bisphosphonate treatment of bone fibrous dysplasia in McCune-Albright syndrome. *Journal of pediatric endocrinology & metabolism : JPEM.* May 2006;19 Suppl 2:583-593.
10. Parisi MS, Oliveri MB, Mautalen CA. Bone mineral density response to long-term bisphosphonate therapy in fibrous dysplasia. *Journal of clinical densitometry : the official journal of the International Society for Clinical Densitometry.* Summer 2001;4(2):167-172.
11. Plotkin H, Rauch F, Zeitlin L, Munns C, Travers R, Glorieux FH. Effect of pamidronate treatment in children with polyostotic fibrous dysplasia of bone. *The Journal of clinical endocrinology and metabolism.* Oct 2003;88(10):4569-4575.
12. Majoor BC, Appelman-Dijkstra NM, Fiocco M, van de Sande MA, Dijkstra PS, Hamdy NA. Outcome of Long-Term Bisphosphonate Therapy in McCune-Albright Syndrome and Polyostotic Fibrous Dysplasia. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* Feb 2017;32(2):264-276.
13. Boyce AM, Kelly MH, Brillante BA, et al. A randomized, double blind, placebo-controlled trial of alendronate treatment for fibrous dysplasia of bone. *The Journal of clinical endocrinology and metabolism.* Nov 2014;99(11):4133-4140.
14. Liens D, Delmas PD, Meunier PJ. Long-term effects of intravenous pamidronate in fibrous dysplasia of bone. *Lancet.* Apr 16 1994;343(8903):953-954.
15. Boyce AM, Chong WH, Yao J, et al. Denosumab treatment for fibrous dysplasia. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* Jul 2012;27(7):1462-1470.
16. Benhamou J, Gensburger D, Chapurlat R. Transient improvement of severe pain from fibrous dysplasia of bone with denosumab treatment. *Joint, bone, spine : revue du rhumatisme.* Dec 2014;81(6):549-550.
17. Ganda K, Seibel MJ. Rapid biochemical response to denosumab in fibrous dysplasia of bone: report of two cases. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* Feb 2014;25(2):777-782.

18. Eller-Vainicher C, Rossi DS, Guglielmi G, et al. Prompt clinical and biochemical response to denosumab in a young adult patient with craniofacial fibrous dysplasia. *Clinical cases in mineral and bone metabolism: the official journal of the Italian Society of Osteoporosis, Mineral Metabolism, and Skeletal Diseases.* Sep-Dec 2016;13(3):253-256.
19. Collins MT, Kushner H, Reynolds JC, et al. An instrument to measure skeletal burden and predict functional outcome in fibrous dysplasia of bone. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* Feb 2005;20(2):219-226.
20. Parisi MS, Oliveri B, Mautalen CA. Effect of intravenous pamidronate on bone markers and local bone mineral density in fibrous dysplasia. *Bone.* Oct 2003;33(4):582-588.
21. Chapurlat RD, Hugueny P, Delmas PD, Meunier PJ. Treatment of fibrous dysplasia of bone with intravenous pamidronate: long-term effectiveness and evaluation of predictors of response to treatment. *Bone.* Jul 2004;35(1):235-242.
22. Lala R, Matarazzo P, Bertelloni S, Buzi F, Rigon F, de Sanctis C. Pamidronate treatment of bone fibrous dysplasia in nine children with McCune-Albright syndrome. *Acta paediatrica.* Feb 2000;89(2):188-193.
23. Kos M, Luczak K, Godzinski J, Klempous J. Treatment of monostotic fibrous dysplasia with pamidronate. *Journal of cranio-maxillo-facial surgery : official publication of the European Association for Cranio-Maxillo-Facial Surgery.* Feb 2004;32(1):10-15.
24. Eastell R, Christiansen C, Grauer A, et al. Effects of denosumab on bone turnover markers in postmenopausal osteoporosis. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* Mar 2011;26(3):530-537.
25. Amgen, Inc. Prolia (denosumab) prescribing information. 2010 updated 2014.
26. Boyce AM, Bhattacharyya N, Collins MT. Fibrous dysplasia and fibroblast growth factor-23 regulation. *Current osteoporosis reports.* Jun 2013;11(2):65-71.
27. Anastasilakis AD, Yavropoulou MP, Makras P, et al. Increased osteoclastogenesis in patients with vertebral fractures following discontinuation of denosumab treatment. *European journal of endocrinology / European Federation of Endocrine Societies.* Jun 2017;176(6):677-683.
28. Tsourdi E, Langdahl B, Cohen-Solal M, et al. Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS. *Bone.* Dec 2017;105:11-17.


FIBREUZE DYSPLASIE
12
jaar