

Prompt clinical and biochemical response to Denosumab in a young adult patient with craniofacial fibrous dysplasia

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Summary

Background. We report on the clinical and biochemical outcomes in 20-year-old male suffering from active craniofacial monostotic fibrous dysplasia (MFD) of the left mandible treated with the RANK-L inhibitor, Denosumab, following unsatisfactory responses to prior long-term bisphosphonates therapy. **Results:** The patient had been treated over 9 years with pamidronate (cumulative dose of 810 mg) with incomplete control of pain. Following initiation of Denosumab 60 mg subcutaneously, bone pain and bone turnover markers (osteocalcin, total and bone alkaline phosphatase and carboxy-terminal cross-linking telopeptide of type I collagen) were monitored over a 27 months period. Few hours after the first administration, the patient demonstrated a complete pain disappearance and after 4 weeks bone turnover markers fell within the normal range. Three months after Denosumab initiation the patient reported a pain reactivation that required a second administration, which again led to the pain disappearance. Subsequently, Denosumab was administered according to the pain reappearance and the injection was always followed by complete pain relief. However, a gradual shortening of

the pain-free interval between administrations was observed, ranging from 90 days to 75 days. All bone turnover markers stayed in the lower half of the normal range, even at the moment of pain reappearance, suggesting that the effect of Denosumab on pain depends on mechanisms other than bone resorption suppression. No side effects were reported by the patient during the follow-up. **Conclusion.** Denosumab appears to be effective in reducing bone turnover and bone pain in adult patients with active MFD.

KEY WORDS: fibrous dysplasia; denosumab; bisphosphonates.

Introduction

Fibrous dysplasia (FD) is a group of skeletal disorders characterized by a non-malignant condition in which normal bone and marrow are replaced by immature woven bone and dense fibrotic stroma. Patients may exhibit involvement of one (monostotic fibrous dysplasia, MFD) or multiple bones (polyostotic fibrous dysplasia, PFD) or may have McCune-Albright syndrome, characterized by PFD, café-au-lait skin macules and endocrinopathies (1). Some of these disorders, such as the McCune-Albright syndrome, are caused by somatic activating mutations in the α -subunit of the stimulatory G-protein (Gsa) encoded by the GNAS gene, while other forms, such as cranio-facial dysplasia with mandibular involvement, also known as cherubism, are caused by the heterozygous mutations of SH3NP2 gene (2, 3).

Craniofacial MFD is a common type of FD and the zygomatic-maxillary complex is a frequently involved region (1). Patients with FD may present with bone deformity, bone pain and/or neurological compromise and the bisphosphonates have been proposed for reducing pain and lesion growth (4). However, the available studies demonstrated variable results on the efficacy of bisphosphonates in this disease and no guidelines are available regarding how to address the therapy of choice in FD.

Denosumab (Dmab), a fully-humanized monoclonal antibody to the receptor activator of nuclear factor kappa-B ligand (RANKL) has been approved for the treatment of osteoporosis and bone metastases from solid tumours in adults (5) and its use in bone diseases other than osteoporosis and bone metastases is off-label. However, in FD, Dmab is of great interest since in vitro studies suggested that in FD Gsa mutation dramatically upregulate RANKL expression (6).

Up to now, Dmab treatment has been successfully used in few patients with PFD, (7-10) but no data are available on craniofacial MFD patients. We describe the first young adult patient with craniofacial MFD, treated with periodic Dmab administration during a 27 month follow-up.

Methods and results

A 20-years-old boy was referred to our Metabolic Bone Diseases Outpatients Clinic in July 2013 for a craniofacial MFD, diagnosed

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during childhood. The patient had been firstly admitted at the Maxillofacial Surgery Department at the age of 10, for a left mandibular deformity associated with severe pain resistant to common analgesic. Radiograph, computed tomography (Figure 1) and bone scans confirmed the presence of craniofacial MFD involving the left mandible. There were no other skeletal deformities, no café-au-lait hyperpigmentation and no features suggesting endocrine diseases. At diagnosis the patient was 140 cm tall, his body weight was 40 Kg and all the routine and hormonal evaluations and calcium-phosphate metabolism were normal. Therefore, he was treated with a fixed dose of 90-mg pamidronate/year (2.25-1.5 mg/kg/year, 30 mg every three months) with an incomplete reduction of pain scores.

In July 2013, at the age of 20, the patient was referred to our outpatient Clinic for Metabolic Bone Diseases. The biochemical tests showed a vitamin D deficiency with normal serum albumin-adjusted calcium (11), phosphate, PTH and creatinine levels. Serum carboxy-terminal cross-linking telopeptide of type I collagen levels (β -CTX, measured by chemiluminescence, Liason XL, Diasorin Italy) were in the upper part of the normal range, while osteocalcin levels (measured by chemiluminescence, Diasorin Italy) and total and bone alkaline phosphatase activity were normal (Table 1). A Dual energy X-ray absorptiometry scans (Hologic Discovery, Bedford MA, USA) at lumbar spine (LS, precision 1.0%) and femoral neck (FN, precision 1.8%) showed that spinal bone mineral density (BMD) was low (LS Z-score -1.6, FN Z-score -0.8). The patient calcium intake from dairy products evaluated at baseline was about 900 mg/day. He was supplemented with 300.000 IU of cholecalciferol once and 500 mg of calcium and 400 IU of cholecalciferol daily. At that time the pain level was evaluated 8-9/10 on an analogue scale (visual analogue scale, VAS).

We treated the patients with Dmab 60 mg subcutaneously (60mg-Dmab) after the informed consent for the off-label treatment was obtained by the patient and the treatment was permitted by the regional law. Few hours after the drug administration, a complete pain disappearance (0/10 VAS) was observed. One month after, β -CTX levels were reduced, PTH were mildly increased and hypovitaminosis D persisted. Therefore, he was supplemented with 300.000 IU of cholecalciferol. Three months after the first 60mg-Dmab dose, bone turnover markers and calcium-phosphate parameters were within the normal range. However, the patient reported an acute reappearance of the pain (8-9/10 VAS), and, therefore, a second 60mg-Dmab dose was given. Since the hypovitaminosis D was still present, a monthly supplementation with 100.000 IU of cholecalciferol was introduced and celiac disease was ruled out. As previously, few hours after the second 60mg-Dmab administration, the pain completely disappeared (0/10 VAS). Three months after the second 60mg-Dmab administration, the bone turnover and calcium-phosphate parameters were normal (Table 1). However, as the patient reported a pain reappearance (8-9/10 VAS), a third 60mg-Dmab dose was administered, with the pain disappearance after few hours (0/10 VAS).

Subsequently, Dmab was given every three months with a slight shortening of the pain-free interval between the administrations (Table 1). The patient's mother reported that after every Dmab administration, the patient had also an improvement of the craving desire and of the sense of well-being and he could restart physical activity. The calcium-phosphate parameters remained normal and BMD at both spine and femur significantly increased. The 25-hydroxy-vitamin D levels remained slightly low for some months (but above 25 ng/mL) and the markers of bone turnover were normal, with the exception of the reduced β -CTX levels (Table 1). To date, the entire duration of the treatment has been 27 months.

The computed tomography performed at the last follow-up visit



Computed Tomography (CT) appearance of the patient's mandible affected with fibrous dysplasia at the first visit.

Legend: Mandible CT - axial view - bony window. The image shows an expansive mass of the left mandible with thickened condyle (arrows), intact cortical bone and medullary space composed of ossified and non-ossified regions. In particular, hazy radiolucent lesions are associated with widened diploic space and osseous expansion in an outward direction.

showed a hyperostotic, sharply defined productive process partially obliterating the mandible canal with prevalent area of sclerosis, with a cortical bone expansion in a smooth and continuous shape. Treatment with Dmab has been well tolerated and no hypocalcemic events or other unwanted effects were observed during the treatment. The calcium intake from dairy products and the oral calcium supplementation did not vary during the follow-up.

Discussion

This case suggests that in craniofacial MFD the treatment with Dmab every three months results in a rapid and complete disappearance of pain, associated with a profound reduction of β -CTX levels. The duration of the Dmab effect, both in terms of pain relief and bone turnover suppression, was stable during the 27 months follow-up.

The finding of a successful effect of Dmab even in craniofacial MFD is consistent with previous studies, reporting the efficacy of Dmab in controlling PFD bone pain (7-9). The better biochemical and clinical response with Dmab as compared with bisphosphonates, might be explained by the fact that Dmab not only induces osteoclasts apoptosis but also affects osteoclasts recruitment from the precursor cells (12) and that Dmab directly inhibits RANKL levels, that are particularly elevated in FD.(6) However, we cannot exclude that the incomplete reduction of the pain scores during the period of pamidronate treatment was due, at least in part, to the relatively low dose used (13).

Interestingly, the bone pain relapsed in spite of the presence of suppressed bone resorption and Dmab led to pain relief notwithstanding the presence of low bone turnover. In addition, the pain relief was independent of an important reduction of the mandible

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Table 1 - Pain score, calcium metabolism parameters, bone turnover markers and bone mineral density during denosumab (Dmab) treatment.

Days	Normal Values	Day 0	Day 44	Day 89	Day 176	Day 261	Day 272	Day 336	Day 422	Day 468	Day 560	Day 651	Day 740
Pain (0/10)	0-10	8-9	0	8-9	8-9	8-9	0	8-9	8-9	0	0	0	0
Caalbadj (mg/dL)	8.4-10.2	9.5	8.6	9.0	9.9	9.7	9.4	8.8	9.1	9.4	8.9	8.8	9.3
Serum Phosphate (mg/dL)	2.7-4.4	3.4	3.0	3.1	3.0	3.0	3.1	3.8	3.3	3.2	2.8	3.1	3.2
Parathyroid hormone (pg/mL)	15-65	43.5	85.1	59.3	34.2	35.2	31.1	76.4	75.4	51.8	62.0	54	55
β-CTX (pg/mL)	140-1350	1180	119.6	160.7	145.8	152.2	89.6	113.0	94.8	85.7	80.0	93	88
ALP (U/L)	40-129	75	69	53	54	57	43	50	46	52	48	51	48
Bone ALP (U/L)	8-95.5	34.5	38.6	29.0	20.0	11.4	13.3	24.0	11.5	16.1	8.2	9.3	9.0
Osteocalcin (ng/mL)	4.6-65.4	54.8	40.1	23.3	13.1	9.2	11.8	12.7	11.4	9.1	8.7	11	9.0
25OHVitaminD (ng/mL)	30-150	22.9	17.5	17.8	33.7	26.2	48.2	37.0	24.9	28.3	42.5	35.1	41.1
Lumbar spine BMD (g/cm ²)	n.a.	0.919	-	-	-	-	-	-	-	-	1.004 ^a	-	-
Lumbar spine BMD (Z-score)	n.a.	-1.6	-	-	-	-	-	-	-	-	-0.8	-	-
Femoral Neck BMD (g/cm ²)	n.a.	0.824	-	-	-	-	-	-	-	-	0.911 ^b	-	-
Femoral Neck BMD (Z-score)	n.a.	-0.8	-	-	-	-	-	-	-	-	-0.1	-	-
	↑			↑	↑	↑		↑	↑	↑	↑	↑	↑
Dmab administered on Day	0			89	176	261		342	422	497	574	651	740

Data are available for about 25 months follow-up period. Dmab 60 mg subcutaneously was administered on day 0, day 89, day 176, day 261, day 342, day 422, day 497, day 574, day 651 and 740. Pain 0/10: evaluated by the visual analogue scale (Aitken RCB. 1969 Measurement of feelings using visual analogue scales. Proc Royal Soc Med. 62:989-993), Caalbadj: serum calcium levels, adjusted for serum albumin levels (according to the formula: Caalbadj (mg/dl)= total calcium + (4 - albumin mg/dl) x 0.8). β-CTX: serum cross-laps. ALP: Alkaline phosphatase total activity. Bone ALP: bone alkaline phosphatase. BMD: Bone mineral density. a+9.5% and b+10.5% vs day 0. n.a.: not applicable. -: not available.

lesion, as described in FD patients treated with bisphosphonates (4). This suggests that Dmab may reduce pain acting on mechanisms other than the inhibition of bone resorption, such as the indirect reduction of interleukin 6 (IL-6). Indeed, RANKL, highly expressed on dendritic cells (DCs), increases DCs survival and enhances expression of multiple activating cytokines, including IL-6, which is overexpressed in patients with FD (4, 14, 15). As compared with PFD patients treated with Dmab (7-10) our craniofacial MFD patient presented a totally relief of pain (16). This is possibly due to the minor extension of the bone lesions in craniofacial MFD in respect with PFD.

The stable duration of Dmab efficacy in our patient, in terms of both pain relief and bone turnover suppression, suggests that craniofacial MFD patients may require 60mg-Dmab administration every 3 months. However, previous studies suggested the possibility to use this drug as a "spot-therapy", only during pain reactivation, reducing the risk of frozen bone and osteonecrosis of the jaw (6-10). However, it must be observed that our patient needed to be treated with relatively high Dmab doses (i.e. 240 mg/year) to obtain the pain relief and that during the follow-up no drug holiday could be applied. Therefore, the long-term safety of this Dmab treatment schedule might be a matter of concern in these subjects (17).

Our patient showed a transient secondary hyperparathyroidism and hypovitaminosis D. The increase of PTH levels after the first Dmab administration is in keeping with data in patients with osteoporosis or FD treated with intravenous bisphosphonates or Dmab (9, 10) The persistent hypovitaminosis D could be due in part to the elevated consumption due to the hyperactivation of 1-α-hydroxylase enzyme, secondary to PTH increase. However, since 1,25(OH)₂ vitamin D is 1000 times less concentrated than 25(OH)D this mechanism could not entirely explain the persistent hypovitaminosis D. On the other hand, the persistence of hypovitaminosis D could be due to the effect of Dmab on fibroblast growth factor 23 (FGF-23) levels. Indeed, some FD patients present elevated plasma FGF-23 levels that directly down-regulate renal 1α-hydroxylase (6). Dmab may determine a FGF-23 levels decrease and a correspondent 1,25 hydroxyvitamin D increase, similarly to what has been described for pamidronate (18).

In summary, this clinical case shows that Dmab may be successfully used in young adults with craniofacial MFD. Although this drug is well tolerated and consents an ideal adherence and persistence to treatment in osteoporosis (19), we emphasize that the use of Dmab in FD is off-label. However, the present data suggest that this drug may represent a new option for the treatment of this condition.

Competing interest

The authors declare that they have no competing interests.

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