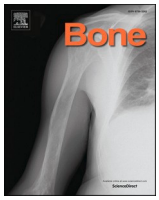
Bone 174 (2023) 116819

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone



Rapid Communication

Denosumab use in bone fibrous dysplasia refractory to bisphosphonate: A retrospective multicentric study

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ARTICLE INFO

Keywords:
Fibrous dysplasia
Pain
Denosumab
RANKL

ABSTRACT

Introduction: Increased RANKL expression is observed in the bone tissue of fibrous dysplasia of bone/McCune-Albright syndrome (FD/MAS). In one animal model of FD/MAS, the inhibition of RANKL reduced tumor volume. A beneficial effect of denosumab on pain in patients refractory to bisphosphonates has been reported, but without systematic quantification of pain improvement. This work describes the clinical experience of our group on the efficacy on pain of denosumab treatment, along with safety, in FD/MAS patients refractory to bisphosphonates.

Materials and methods: We have conducted a retrospective multicenter study in 6 academic rheumatology centers in France. We have collected patients and FD/MAS characteristics, duration of prior exposure to bisphosphonates, denosumab treatment modalities (dosage - administration regimen - number of courses); evolution of pain evaluated by Visual Analogic Scale (VAS).

Results: 13 patients were included (10 women and 3 men) 45 years on average, 5 MAS, 4 monostotic and 4 polyostotic forms. The average duration post-diagnosis of FD/MAS was 25 years and the mean duration of prior exposure to bisphosphonates was 4.7 years. Pain could be analyzed in 7 patients, showing a significant improvement from a mean VAS of 7.8 to 2.9 (−4.9 points, $p = 0.003$). In one patient with fronto-orbital FD/MAS, a 30 % decrease in lesional volume, assessed by MRI, was observed within 6 months of treatment, that was sustained over the following 12 months. Treatment regimens were heterogeneous. No hypercalcemia was observed after treatment cessation and the clinical tolerance was good.

Discussion: This study suggests that denosumab reduces pain in patients with DF/MAS refractory to bisphosphonates, and quantifies this improvement for the first time in a multicenter study. In our cohort, no patients who discontinued denosumab developed hypercalcemia and clinical tolerance was overall good. This study also provides encouraging data regarding lesion volume control. Further controlled studies are required to determine the place and modalities of the denosumab treatment of FD/MAS.

Conclusion: Denosumab significantly decreased pain in FD/MAS refractory to bisphosphonate. This study paves the way for a randomized clinical trial to validate and standardize the prescription of denosumab in FD/MAS.

1. Introduction

Fibrous dysplasia (FD)/Mc Cune Albright Syndrome (MAS) is a rare bone disorder, due to somatic variants of the *GNAS* gene, which encodes the α-subunit of the Gs signaling protein, leading to increased production of cAMP [1]. This overproduction impairs osteoblastic differentiation. The *GNAS* mutated cells synthesize a disorganized fibrous bone matrix and are also responsible for local increase IL-6 (Interleukin 6) and

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https://doi.org/10.1016/j.bone.2023.116819
Received 29 November 2022; Received in revised form 29 May 2023; Accepted 6 June 2023
Available online 8 June 2023

RANK-L (Receptor Activator of Nuclear Factor- κB Ligand) and systemic elevated in FGF23 (Fibroblast Growth Factor 23) [2,3]. Clinically, fibrous dysplasia can be an isolated bone disease or part of the Mc Cune Albright syndrome (MAS) including FD, hyperfunctional endocrinopathies and "café-au-lait" macules. Patients can present asymptomatic form, or severe impairment as bone pain, bone deformity, fracture, neurologic compression, renal phosphate wasting and a variety of tumors [4]. There is currently no cure for FD/MAS. A pharmacological treatment is proposed for patients who experienced pain or in case of local complication. The treatment is generally based on bisphosphonates, with pamidronate as first-line treatment and zoledronate as second-line treatment [1]. Despite this treatment, some patients continue to experience bone pain. One of the hypotheses for inadequate efficacy of bisphosphonates is that their action requires matrix incorporation, which is largely decreased in fibrous dysplasia lesions [5].

Because of the overexpression of RANK-L by mutated cells and because inhibition of RANK-L does not require matrix incorporation [5], denosumab, a fully human monoclonal antibody that inhibits RANK-L, has emerged as a potential treatment of FD. Since 2012, several cases of FD/MAS treated by denosumab have been reported in the literature, with some benefit on pain, but pain improvement was rarely quantified [6]. Side effects were reported mainly for two pediatric patients who developed symptomatic hypercalcemia after the end of denosumab exposure [7,8]. All studies were monocentric and retrospective in a limited number of patients, so we need to accumulate more data regarding the efficacy of denosumab on pain and evaluate its effects on lesional volume, as well as to confirm its safety and clarify the most effective administration modalities (dose/frequency) as well as discontinuation modalities.

In this context, we conducted a multicenter, retrospective observational study to report the experience of the French network of FD centers in the use of denosumab in FD/MAS patients with refractory pain despite bisphosphonate treatment.

2. Material and methods

2.1. Study design

This study is a multicenter, retrospective, observational study, to determine the effect of denosumab on pain in the treatment of FD/MAS. The study has been conducted in 6 rheumatology academic centers in France (Lyon, Bordeaux, Lille, Caen, Toulouse, Nice). The decision to start treatment with denosumab was made for each patient in agreement with the reference center. The study did not interfere with routine care. The authorization to use the reference center database of medical records has been provided by the CNIL.

2.2. Outcome measurements

The primary endpoint was the change in pain assessed by visual analog scale (VAS) before and after treatment with denosumab, ranging from 0 (no pain) to 10 (maximal pain). A change in dosage or frequency of denosumab administration was collected and considered as a new line of therapy. In addition, the following data were collected: height, weight, date of birth, date of diagnosis, type of fibrous dysplasia (monostotic, polyostotic or MAS), previous treatments used before denosumab, duration of bisphosphonate use before denosumab, concentration of serum biochemical markers of bone turnover during denosumab treatment, clinical and biological side effects, volumetric evaluation of lesion (CT or MRI) if available.

2.3. Patients

Patients had FD/MAS with persisting bone pain after use of one or more bisphosphonate and were treated with denosumab between January 2012 and January 2022.

2.4. Statistical analysis

Quantitative variables have been described with their mean and standard-deviation, or median and first and third quartiles; and qualitative variables by their frequency. Missing data were not imputed. According to the data distribution, groups were compared using either paired Student's t or Mann-Whitney tests. A p value lower than 0.05 was considered as significant.

3. Results

3.1. Patients characteristics and therapeutic regimens

Thirteen patients have been included: 10 women and 3 men, mean age 45 ± 14 years. Five had MAS, 4 had monostotic and 4 polyostotic FD. The average duration of the disease was 25 ± 16 years (7 to 64 years). The average duration of previous exposure to bisphosphonates was 4.7 ± 2.8 years (1–10 years). Baseline VAS was 7.8/10 (±1.99) (Table 1). The different modalities of administration (frequency - dose) of denosumab are presented in Table 2: 13 patients had one line of denosumab, 6 patients 2 lines, and 2 patients 3 lines. Doses and frequencies of denosumab administration were variable between and within centers, because these were off label prescription. Two patients received tocilizumab as a second-line and one as third line.

3.2. Pain evaluation

Among the 13 patients, VAS before and after first line of denosumab was available for 7 patients (see Fig. 1). Denosumab improved pain in all patients, except one (patient 9) and the variation was significant ($p = 0.003$). Pain was improved on average by 4.9/10 points (CI 95 % 2.4–7.38) (mean decrease from 7.8 to 2.9). VAS after 2 lines of denosumab was available only for 3 patients and for 1 patient after line 3. The individual trajectories of pain of the 7 patients for whom VAS were available before and after the introduction of the first line of denosumab are presented in Fig. 2.

3.3. Lesional volume evolution

Assessment of lesional volume evolution was available for only one patient (number 11), evaluated by MRI. This patient had a craniofacial FD/MAS responsible for exophthalmos. Before denosumab treatment the lesional volume was 47 cm^3, 3 months after the initiation of denosumab treatment the lesional volume was 44 cm^3 and at 6 months 33 cm^3 (29 % of decrease after 6 injections). At 12 and 18 months, the volume was stabilized at 32 cm^3 (Fig. 3).

3.4. Safety

Adverse events included: right femur shaft fracture in the dysplastic

Table 1
Table of demographic, clinical and therapeutic characteristics of patients before treatment with denosumab. VAS: Visual analogic scale; BP: Bisphosphonates; SD: standard deviation.

Sex	10 women - 3 men
Age at denosumab introduction (year) (mean ± SD; min; max)	45 ± 14; 25; 72
BMI (mean ± SD; min; max); 3 not known	27.3 ± 6.6; 19.3; 39.6
FD/MAS type	5 MAS; 4 monostotic; 4 polyostotic
Average duration of FD/MAS (year) (mean ± SD; min; max)	25.1 (±16; 7; 64)
VAS (mean ± SD) before BP; 3 not known	7.8 (±1.99)
Average duration of exposure to bisphosphonates (year) (Mean ± SD; min; max)	4.7 (±2.8; 1; 10)

Table 2
Summary of the different treatment regimens used. N.A: not applicable. P: patient.

	Line 1	Line 2	Line 3	Cumulative dose on January 2022/ other comments
P1	DENOSUMAB 120 mg 1 injection	DENOSUMAB 60 mg 1 injection	TOCILIZUMAB 162 mg/month	180 mg
P2	DENOSUMAB 120 mg/3 months; 2 injections Ongoing	N.A	N.A	240 mg
P3	DENOSUMAB 60 mg/month 3 injections	DENOSUMAB 120 mg/3 months Ongoing	N.A	300 mg/failure at 60 mg/2 months for pain >3, switch to 120/3 months
P4	DENOSUMAB 120 mg/4 months 2 injections	DENOSUMAB 60 mg/6 months	DENOSUMAB 60 mg/3 months; Ongoing	540 mg/failure for pain rebound under 60 mg/6 months dosage, shortening interval injection to every 3 months
P5	DENOSUMAB 60 mg once 1 injection	TOCILIZUMAB 162 mg/month 6 injections	N.A	60 mg/failure for pain >3 VAS 7/10 after TOCILIZUMAB
P6	DENOSUMAB 120 mg/2 months; 4 injections	DENOSUMAB 60 mg/month 8 injections	N.A	960 mg/ denosumab stopped without relay by another treatment. No rebound reported.
P7	DENOSUMAB 120 mg/2 months; 4 injections	Pamidronate 180 mg	Pamidronate 180 mg	480 mg/switch on patient request to bisphosphonates after 4 injections. VAS after each pamidronate: 4 and 5/10
P8	DENOSUMAB 120 mg/2 months; 2 injections	DENOSUMAB 120 mg/2 months 2 injections	DENOSUMAB 120 mg/3 months Ongoing	840 mg
P9	DENOSUMAB 60 mg/6 months 3 injections	TOCILIZUMAB 162 mg 9 injections in 6 months	N.A	180 mg failure for short effectiveness VAS 0/10 after TOCILIZUMAB
P10	DENOSUMAB 120 mg/3 months; 7 injections	Zoledronate 5 mg	N.A	840 mg/failure for persistent pain
P11	DENOSUMAB 120 mg/ month 6 injections	DENOSUMAB 120 mg/3 months 6 injections	DENOSUMAB 120 mg/6 months/ ongoing	1560 mg/severe orbital damage, tapering decided after national expert discussion at each line
P12	DENOSUMAB 120 mg/3 months; 8 injections	DENOSUMAB 60 mg Ongoing	N.A	>960 mg/ tapering to reach minimum effective dose
P13	DENOSUMAB 120 mg once 1 injection; ongoing	N.A	N.A	120 mg/first injection just before end of the study inclusion

zone 5 months after first denosumab injection for patient 1 in whom the treatment was temporarily stopped; metatarsal fracture for patient 2, no treatment discontinuation; nausea despite dose reduction for patient 6, leading to treatment discontinuation; stented coronary artery disease for patient 8, leading to treatment discontinuation; epigastralgia for patient 11, no treatment discontinuation. No hypercalcemia was reported for the 5/13 patients who discontinued denosumab. Transient, non-symptomatic and expected hypophosphatemia has been reported for patients 1, 2, 4 and 12.

4. Discussion

This study showed a significant improvement in pain with denosumab in 6 out of 7 adult patients with different types of FD/MAS, with an average 4.9 points decrease of VAS, which is clinically relevant. This result is consistent with data available in the literature, mostly case reports, showing that the use of denosumab is effective to control pain in FD/MAS. [7,9–15]. In our series, only one patient (number 9) did not improve. This patient with polyostotic FD/MAS (spine and rib involvement) was treated by 60 mg/6 months for 18 months (3 injections), and although he reported a transient benefit from denosumab immediately after the injections, he wanted surgical management so we cannot rule out the hypothesis that he overestimated his pain to fulfil surgical criteria. This study therefore provides important data on the quantitative evolution of pain under treatment, reinforcing the few available data [9,12,14,16].

Denosumab efficacy on lesional volume was assessed in only one patient (number 11), who received the highest dose of denosumab (cumulatively 1560 mg), with a significant decrease of the volume of his fronto-orbital FD/MAS. Of note, we did not observe any subsequent relapse of lesion growth despite the progressive tapering of the treatment interval. This observation is in agreement with Van Der Bruggen and coll. who showed in 8 patients with FD/MAS treated by denosumab and compared to 7 FD/MAS not treated by denosumab a significant decrease in lesion activity and volume, by monitoring them by ^{18}FNa PET CT [8]. This result is particularly encouraging, because despite common good pain control with bisphosphonates, they have not reduced lesion volume or activity [17].

In France, the initiation of denosumab for bisphosphonates resistant FD/MAS is the responsibility of the regional expert centers. However, we observe a certain disparity in treatment administration protocols, in terms of dose and frequency. In their study, Majoor and coll. propose an injection of denosumab 60 mg every 3 months as a promising dose for good control of bone turnover markers [18]. In our study, the dosage of denosumab 120 mg was the most frequently prescribed. In this context of retrospective study, the frequency of administration was not comparable between individuals, that does not allow us to draw any conclusion on the optimal administration regimen to be proposed. Thus, it appears necessary to set up a randomized controlled trial in order to establish clear recommendations and to harmonize practices.

In addition to the modalities of administration of denosumab, it will be necessary to establish a therapeutic sequence and the modalities of denosumab withdrawal. In this regard, Palmisano and coll. showed in a mouse model of FD/MAS a near-normalization of dysplastic bone using a mouse-specific inhibitor of RANK-L [19]. Unfortunately, a lesion recurrence and an overshoot of bone turnover, which was expected, were observed 4 weeks after the end of the treatment [19]. However, the near-normalization of the histology can give us hope for structural improvement of FD/MAS with denosumab, which remains to be proven in humans. Also, in order to avoid the bone remodeling overshoot well known in postmenopausal osteoporosis, it is recommended to provide bisphosphonates at the end of the denosumab therapeutic sequence, especially since the histological normalization could induce a better matrix integration of the bisphosphonate [5,19].

The second interest of this work is to provide data on the tolerance of denosumab in this FD/MAS adult population. Side effects were mild. No symptomatic case of hypocalcemia after injection was reported. No symptomatic hypercalcemia was reported during tapering of doses. These results, however, should be interpreted with caution because of missing data. Thus, our collection of bone turnover markers is inadequate. Serum calcium was measured more systematically because this is

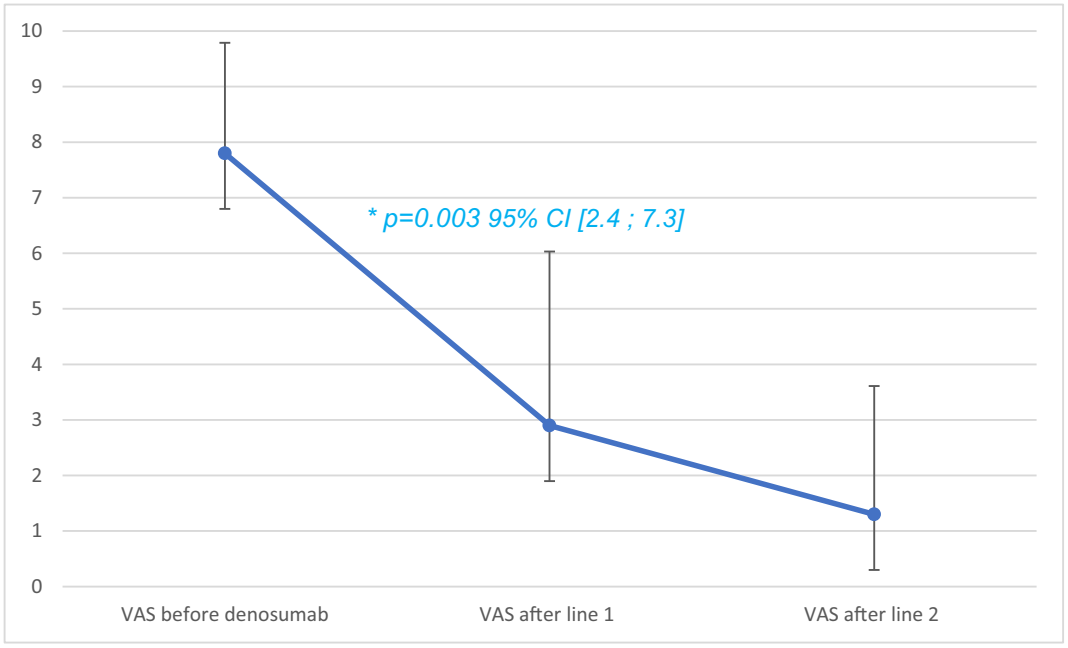

Fig. 1. Mean VAS in patients before and after lines of denosumab injection. After line 1 n = 7; After line 2 n = 3. VAS: visual analogic scale.

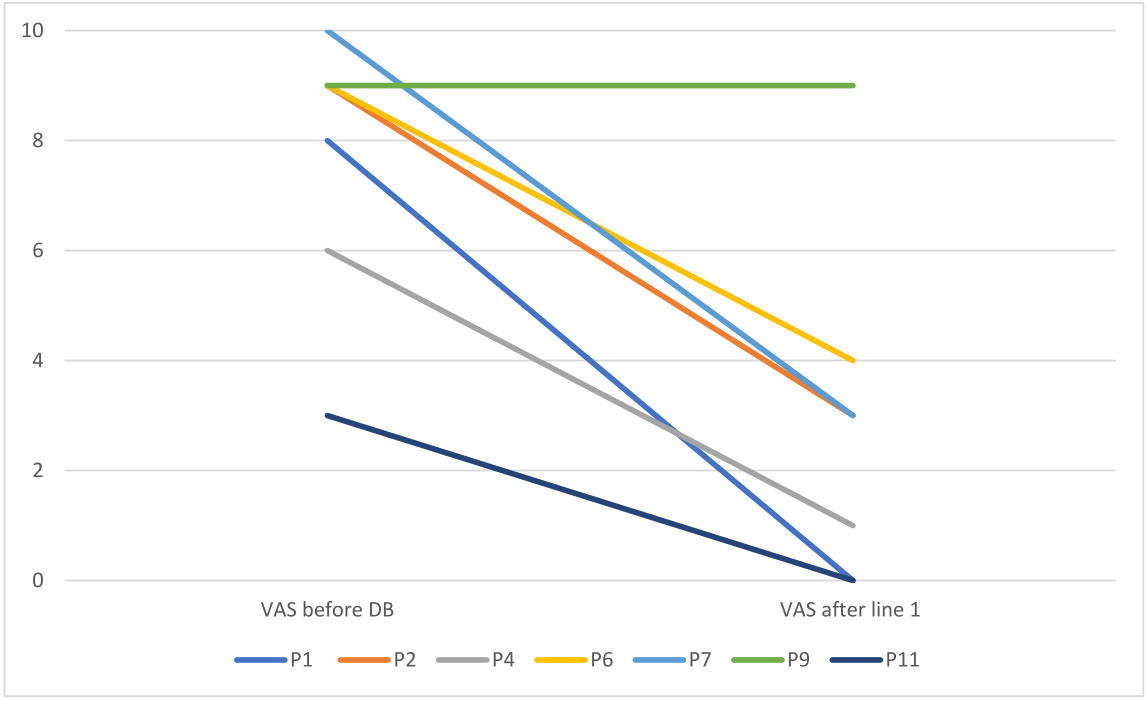

Fig. 2. Individual pain trajectory of the 7 patients for whom VAS were available before and after the introduction of the first line of denosumab. DB: denosumab; P: patient; VAS: visual analogic scale.

part of the regular clinical monitoring, so we can have confidence that we did not miss hypercalcemia cases. This is of particular concern, given the recent results by De Castro et al., observing one case out of 8 patients [20]. Two cases of hypercalcemia have been reported in children after denosumab discontinuation [7,8]. Moreover, in their study, Meier and coll. looked at the biological data during denosumab discontinuation, and no symptomatic hypercalcemia were reported (only one asymptomatic hypercalcemia at 2.7 mmol/l) in their adult population [9]. They did not observe any rebound in pain yet [9]. We did not have the data to assess the possibility of a pain rebound effect upon discontinuation of treatment, but for patient 4-8-11-12, we note that increasing intervals between the injections or decreasing the doses of denosumab did not result in rebound in pain. Patient 1 had a shaft femoral fracture in dysplastic zone 5 months after a first injection of denosumab 120 mg, leading to the discontinuation of the treatment while the efficacy on pain was remarkable (VAS 0/10 for 5 months). The hypothesis of an atypical femoral shaft fracture was discussed as the alkaline phosphatase was low and the patient had prolonged prior exposure to bisphosphonates: semi-annual pamidronate from 2002 to 2010, annual zoledronate from 2010 to 2011, 6 injections of tocilizumab

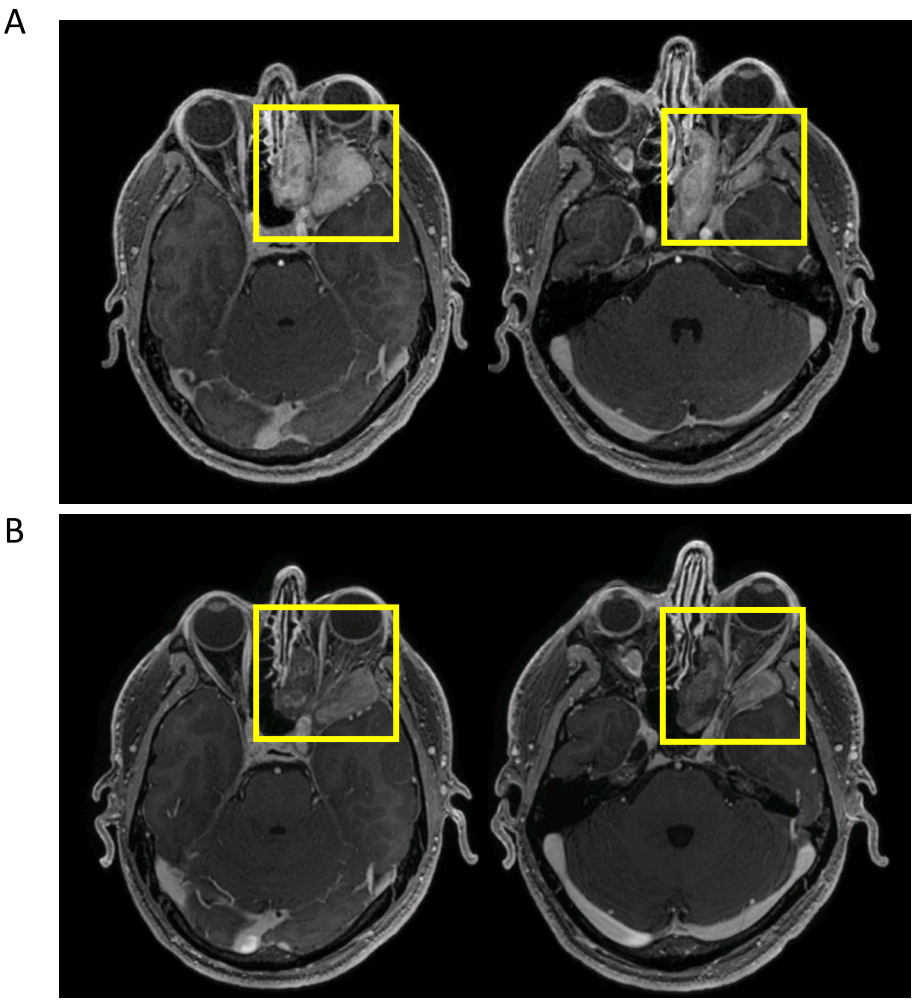

Fig. 3. Representative MRI sections of tumor volume decrease on denosumab. A. Sagittal sections T1 sequence with gadolinium injection, before the start of denosumab treatment (total volume measured by neuroradiologist: 47 cm^3) B. Sagittal T1-sequence sections with gadolinium injection, 18 months after denosumab introduction (total volume measured by neuroradiologist: 32 cm^3).

from 2013 to 2014, then semi-annual pamidronate from 2017 to 2018 (interrupted for atrial fibrillation), and finally 2 injections of zoledronate in 2020, the last of which was in March 2020, just prior to the denosumab injection. However, after expert group discussion, as the fracture occurred in dysplastic bone, denosumab was reintroduced at a lower dosage and the pain disappeared thereafter.

Our study has several limitations. First, the sample size is small. However, our series remains comparable to previously published series on the topic, with Majoor and coll and Van Der Bruggen and coll working on 12 and 15 patients respectively [8,18]. Also, we are lacking a control group. Patients who would have continued the bisphosphonates despite failure might have constituted this group. Ethically, however, it is challenging to propose to pursue a failing therapy. So, in our current practice, these patients were offered denosumab or sometimes tocilizumab. Also, our study population is heterogeneous in terms of denosumab administration dosage, frequency and duration, but this reflects the practical use of denosumab in this off-label situation, before any specific randomized trial is conducted. In addition, as a retrospective study, data are missing. Specifically, we were not able to analyze the bone turnover markers. Two other studies found that bone turnover markers were suppressed with denosumab. Indeed, in their work Majoor and coll showed that alkaline phosphatase was normalized in 7 of their 12 patients and decreased by at least 50 % for all their patients [18]. Similarly, Meier and coll showed that CTX and alkaline phosphatase were normalized in 2/3 of their patients [9]. Very recently, these results were supported by the study conducted by de Castro et al. also showing suppressed bone turnover on denosumab. [20]

5. Conclusion

In conclusion, we observed substantial efficacy of denosumab on pain, in patients with painful FD/MAS refractory to bisphosphonates. Therefore, our results support the implementation of a placebo-controlled trial to establish the appropriate administration modalities and quantitatively confirm the efficacy of denosumab on pain.

CRediT authorship contribution statement

D. Gensburger: Data curation, Investigation, Resources, Supervision. **M.C. Trojani:** Data curation, Writing original draft, Writing – review & editing. **F. Bagouet:** Data curation. **B. Cortet:** Data curation. **G. Couture:** Data curation. **C. Marcelli:** Data curation. **N. Mehsen Cetre:** Data curation. **V. Breuil:** Conceptualization, Data curation, Supervision. **R. Chapurlat:** Data curation, Supervision, Writing – review & editing.

Declaration of competing interest

None.

Data availability

Data will be made available on request.

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