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Original article

Denosumab for treating aneurysmal bone cysts in children

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ABSTRACT

Background: Aneurysmal bone cyst (ABC) is a benign tumour whose progression involves the RANK/RANKL signalling pathway. Surgery is the reference standard treatment but carries risks that vary with the site of the tumour. Denosumab is a human monoclonal IgG2 antibody that targets the RANK/RANKL pathway and may therefore hold promise for inhibiting ABC progression. The objective of this study was to evaluate denosumab use in paediatric patients (younger than 18 years) with ABC and to describe the clinical and radiological outcomes, as well as the side effect profile.
Hypothesis: Denosumab is a viable option in children with ABC refractory to standard treatments.
Material and methods: We retrospectively reviewed the medical files of paediatric patients given denosumab to treat ABC in any of 32 centres affiliated with the French Paediatric Cancer Society (Société Française du Cancer de l'Enfant, SFCE) and French Sarcoma Group (Groupe Sarcome Français, GSF-GETO). We identified 5 patients treated between March 2015 and June 2018. Median age was 8 years (range, 7–17 years). Pain was a symptom in all 5 patients and neurological deficits were present in 3 patients. Surgery was performed in 4 patients, either before ($n = 3$) or after ($n = 1$) denosumab therapy; the remaining patient had no surgery. Denosumab was given as monthly injections in a dosage of 70 mg/m^2 for a median of 12 months (range, 4–23 months). The clinical outcomes and changes in computed tomography and/or magnetic resonance imaging findings were evaluated.
Results: Abnormalities in calcium and phosphate levels secondary to the ABC occurred in 2 patients. At median of 24 months (range, 0–28 months) after denosumab initiation, all 5 patients were free of pain, and the neurological deficits in 3 patients had improved. Central remineralisation and cortical reconstitution were demonstrated consistently by the imaging studies.
Discussion: Denosumab is a viable treatment option in selected paediatric patients with inoperable ABC. The immediate adverse effect profile is acceptable. A larger study with a longer follow-up would be welcome to further assess the contribution of denosumab to the treatment of ABC.
Level of evidence: IV.

1. Introduction

Aneurysmal bone cyst (ABC) is a benign tumour of variable aggressiveness that shares features with giant cell tumour of bone (GCTB) [1], including overexpression of the receptor-activator of nuclear κB ligand (RANKL), which influences bone metabolism by activating both osteoblasts and osteoclasts [2]. ABC can raise treatment challenges related to the aggressiveness or location of the tumour [3]. The reference standard is curettage with or without filling of the defect. Selective embolisation [4] and sclerosing agent injection into the tumour [5] are other options. ABCs located in the axial skeleton may be difficult to treat surgically and have

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been reported to recur locally in 14% of cases after curettage alone [6].

Denosumab is a human monoclonal IgG2 antibody that targets RANKL, thereby decreasing bone resorption by impairing osteoclast formation, function, and survival [7]. This innovative drug has been proven effective in the treatment of GCTB and has radically changed the management of these tumours [8]. Denosumab was granted a license for use in GCTB in France 2015. The approved indication is GCTB in adults and skeletally mature adolescents with a body weight of 38 kg or more.

The RANK/RANKL pathway is also involved in the pathophysiology of ABC [2]. Several reports of denosumab therapy for severe ABC have been published [1,9]. Nevertheless, denosumab is not licensed for use in ABC. Furthermore, few data are available on denosumab therapy in paediatric patients.

The objective of this multicentre retrospective study was to evaluate denosumab use in paediatric patients (younger than 18 years) with ABC and to describe the clinical and radiological outcomes, as well as the side effect profile. The working hypothesis was that denosumab is a viable option in children with ABC refractory to standard treatments.

2. Material and method

2.1. Patients and treatment

To perform a preliminary evaluation of the effects of denosumab in paediatric patients with ABC, we invited centres belonging to the French Paediatric Cancer Society (Société Française du Cancer de l'Enfant, SFCE) and French Sarcoma Group-Bone Tumour Study Group (Groupe Sarcome Français-Groupe d'Étude des Tumeurs Osseuses, GSF-GETO) to report paediatric cases of ABC treated with denosumab, for inclusion into a retrospective study. Five patients with ABC diagnosed between January and August 2015 were identified, 3 males and 2 females with a median age at diagnosis of 8 years (range, 7–17 years). Histological documentation of the diagnosis was obtained by examination of a biopsy taken before or during surgery in all 5 patients.

The decision to use denosumab was made during a multidisciplinary discussion in all 5 patients. The dosage was 70 mg/m^2, up to a maximum of 120 mg by intravenous injection in patients weighing more than 38 kg. All 5 patients received a weekly injection for 4 weeks then a monthly injection, on a day-hospital basis. Calcium and vitamin D supplements were prescribed routinely. Median denosumab therapy duration was 12 months (range, 4–23 months) and median follow-up after denosumab discontinuation was 24 months (range, 0–28 months). A follow-up computed tomography (CT) scan was obtained 6 months after denosumab initiation in all 5 patients.

2.2. Data collection

We reviewed the medical files of the 5 included patients. The histological reports were reviewed by a pathologist belonging to the referral network for bone sarcomas and intermediate malignancy tumours (Réseau de référence pour la prise en charge des sarcomes osseux et tumeur à malignité intermédiaire, RESOS). Information was recorded about pain control, changes in the neurological deficits as assessed using the National Foundation for Infantile Paralysis scale, surgical complications, and side effects of denosumab. Available imaging studies were reviewed to assess tumour size based on Response Evaluation Criteria In Solid Tumours (RECIST) criteria, CT attenuation, and magnetic resonance imaging (MRI) signal.

3. Results

3.1. Patient #1

This 8-year-old boy had an ABC in L4 with back pain and a neurological deficit in the distribution of the L4 root (NFIP: 2/5). L4 vertebrectomy with L3-L5 fusion was performed. A first recurrence was treated by L4 embolisation and a further recurrence by additional surgical excision performed abroad. He was then seen in France for a third recurrence manifesting as a neurological deficit (NFIP: 2/5) with MRI evidence of tumour progression. Denosumab therapy was decided during a multidisciplinary discussion. An episode of hypocalcaemia 2 months after denosumab initiation was controlled by increasing the calcium supplement dosage. The pain resolved after 4 months on denosumab, which was used for 17 months in all. He experienced 3 episodes of hypercalcaemia 3, 5, and 6 months after denosumab discontinuation, which were managed by hospital admission and bisphosphonate therapy. Six months after the last denosumab dose he had a persistent mild neurological deficit (NFIP: 4/5).

3.2. Patient #2

A 14-year-old girl had an ABC involving S2 and S3 and responsible for back pain with no neurological deficit (Fig. 1). Surgery was not performed initially due to the large size and extension into the sacral canal of the tumour. Biopsy results confirmed the diagnosis of ABC. The treatment plan involved surgery performed 4 months after denosumab therapy given to facilitate the procedure. She was free of pain 1 month after denosumab initiation. Curettage of the lesion with filling of the residual cavity and decompression laminectomy was performed. The post-operative course was satisfactory. The histological examination of the operative specimen showed heavily ossified fibrotic tissue that had lost the septate structure typical of ABC. The physical findings and levels of calcium and phosphate were normal 2 years after denosumab discontinuation.

3.3. Patient #3

This 8-year-old boy presented with a lesion in C5 and C6, neck pain, and paralysis of the left shoulder (NFIP: 1/5) (Fig. 2). A biopsy was taken and the nerve roots were released. The histological findings confirmed the diagnosis of ABC. After the procedure, the pain abated and the neurological deficit began to improve. Denosumab therapy was started 1 month later given the absence of any validated surgical or interventional radiological procedure for the treatment of ABCs involving the cervical spine. After 2 months on denosumab therapy, he was free of pain and had recovered normal neurological function (NFIP: 5/5). Vitamin D deficiency was diagnosed 11 months after denosumab initiation and managed by supplemental vitamin D. Denosumab was given for 1 year. An episode of hypercalcaemia developed 5 months after denosumab discontinuation. Although the patient remained free of symptoms, an MRI scan obtained 10 months after denosumab discontinuation (Fig. 2d) showed enlargement of the lesion, prompting the re-initiation of denosumab therapy. One year later, the patient was still symptom-free and the CT scan findings were satisfactory (Fig. 2e).

3.4. Patient #4

A 7-year-old girl with groin pain as the only symptom was found to have a lesion in the left femoral neck (Fig. 3). A biopsy was taken, followed by curettage of the lesion, bone grafting, and plate fixation. A recurrence diagnosed 3 months later was managed by oncological

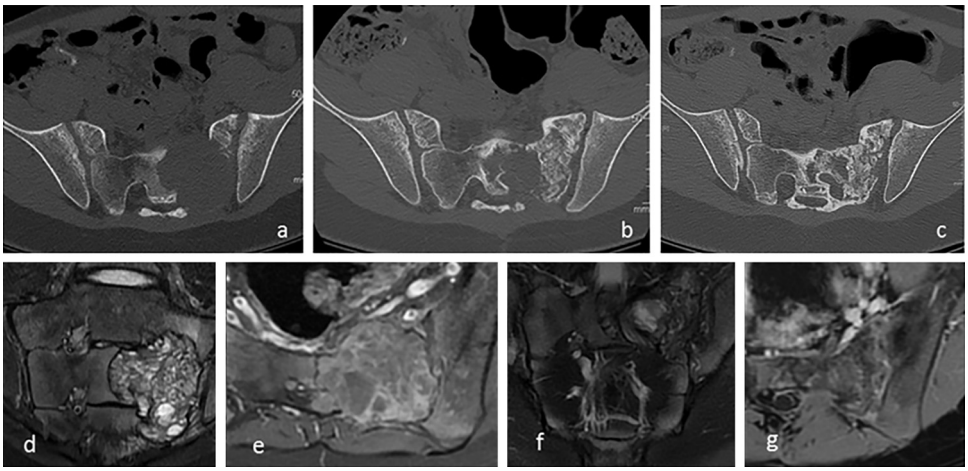

Fig. 1. Patient #2 a, b, and c: Computed tomography scans, (a) at diagnosis, (b) 6 months after denosumab initiation showing mineralisation of the lesion in a centripetal direction, and (c) 10 months after denosumab initiation showing cortico-medullary dedifferentiation and cortical thickening with no change in size (RECIST); d, e, f, and g: Magnetic resonance imaging, T2-weighted coronal view and T1-weighted axial view; (d and e) before denosumab therapy, cystic images with fluid-fluid levels indicating the presence of blood, with contrast enhancement of the lesion; (f and g), 10 months after denosumab initiation, the cystic images and fluid-fluid levels are no longer visible and the contrast enhancement is less marked.

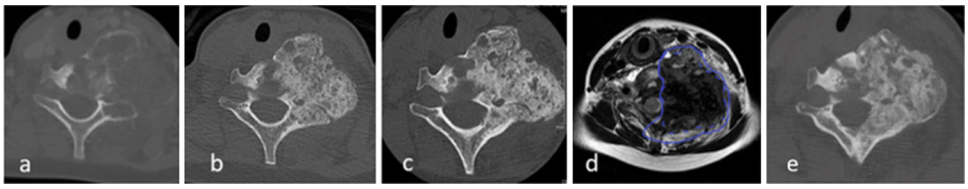

Fig. 2. Patient #3 a, b, c, and d: Computed tomography and magnetic resonance imaging, axial views; (a) at diagnosis; (b) 6 months after denosumab initiation; (c) 12 months after denosumab initiation; and (d) 4 months after denosumab discontinuation, with a dotted line to indicate the cyst contours; 10 months after denosumab discontinuation, the solid line delineating the cyst contours indicates an increase in size; e: Computed tomography, axial view 12 months after the resumption of denosumab therapy.

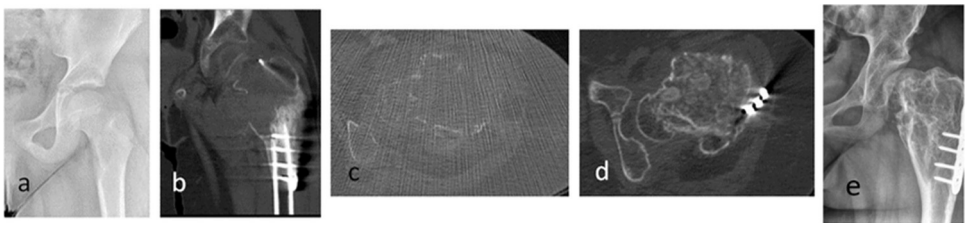

Fig. 3. Patient #4 a: Radiograph of the hip at diagnosis; b: Computed tomography, coronal view after curettage, defect filling, and plate fixation; c: Computed tomography, axial view showing a recurrence despite the two previous surgical procedures; d: Computed tomography 6 months after denosumab initiation showing reconstitution of the cortex peripherally and cortico-medullary dedifferentiation centrally, with no change in size (RECIST); e: Hip radiograph at last follow-up 32 months after denosumab initiation.

excision followed by immobilisation using an ilio-femoral external fixator. A second recurrence diagnosed 3 months later prompted the administration of denosumab, which was given for 4 months. The pain resolved 2 months after denosumab discontinuation. She was symptom-free 42 months after the initial diagnosis and 28 months after denosumab discontinuation.

3.5. Patient #5

This 17-year-old boy with low back pain and mild motor loss in the right lower limb (NFIP: 4/5) was found to have a lesion in L3 (Fig. 4). Two sclerosing agent injections into the lesion were performed, followed by L3 vertebrectomy and L1-L5 fusion. An MRI scan obtained 6 months later showed a recurrence, prompting a decision to administer denosumab. The CT scan changes were satisfactory 6 months after denosumab initiation (Fig. 4). After 15 months on denosumab, the patient was free of pain and had no residual neurological deficit (NFIP: 5/5). He was still symptom-free (NFIP: 5/5) 23 months after the initiation of denosumab therapy, which was continued due to concern about a local recurrence.

4. Discussion

In our 5 patients aged 7 to 17 years, denosumab given to treat inoperable or refractory ABC induced clinical and radiological improvements, confirming our working hypothesis.

The denosumab administration modalities and the strategy for monitoring treatment efficacy and safety were identical in all 5 patients and consistent with recommendations for the treatment of GCTB [8]. The diagnosis was confirmed by histological findings typical for ABC in all 5 patients. Denosumab therapy consistently provided complete pain relief, while also substantially improving the neurological deficits, in keeping with earlier data [10]. The imaging study results also indicated beneficial effects of denosumab. Thus, by Computed Tomography (CT), lesion size was unchanged (RECIST) and remineralisation of the lesion with reconstitution of the cortex was obtained. MRI showed disappearance

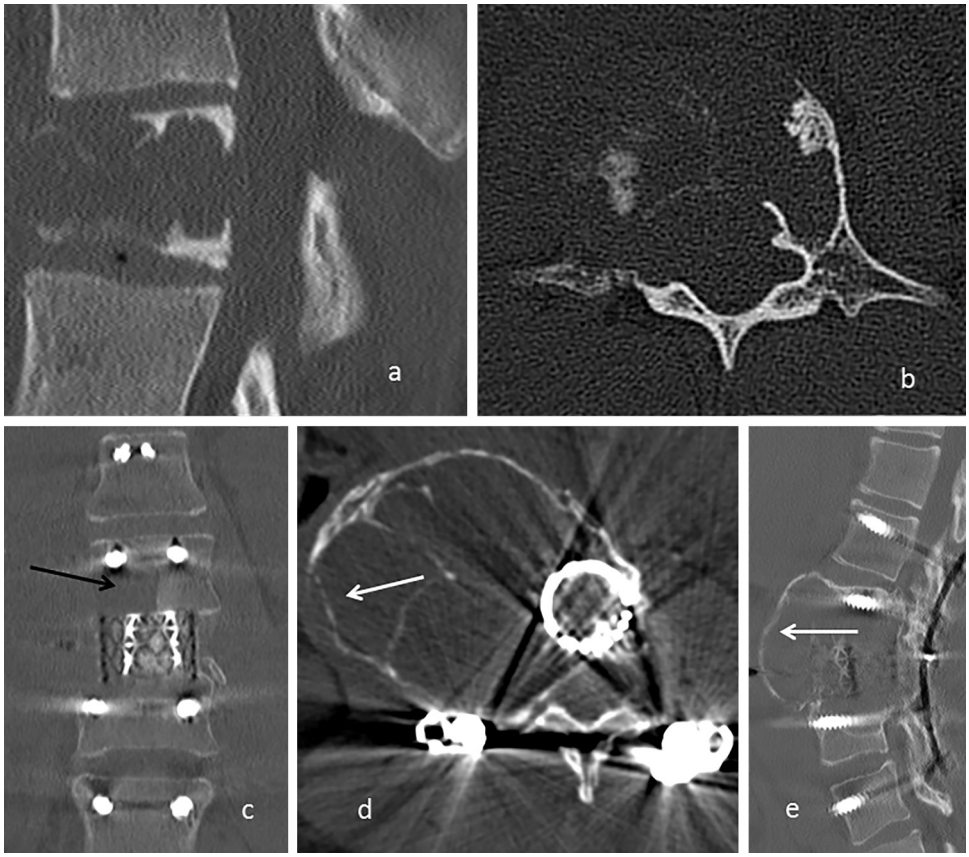

Fig. 4. Patient #5 a and b: Computed tomography (CT), sagittal and axial views showing osteolysis with a pathological fracture of L3; c: CT, recurrence 6 months after surgery (black arrow); d and e: CT 6 months after denosumab initiation, cortical bone is visible peripherally and along the septa within the lesion (white arrows), while the size of the lesion is unchanged (RECIST).

of the cystic lesions and fluid-fluid levels, as well as a decrease in contrast enhancement.

Curettage with filling of the defect, embolisation, and sclerosing agent injection into the lesion are currently the standard treatments for ABC but may be challenging to use if the ABC is aggressive or involves the axial skeleton, where difficulties in accessing the tumour increase the risks of incomplete curettage followed by recurrence [6] and of damage to important neighbouring structures. Embolisation is technically demanding at certain sites [9]. Sclerosing agent injection produces local inflammation and carries a risk of thromboembolism [10]. Our patients #1 and #5, who had involvement of the lumbar spine with neurological deficits, were given denosumab after experiencing failure of embolisation or sclerosing agent injection. In patient #2, who had a sacral ABC, the decision taken during the initial multidisciplinary discussion consisted in using denosumab as a neoadjuvant treatment, to facilitate subsequent surgery. Patient #3 had a cervical ABC that was considered unamenable to any of the standard treatments. The only invasive treatment in this patient therefore consisted in taking a biopsy and releasing the nerve roots to improve neurological function. Finally, neither embolisation nor sclerosing agent injection was performed in patient #4, as the failure of oncological resection was considered during the multidisciplinary discussion to indicate a low likelihood of achieving benefits from any other invasive treatments. Bisphosphonate therapy has been reported in patients with ABC [11] and has a similar mechanism of action to that of denosumab, i.e., inhibition of osteoclastic bone resorption. However, bisphosphonates were not used here, as they carry a risk of osteonecrosis of the jaw.

A beneficial effect of denosumab used as neoadjuvant therapy cannot be established definitively based on our findings in a single patient. The histological findings in our study of cyst remodelling with marked ossification constitute objective evidence of the efficacy of denosumab therapy. In a study of patients with GCTB, Müller et al. [12] reported difficulties in lesion curettage due to the bone sclerosis induced by prior denosumab therapy. Nevertheless, these histological changes combined with lesion shrinkage have been suggested to facilitate subsequent surgery [1,10]. No complications occurred in our patient given neoadjuvant denosumab therapy.

Further tumour progression after denosumab discontinuation occurred in only 1 of our 5 patients. The optimal duration of denosumab therapy that minimises the risk of tumour progression after discontinuation remains to be determined. Local GCTB recurrence after denosumab discontinuation has been reported [12]. Of 27 patients with GCTB studied by Rekhi et al. [13], 5 (18.5%) experienced a recurrence after denosumab therapy followed by curettage. Rutkowskiet al. [14] reported a 21% recurrence rate at a median of 6 months after neoadjuvant denosumab followed by surgery for GCTB. Median denosumab treatment duration in our patients was 12 months (range, 4–23 months) and a single patient experienced further tumour progression after denosumab discontinuation. However, the treatment strategies varied across patients: 1 patient received neoadjuvant denosumab, another received denosumab alone, and the remaining 3 patients took denosumab as adjuvant therapy to one or more surgical procedures. Tumour progression is a more appropriate term than recurrence for our patient #3, as surgery was not performed. Longer follow-ups are needed to better assess the risk of tumour progression or recurrence after denosumab discontinuation. In a study of 9 patients with

ABC, Kurucu et al. [10] observed further tumour progression during denosumab therapy in 1 patient and recurrence after denosumab discontinuation in 2 patients. Based on data from patients with GCTB or ABC, Dubory et al. [1] suggested that the risk of recurrence may be high if over 10% of viable tumour cells persist after denosumab discontinuation. Given the histological similarities between the two tumour types, the data obtained in patients with GCTB are relevant to patients with ABC.

Hypocalcaemia and/or hypocalcaemia occurred in 2 of our patients. Similarly, Chawla et al. [8] reported hypocalcaemia in 15% of patients during denosumab therapy and Kurucu et al. [10] observed hypercalcaemia after denosumab discontinuation in 22% of patients. Hypercalcaemia after stopping denosumab may be life-threatening [15] and requires emergent treatment with restoration of the fluid and electrolyte balance and administration of a bone resorption inhibitor. In our study, hypercalcaemia occurred in patients #1 and #3, in whom the duration of denosumab therapy was 17 months and 12 months, respectively. Kurucu et al. [10] also reported hypercalcaemia after long treatment durations of more than 1 year. These data suggest a possible higher risk of rebound hypercalcaemia when denosumab therapy is prolonged. This complication requires close patient follow-up after denosumab discontinuation as recommended for the treatment of GCTB, with a visit and serum calcium and phosphate assays after 6 months then once a year.

No information is available to date on the safety profile of denosumab in children younger than 12 years of age. One of the obstacles to the use of denosumab in the rare cases of paediatric GCTB is the absence of phase I data. Nevertheless, denosumab therapy is considered acceptable in these exceedingly rare cases. A pressing need exists for additional data.

5. Conclusion

ABC in children can result in challenging therapeutic situations for which denosumab may be a viable option. When used as neoadjuvant or adjuvant therapy to surgery, denosumab is effective in controlling the symptoms and providing a lasting radiological response. Denosumab can induce disturbances in calcium level regulation, which respond to symptomatic treatment but warrant that decisions to use denosumab be taken only during multidisciplinary discussions. A larger study with a longer follow-up is needed to confirm our findings and to determine the optimal duration of denosumab therapy used to treat ABC.

Disclosure of interest

FG is a consultant for AMGEN.

The other authors declare that they have no competing interest.

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None.

Contributions of each author

A.B. (radiologist) selected and commented the images.

N.G., L.B., and N.E.W. (oncologists) and C.M. (surgeon) contributed to recruit and to study the patients.

F.D. (pathologist) reviewed the pathology reports of all the study patients.

F.G. (surgeon) and P.M.B. (oncologist) conceived and designed the study and contributed to draft and to revise the manuscript for important intellectual content before submission.

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