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Experience with denosumab in the treatment of bone diseases in pediatrics at a tertiary care hospital

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ABSTRACT

Denosumab has been shown to improve post-surgical morbidity in resectable lytic bone neoplasms with high RANK-L expression and to halt disease progression in unresectable cases. Intra- and post-treatment adverse effects have been reported.

We conducted a prospective, descriptive study including six patients with lytic bone neoplasms treated with denosumab. The median age at onset treatment was 7.4 years, and the male-to-female ratio was 5:1. Five patients showed a favorable response. All patients developed hypocalcemia and hypophosphatemia during treatment, requiring adjustments in calcium and ergocalciferol/cholecalciferol supplementation (6/6), the addition of calcitriol (5/6), and phosphate salts (3/6).

Metaphyseal bands were observed in 4 out of 6 patients. No fractures were reported, and most patients did not show evidence of impaired growth.

Four patients experienced post-treatment hypercalcemia. Risk factors included younger age, a higher number of doses, and the presence of metaphyseal bands.

Keywords: *denosumab; hypercalcemia; bone neoplasms; aneurysmal bone cysts; giant cell tumor.*

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INTRODUCTION

The receptor activator of nuclear factor kappa B (RANK) is a membrane protein expressed on the surface of osteoclasts, playing a crucial role in their differentiation, survival, and function. It is stimulated by RANK ligand (RANK-L), which promotes resorption,[1-3] and is inhibited by osteoprotegerin (OPG).

Denosumab is a subcutaneously administered monoclonal antibody that binds to RANK-L and inhibits its interaction with RANK, leading to reduction of bone resorption. It was initially indicated for the treatment of osteoporosis in postmenopausal women and has been expanded to other bone conditions.[2]

Aneurysmal bone cyst (ABC), giant cell tumor (GCT), and central giant cell lesion (CGCL) are lytic bone neoplasms characterized by abundant multinucleated giant cells with high expression of RANK-L [4,5] which promotes tumor expansion and local destruction.

These lesions can potentially penetrate the bone cortex and cause fractures.[6,7] GCT may also undergo malignant transformation and develop metastases.[2,8]

Treatment with denosumab in these tumors aims to increase ossification. Multiple studies have demonstrated its high efficacy in improving postoperative morbidity in resectable forms and halting progression in unresectable forms,[6,7,9,10] with good tolerance. There is limited data on its use in growing patients. Adverse effects were reported during treatment (hypocalcemia, hypophosphatemia, and metaphyseal calcium and phosphorus deposits visible on radiographs as hyperdense bands) and after its discontinuation (rebound hypercalcemia). In addition, there is particular concern about the compromise of linear growth and the risk of fractures in the interface zone between healthy bone and metaphyseal deposits.[2,7]

At the end of 2023, a recommendation on denosumab treatment for RANK-related disorders in children and adolescents was published by experts from six countries. Follow-up protocols were defined, and the use of bisphosphonates (pamidronate/zoledronate) was incorporated as long-acting antiresorptive agents for the prevention of rebound hypercalcemia.

In 2022, the use of denosumab was extended at the Hospital de Pediatría Prof. Dr. Juan P. Garrahan for children under 18 years of age with ABC, CGT and CGCL.

Given the limited information available at the time, we initiated a prospective study to evaluate the frequency of adverse effects and the therapeutic strategies employed to manage them. The research protocol was approved by the Institutional Review Board of Garrahan Hospital under registration number 1700. Follow-up was conducted from February 2022 to December 2024.

Oncology determined the indication, dose, and frequency of denosumab by bibliographic recommendations. Periodic growth checks, phosphocalcic profile laboratory tests were performed before starting treatment and before each dose, and lower limb X-rays were taken (at 12 months or earlier if hypercalcemia occurred).

All patients started a diet rich in dairy products, calcium carbonate supplementation (500-1000 mg/day of elemental calcium depending on age), and prophylaxis with ergo/cholecalciferol 1,000-1,500 IU/day in cases of 25-hydroxyvitamin D (25[OH]D) sufficiency, or treatment with 3,000 IU/day in cases of deficiency.

Adjustments were made according to the control laboratories' before each infusion and at quarterly 25(OH)D checks. In mild hypocalcemia, calcium carbonate supplements were increased by 48 to 72 hours post-infusion. In moderate hypocalcemia, the increase was indicated to be permanent. In persistent hypocalcemia and/or with increased parathyroid hormone (PTH), calcitriol was added. In persistent hypophosphatemia, treatment with phosphorus salts was indicated. In severe hypocalcemia or hypophosphatemia, intravenous correction was suggested according to CIME guidelines.[11]

When treatment was discontinued, patients were informed about red flags and advised to have monthly laboratory monitoring.

The following variables were analyzed:

- Demographic: age at denosumab initiation and discontinuation, sex, type of primary tumor, and location.
- Treatment with denosumab: dose (in mg/m^2 and absolute) and number of doses received.
- Biochemical: serum calcium, serum phosphate, 25(OH)D, and PTH.
- Clinical: weight and height at the start and end of treatment, report of fractures, presence of symptoms of hypocalcemia, hypercalcemia, or hypophosphatemia.
- Imaging: presence of metaphyseal bands visible as hyperdense areas in radiographs.
- Therapeutic: type of drug and dose.

CASE DESCRIPTIONS

Demographic and treatment data with denosumab

Six patients treated with denosumab were included (*Table 1*), with a median age at treatment initiation of 7.4 years (range, 3.25-15 years) and a male-to-female ratio of 5:1.

Patient #5 presented malignant behavior with lung metastasis (requiring systemic chemotherapy), and patient #6 had a previous diagnosis of Noonan syndrome.

Images of the primary tumors are shown in *Figure 1*.

Patients underwent weekly cycles during the first month and monthly cycles during the subsequent months, at a dose of 70 mg/m² per dose (maximum 120 mg), with a median of 18 doses (range, 7-22).

Clinical and imaging response to treatment with denosumab

All patients, except #5 with GCT, had a favorable response to treatment with denosumab (*Table 1*). This response (clinical and/or imaging) was evident during the first treatment cycles (between 3 and 5). In 2 patients, tumor resectability was achieved, and in 3 patients, local control with symptomatic improvement was achieved (*Figure 2*).

None have presented with recurrence or progression to date, with a median follow-up from the start of treatment of 32 months (range, 15-39 months).

Intratreatment adverse effects with denosumab

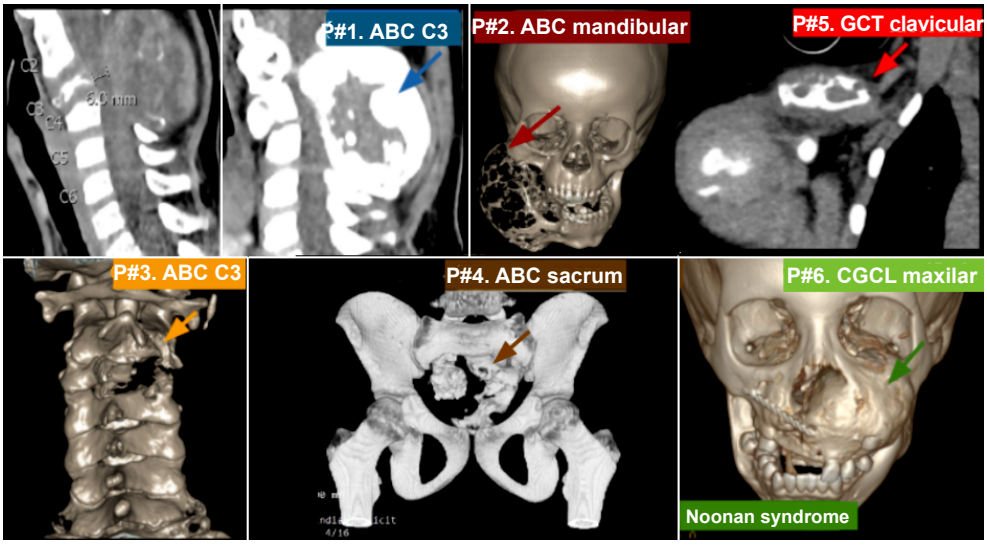
All patients presented hypocalcemia and hypophosphatemia (minimum values of 7.5 mg/

Table 1. Demographic and treatment variables with denosumab

Patient	Diagnosis		Sex	Age at denosumab initiation (years)	Age at denosumab discontinuation (years)	Denosumab treatment		
	Tumor	Location				Number of doses (n)	Imaging response	Clinical response
#1	ABC	C3	M	5.83	7.58	22	Post-cycle No. 3: Increased the anteroposterior diameter of the spinal canal with stable tumor size and increased peripheral bone density.	Post-cycle No. 3: Removal of the halo vest.
#2	ABC	Mandibular	M	4.08	4.5	7	Post-cycle No. 4: Slight increase in sclerosis/eccentric ossification and some septa of the lesion, with no significant changes in volume.	Post-cycle No. 2: Improvement in pain and mouth opening. Postcycle no. 4: Possibility of tumor excision.
#3	ABC	C3	M	15	17.25	18	Post-cycle No. 5: Diffuse sclerotic reaction and decreased soft tissue involvement.	Post-cycle No. 5: Removal of the halo vest
#4	ABC	Sacrum	M	9.08	10.75	18	NA	Pain relief.
#5	GCT	Clavicular	F	3.25	3.91	10	Post-cycle No. 3: Progression of primary tumor and metastatic lesions.	Clinical increase in tumor size.
#6	CGCL	Maxilar	M	10.83	12.16	19	Post-cycle n.° 6: Slight size reduction and marked increase in density, and slight increase in air space in both nostrils.	Post-cycle n.° 2: Clinical reduction in size. Post-cycle n.° 15: Possibility of tumor excision (awaiting surgical resolution).

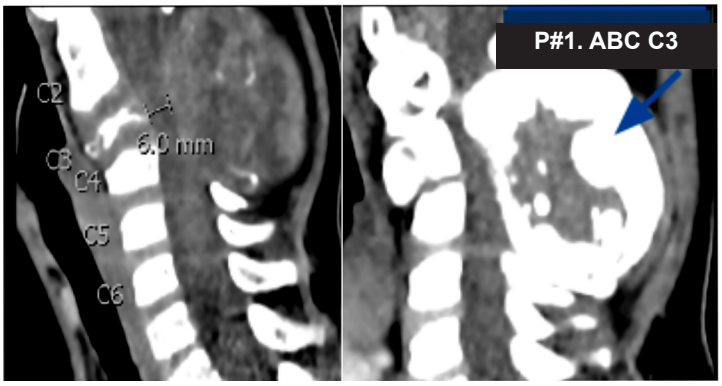
ABC: aneurysmal bone cyst; GCT: giant cell tumor; CGCL: central giant cell lesion; C3: third cervical vertebra; M: male; F: female; NA: not available.

Figure 1. Imaging studies of the six patients before starting denosumab



P: patient; ABC: aneurysmal bone cyst; GCT: giant cell tumor; CGCL: central giant cell lesion; C3: third cervical vertebra. The arrows indicate the primary tumor.

Figure 2. Computed tomography of patient #1 before treatment and 12 months after denosumab



On the left, an expansive formation is observed, with its epicenter at C3, measuring 56 × 74.3 × 54.8 mm and compromising the entire vertebral body, thereby reducing the spinal canal space to 6 mm and causing anterior displacement of the spinal cord. On the right, there is a marked increase in the density of the peripheral sectors of the lesion, with an increase in the anteroposterior diameter of the spinal canal to 11.1 mm.

dl and 2.2 mg/dl, respectively). Hypocalcemia occurred after a median of 1.5 doses (range, 1-6), and hypophosphatemia occurred after a single dose (range, 1-6). They were asymptomatic, except for one patient who presented mild symptoms of hypocalcemia. PTH levels during hypocalcemia were available in 3 of 6 patients, with a range of 145-456 pg/mL (normal value <95).

These adverse effects required adjustments to calcium carbonate and ergo/colecalciferol supplements in all cases, the addition of calcitriol in 5 of 6 patients, and phosphorus salts in 3 of 6. The mean treatment doses were 79.6 mg/kg/day (41.9 SD) for elemental calcium, 3,000 IU/day for ergo/cholecalciferol, 56.7 ng/kg/day (22.7 SD) for calcitriol, and 36 mg/kg/day (7.6 SD) for phosphorus salts.

Post-treatment adverse effects with denosumab

Four patients developed rebound hypercalcemia, of whom only one had received preventive bisphosphonate therapy according to guidelines published in late 2023.[7] Two of six patients never developed hypercalcemia and had

not received prophylactic treatment.

Patients who developed hypercalcemia started treatment at a median age of 7.4 years (range 3.25-10.83) and received a median of 18.2 doses (range 10-22). In all cases, PTH levels during hypercalcemia were less than 20 pg/mL.

The three patients who developed hypercalcemia and did not receive preventive bisphosphonates presented severe symptomatic hypercalcemia (median 17 mg/dl, with a narrow range of 16.4-17), detected with a median time from denosumab discontinuation of 15 weeks (range 6-16). The most common symptoms were gastrointestinal, renal function impairment, and asthenia/adynamia. All patients were treated with hyperhydration, furosemide, and bisphosphonates (administered between 2 and 4 doses) according to their response. In patient #6, preventive treatment with bisphosphonates (zoledronate 0.025 mg/kg/dose) was indicated 4 and 8 weeks after the last dose of denosumab. He received the first dose correctly, but not the second, due to family difficulties in accessing medical care. Fifteen weeks after the last denosumab dose, moderate asymptomatic hypercalcemia (13.4 mg/dL) was detected, which responded favorably to a new dose of zoledronate, resulting in subsequent normalization of calcium levels.

Radiographs showed metaphyseal bands in 4 of 6 patients (*Figure 3*).

Figure 3. Evidence of metaphyseal bands in the lower limbs in patient #1

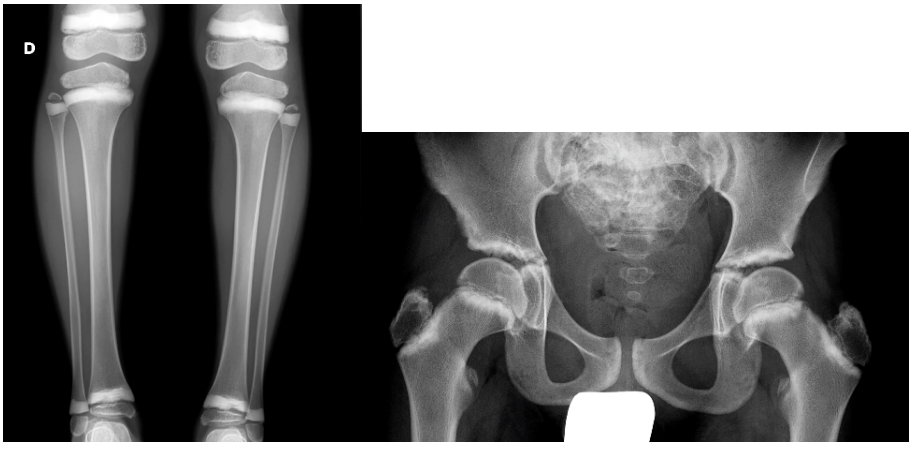
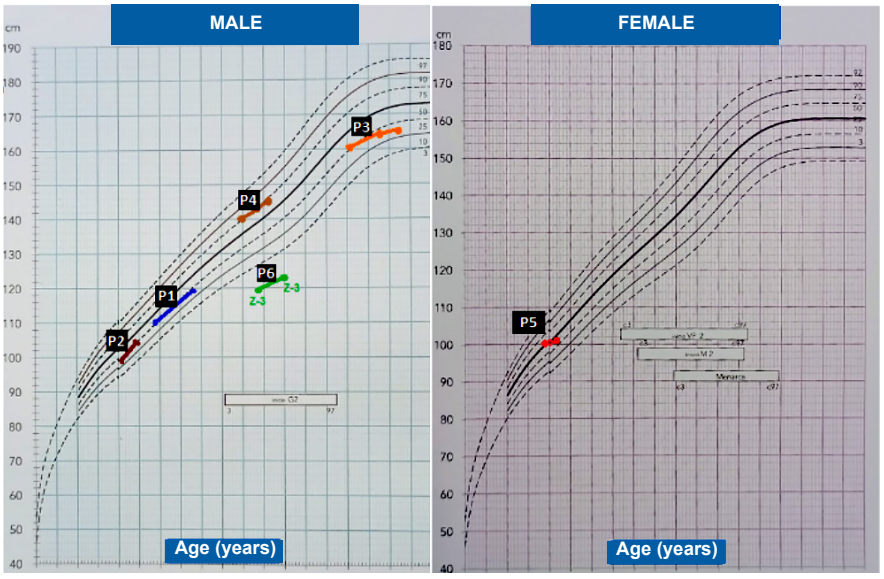


Figure 4. Evaluation of the linear growth



No fractures were recorded during or post-treatment.

In most patients, no growth impairment was observed during treatment with denosumab, except in patient #5, who required chemotherapy due to metastatic behavior (*Figure 4*). Patient #6 had short stature secondary to Noonan syndrome, maintaining a value of -3 SD both before and after treatment.

Pre-, intra-, and post-treatment assessment data on phosphocalcic metabolism are detailed in *Table 2*.

DISCUSSION

As reported in the literature, our cohort showed a male predominance in ABC, but not in CGT.[12,13] Only one patient presented a predisposing syndrome (Noonan syndrome, an entity associated with CGCL).[14]

The doses and dosages of denosumab were those recommended,[7] and the patients showed clinical benefits.

In healthy pediatric skeletons, there is a coupling between bone formation and resorption, favoring the former, a process known as modeling.[2] Denosumab is a potent inhibitor of resorption, not only at the intratumoral level, but also in healthy bone, resulting in a profound alteration of this balance. The increased calcium and phosphorus requirements caused by tumor ossification and the inability to obtain them from skeletal deposits (due to the antiresorptive effect of the drug) lead to the need for supplementation of these minerals. Despite supplementation, all our patients presented hypocalcemia and hypophosphatemia, but these were mainly asymptomatic, with no need for intravenous corrections.

The adjustment of treatment to correct hypocalcemia, by increasing calcium supplementation, ergo/cholecalciferol, and the addition of calcitriol, also improved hypophosphatemia. This can be attributed to the decrease in PTH levels, which reduces its phosphaturic effect and promotes the normalization of phosphatemia, requiring phosphorus salts only in forms that are refractory to these measures. We found no reports in the literature on the use of calcitriol for preventing hypocalcemia and hypophosphatemia; however, it could be a promising strategy for future patients.

After denosumab administration, the etiology of hypercalcemia is caused by the abrupt loss of the antiresorptive effect (given its rapid on-off effect) in patients with high bone turnover,[7] which leads to an increase in calcemia that exceeds the renal capacity of calcium excretion. This was the most serious adverse effect in our cohort, with a risk to life. Risk factors appear to include younger age at the start of treatment, a higher number of doses administered, and the presence of metaphysical bands on X-rays, which correlate with greater bone deposition. The time to detection was somewhat shorter than in previous reports, and

Table 2. Evaluation of phosphocalcic metabolism before, during, and after treatment

Patient	Pre-treatment			Intra-treatment								Post-treatment			
	25(OH)D defficiency	Ergo/colecalciferol (U/day)	Elemental calcium (mg/day)	25(OH)D defficiency	25(OH)D minimum (ng/ml)	Hypocalcemia	Cycles until first hypocalcemia (n)	Minimum calcemia	Hypophosphatemia	Cycles until first hypophosphatemia (n)	Minimum phosphatemia (mg/dl)	Hypercalcemia	Time to first hypercalcemia (weeks)	Metaphyseal bands	Fractures
#1	Yes	3000	1000	-	9.1	Yes	3	8	Yes	6	2.6	Yes	15	Yes	No
#2	No	1000	500	Yes	17.3	Yes	2	7.6	Yes	1	3	No	-	No	No
#3	Yes	3,000	500	-	10.1	Yes	1	7.9	Yes	1	2.4	No	-	No	No
#4	No	1500	1000	Yes	NA	Yes	1	7.5	Yes	6	2.3	Yes	16	Yes	No
#5	No	1200	500	Yes	16.5	Yes	1	7.7	Yes	1	2.2	Yes	6	Yes	No
#6	No	1000	1000	Yes	16.5	Yes	6	8.5	Yes	1	2.5	Yes	15	Yes	No

NA: not available.

in patients without preventive zoledronate, it was severe and symptomatic, requiring hospitalization and the use of bisphosphonates.

Following the latest recommendations, preventive administration of zoledronate was indicated in patient #6. Given the delay in the administration of the second dose, hypercalcemia could not be avoided, but it occurred with lower values (13.6 vs. 17 mg/dl) and was asymptomatic. Hypercalcemia could be prevented with an appropriate bisphosphonate regimen in future patients.

Rebound hypercalcemia and metaphyseal bands did not occur in patient #2 (who received only seven doses) or in patient #3 (aged 15 years with metaphyseal fusion at the start of denosumab).

We did not observe secondary growth impairment secondary to denosumab, and no intra- or post-treatment fractures were reported.

The optimal duration of treatment with denosumab is still unknown. There are reports of treatments lasting only 3 to 6 months that have been effective in inducing sustained remission.[15,16] A less intensive treatment regimen would reduce the risk of rebound hypercalcemia. However, further studies are needed, particularly randomized multicenter studies.

The limitations of our study were the small number of patients, the different etiologies involved, and the lack of long-term follow-up.

In our experience, denosumab was associated with intra- and post-treatment adverse effects. Given the favorable oncological results, we believe it is crucial to continue developing strategies to minimize the adverse effects associated with denosumab. ■

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