ORIGINAL ARTICLE
TUMOR/INFECTION
http://dx.doi.org/10.1590/S1808-185120222101253789

LONG-TERM USE OF DENOSUMAB IN GIANT CELL TUMORS AND VERTEBRAL ANEURYSMAL BONE CYSTS

USO PROLONGADO DE DENOSUMAB NO TUMOR DE CÉLULAS GIGANTES E CISTOS ÓSSEOS ANEURISMÁTICOS VERTEBRAIS

USO PROLONGADO DE DENOSUMAB EN TUMOR DE CÉLULAS GIGANTES Y QUISTES ÓSEOS ANEURISMÁTICOS VERTEBRALES

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ABSTRACT

Introduction: Denosumab is a human monoclonal antibody that binds to the receptor activator of nuclear factor kB (RANKL), it is used in the treatment of Osteoporosis. The Giant Cell Tumor (GCT) and the Aneurysmal Bone Cyst (ABC) use the same RANKL, and for this reason this drug began to be used for its treatment. There is consensus on the use, dose-time and 12-month duration for Denosumab treatment of GCT. Not so for ABC. In unresectable, disabling or recurrent tumors, its use could be for life. The adverse events of the habitual use of the drug are known, but it is not known if these increase with time. The objective of the present work is to identify the possible adverse events of treatment with Denosumab for more than 12 months. Material and Method: Series of cases with a diagnosis of GCT or ABC in spine, treated with Denosumab for more than 12 months. Adverse events are: arthralgia, fatigue, spinal pain, pain in extremities, headache, hypokalaemia, hypocalcemia, osteonecrosis of the jaw, malignant transformation, pathological fractures. Results: Eight patients, 6 TCG and 2 ABC, with a mean age at diagnosis of 25,6 years; presenting a mean treatment of 4.18 years (range 1.7 - 8.7). Of 6 operated patients, 4 had recurrence (2 to 36 months after surgery). One patient had to suspend treatment due to necrosis of the jaw, another hypocalcemia, both returned to treatment when stabilized. Conclusions: A minor adverse event (hypocalcemia) and a major adverse event (jaw bone necrosis) were observed. ***Level of Evidence IV; Original.***

Keywords: Giant Cell Tumor of Bone; Bone Cysts; Aneurysmal; Tumor; Denosumab; Spine.

RESUMO

Introdução: O denosumab é um anticorpo monoclonal humano que se liga ao receptor ativador do fator nuclear kB (RANKL), sendo utilizado no tratamento da Osteoporose. O Tumor de Células Gigantes (TCG) e o Cisto Ósseo Aneurismático (CAO) utilizam o mesmo RANKL, por isso esse medicamento passou a ser utilizado para seu tratamento. Há consenso sobre o uso, o tempo de dosagem e a duração de 12 meses para o tratamento com Denosumabe de TCG. Não é assim para CAO. Em tumores irressecáveis, incapacitantes ou recorrentes, seu uso pode ser vitalício. Os eventos adversos do uso habitual do medicamento são conhecidos, mas não se sabe se aumentam com o tempo. O objetivo do presente trabalho é identificar os possíveis eventos adversos do tratamento com Denosumabe por mais de 12 meses. Material e Método: Série de casos com diagnóstico de TCG ou CAO na coluna, tratados com Denosumabe por mais de 12 meses. Os eventos adversos são: artralgia, fadiga, dor na coluna, dor nas extremidades, cefaleia, hipocalemia, hipocalcemia, osteonecrose da mandíbula, transformação maligna, fraturas patológicas. Resultados: Oito pacientes, 6 TCG e 2 LRA, com média de idade ao diagnóstico de 25,6 anos; apresentando um tratamento médio de 4,18 anos (variação 1,7 - 8,7). Dos 6 pacientes operados, 4 tiveram recorrência (2 a 36 meses após a cirurgia). Um paciente teve que suspender o tratamento por necrose da mandíbula, outro hipocalcemia, ambos voltaram ao tratamento quando estabilizados. Conclusões: Um evento adverso menor (hipocalcemia) e um evento adverso maior (necrose óssea da mandíbula) foram observados. ***Nível de Evidência IV; Original.***

Descritores: Tumor de Células Gigantes de Osso; Cistos Ósseos Aneurismáticos; Tumor; Denosumab; Coluna.

RESUMEN

Introducción: El Denosumab es un anticuerpo humano monoclonal que se une al receptor activador del factor nuclear kB (RANKL), se lo utiliza en el tratamiento de Osteoporosis. El Tumor de Células Gigantes (TCG) y el Quiste Óseo Aneurismático (QOA), utilizan los mismos RANKL, y por ello se comenzó a utilizar esta droga para su tratamiento. Existe consenso en la utilización, dosis-tiempo y 12 meses

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Received on 06/30/2021 accepted on 01/18/2022
Reviewed by: Dr. Helton Delfino

de duración para el tratamiento con Denosumab del TCG. No así para el QOA. En tumores irresecables, incapacitantes o con recidiva, su uso podría ser de por vida. Se conocen los eventos adversos de la utilización habitual de la droga, pero no se sabe si estas aumentan con relación al tiempo. El objetivo del presente trabajo, es identificar los posibles eventos adversos del tratamiento con Denosumab por más de 12 meses. Material y Método: Serie de casos con diagnóstico de TCG o QOA de columna, tratados con Denosumab por más de 12 meses. Los eventos adversos son: artralgias, fatiga, raquialgia, dolor en extremidades, cefalea, hipopotasemia, hipocalcemia, osteonecrosis de mandíbula, transformación maligna, fractura patológica. Resultados: Ocho pacientes, 6 TCG y 2 QOA, con promedio de edad al diagnóstico de 25,6 años; presentando una media de tratamiento de 4.18 años (rango 1,7 – 8,7). De 6 pacientes operados, 4 presentaron recidiva (2 a 36 meses después de la cirugía). Un paciente se debió suspender el tratamiento al presentar una necrosis de mandíbula, otro hipocalcemia, ambos retornaron al tratamiento al estabilizarse. Conclusiones: Se observa un evento adverso menor (hipocalcemia) y un evento adverso mayor (necrosis ósea de mandíbula). ***Nivel de Evidencia IV; Original.***

Descriptores: Tumor *Óseo de Células Gigantes; Quistes Óseos Aneurismáticos; Tumor; Denosumab; Columna.*

INTRODUCTION

Denosumab is a human monoclonal antibody (IgG2) that binds with high affinity and specificity to the receptor activator of nuclear factor kB ligand (RANKL). The interaction of this ligand with the receptor (RANK) promotes the activation, differentiation, and migration of the osteoclasts and the osteoclast precursors, favoring bone resorption. Denosumab acts to inhibit this interaction and, thus, the activity of the osteoclastic cells.[1,2]

Denosumab was initially used for the treatment of osteoporosis in postmenopausal women. Some time later, when the involvement of RANKL in the pathogenesis of some osteolytic tumors was demonstrated,[3] denosumab began to play a leading role in treating them. Its inhibitory action was shown to be effective for both normal and tumoral cells, acting on the disproportionate bone destruction and lysis produced by the superexpression of RANKL by these neoplastic cells.[4]

There is consensus around the treatment of giant cell tumors (GCT) and there are increasingly more articles related the use of denosumab for aneurysmal bone cysts (ABC). Given both the satisfactory results achieved using denosumab in patients with GCT[5-8] and the similarity of its pathogenesis to that of ABC,[9] the same treatment began to be used as an innovative therapeutic option for the latter.[10-12]

In the bibliography, there are several scientific studies reporting the ideal treatment dosage and duration as 120 mg administered subcutaneously once a month for 12 months.[13] The indications for this treatment are tumor recurrences, in intralesional resections as neoadjuvant therapy or in cases where complete resection is difficult due to the location and the possible consequences that may occur. Regarding the latter, prolonged treatment has the benefit of stopping tumor progression and relieving symptoms.[14] However, there is still no consensus around the appropriate duration of treatment beyond 12 months, the dosage interval, the presence of adverse effects due to cumulative toxicity, or the consequences that may occur by suspending it after this period.

The objective of the present study was to identify the possible adverse events resulting from treatment with denosumab for more than 12 months, its effects on osteolytic vertebral tumors, and dose management.

METHODS

We analyzed a series of cases diagnosed with GCT or ABC of the spine, treated with subcutaneous denosumab continuously for 12 months, evaluating age at diagnosis, presence of previous surgery, tumor recurrence, and any adverse events that required suspending, restarting, or modifying the doses administered.

Among the most described intratreatment adverse effects described in the literature are arthralgia, fatigue, spinal pain, pain in the extremities, headache, hypokalemia, hypocalcemia, osteonecrosis of the jaw, malignant transformation, and pathological fracture.

RESULTS

We present 8 patients (6 women and 2 men), all of them currently in treatment, with a mean age at diagnosis of 25.6 years (ranging from 14 to 39) and an average treatment duration of 4.17 years (ranging from 1.7 to 8.7).

Six patients had GCT; 1 cervical, 1 thoracic, 2 thoracolumbar, and 2 sacral (Figure 1), one of whom had a polyostotic variant associated with involvement of both femurs. Two of the patients had ABC, 1 thoracic and 1 lumbar.

Six patients had a history of previous surgery, recurrence being the indication for denosumab in 4 of them (from 2 to 36 months after the first surgery) and intralesional resection in another case (Figure 2). All the patients had good results in controlling the lesion (with a decrease in mass and better pain control), which justified the use of denosumab.

Treatment had to be discontinued in 1 patient due to jaw necrosis following removal of a molar 3 months before its presentation. After 9 months, treatment was reinitiated with 60 ml/5 months.

Another adverse event that required suspension of a treatment dose was hypocalcemia, confirmed in a previous control (Table 1).

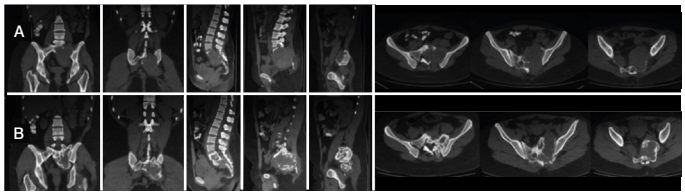

Figure 1. Patient 1, with GCT of the sacrum. Female, 36 years of age at the time of diagnosis, medical consultation for mechanical low back pain, diagnosis performed by fine needle aspiration biopsy. A – Tomography images from March 2016 showing lytic lesion affecting the sacrum. B – Tomographic study from December 2019 showing the evolution of the lesion after 45 months of pharmacological treatment.

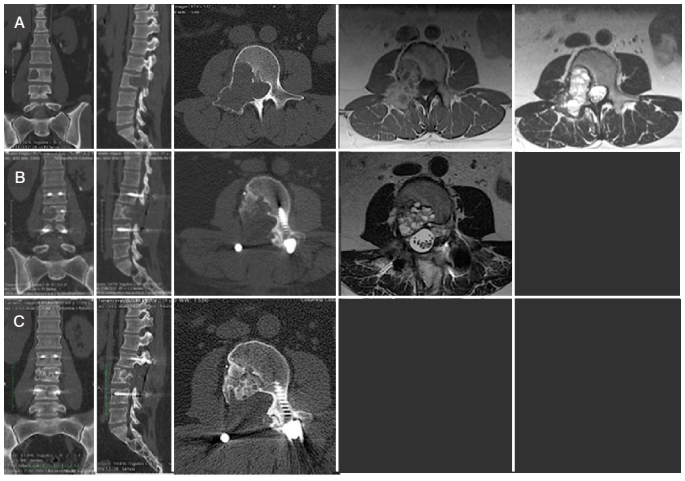

Figure 2. Patient 4, with ABC. Female, 38 years of age at the time of diagnosis, treated by wide resection, who presented lesion recurrence 24 months after surgery. Treated since that time with denosumab. A – Preoperative tomography and resonance images showing the lytic lesion affecting the posterior arch and right body of L3. B – Tomographic and magnetic resonance study two years following surgery. C – Tomographic study after 18 months of pharmacological treatment.

Table 1. Epidemiological patient data.

Patient	Sex	Age at diagnosis (years)	Diagnosis	Location	Previous surgery	Recurrence time (months)	Start date	Adverse event
1	F	36	GCT	Sacro	No	0	03/04/2016	Hypocalcemia
2	F	26	GCT	L3	Yes	36	09/06/2016	No
3	M	39	GCT	C5	Yes	5	11/1/2012	Necrosis of the jaw
4	F	38	ABC	L3	Yes	24	11/10/2016	No
5	M	13	GCT	T11	Yes	2	06/12/2018	No
6	F	16	ABC	T6	Yes, Intralesional	0	09/26/2017	No
7	F	14	GCT	Sacrum and femurs	No	0	12/01/2017	No
8	F	24	GCT	T12	Yes	0	06/07/2019	No

F = female, M = male, GCT = giant cell tumor, ABC = aneurysmal bone cyst.

DISCUSSION

The use of denosumab to treat GCT and ABC has been the subject of recent studies with good clinical and radiographic results. There are protocols for the administration of doses of 120 mg per month for 12 months. There is still no consensus around the treatment of ABC, but the same scheme as that used for GCT is followed. However, there are situations where prolonged use of this drug is necessary.[15]

In our work, we reported on 7 cases of patients diagnosed with GCT and ABC in which denosumab had to be used for more than 12 months, either due to tumor recurrence, unresectable tumors, or after intralesional resection, the mean duration of treatment being 3.5 years.

Since denosumab began to be used for these types of tumors, complications such as arthralgia, fatigue, spinal pain, pain in the extremities, headache, hypokalemia, hypocalcemia, hypercalcemia (mainly in the pediatric population), osteonecrosis of the jaw, malignant transformation, and pathological fractures have been reported.[2,16-22] However, it is not yet clear whether prolonged treatment would favor appearance of new complications and whether the dose administered should be adapted to said treatment.

Sambri et al.[23] studied 26 patients with aggressive GCT in the sacrum and pelvis who were treated with denosumab for a mean duration of 65 months. Of these, only three had complications: hypocalcemia, osteonecrosis of the jaw, and a malignant transformation to osteosarcoma. The authors believe that prolonged treatment with denosumab is a suitable alternative to be considered in GCT of this nature.

On the other hand, Palmerini et al.[24] conducted a study to evaluate the long-term toxicity of denosumab in GCT patients. They demonstrated substantial clinical and radiographic benefits in treatment between 6 and 115 months of duration and reported the appearance of dose-dependent osteonecrosis of the jaw in 6% of the patients, more frequent in patients with previous dental comorbidities. They suggest evaluating periods of interruption or lower doses in patients for whom denosumab is the only alternative.

In a multicenter study with 532 patients treated with denosumab for an average of 58 months, Chawla et al.[4] reported an increased frequency of the appearance of osteonecrosis of the jaw with increased exposure to denosumab, preceded by tooth extraction and dental infections in 75% and 50% of these cases, respectively. They recommend periodic dental check-ups, promoting good dental hygiene, and suspending the treatment before an invasive procedure, only resuming it when the oral mucosa is completely healed. However, despite the appearance of these complications, they consider that treatment with denosumab in patients with unresectable GCT or in those whose resection is accompanied by severe morbidity, to be favorable.

The use of denosumab for more than 12 months is still a controversial topic, but our study, as well as other articles in the world literature, show that this treatment in candidate patients has beneficial results despite the documented complications.

CONCLUSIONS

In the present series of 8 cases with treatment longer than 12 months, we observed a minor adverse event (hypocalcemia) and a major adverse event (osteonecrosis of the jaw) due to removal of a tooth without prior suspension of the drug. The drug was discontinued for 9 months and subsequently prescribed at a lower dose.

All authors declare no potential conflict of interest related to this article.

CONTRIBUTIONS OF THE AUTHORS: All authors made significant individual contributions to this manuscript. PLB: Planning, selection of the patients, patient admission, data analysis, image management, editing of the final document; MC: theoretic support, writing of the draft, and translation; FLZ, RC, CS, JLM, EGG, AMS: Selection of the patients, editing of the draft and final text.

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