

Case Report

Denosumab Related Osteonecrosis of the Jaws as Consequence of Osteoporosis Treatment- A Case Series

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Abstract: Bisphosphonate-related osteonecrosis of the jaws represents a widely studied pathology. Moreover, some cases of ONJ related to the use of Denosumab have also been described recently. Denosumab is a human monoclonal antibody. It is bound with high affinity and specificity to nuclear factor kappa beta activating factor ligand (RANKL) and prevents Rank activation with reduction bone reabsorption. However, medium and long term effects of this drug are not unknown yet. The main goal of the present report is twofold. First, we point out the serious complications that these drugs might provoke. Second, we describe four cases of Denosumab related ONJ in order to expand the knowledge about the proper management of this rare complication.

Keywords: Denosumab, osteonecrosis of the jaw, osteoporosis, conservative treatment

INTRODUCTION:

Bisphosphonate-related osteonecrosis of the jaws was first described in 2004 by Ruggiero [1]. This author related this disease with the intravenous administration of bisphosphonates in patients affected by bone metastases of solid tumors. The diagnostic classification of this condition was initially proposed in 2009 [2]. However, it was modified in 2014 to include other antiresorptive and antiangiogenic drugs [3]. Three main diagnostic parameters was established in this new classification:

- 1- Previous or current treatment with antiresorptive and/or antiangiogenic drugs;
- 2- Intraoral bone exposure or intraoral either external fistula lasting more than 2 months;
- 3- No evidence of jaw radiotherapy in patient's medical history;

Denosumab is a human monoclonal non-chimeric antibody (IgG2). It is bound with high affinity and specificity to nuclear factor kappa beta activating factor ligand (RANKL) and prevents Rank activation. Hence, Denosumab reduces osteoclast function and bone reabsorption [4]. However, medium and long term effects of this drug are not unknown yet. Nowadays, two drugs that contain Denosumab exist. Specifically, Prolia® and Xgeva® have been formally approved by European Medicines Agency. Prolia is indicated for

treating ordinary postmenopausal osteoporosis, as well as in men with osteoporosis and high risk of fracture. Moreover, this drug is also authorized to mitigate the bone reabsorption related with the hormone therapy of prostate cancer. In contrast, Xgeva is indicated to prevent oncological complications as pathological fractures, spinal cord compression and side effects of radiation treatment.

The main goal of the present report is twofold. First, we point out the serious complications that these drugs might provoke. Second, we describe four cases of Denosumab related osteonecrosis of the jaws in order to expand the knowledge about the proper management of this rare complication.

CASE REPORTS:**Case 1:**

89 years old Caucasian female with a personal history of type 2 diabetes and significant osteoporosis treated with alendronate (one tablet of 70 mg weekly), calcium supplements and cholecalciferol from 2003 to 2012. However, alendronate was changed to Prolia® (60 mg/ one subcutaneous injection every 6 months) due to the appearance of two pathological fractures in 2012. Specifically, treatment with Prolia® was continued until July 2014. In this span of time (April 2014) patient was submitted to surgical extraction of mandibular incisors. Consequently, patient began

presenting clinical symptoms of ONJ with the appearance of induration of the submental area and extraoral fistula. Thus, patient was referred to outpatient department of Maxillofacial Service by family doctor. After a careful examination we decided to perform a head and neck CT in order to achieve a proper diagnosis. CT images showed the presence of a serious ONJ (Fig. 1) (ONJ EIII). Against this backdrop, we choose to treat the case with conservative approach. In fact, we carried out the drainage of mandibular abscess. Besides, we prescribed oral antibiotic treatment with amoxicillin clavulanate 875/125mg every 8 hours for 15 days. Additionally, the patient was instructed to make mouthwash with chlorhexidine. Patients responded well to treatment and no recurrences were evidenced during the follow-up.

Case 2:

68 years old Caucasian female with postmenopausal osteoporosis treated with alendronate (one tablet of 70 mg weekly), calcium supplements and cholecalciferol from 2000 to 2012. However, alendronate was changed to Prolia® (60 mg/ one subcutaneous injection every 6 months) in 2012 and this treatment was continued until June 2014. In September 2014, the patient was undergoing oral surgery to extract several teeth. In November 2014, patient was referred to our service due to the appearance of an oral ulcer in mandibular third quadrant. Thus, an orthopantomography (Fig. 2) and oral biopsy were carried out. Finally, oral biopsy confirmed the diagnosis of ONJ (ONJ stage EII). As in the previous case, we treated the case with conservative approach. Oral antibiotic treatment with amoxicillin clavulanate 875/125mg every 8 hours for 15 days and mouthwash with chlorhexidine were indicated. As before, the patient remained asymptomatic during the follow up.

Case 3:

75 years old Caucasian female who received during 20 years BFF (150 mg of ibandronic acid every month) to treat a severe osteoporosis (secondary to long-term treatment with corticosteroids). Nevertheless, ibandronic acid was changed to Prolia® in 2014 (60 mg/ one subcutaneous injection every 6 months). In February 2015, patient experienced signs of ONJ as pain and intraoral bone exposure after the extraction of multiple teeth in the left side of the jaw. Consequently, patient was referred to outpatient department of maxillofacial service. ONJ diagnosis was made with orthopantomography and face CT (ONJ stage II). In this context, we order the suspension of the drug immediately. As before, patient was treated with conservative approach (oral antibiotic treatment with amoxicillin clavulanate 875/125mg every 8 hours for 15 days and mouthwash with chlorhexidine). To date, no recurrences were evidenced during repeated patient examinations.

Case 4:

55 years old Caucasian female who received during 6 years alendronate (one tablet of 70 mg weekly) for treating a severe osteoporosis (secondary to long-term treatment with corticosteroids). Notwithstanding, alendronate was changed to Prolia® in 2010 (60 mg/ one subcutaneous injection every 6 months). In 2013, patient began presenting cyclic joint swelling and joint pain without bone exposition (ONJ stage 0). As before, orthopantomography and face CT confirmed the diagnosis. In view of that, we recommended the suspension of Prolia® and we treat the pathology with a conservative approach (oral antibiotic treatment with amoxicillin clavulanate 875/125mg every 8 hours for 15 days and mouthwash with chlorhexidine). No complications were evidenced during patient follow-up.

Table-1: Summary of the cases

	Age	Risk Factors	BFF treatment time and route of administration	Denosumab treatment time	ONJ stage	Indiations to use Denosumab	ONJ Treatment
Case 1	89	Oral surgery procedures type 2 diabetes	oral treatment during 10 years	2 years	III	Severe osteoporosis with high risk of pathological fractures	Abscess drainage + Conservative treatment
Case 2	68	Oral surgery procedures	oral treatment during 12 years	2 years	II	postmenopausal osteoporosis	Conservative treatment
Case 3	75	Oral surgery procedures long-term treatment with corticosteroids	oral treatment during 20 years	1 years	II	Severe osteoporosis with pathological fractures	Conservative treatment
Case 4	55	long-term treatment with corticosteroids	oral treatment during 6 years	3 years	0	postmenopausal osteoporosis	Conservative treatment



Fig-1: CT image of bilateral Denosumab related osteonecrosis of the jaws.



Fig-2: Radiographic image of Denosumab related ONJ in mandibular third quadrant.

DISCUSSION:

Bisphosphonate-related osteonecrosis of the jaws represents a widely studied pathology. However, recently, some cases of osteonecrosis of the jaws related to the use of Denosumab have also been described in oncological patients [8,9]. In addition, Neuprez A. *et al* described the first case of Denosumab related ONJ in an osteoporosis patient underwent oral surgery [10].

Despite the efforts of scientific community, the pathogenesis of ONJ related with antiresorptive agents has not been fully clarified [4]. In this sense, the association of poor jaws coverage, inhibition of bone metabolism produced by this medication and high

population incidence of periodontal and dental disease could explain the frequent affectionation of these bones [11]. Furthermore, the expression of this disease may be facilitated by dental procedures (case 1, 2 and 3), diabetes and long-term steroid use (case 1 and 3) [12].

In our cases, a cause and effect relationship between the use of Denosumab and ONJ was established using the Karch-Lasagna causality scale [13]. Indeed, a temporal association between the use of Denosumab and ONJ was evidenced. Moreover, all patients experienced a clear clinical improvement after the suspension of Denosumab.

In this line, several studies showed that Denosumab could be associated with an higher risk of ONJ compared to zoledronic acid ($p>0,05$) [15]. Notwithstanding, Denosumab does not present antigenic activity and it is not incorporated into the bone matrix [14]. This may explain the great response to conservative treatment of our cases [16]. As stated before, oral surgery, tooth extraction, poor oral hygiene and dental prostheses have been proposed as independent risk factors for the development of ONJ. Therefore, an accurate oral examination before the beginning of bisphosphonate treatment is mandatory. The existence of dental pathology need to be diagnosed and treated prior to the commencement of antiresorptive treatment. This attitude might reduce the frequency of ONJ.

Importantly, we would like to highlight that there are no elements to determine the necessary waiting time to perform dental procedure after the suspension of antiresorptive treatment. It is important to note that although the relationship between oral bisphosphonate and Denosumab with ONJ exists, according to us this risk is relatively low if considering the great sample of patients who take this medication (5.1 million over 55 years) [17].

CONCLUSION:

Stemmatologists, oral surgeons and maxillofacial surgeons need to be aware of the risks associated with antiresorptive and antiangiogenic drugs. Diagnosis of oral pathology before starting the antiresorptive treatment is mandatory. This might reduce the frequency of ONJ related to these drugs.

Conflict of interests:

The authors declare that they have no conflict of interests.

Ethical standards:

Authors declare we that they have taken into account the ethical responsibilities.

Authors' contributions:

All authors participated in the creation of manuscript.

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Informed Consent:

All patients agreed to participate in the study, and all of these signed the informed consent.

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