

Original Article

Clinical attitude regarding denosumab drug-holiday for dental extraction in oncologic patients: a national survey

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Abstract – Introduction: Denosumab is indicated in oncology to reduce tumoral development. However, this medication may cause osteonecrosis of the jaw, especially after dental extractions. Drug holiday has been proposed to decrease the risk of osteonecrosis of the jaw. This survey aimed to assess the management of drug holidays for patients who needed both dental extraction and denosumab. **Methods:** A questionnaire was sent to a panel of healthcare professionals. **Results:** Of the 33 practitioners interviewed, 28 undertook or “were used to” dental extractions in patients on denosumab. 25% (7/28) of the practitioners questioned did not stop patients from taking denosumab before dental extraction and 75% (21/28) used a drug holiday. For those who stopped the treatment, 33% (7/21) waited 2 months before performing dental extraction and 38% (8/21) waited 2 months after the dental extraction before reintroducing the molecule; 2 months being the median duration in both cases. In addition, 89% (25/28) of practitioners, modified their surgical procedure for these patients. **Conclusion:** Despite a small number of responders, it seemed that a drug holiday of at least 2 months is mandatory before performing tooth extraction. The issue of the drug holiday should always be raised with the patient’s oncologist.

Introduction

Denosumab is a human monoclonal antibody indicated in oncology and administered by subcutaneous injection at 120 mg every 4 weeks [1]. This drug prevents bone complications in adult patients with advanced malignancy with bone involvement, for patients with giant cell bone tumors unresectable or for which surgical resection is likely to cause severe morbidity [2]. It interferes in RANKL/RANK complex by playing osteoprotegerin role which conduce to inhibit osteoclastic activity and therefore to stop bone resorption [3]. It results in a limitation of tumor development [4].

However, patients undergoing this treatment are at significant risk of developing osteonecrosis of the jaw after dental extractions [5–7]. Indeed, it reduces bone remodeling via its anti-osteoclastic activity, but osteoclasts are also necessary for the socket’s healing by remodeling the new bone matrix with a peak of activity at the 14th day after the dental extraction.

Osteonecrosis of the jaw is defined clinically by the AAOMS (American Association of Oral and Maxillofacial Surgeons) as

the exposure of a necrotic bone and must fulfill several conditions [8]:

- The patient must receive or have received a treatment which may induce osteonecrosis.
- The bone must be exposed or accessible via a fistula for more than eight weeks.
- The patient must not have received radiotherapy, nor have metastasis in the necrotic area.

Osteonecrosis in a patient treated with denosumab is called DRONJ (Denosumab Related Osteo Necrosis of the Jaw). The incidence of DRONJ in the context of cancer ranges between 0.5% and 2.1% after one year of treatment, 1.1% and 3% after two years, and between 1.3% and 3.2% after three years [9]. One of the main precipitating factors of such osteonecrosis of the jaw is dental extraction [10].

Adapting the tooth extraction protocol for these patients constitutes a significant means of preventing the occurrence of these lesions. This procedure has already been standardized by the SFSCMFCO (French Society of Stomatology, Maxillofacial Surgery and Oral Surgery) since 2013 and a drug holiday was proposed but without a specified duration [11,12]. It is important to note that the maximum serum concentration of denosumab is reached on the tenth day, and then decreases over 5 months with a half-life of 25.8 days [13]. Therefore, it seems coherent to consider a drug holiday given that this

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Determination of a drug holiday for performing dental extractions in patients treated with Xgeva®.

Xgeva® (DENOSUMAB) is indicated in oncology to reduce tumor development. However, this molecule may promote the occurrence of osteonecrosis of the jaw, particularly in the case of dental extraction.
We aim to assess the drug holiday used in practice.

The answers to this questionnaire are anonymous.
We thank you for your help in this work.

1. Do you perform dental extractions for patients on Xgeva®? *

Yes

No (go directly to question 7)

2. If yes, do you stop Xgeva® before performing a dental extraction?

Yes

No

3. How long do you wait between stopping Xgeva® and performing the dental extraction?

0 1 2 3 4 5 6

months

4. How long do you wait between the dental extraction and resuming Xgeva® treatment?

0 1 2 3 4 5 6

months

5. Do you modify your surgical procedure when performing an extraction in these patients?

Yes

No

6. In this case, does your protocol include: (multiple responses possible)

Antibiotic prophylaxis

Hemostasis protocol (collagen sponge, sutures)

Other...

7. You are:

Dental surgeon

Stomatologist

Maxillo-facial surgeon

Other...

8. You practice: (several answers possible)

In private practice

In a hospital

Other...

Fig. 1. Questionnaire: 8 questions on Google Form.

molecule has an elimination rate that is much faster than some bisphosphonates (10.5 years for alendronate) because it does not incorporate into bone [14,15]. The objective of this survey was firstly to identify whether practitioners use a drug holiday, and secondly, for those that did, how long they stopped this molecule for.

Method

A panel of healthcare professionals were asked to complete a questionnaire (Fig. 1). This one was disseminated online (Google Forms) through a scientific community (the French Society of Oral Surgery (SFCO)) and was made accessible for two months (12.06.2020–12.08.2020).

Results

33 healthcare professionals responded. Of the sample, 29 were dental surgeons (general practitioners, specialized in oral surgery or in oral medicine) and 4 were stomatologists (Fig. 2a). 8 worked only in private practices, 15 worked only in hospitals, and 10 work in both contexts (Fig. 2b).

Of the 33 people interviewed, 28 undertook dental extractions in patients on denosumab.

21 out of 28 used a drug holiday to perform it (Fig. 2c).

For those who stopped denosumab (21/28), 5 waited 1 month before performing dental extraction; 7 waited 2 months, 4 waited 3 months, 4 waited 4 months, and 1 waited 5 months (Fig. 2d). The median time interval was 2 months, and the average 2.47 months.

After the dental extraction, 1 waited 2 weeks before reintroducing the molecule; 4 waited 1 month, 8 waited 2 months, 6 waited 3 months, and 2 waited 4 months (Fig. 2e). The median time interval was 2 months, and the average 2.21 months.

25 out of 28 people questioned modified their surgical procedure for these patients (Fig. 2f). For example, 24 used prophylactic antibiotic treatment, 16 achieved hemostatic protocol (collagen sponge, suture), 6 hermetically closed the area using sutures (\pm /– with muco-periosteal flap) in order to have the least possible bone exposure, 5 disposed PRF (Platelet Rich Fibrin) (Fig. 3), and less than 8% applied other methods such as biological glue (2/28), anesthesia without adrenaline (2/28), or general anesthesia (1/28).

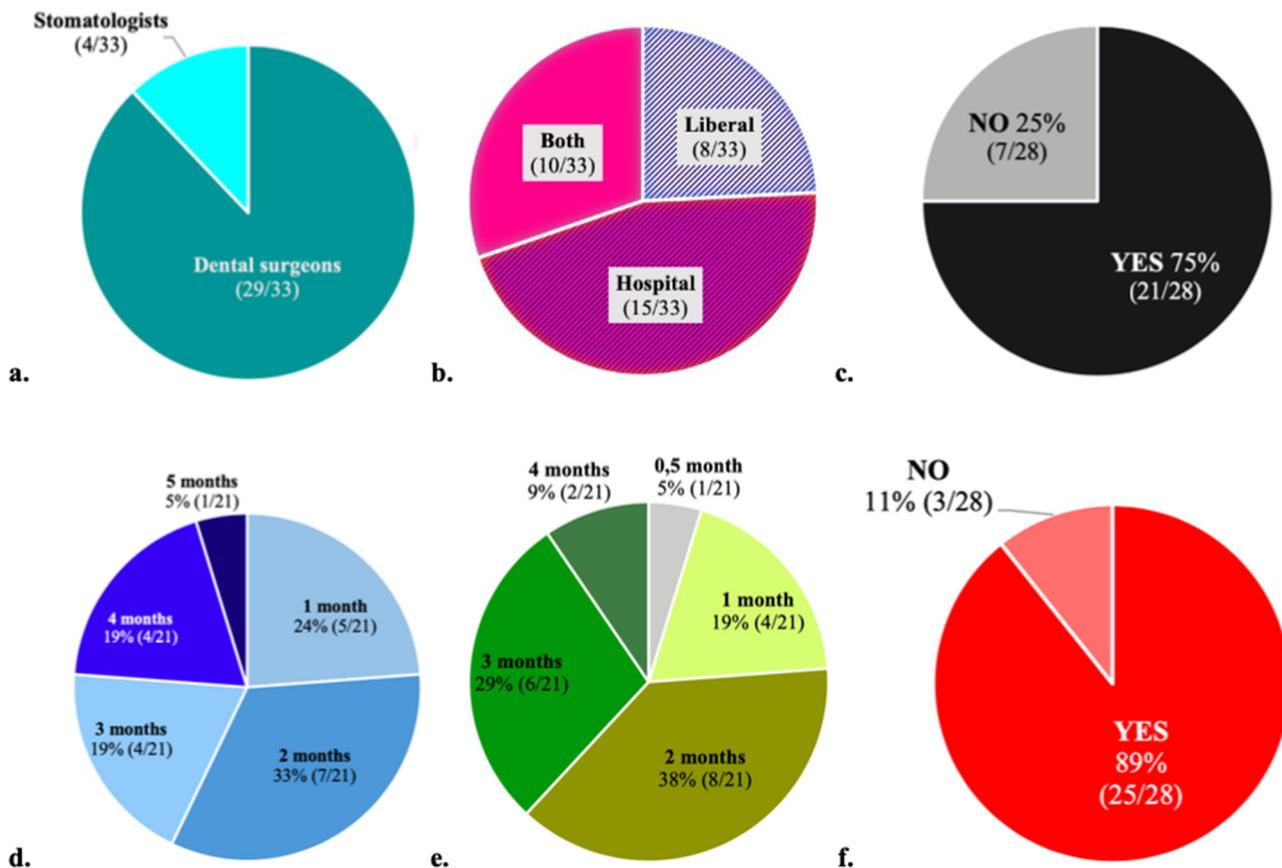


Fig. 2. (a to f): Results: a. Profession; b. Practice; c. Do you stop denosumab before having a dental extraction?; d. How long do you wait between stopping denosumab and dental extraction?; e. How long do you wait between dental extraction and reintroducing denosumab?; f. Do you modify your surgical procedure during extraction in these patients?

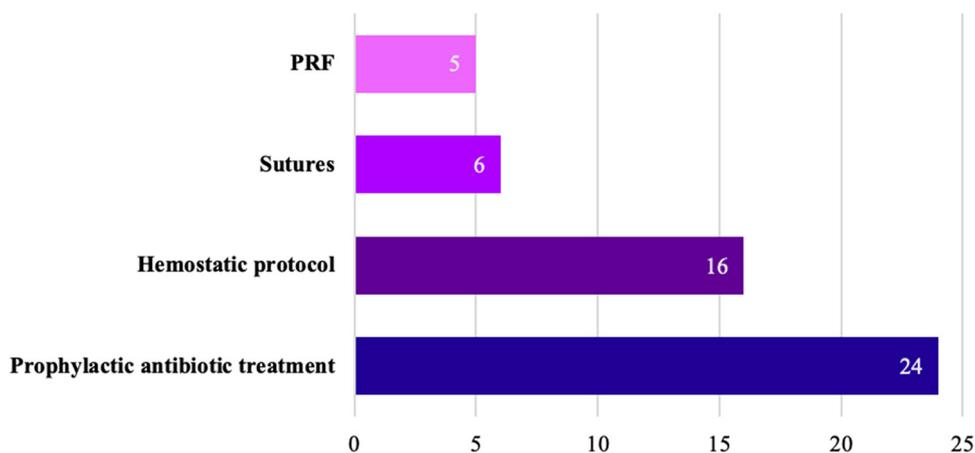


Fig. 3. Question 6: Protocol modifications.

Discussion

In regard to the surgical procedure, 90% of practitioners questioned modify their protocol. The French recommendations are above all for bisphosphonates [12]. It could be applied to

denosumab, also an anti-osteoclastic molecule. They suggest reducing inflammation or local infection before surgery with periodontal care, daily mouthwashes with chlorhexidine 0.2%, and antibiotic prophylaxis and postoperative antibiotics [16–18].

The surgical procedure needs to be as less traumatic as possible, with alveolar regularization and the closure of the wound without tension [18,19]. Depending on studies a full thickness flap can be used [18–20]. Few data are available about anesthesia, only one study contraindicates the use of intra-ligament or intra-papillary anesthesia. No study excludes the use of vasoconstrictors.

In this survey, both prophylactic antibiotic treatment and hermetic closure of the area with sutures comply with the recommendations [12].

The practitioners questioned agreed that the molecule must be stopped when undertaking a dental extraction. Indeed, 75% of surgeons interviewed used a drug holiday. The waiting period before performing the dental avulsion was most commonly two months, more than twice the half-life of the molecule, and practitioners reintroduced the molecule on average 2 months after dental extractions. However, osteoclastic cells intervene in the first month of sockets healing with a peak of activity at the 14th day after extraction [21]. Denosumab only had an effect on these osteoclastic cells, so theoretically, this medication could be reintroduced one month after the extraction.

The oncological benefit of denosumab should not be forgotten. The drug holiday must be as short as possible to manage metastasis development and its symptomatology. During this break the follow-up is essential and tumor markers and tumor development must be monitored. The absence of necrosis of the jaw is obviously meaningless without the absence of tumor progression.

Concerning literature, the recommendations are blurry, especially concerning denosumab. In fact European and French recommendations (2009 and 2013) only talk about bisphosphonate; and the drug-holiday mentioned for this medication must be discussed with the prescribing doctor [12,22]. An international consensus from the International Task Force on ONJ suggested to withhold denosumab for oral surgery until the socket's healing but there is no evidence [10,23]. Finally, the American Dental Association Council on Scientific Affairs conclude that there is no sufficient proves to stop anti-resorptive drug therapy before a dental extraction to prevent Antiresorptive Agent-Related Osteonecrosis of the Jaw (ARONJ) [24].

Thus, the shift between practices and recommendations is still high. Too little studies are available about these subject, and there are not enough proofs to recommend denosumab drug-holiday. However, this must be even more considered if denosumab time exposure is important because ONJ incidence increases overtime from 0.5% to 2.1% after one year, to 1.1% to 3% after 2 years, and 1.3% to 3.2% after 3 years [9]. The time-related evolution of the occurrence of ONJ showed the molecule impregnation, and a drug-holiday appear more evident. Practitioner's habits are based on subjective clinical experience. Further studies (including a prospective trial) are required to determine which time interval is required, while taking exposition duration and oncologic constraints into account.

Conclusion

In the literature, the recommendation for a dental extraction procedure is already known for patients on denosumab. However, despite this recommendation, zero risk does not exist. The question is: is it possible to reduce ONJ even further by withholding denosumab?

There is no answer in the literature, however, this survey has shown that in practice healthcare professionals do stop denosumab before performing dental extraction. The results show that the average drug holiday duration for denosumab is two months before and two months after the dental extraction. This drug-holiday must be discussed with the patient's oncologist while taking into account denosumab exposition duration and oncologic constraints.

Conflicts of interest: All authors state that they have no conflicts of interest.

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