

Osteonecrosis of the jaw in patients taking Atorvastatin: Case series

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Abstract

Osteonecrosis of the jawbones commonly seen in patients taking bisphosphonates, denosumab, and several antiangiogenic medications with several oral factors such as tooth extraction or dental infection. Currently, patients taking Simvastatin, a medication commonly used to treat hypercholesteremia, were reported of developing osteonecrosis of the jaw. Thus, it is important that clinicians know about the risk of osteonecrosis for patients taking this hypercholesteremia medication. It is not known if the undesirable effect only occurs with Simvastatin or other types of statin medication. We report in detail three cases of osteonecrosis of patients taking Atorvastatin calcium, a second-generation statin medication.

Keywords: *bisphosphonate, MRONJ, mevalonate pathway, osteonecrosis, statin*

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Introduction

Medication-related osteonecrosis of the jaw (MRONJ) can be diagnosed when a patient treated with bone modifying agents or angiogenesis inhibitor presented with the exposed bone for more than eight weeks, without a history of radiation therapy (He *et al.*, 2020). When a patient taking medications known to induce MRONJ, coupled with several oral factors such as dental infection, ill-fitting denture, tooth extraction, or other dental surgery procedures, the development of MRONJ

could be triggered (Fede *et al.*, 2018). Common medications associated with MRONJ include bisphosphonate, denosumab, and bevacizumab (He *et al.*, 2020).

Recently, three cases of osteonecrosis of the jaws in patients taking Simvastatin were reported (Giladi *et al.*, 2020; Samieirad *et al.*, 2021). We want to add three more cases of patients taking Atorvastatin calcium for the treatment of hypercholesteremia, presented with osteonecrosis following the tooth extraction procedure. This manuscript was prepared according to the CARE Guidelines

for reporting case reports and case series (Riley *et al.*, 2017).

Case description

Three patients taking Atorvastatin, prescribed by the physician for the treatment of underlying hypercholesteremia. All of them went to the dental practice for tooth extraction procedures. Normal tooth extraction was performed smoothly. Subsequently, the patients developed exposure of necrotic bone after the tooth extraction procedure in both the maxilla and mandible. The patients also complained of pain at the extraction socket, after the procedure.

None of the patients have undergone radiation therapy, taking steroid and

bisphosphonate medications, or smoking. Two of the patients were also diagnosed diabetes mellitus. Clinical diagnosis of osteonecrosis of the jaw was made for all cases, based on the complain and the clinical presentation of necrotic bone exposure and the non-healing extraction socket.

The treatments done for the management of osteonecrosis include surgical debridement of the necrotic bone and primary wound closure technique. All patients were reviewed until healing of the extraction area. The cases took up to four months duration for healing. The cases were reviewed again after six months to confirm the healing. The details about the three cases are summarized in Table 1, and one case is illustrated in Figure 1 and Figure 2.

Table 1. Summary of cases.

Case	Age/ gender	Atorvastatin calcium dosage	Location	Surgical procedure	Duration for healing
1	53, Male	80mg	Mandible	Extraction 36	Three months
2	71, Female	10mg	Maxilla	Extraction 11 and 12	Four months
3	61, Male	10mg	Mandible	Extraction 33	Three months



Figure 1. Osteonecrosis in the maxilla after extraction of 11 and 12 (Case 2)



Figure 2. Wound debridement and suture placed in Case 2.

Discussions

According to the American Association of Oral and Maxillofacial Surgeons, MRONJ can be defined by clinical presentation by ongoing or history of antiangiogenic or antiresorptive drugs, absent of history of radiation therapy and metastasis to the jaw, and exposed bone or presence of an intraoral or extraoral fistula in the maxillofacial region persisting for more than 8 weeks (Ruggiero *et al.*, 2014). Even though our cases did not satisfy the first criteria, the clinical presentation are similar to the reported MRONJ cases.

MRONJ is a serious adverse reaction developed by patients taking certain medications resulting in the destruction of maxillary and mandibular bone. The common medications associated with MRONJ are used in the treatment of osteoporosis and cancer. The condition is a challenge to clinicians because the treatment is not easy (Beth-Tasdogan *et al.*, 2017). The pathophysiology of MRONJ is still not well understood, and TGF- β 1 signalling pathway is considered a vital element of the development of MRONJ, by disrupting the balance of osteoclast and osteoblast activity

during the bone remodelling of the jaw bone. Other factors that can cause MRONJ include

the particular characteristic of the jaw, oral infection, and altered angiogenesis (He *et al.*, 2020).

Statin drugs are HMG CoA reductase inhibitors that disrupt cholesterol production by inhibiting the conversion of HMG CoA enzyme to mevalonate (Uzzan *et al.*, 2007). Similar action can be seen in bisphosphonates containing nitrogen through its R2 chain, also inhibit the HMG CoA reductase and consequently disrupting the mevalonate pathway (Giladi *et al.*, 2020). Thus, Giladi *et al.* highlighted a common mechanism for bisphosphonates and statins in the development of osteonecrosis for patients taking prolonged, high dosage statin when publishing the first case report about this issue (Giladi *et al.*, 2020).

Underlying systematic diseases, such as diabetes mellitus (DM), could be one of the risk factors for patients developing MRONJ. DM can alter the bone remodelling, increase apoptosis of osteoblast and osteocyte, altering the immune response, in addition to microvascular damage and oxidative stress

(He *et al.*, 2020). However, the exact relationship between DM and MRONJ is still debatable and not conclusive (Peer & Khamaisi, 2015). Two of our MRONJ patients have an underlying DM in addition to hypercholesteremia. The other two reported cases by Giladi *et al.* did not have DM (Giladi *et al.*, 2020) while Samieirad *et al.* did not mention the DM status for their patient (Samieirad *et al.*, 2021).

The treatment of MRONJ is challenging and requires a long-term treatment plan. The symptoms of MRONJ may lead to a resolution of 12 months (Hinson *et al.*, 2015). Over half of the MRONJ resolved, about a quarter of the cases did not heal, while the balance developed recurrence (Beth-Tasdogan *et al.*, 2017). The standard treatment plan for managing MORNJ can be divided into nonsurgical or surgical management. The nonsurgical approach includes the use of antiseptic rinse, prescription of antibiotics. The surgical intervention includes debridement and resection of the involved area (Ruggiero *et al.*, 2014). Hyperbaric oxygen can be added to the treatment plan. However, there were no significant differences in the addition of hyperbaric oxygen with the standard care (Beth-Tasdogan *et al.*, 2017). Our patients were treated with surgical debridement and biweekly to monthly review until complete healing of the necrotic area. Similar treatment approach was utilized for the other three cases if MRONJ with Simvastatin history. However, Giladi *et al.* mentioned that their cases did not respond well so debridement (Giladi *et al.*, 2020), while Samieirad *et al.* included platelet rich fibrin (PRF) adaptation to the surgical site and it responded well (Samieirad *et al.*, 2020).

Conclusions

The association between statin and MRONJ is still not well established due to the limited number of patients in the case series. However, further investigations and research is required to conclude the additional side effect of this medication.

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