

# Jaw Osteonecrosis in Patients Receiving Oral Bisphosphonates Therapy

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## Abstract

We describe the cases of three patients, under the care of the rheumatology service, who presented with osteonecrosis of the jaw whilst on oral bisphosphonate therapy. The first case is of a 74-year-old woman with a 12 year history of sero-negative inflammatory arthritis, having been on oral steroids for 11 years, Methotrexate for the preceding 6 years, and oral bisphosphonates for 9 years. Clinical and radiographic examination revealed extensive jaw necrosis. The second patient was a 72-year-old woman with temporal arteritis, on long term oral steroids, and oral bisphosphonates presenting with jaw osteonecrosis. The third case is of an 81-year-old lady with a diagnosis of Polymyalgia Rheumatica on reducing dose of prednisolone along with calcium and vitamin D3 and oral bisphosphonate therapy as part of steroid induced prophylaxis guidelines. On reviewing the literature regarding bisphosphonate-associated osteonecrosis of the jaw, there is indeed recognition of this occurring with oral bisphosphonates. However, this is far less common than with intravenous preparations. Reports to the UK MHRA regarding adverse reactions have shown 53 cases of osteonecrosis of the jaw associated with oral bisphosphonates, but this is thought to represent under-reporting. We suggest consideration of patient counselling and consent, and preventive dental work prior to initiation of oral bisphosphonate therapy.

## Keywords

Jaw Osteonecrosis, Oral Bisphosphonates

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## 1. Introduction

Jaw osteonecrosis is a rare side effect of bisphosphonates therapy usually related to intravenous preparations. We hereby present a case series of 3 patients with osteonecrosis of the jaw secondary to oral bisphosphonates

therapy. This suggests that this condition may be under reported and consideration of dental clearance before the start of the therapy.

## 2. Case 1

A 74-year-old woman, with a 12 year history of sero-negative inflammatory arthritis, Osteoporosis and Ischaemic Heart Disease presented in March 2007, complained of recently losing two teeth in the upper left jaw, with an associated vague ache and offensive smell. Clinical examination revealed extensive jaw necrosis affecting the left maxilla in an area measuring 2.5 cm. Radiographic examination suggested extension towards the left maxillary sinus.

Oral steroids (prednisolone 5 to 7.5 mg daily) had been used to control her inflammatory arthritis over the preceding 11 years, with Methotrexate 7.5 mg weekly being introduced 6 years prior to her presentation. She had been on oral bisphosphonates since June 1998 in the form of Etidronate, being changed to Alendronate 10 mg daily in September 2000 (as Bone Densitometry showed deterioration of hip osteoporosis), converted to 70 mg weekly in November 2003.

Alendronate and Methotrexate were both discontinued at time of presentation. She was commenced on oral amoxicillin and chlorhexadine mouthwashes, along with being given advice regarding oral hygiene. Hydroxychloroquine 200 mg twice daily for 3 months and subsequently daily was commenced as an to control her inflammatory arthritis, without DMARD therapy following the withdrawal of Methotrexate. Over a period of 2 years she clinically settled, with no progression of osteonecrosis.

## 3. Case 2

A 73-year-old woman presented after referral from her General Dental Practitioner to the maxillofacial surgeons with exposed bone in the lower right 6/7 region as well as lower central incisors. She had a history of temporal arteritis for which she took oral corticosteroids (prednisolone 7.5 mg daily), and a right wrist fracture following a fall 3 years previously. She had been on oral bisphosphonates in the form of risedronate 35 mg weekly (bone scan showing osteopenia), in addition to oral calcium and vitamin D supplementation.

She was managed conservatively with oral hygiene measures, including chlorhexadine mouthwashes, and removal of a small, mobile section of bone. The patient discontinued the bisphosphonate herself, and repeat bone densitometry showed mild osteopenia (total hip T-score  $-1.0$ )—an improvement of 2.5% in comparison of her scan 3 years previously. She remains under maxillofacial and rheumatological follow-up.

## 4. Case 3

An 81 years old woman presented to the maxillofacial surgeon in our hospital with a history of a discharging sinus with ulcer in UL4 canine premolar region in March 2011. She was on long term reducing dose oral prednisolone therapy for her diagnosis of polymyalgia rheumatica, and is currently on prednisolone 7.5 mg daily. She has been taking oral bisphosphonates, namely risedronate 35 mg once weekly, along with calcium and vitamin D3 twice daily for the bone protection as per steroid induced osteoporosis [SIO] prophylaxis guidelines.

She was managed with removal of UL4 and draining of pus. The affected area was explored and the pathological picture was deemed consistent with osteonecrosis of the maxillary region. Risedronate has subsequently been discontinued. On a recent clinic review there was some evidence of healing in her left maxilla but there was still some exposed bone. She is being followed by the maxillofacial surgeons and remains on tapering dose of steroids.

## 5. Discussion

Osteonecrosis of the jaw is a recognised side-effect of bisphosphonate therapy, but is more usually associated with intravenous bisphosphonates. Reports of osteonecrosis of the jaw associated with Zoledronic acid and Pamidronate first appeared in 2003 [1] [2], these both being intravenous preparations. An association between oral bisphosphonate therapy and osteonecrosis of the jaw has become increasingly recognised, with multiple case reports and case series.

An Australian prospective study published in 2007 by Mavrokokki *et al.* estimated the incidence associated with oral alendronate to be from 1 in 8470 to 2260 cases (0.01% - 0.04%) [3]. In this study the risk of develop-

ing osteonecrosis increased by greater than four times in those patients who underwent dental extraction.

In 2009, Sedghizadeh *et al.* published an institutional study, having retrospectively identified those patients on alendronic acid treated by their dental unit, and identified 9 of 208 patients who were also undergoing therapy for osteonecrosis of the jaw [4]. All were taking alendronic acid for osteoporosis.

A recent review of the literature by Assael, published in a supplement to the *Journal of Maxillofacial and Oral Surgery* concentrating on Bisphosphonate-Associated Osteonecrosis of the Jaw suggested a risk of 1:10,000 to 1:100,000, however increasing dramatically after dental extraction [5]. The literature also suggests that smoking, diabetes, steroid use (as in both of our patients), infection and immune disorders appear to be important comorbidities.

In the UK, the MHRA Yellow Card scheme provides us with an idea as to the prevalence of bisphosphonate associated osteonecrosis. The Drug Analysis Prints from the MHRA website lists 58 reports of osteonecrosis of the jaw with Alendronic Acid, 9 reports associated with Risedronate, 19 with Ibandronate, 29 with Pamidronate, and 127 with Zoledronic Acid [6]. Alendronic acid and risedronate are only available in the UK as oral preparations, Ibandronate as both oral and parenteral preparations, and Zoledronic Acid and Pamidronate as intravenous preparations only. It is, however, difficult to interpret these figures-only Ibandronic Acid and Aclasta<sup>®</sup> (one of the two preparations of Zoledronic Acid available in the UK) are “black triangle items”, where the MHRA requests that all suspected adverse reactions be reported. The number of unreported cases is unknown. Without knowing the number of patients taking each preparation in the UK it is impossible to give a “risk”; however, the number of cases reported via the yellow card scheme exceeds the number of cases published in the literature.

## 6. Conclusion

Osteonecrosis of the Jaw is recognised to be associated with both intravenous and oral bisphosphonate use. The former is of greater concern with regard to increased risk. The risk of developing bisphosphonate-associated osteonecrosis of the jaw appears minimal with oral bisphosphonates compared to intravenous preparations; however consideration should be made to patient counselling, consent and preventative dental work prior to the commencement of oral bisphosphonate therapy.

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