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Periodontal Disease, Dental Implants, Extractions and Medications Related to Osteonecrosis of the Jaws

Abstract: Patients taking bisphosphonates and other anti-resorptive drugs are likely to attend general dental practice. The term 'bisphosphonate' is often immediately associated with osteonecrosis of the jaws (ONJ). Risk assessment and subsequent management of these patients should be carried out taking into account all the risk factors associated with ONJ. The introduction of newer drugs, also shown to be associated with ONJ, demands increased awareness of general dental practitioners about these medications.

CPD/Clinical Relevance: This paper provides an update on medication-related ONJ and considers the effects of anti-resorptive drugs on the management of patients needing exodontia, treatment for periodontal disease and dental implant placement.

Dental Update 2015; 42: 878–889

Routine medical history screening in general dental practice will reveal patients taking nitrogen-containing bisphosphonates (N-BPs) and other anti-resorptive drugs, used most commonly in oncology patients with metastatic disease and in the treatment of osteoporosis in post-menopausal women.

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The term 'bisphosphonates' (BPs) can immediately prompt concerns of drug-related osteonecrosis of the jaws (ONJ), a reported complication of certain drug groups; N-BPs being the most documented family of drugs associated with a higher risk. Recently approved anti-resorptive agents, such as denosumab and other anti-angiogenic drugs used in oncology, have also been associated with ONJ and are expected to be used increasingly in the future; hence the American Dental Association Council on Scientific Affairs expert panel proposed all cases of ONJ related to the administration of anti-resorptive therapeutic agents to be termed 'anti-resorptive agent-induced ONJ' (ARONJ) in 2011;[1] this term has now been updated to 'medication-related ONJ' (MRONJ) by the American Association of Oral and Maxillofacial Surgeons (AAOMS),[2] allowing inclusion of the effects of anti-angiogenic agents.

Currently there are no guidelines from British institutions on the management of patients taking drugs associated with ONJ. Expert panels from other countries, however, have produced recommendations on the management of these patients.[2-6] The aim of this article is to revise ONJ, and to review the current literature on the potential effects of anti-resorptive drugs on the management of patients needing exodontia, treatment for periodontal disease and dental implant placement.

MRONJ: Diagnosis, aetiology, epidemiology and risk factors

The diagnosis of MRONJ is based on the presence of exposed bone or bone that can be probed through an intra-oral or extra-oral fistula(e) in the maxillofacial region that has persisted for more than eight weeks in the absence of radiotherapy or obvious metastatic disease to the jaw, on a background of current or previous treatment with anti-resorptive or anti-angiogenic agents.[2] The AAOMS have produced a recommended staging system for MRONJ (Table 1).

Stage	Characteristics
At risk category	No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates
Stage 0	No clinical evidence of necrotic bone, but non-specific clinical findings, radiographic changes or symptoms
Stage 1	Exposed and necrotic bone, or fistulae that probes to bone, in patients who are asymptomatic and have no evidence of infection
Stage 2	Exposed and necrotic bone, or fistulae that probes to bone, associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage
Stage 3	Stage 2 patients and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone (ie inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture, extra-oral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible or sinus floor

Table 1. AAOMS staging system for MRONJ.[2]

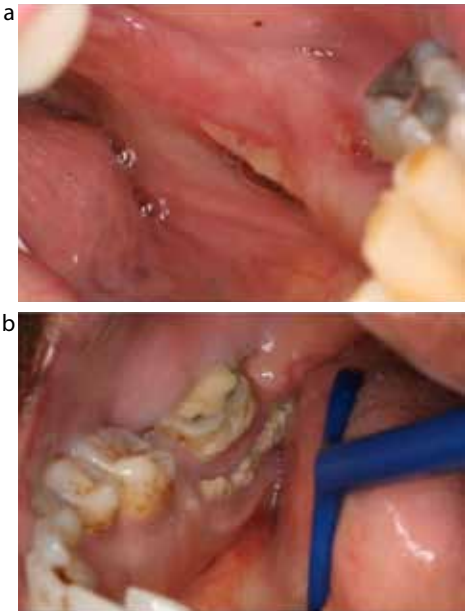

Figure 1. (a) MRONJ in the lingual sulcus of a denture wearer who had a history of 3 years of alendronate therapy; stage 1. **(b)** MRONJ in a similar region in a non-denture wearer who had a history of 90 doses of zometa; stage 1.

The first case of ONJ-related to bisphosphonate use (BRONJ) was reported in 2003,[7] though the full pathophysiological mechanism(s) of MRONJ is (are) yet to be fully understood. Current theories are centred on the drug's inhibitory role on osteoclastic bone resorption that affects bone remodeling, endothelial cell angiogenesis (certain drugs) and the presence of infection and/or inflammation.[8]

MRONJ is more commonly associated with the mandible compared to the maxilla (2:1) but can also affect both jaws in any one particular patient.[9,10] The published incidence of MRONJ varies (Table 2). Oncology patients are at a higher risk for MRONJ than those treated for osteoporosis since the anti-resorptive drugs used in this group are administered at higher doses, more frequently (ie monthly in oncology versus yearly or 6-monthly in osteoporosis indications) and parenteral administration allows greater drug exposure[11-13] (Table 2). Increased duration of the drug therapy has been reported as a risk factor for ONJ related to denosumab,[14,15] IV N-BPs[14] and oral N-BP use,[16-18] as has concomitant corticosteroid use.[15] Information on the association of ONJ with anti-angiogenic agents (in the absence of bisphosphonate therapy) is limited to case reports, and the incidence from a large analysis of patients treated with bevacizumab has been quoted in Table 2. The presence of certain genes[19] and other medical co-morbidities, such as anaemia and diabetes,[15] have been mentioned as risk factors, however further research is needed in these areas.

In addition to these systemic factors, local risk factors include denture wearing[23] (Figure 1a and 2), the presence of inflammation or infection in the structures supporting the teeth[4,30] and procedures stimulating the bone around the teeth, such as extractions (Figure 3), implant placement, and periodontal treatment; all of which are procedures commonly carried out in general dental practice. The second part of this article addresses the risk of ONJ for these procedures in patients on anti-resorptive drugs, predominantly N-BPs.

Extractions (and other dento-alveolar surgery)

Dental extractions have been used in animal ONJ models[31] and dento-alveolar surgery has been suggested as an inciting event for the development of ONJ in patients on anti-resorptive drugs.[9,15,23,30,32] In one example, in a case control study of cancer patients exposed to anti-resorptive drugs, patients with a history of tooth extraction were associated with a 16-fold increased risk for ONJ when compared to cancer patients without ONJ,[30] implicating the tooth extraction as a risk factor itself in addition to the IV use of the anti-resorptive agent. In addition to the extraction process causing local trauma, the presence and contribution of dental infection to the development of ONJ should not be excluded from the equation, as most dental extractions are carried out on teeth with periodontal disease or periapical pathology.

Although the risk of ONJ is much smaller in patients on oral N-BPs, there have been numerous cases of ONJ in patients taking oral BPs[33] and, as previously discussed, other systemic and/or local factors can increase this risk, such as greater than 4 years of BP therapy or concomitant corticosteroid or anti-angiogenic medication use.

MRONJ: Patient group	Risk level for ONJ	Approximate incidence of MRONJ (%)*	References
Cancer patients	**High**		
Zoledronate		0.7–6.7	Qi *et al* 2014[20] Coleman *et al* 2011[21] Mauri *et al* 2009[22]
Denosumab		0.7–1.9	Vahtsevanos *et al* 2009[23]
Bevacizumab		0.2	Scagliotti *et al* 2012[24]
Bevacizumab + Zoledronate		0.9	Qi *et al* 2014[20] Guarneri *et al* 2010[25]
Osteoporosis patients	**Low‡**		
Oral bisphosphonates		0.00038–0.21	Lo *et al* 2010[18] Felsenberg and Hoffmeister 2006[26] Malden and Lopes 2012[27]
Intravenous bisphosphonates		0.017–0.04	Grbic *et al* 2010[28] Papapoulos *et al* 2012[29]

Table 2. Incidence of MRONJ with associated anti-resorptive and anti-angiogenic agents. *It must be noted that incidences vary with the size of the studies; detailed investigation of each study is strongly advised. ‡'Low' risk, does not indicate 'No risk'.

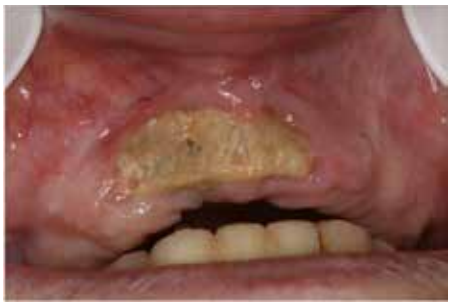

Figure 2. MRONJ lesion in the anterior maxilla of a patient with a history of 57 doses of zometa. Despite the size of the lesion, this patient was asymptomatic and there was no evidence of infection on clinical examination; stage 1.

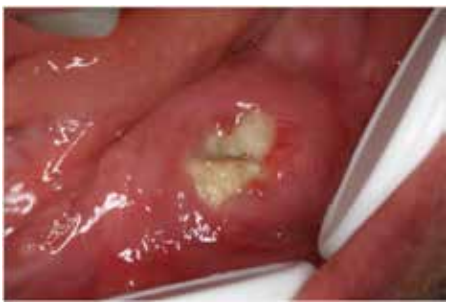

Figure 3. Post-dental extraction MRONJ; stage 2 based on symptoms of pain, and signs of exposed bone, erythema and a purulent discharge on clinical examination.

Recommendations by AAOMS for oral surgery in patients on oral BPs have been summarized in Table 3.

Patients with a background of intravenous administration of anti-resorptive or anti-angiogenic agents, especially cancer patients, should be treated with extreme caution and careful planning, often with multidisciplinary input. For this group of patients, AAOMS recommend:

- Where possible, delay the start of intravenous anti-resorptive or anti-angiogenic treatment for cancer therapy in order to optimize dental health, including extraction of non-restorable teeth and those of poor prognosis and any other necessary elective dento-alveolar surgery. If systemic conditions permit, delay the therapy until the extraction site has undergone mucosalization (14–21 days) or until there is adequate osseous healing.
- Avoid procedures that involve direct osseous injury and non-restorable teeth may be treated by removal of the crown and endodontic treatment of the remaining roots.

In many circumstances, dento-alveolar surgery cannot be avoided. Studies have looked at other factors such as pre- and post-operative antibiotic treatment, antibacterial mouthwashes, drug holidays and alternative methods of exodontia that could potentially reduce the risk of ONJ in patients undergoing dento-alveolar surgery whilst taking BPs.

Antibiotics

To date there is no clear consensus for the use of peri-operative antibiotics during dento-alveolar surgery in the prevention of BRONJ. A study on rats treated with pamidronate and dexamethasone with and without (control) perioperative antibiotics undergoing dento-alveolar surgery demonstrated a significant decrease in BRONJ[34] when antibiotics were used. A case series of 43 oncology patients with a history of zoledronate therapy underwent single or multiple extractions with a preventive protocol consisting of the removal of alveolar bone supported with antimicrobial therapy (antibiotics and mouthwash) showed encouraging results with no evidence of BRONJ at 12 month follow up.[35] The average duration of BP therapy was, however, only 16.2 months and there were no controls in this study. Similarly, in a retrospective analysis

Oral bisphosphonates (BPs): Recommendations by AAOMS
Prior to starting anti-resorptives for osteoporosis: ■ Education of the potential risks of MRONJ as the anti-resorptive therapy is likely to exceed beyond 4 years of treatment ■ Emphasis on the importance of optimizing dental health throughout this treatment period ■ If implants are to be considered, informed consent should be provided related to the long-term possibility of implant failure and low risk of developing ONJ if the anti-resorptive is continued. Regular review and discussion with the prescribing physician to consider alternate dosing of the BPs, drug holidays, or an alternative to the BP therapy is advised
Oral BPs < 4 years and have no clinical risk factors* ■ No alteration or delay in the planned surgery (all procedures common to oral and maxillofacial surgeons, periodontists and other dental providers)
Oral BPs < 4 years and have also taken corticosteroids or anti-angiogenic medications concomitantly ■ Liaise with the prescribing provider to consider drug holiday for at least 2 months prior to oral surgery, if systemic conditions permit ■ Anti-resorptive should not be restarted until osseous healing has occurred
Oral BPs > 4 years and with or without any concomitant medical therapy ■ Liaise with the prescribing provider to consider drug holiday for at least 2 months prior to oral surgery, if systemic conditions permit ■ Anti-resorptive should not be restarted until osseous healing has occurred

Table 3. AAOMS recommendations based on clinical experience;[2] *eg concomitant use of corticosteroid or anti-angiogenic medications.

No evidence of detrimental effects	
	Madrid and Sanz, 2009[58] Fugazzotto *et al* 2007[59] Grant *et al* 2008[60] Memon *et al* 2012[61]
Negative effects	
■ Delayed wound healing ■ Failure to osseointegrate ■ Failure post osseointegration	Wang *et al* 2007[62] Yip *et al* 2012[63] Yip *et al* 2012[63] López-Cedrún *et al* 2013[64] Shirota *et al* 2009[65] Bedogni *et al* 2010[66]

Table 4. Summary of cited papers on the effects of oral bisphosphonates (BPs) on dental implants.

of multiple myeloma patients receiving IV BP, when comparing 'high risk' procedures (eg tooth extraction) carried out with antibiotic prophylaxis to 'high risk' procedures without prophylaxis, it was found that patients in the first group (prophylaxis group) had a significantly reduced the risk of ONJ ($p = 0.012$).[36] The prophylaxis regimen used in this study consisted of an oral dose of amoxicillin-clavulanate 1g twice daily, or much less frequently, in case of intolerance or allergy, an oral dose of levofloxacin 500mg once daily, both from 1 day before to 3 days after any dental procedure.

Chlorhexidine mouthwash

Pre- and post-extraction use of chlorhexidene mouthwash has been suggested in guidelines;[4,37] recommended regimens vary from twice daily use for 15 days followed by review or for as long as 2 months, depending on healing.

Alternative techniques

'Atraumatic' extractions using orthodontic elastics around the roots of teeth to cause slow and gradual exfoliation of teeth have been suggested by few authors, however, the practicality of this suggested technique for use in general practice is questionable and follow-up period in both studies was only nine months or less.[38,39] Another author has suggested the avoidance of vasoconstrictors in local anaesthetic, however, there is limited evidence to support this.[17]

Drug holiday

A bisphosphonate drug holiday is currently a controversial suggestion. The Food and Drug Administration (FDA) have stated that there is no evidence for the initiation or duration of a drug holiday.[17,40] Despite little evidence to support it, it has been advocated by various panels (AAOMS and CAOMS) for patients on intravenous BPs, and even for patients on oral BPs for osteoporosis with prolonged exposure and/or co-existing risk factors, based on the theoretical benefit it may have.[2,41] Denosumab on the other hand has a significantly different mechanism of action and a relatively short half-life compared with that of bisphosphonates which accumulate in bone, therefore a drug holiday may be beneficial.[42] The prescribing physician and the dental practitioner should consider the appropriateness of a drug holiday on an individual basis, depending on the risks and benefits of ceasing anti-resorptive therapy and the alternative or urgency of the dento-alveolar surgery.

MRONJ and periodontal disease

Presence of periodontal disease

Although the treatment for periodontal disease is not recognized as a 'high-risk' procedure causing obvious trauma to the supporting tissues, the presence of this chronic low-grade inflammatory disease itself has been suggested as a risk factor in the development of MRONJ.[9,43] Although the mechanism in which periodontal disease may

contribute to ONJ needs further research, periodontal pathogens, such as Prevotella, Porphyromonas and Fusobacterium, have been isolated in BRONJ lesions.[44,45] In a large case series by Marx *et al*, 84% of the patients with BRONJ presented with periodontal disease (29% had advanced disease).[9] Furthermore, animal studies have shown ONJ or ONJ-like lesions develop in rodents given high doses of zoledronic acid, with existing laboratory-induced periodontitis[46,47] and periapical pathology.[48] An association between BRONJ incidence and alveolar bone loss due to periodontal disease in patients receiving intravenous BP therapy has also been observed.[49]

On the contrary, other animal and human studies have shown some benefits of oral BPs on induced periodontitis models and periodontal disease, respectively.[50-54] Many of these prospective studies were carried out early in the millennium when the concept of BRONJ was only just emerging and they are based on the expectation that osteoclastic resorption of bone in periodontal disease is reduced by BPs. Improved outcomes of non-surgical treatment or periodontal disease in patients on BPs, compared to patients on a placebo drug, in terms of significantly improved clinical attachment level (CAL), bleeding on probing[53] and probing depths (PD)[53,54] have been shown. Although in the absence of osteoporosis BPs would not be recommended as an adjunct to routine periodontal treatment, the latter studies suggest that positive clinical outcomes in periodontal therapy are achievable in patients on BPs; neither study described cases of ONJ. Using similar hypotheses, more recent studies have shown significantly improved PD reduction, CAL gain, and improved bone fill in chronic and aggressive periodontal disease at 6 months using a locally applied gel containing a high concentration of alendronate.[55,56] The studies cannot comment on the long-term clinical, histologic and radiographic effect of the treatment.

Management of periodontal disease

The principles of management of periodontal disease remain the same in all patients whether they are taking anti-resorptives or not; preventive care, early detection, early non-surgical management with regular monitoring and maintenance. Since periodontal disease is a known risk factor for ONJ, efforts should be made to prevent the development and progression of the disease, ultimately reducing the likelihood of future infections in the tooth-supporting tissues, particularly in patients on parenteral anti-resorptives or anti-angiogenic agents. Routine non-surgical periodontal treatment is not contra-indicated in any patient group, however, procedures involving direct osseous injury, including surgical periodontal treatment, are best avoided in patients on anti-resorptive and anti-angiogenic therapy for oncology purposes.[2]

Teeth with severe periodontal involvement requiring extraction are often less surgically demanding owing to the reduced alveolar bone height surrounding the tooth. However, these teeth should be disregarded as a risk in patients with IV BP use. In a single centre, BRONJ was diagnosed in 9 patients, following removal of 'hopeless' teeth with severe periodontal involvement; all these patients had had IV bisphosphonate drug therapy.[57] It is unclear whether the presence of periodontal disease or the surgical procedure was the initiating factor in this study, however, many of the reported cases of ONJ following dental extractions occur in teeth with existing periodontal or periapical pathology, suggesting the role of dento-alveolar disease in ONJ.

MRONJ and dental implants

Implants are an increasingly common treatment requiring careful surgical planning. For dental patients, costly treatment such as this carries expectations for success and longevity. Amongst other factors, the process of osseointegration of the dental implant is critical to the implant's survival. For this reason, questions arise when considering dental implants on patients who are taking medications that affect bone remodelling, ie anti-resorptives: *does placing implants in patients taking anti-resorptive medications increase risk of ONJ and, furthermore, is the success rate of the implant affected?* Since the placement of a dental implant is a traumatic procedure with bone removal at the osteotomy site, similarly to dento-alveolar surgery, it is contra-indicated in patients who have taken anti-resorptives for cancer by numerous expert panels.[2,3,58] The incidence of ONJ associated with dental implants and anti-resorptive drugs for osteoporosis, however, remains uncertain within the literature. A summary of the papers cited in this article is shown in Table 4.

A systematic review of one prospective and three retrospective human studies by Madrid and Sanz concluded that there was no evidence that placement of implants in patients on oral BPs (< 4 years) was associated with ONJ in the short follow-up period.[59] Some of the studies included were, however, of poor quality; one study had no control group;[60] another followed patients up by questionnaires rather than clinical examination.[61] The success rates of implants placed in the oral BP groups were high (95–100%), comparable to the control groups with no N-BP treatment (96.5–100%), however, the studies were unable to report on the long-term outcome of both implant success or development of ONJ. Crestal bone changes at the second stage of implant placement were compared in oral BPs users and a control group by Memon *et al*, with no significant differences seen between the groups.[62]

Case reports and case series have reported a spectrum of complications associated with implant placement in bisphosphonate patients, such as delayed wound healing at site of placement,[63] failure to osseointegrate[64] and subsequent failure of the implant post-osseointegration.[65-67] Several studies have looked into possible mechanisms for failure of dental implants in patients taking BPs, concluding that BPs significantly reduce alveolar bone turnover and wound healing, thereby increasing the risk for ONJ and implant failure.[68] However, only a few studies take into consideration the role of co-existing conditions, such as hypertension, corticosteroid use and smoking status. As previously discussed, the presence of infection has been indicated as a risk factor for ONJ, however, authors describing ONJ associated with dental implants do not mention peri-implant disease, a potential source of infection. A study looking at failed implants in middle-aged women found a significant odds ratio of 2.5 for a history of oral BP use.[64] Failure was defined by unsuccessful osseointegration or mobility once the implant had osseointegrated. In a case series of 27 patients, ONJ presenting less than 6 months from the time of implant placement (classified as surgically related) was observed in six patients (22.2%).[69] ONJ occurred in patients with oral BPs as well as IV treatment. ONJ took longer to present (mean: 68 months) following

implant placement in patients on oral BPs (alendronic acid) compared to patients who had a history of IV zolendronic acid use (mean: 16.4 months), emphasizing the need for long-term follow-up for any patient on BPs. In their cohort, four patients developed ONJ even though BP use commenced after implant placement. Notably, in this group, two patients had already had implant(s) *in situ* for over 9 years but developed BRONJ within 4 months of commencing IV BPs; rapid progression compared to one of the other patients whose BRONJ took longer to develop (156 months) after starting oral BPs.

With limited knowledge on the long-term affects of oral BPs on dental implants, when considering treatment patients should be warned of the risks of ONJ prior to implant treatment, and cases should be selected carefully, taking into consideration other systemic and local factors. AAOMS have suggested an informed consent process should be undertaken prior to implant placement in patients on oral BPs (Table 3) owing to the long-term possibility of implant failure and low risk of developing ONJ if the anti-resorptive is continued. This advice is based on a study evaluating the effects of intravenously administered BPs on bone healing after tooth extraction and osseointegration of dental implants in a rabbit model, where the experimental group demonstrated good initial stability at 4 weeks but impaired healing around the implants at 8 weeks compared to the control.[70] The conclusions we are able to draw from this study are limited.

Interestingly, studies involving local application of BP to implant surfaces have been carried out with positive results in animal[71-73] and human[74] models without causing ONJ. The local delivery of the anti-resorptive agents have shown improved early fixation, increased bone density, both close to and further away from the screw.[75] The long-term clinical outcome of BP coatings on dental implants is an area of future research.

Conclusion

Medication-related ONJ is a complex, multi-factorial process. The key to the management of patients at risk for ONJ in primary care involves taking a thorough medical history and understanding the indications and nature of any anti-resorptive or anti-angiogenic therapy, which will subsequently determine their dental management. Cancer patients are at a higher risk of ONJ than patients with osteoporosis and should be managed with caution, however, oral health screening and preventive care would benefit any patient receiving these agents. Dentists should familiarize themselves with the names and indications of newer agents associated with ONJ to help identify those patients at higher risk for the disease. Dental extractions and periodontal disease have been identified as risk factors for ONJ, especially in high risk patients, and the long-term success rates of implants in oral BP users is yet to be determined, as does the long-term outcomes of locally applied BPs in animal and human models.

Acknowledgements

The authors would like to thank the Department of Oral Surgery, Guy's and St Thomas' NHS Foundation Trust for their contribution of clinical photos.

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See page 892 of this issue