

A review of the clinical implications of bisphosphonates in dentistry

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ABSTRACT

Bisphosphonates are drugs that suppress bone turnover and are commonly prescribed to prevent skeletal related events in malignancy and for benign bone diseases such as osteoporosis. Bisphosphonate associated jaw osteonecrosis (ONJ) is a potentially debilitating, yet poorly understood condition. A literature review was undertaken to review the dental clinical implications of bisphosphonates. The present paper briefly describes the postulated pathophysiology of ONJ and conditions with similar clinical presentations. The implications of bisphosphonates for implantology, periodontology, orthodontics and endodontics are reviewed. Whilst bisphosphonates have potential positive applications in some clinical settings, periodontology particularly, further clinical research is limited by the risk of ONJ. Prevention and management are reviewed, including guidelines for reducing cumulative intravenous bisphosphonate dose, cessation of bisphosphonates prior to invasive dental treatment or after ONJ development, and the use of serum beta-CTX-1 in assessing risk. In the context of substantial uncertainty, the implications of bisphosphonate use in the dental clinical setting are still being determined.

Keywords: Bisphosphonates, bone, cancer, osteonecrosis, prevention.

Abbreviations and acronyms: AAOMS = American Association of Oral and Maxillofacial Surgeons; AmDA = American Dental Association; ASBMR = American Society for Bone and Mineral Research; CCPG = Canadian Consensus Practice Guidelines; HBO = hyperbaric oxygen therapy; MFA = Myeloma Foundation of Australia; NBP = nitrogen-containing bisphosphonate; ONJ = bisphosphonate associated jaw osteonecrosis; OPG = orthopantomograph; ORN = osteoradionecrosis; PMO = post-menopausal osteoporosis; RANKL = receptor activator of nuclear factor- κ B ligand; SRE = skeletal related event.

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INTRODUCTION

Bisphosphonates are drugs used to suppress bone turnover, primarily through effects on osteoclasts. The more potent nitrogen-containing bisphosphonates (NBPs) are favoured in clinical applications today. They are intravenously administered to prevent skeletal related events (SREs) associated with malignancy and severe forms of osteogenesis imperfecta. Intravenous (IV) pamidronate (Novartis Pharmaceuticals, North Ryde, NSW, Australia) and zoledronic acid (Novartis Pharmaceuticals, North Ryde, NSW, Australia) are used in this clinical setting, often monthly in the initial treatment phase. Less potent NBPs such as alendronate (Merck & Co., Inc., Whitehouse Station, USA) and risedronate (Sanofi-Aventis, Macquarie Park, NSW, Australia) are also administered orally and used in the management of non-malignant bone disorders such as osteoporosis and Paget's disease of bone. The value of alendronate and risedronate in the management of post-menopausal osteoporosis (PMO) has been compared to placebo and

supplements of calcium and/or Vitamin D, and assessed in meta-analyses of randomized controlled clinical trials. Both reduce vertebral, non-vertebral and hip fractures by 16 to 45%.^{1,2} Complications of bisphosphonate use, including oral and oesophageal ulceration, relate to improper oral drug use. More recently annual IV zoledronic acid has also been shown to be effective in reducing vertebral fractures, non-vertebral fractures and hip fractures by 70%, 25% and 41%, respectively.³ The number of patients needed to treat to prevent one fracture was as low as 13 for prevention of vertebral fractures with zoledronic acid, compared with the very low risk of jaw osteonecrosis of 1:3862 in the same study. Thus, the benefit/risk ratio greatly favours treatment with bisphosphonates in osteoporosis. The reader is referred to a review article for further discussion of the pharmacokinetics of bisphosphonates.⁴

Bisphosphonate use has been linked to jaw osteonecrosis, particularly the use of NBPs in the setting of malignancy. Called bisphosphonate associated jaw osteonecrosis (ONJ), the condition presents as an area

of exposed bone in the maxillofacial region. As ONJ is often refractory to treatment, prevention is critical. The condition may progress to secondary maxillary sinusitis, extraoral and intraoral fistula formation, bone sequestration, secondary paraesthesia and pathological fracture, causing significant morbidity. ONJ is exclusively related to the oral cavity, except for rare cases reported in the external auditory canal, hip, tibia and femur,^{5–7} where the contributory role of concomitant glucocorticoid use in some of these cases is uncertain. A number of risk factors for ONJ have been ascertained from longitudinal follow-up of cohorts taking bisphosphonates. Risk factors that have been demonstrated to be statistically significant include duration of bisphosphonate exposure, number of infusions, zoledronic acid, dental extraction and advanced age.^{8–13} Whilst the frequency of ONJ in patients with a history of IV bisphosphonate exposure for malignancy is low, 0.88% to 1.15%, the risk of ONJ after a dental extraction in such patients is 6.7–9.1%, as estimated in an Australian population-based survey.¹⁴ This presents a great concern to dental practitioners managing such patients, especially in the event that invasive procedures, such as tooth extraction, are indicated. The same study reported a lower frequency of ONJ in patients with an oral bisphosphonate exposure history for osteoporosis, 0.01–0.04%, with a 0.09–0.34% risk of ONJ after a dental extraction. Whilst the frequency of ONJ in the osteoporosis group was low, this must be understood in the context of high oral bisphosphonates prescribing levels for osteoporosis, itself a condition expected to increase in incidence as the population ages. Over 300 000 prescriptions were issued for oral NBPs in 2007.¹⁵ Accordingly, dental practitioners can expect to frequently manage patients with an oral bisphosphonate exposure history, and as such need to be informed as to best-practice management.

The pathophysiology of ONJ is poorly understood, and in particular why the condition localizes to the jaws. As discussed in a recent review of bisphosphonates and alveolar bone,¹⁵ it is postulated that bisphosphonates accumulate in human jaws at higher levels than the skeleton generally, as bone turnover in the jaws has been demonstrated to be higher. The consequent oversuppression of bone turnover may compromise jaw healing, both in response to injury (e.g. tooth extraction) and the normal physiological microdamage from occlusion. Several animal models of ONJ have been developed but none to date have reported sustained osteonecrotic jaw lesions, even when dogs were exposed to oral alendronate for three years.¹⁶ However, regions of matrix necrosis in alveolar bone specimens were more significant in the alendronate groups compared with a control, thus supporting the role of oversuppression of bone in ONJ pathophysiology.¹⁶ The closest approximations to ONJ in animal models were osteonecrosis of the ear pinna in

mice following subcutaneous NBP administration,¹⁷ and delayed dental healing post-extraction in rats exposed to zoledronic acid/dexamethasone.¹⁸ However, the pathophysiology may potentially be multifactorial, also involving other factors such as oversuppression of angiogenesis, altered functioning of oral mucosal cells, microbial flora, an anti-inflammatory effect and a genetic predisposition. The reader is referred to a recent review for an in-depth discussion of the potential pathophysiology.¹⁹

As ONJ is a relatively new condition, with knowledge regarding pathophysiology and management constantly expanding, the implications of bisphosphonate use in the dental clinical setting are still being determined. The aim of this paper was to inform clinical decision-making by reviewing the clinical implications of bisphosphonates in dentistry as set out in the current literature, in particular, orofacial conditions with similar presentations to ONJ; different clinical settings; and management and prevention of ONJ.

A literature search was conducted using Medline (ISI) in August 2009 from which a qualitative style review was developed.

REVIEW OF BISPHOSPHONATES IN DENTISTRY

Orofacial conditions with similar presentations to ONJ

Osteoradionecrosis

Osteoradionecrosis (ORN) is caused by radiotherapy to the orofacial structures creating hypoxic, hypocellular and hypovascular tissue. Both ONJ and ORN have necrosis of jaw bones as a common feature, and both are susceptible to secondary infection. The presence of bacteria, and *Actinomyces* species in particular, are frequently observed in cultures and histology from ONJ lesion specimens.²⁰ Hyperbaric oxygen therapy (HBO) has proven beneficial clinically to enhance ORN wound healing and to prevent ORN before surgery in irradiated jaws. HBO produces reactive oxygen and nitrogen species, thereby promoting fibroplasia and angiogenesis by the increase in tissue oxygen gradients and modulating oxygen-sensitive signalling processes critical to osteoclast function.²¹ However, the clinical utility of HBO for ONJ remains to date inconclusive. As recently reviewed,²¹ whilst some case series observed no substantive benefit from HBO,²² other reports suggest HBO may be useful.^{23,24}

Conditions affecting bone turnover

Jaw osteomyelitis, with or without exposed bone, develops rarely in osteopetrosis and pyknodysostosis, both which are genetic disorders in which osteoclast function is impaired.^{25,26} The critical role of reduced osteoclast function in these conditions lends support to

the theory that oversuppression of bone turnover is central to ONJ pathophysiology. In addition, recent media reports announced that cases of jaw osteonecrosis occurred in a trial of zoledronic acid or denosumab (Amgen, Thousand Oaks, CA, USA) for bone metastasis. Denosumab is a fully human monoclonal antibody against receptor activator of nuclear factor- κ B ligand (RANKL). Comparable numbers of jaw osteonecrosis cases occurred in both active treatment groups. However, jaw osteonecrosis has not been reported with most other drugs that reduce bone turnover, including hormone replacement therapy, strontium ranelate, calcitonin and selective oestrogen receptor modulators, though these drugs do have a different mechanism of action to bisphosphonates.

ONJ has some similarities with the condition 'phossy jaw', first observed in the 19th century in individuals exposed to white (yellow) phosphorous in match stick production,²⁷ and indeed a biochemical pathway has been described by which white phosphorous is converted to a compound similar to modern NBPs.²⁸ The condition disappeared when this substance was substituted. Phossy jaw had a similar clinical presentation to ONJ, and a dose-response effect is implicated in both conditions.²⁷ In common with ONJ, early experiments in dogs failed to model phossy jaw.²⁷

Bisphosphonates in different clinical settings

Implants

Dental implants and related bone graft surgery are potential precipitants of ONJ. However, in a prospective three-year follow-up of 50 subjects receiving implants – half with a bisphosphonate exposure history and half without – no cases of ONJ were observed.²⁹ Reviews of implants in 115, 101, 61 and 11 subjects with an oral bisphosphonate exposure history, respectively,^{30–33} found no cases of ONJ, except for one minor small tissue dehiscence. These studies were underpowered by small sample sizes, and the bisphosphonate delivery was all oral, which has a weaker association with ONJ than the potent IV NBPs. Aside from the issue of ONJ, several studies were unable to definitively establish that implant failure rates were substantially affected by a bisphosphonate use history.^{29,30,32,33} A recent South Australian study estimated the risk of implant failure in patients receiving oral bisphosphonates to be 0.88%.¹⁵

Experimentally, the potential of topical bisphosphonate application to enhance osseointegration of dental implants has been investigated in animal models, demonstrated to be of value in some studies,^{34–36} but not in all.^{37,38} Topical applications of bisphosphonate on dental implants in dogs, with and without a calcium-phosphate layer, promoted implant-bone contact^{35,36}

and increased the amount of bone peripheral to implants.³⁴ Despite these potential benefits, the toxic effects on the oral mucosa may potentially contribute to the development of ONJ. Hence, further investigation is unlikely given the ethical issues inherent in undertaking such trials in humans. Studies have described ulceration of gastric mucosa and oral mucosa or tongue after taking oral bisphosphonates, largely in the context of incorrect administration.

Periodontics

The extent to which periodontal disease is present in ONJ cases, i.e. a potential co-morbidity, is uncertain. Whilst periodontal disease has been noted as a co-morbidity in 79–84% of cases,^{12,39} another study found residual alveolar bone levels as measured from orthopantomographs (OPGs) to be comparable between participants with and without ONJ.⁴⁰ Periodontal disease has also been observed to be a precipitant of ONJ, as high as 41% in one study.¹¹ The presence of periodontal disease may necessitate invasive periodontal procedures or dental extraction, and hence increase the risk of ONJ.

The potential beneficial effects of bisphosphonates on periodontal disease have been explored. Administration of systemic bisphosphonates reduced alveolar bone loss in the majority of animal models of experimentally induced and naturally occurring periodontitis, but without significantly affecting clinical periodontal parameters.⁴¹ These promising early findings led to controlled clinical trials in humans, of which four have demonstrated the efficacy of alendronate in reducing alveolar bone loss relative to placebo, but in one study the effect was only noted in a subgroup with low mandibular bone density.^{42–45} In contrast, another controlled clinical trial did not demonstrate bisphosphonate efficacy in reducing alveolar bone mass relative to placebo.⁴⁶ The effects of bisphosphonates on periodontal clinical parameters in controlled clinical trials are somewhat inconclusive. Three trials demonstrated the efficacy of bisphosphonates in significantly improving clinical parameters,^{44–46} but two did not.^{42,47} Thus, bisphosphonates have paradoxical effects in the oral cavity, having potential beneficial effects on periodontal disease, whilst also increasing the risk of ONJ. However, the ethical issues inherent in undertaking such trials are likely to limit further trials in humans.

Orthodontics

Bisphosphonates are very effective in managing osteogenesis imperfecta in children, but no cases of ONJ have been reported, suggesting extractions are not contraindicated in these children.^{48–50} Whilst not fully understood, young age may possibly be a protective factor. As the patient demographic of orthodontists changes to

increasingly include adult patients, more patients with a bisphosphonate exposure history will seek orthodontic care. To date there have been no case reports describing ONJ occurring specifically in the region of orthodontic treatment, but as orthodontic tooth movement involves both bone resorption and formation, bisphosphonates may potentially compromise orthodontic treatment. Indeed, inhibition of orthodontic tooth movement, rather than ONJ, has been described in four cases with a bisphosphonate exposure history.^{51,52} Whilst extraction spaces are preferably closed by bodily movement, root tipping was observed. Caution is advised with invasive diode laser therapy, miniscrew skeletal anchorage devices, mucosal trauma from retainers, orthognathic surgery and tooth extraction. It has also been proposed that patients discontinue their bisphosphonate therapy for a period of time prior to orthodontic treatment,⁵¹ but this would require further investigation before implementation as these drugs have a terminal half-life of approximately 10 years.

In contrast, experiments involving local administration of bisphosphonates in rats have suggested a potential positive role for topical bisphosphonates in orthodontic treatment, inhibiting undesirable movement of anchor teeth and inhibiting post-treatment relapse in a dose dependent manner.^{53,54} However, extrapolation of these animal models to humans needs to be made with caution in light of the risk of ONJ, and as with other aspects already mentioned, such ethical considerations are likely to limit investigation in humans.

Endodontics

In patients with a bisphosphonate exposure history, and especially that administered intravenously, endodontic treatment is the preferred treatment over extraction to minimize ONJ risk. Nonetheless, due to bisphosphonate suppression of bone turnover, the periapical rarefaction may not decrease in size in a manner comparable to patients with normal bone turnover. Two case reports describe development of ONJ in the region of teeth requiring endodontic treatment.⁵⁵ Whilst endodontic treatment itself has not been identified as a precipitant of ONJ, care is advised to minimize the risk. In particular, atraumatic rubber dam placement and avoiding filing beyond the apex are advised, and apicectomy is contraindicated.

Management of bisphosphonate associated jaw osteonecrosis

Diagnosis

The American Society for Bone and Mineral Research (ASBMR) defines a confirmed case of ONJ as an area of exposed bone in the maxillofacial region that did not

heal within eight weeks after identification by a health-care provider, in a patient who was receiving or had been exposed to a bisphosphonate, and had not had radiation therapy to the craniofacial region.⁵⁶ These defining characteristics are consistent with the other major guidelines for ONJ management, namely the American Association of Oral and Maxillofacial Surgeons (AAOMS)⁵⁷ and the American Dental Association (AmDA).⁵⁸ The most recent AAOMS ONJ staging system has introduced Stage 0, a category for non-specific clinical findings and symptoms (Table 1).⁵⁷ This may include oral swelling, infection, and non-healing extraction sockets where exposed bone is not present. Clinicians need to be alert to such early changes as they may progress to frank exposed necrotic bone.

The guidelines have a comprehensive list of differential diagnoses. The ASBMR guidelines specify 10 potential differential diagnoses, including periodontal disease, gingivitis, mucositis, infectious osteomyelitis, sinusitis, periapical pathology due to a carious infection, temporomandibular joint disease, osteoradionecrosis, neuralgia-induced cavitation osteonecrosis and bone tumours.⁵⁶ Radiographs are considered essential to exclude differential diagnoses, particularly malignant lesions. A review of radiographic presentations of ONJ reported findings of osteosclerosis, osteolysis, dense woven bone, thickened lamina dura, subperiosteal bone deposition and failure of post-surgical remodelling, with or without bony sequestrum.⁵⁹ Whilst OPGs are considered an initial screening modality, computed tomography provides superior imaging. The utility of magnetic resonance imaging and nuclear bone scanning for ONJ diagnosis is yet to be clearly established.

Prevention

There is consensus across the guidelines that a comprehensive oral evaluation is recommended prior to

Table 1. The American Association of Oral and Maxillofacial Surgeons staging system for bisphosphonate associated jaw osteonecrosis⁵⁷

At risk	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 and symptoms
Stage 1	Exposed/necrotic bone in asymptomatic patients without evidence of infection
Stage 2	Exposed/necrotic bone associated with infection as evidenced by pain and erythema in region of exposed bone with or without purulent discharge
Stage 3	Exposed/necrotic bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone resulting in pathological fracture, extraoral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible or the sinus floor

initiating IV bisphosphonate therapy.^{56–58,60–65} However, the AmDA also promotes oral evaluation as beneficial either before or early on in oral bisphosphonate therapy,⁵⁸ the AAOMS recommend oral evaluation if oral bisphosphonates have been received in the last three months,⁶³ and the Canadian Consensus Practice Guidelines (CCPG) recommend oral evaluation prior to oral bisphosphonate therapy when appropriate dental care and good oral hygiene are not present.⁶⁰ The Australian Therapeutic Guidelines favour a firm preventive approach, advising a comprehensive oral evaluation and establishment of oral health prior to commencement of all bisphosphonates, including oral.⁶⁵ Whilst IV NBPs for osteoporosis were not available in Australia when these guidelines were published, the authors advise that this preventive approach be extended to patients commencing annual IV NBPs for osteoporosis, in line with recent advice from the Therapeutics Committee of the Australian Dental Association.⁶⁶ If the clinical condition permits, invasive dental procedures and subsequent healing, as evidenced by mucolization (14–21 days) or osseous healing, are best completed prior to commencing IV bisphosphonates.^{56,57,60,63,65} Optimal periodontal health is best achieved prior to commencing IV^{57,63} and oral⁶⁵ bisphosphonates, as is ensuring dentures are well fitted. Whilst patients who have received bisphosphonates for osteoporosis can usually be managed in general dental practices, when NBPs have been administered for malignancy, management should be under the care of a dental specialist in conjunction with the oncology team.⁶⁵

Once bisphosphonate therapy has commenced, patients should be reviewed every six months to ensure that oral health is optimum and encourage oral hygiene. All attempts should be made to maintain the dentition, by performing endodontics rather than extractions where necessary.^{56–58,60,63} The use of orthodontic elastics to promote atraumatic exfoliation has also been proposed. Elective dentoalveolar procedures (e.g. implants, orthodontics and periapical surgery) are not recommended whilst receiving IV bisphosphonates for malignancy.⁵⁶ Routine dental treatment generally should not be modified in patients with an oral bisphosphonate exposure history, though bone recontouring in periodontal disease should be modest,^{56,58} and suppressed bone turnover may compromise healing in periodontal procedures such as flap surgery, bone grafts and guided tissue regeneration.¹⁵ Implant placement in patients with an oral bisphosphonate history needs to be carefully considered,⁶⁵ and the patient informed of the ONJ risk and the risk of implant failure. Whilst the extent of the risk will be affected by cumulative dose and time since bisphosphonate cessation, the risk cannot be definitively quantified. The AAOMS have published guidelines for cessation of oral

bisphosphonates prior to invasive dental procedures⁵⁷ (Table 2), which can be applied to patients who wish to proceed with implant placement. Similar guidelines need to be developed regarding elective dentoalveolar procedures in patients receiving annual IV NBPs for osteoporosis. Suffice to say, careful consideration is warranted. In addition to meticulous oral hygiene, cessation of smoking and limiting alcohol intake is also recommended.⁶⁰

In some instances, invasive dental procedures may be inevitable after bisphosphonates have commenced. Under these circumstances patients must be warned of the possible risk of ONJ, and written informed consent considered. The guidelines are not consistent for advising cessation of bisphosphonates prior to invasive dental procedures^{56,57,60,62,64} (Table 2). Nonetheless, IV bisphosphonates are best ceased at least one month prior to invasive dental procedures, and not recommenced until healing is achieved (systemic condition permitting). Only the AAOMS guidelines are specific regarding cessation of oral bisphosphonates prior to invasive dental procedures,⁵⁷ advising cessation three

Table 2. Guidelines for cessation of oral and intravenous bisphosphonates prior to invasive dental procedures

Guideline	Bisphosphonate exposure history by route of administration	
	Oral	Intravenous
ASBMR ⁵⁶	No specific guidelines given	No guidelines given
AAOMS ⁵⁷	Less than 3 year duration: No change to dosing	No guidelines given
	Less than 3 year duration and corticosteroids:	
	Cease: 3 months prior	
	Recommence: Osseous healing has occurred [†]	
CCPG ⁶⁰	More than 3 year duration: Cease: 3 months prior	Cease: 3–6 months prior Recommence: Full healing [†]
	Recommence: Osseous healing has occurred [†]	
	No specific guidelines given	
Mayo Clinic ⁶²	No guidelines given	Cease: 1 month prior Recommence: Full healing
MFA ⁶⁴	No guidelines given	Low/intermediate risk of SRE: Cease: 2–3 months prior Recommence: 2–3 months after or full healing

[†]If systemic condition permits.

months prior to invasive dental procedures only when bisphosphonate exposure is over three years, or under three years when there is also a concomitant glucocorticoid history. Extractions should always be performed as atraumatically as possible with direct closure of the socket by suturing and antibiotic prophylaxis considered, especially in immunocompromised patients.^{64,65} Two guidelines also recommend prophylactic chlorhexidine mouthwashes.^{58,64} It should be noted that root planing is a low risk invasive procedure,¹⁵ and whilst caution is advised, cessation of bisphosphonates may not be warranted.

A recommendation that serum levels of the bone turnover marker carboxyl-terminal cross-linked telopeptide of type I collagen (beta-CTX-1) be used to predict ONJ risk prior to undergoing an invasive dental procedure in patients with an oral bisphosphonate history has arisen from two observational studies.^{39,67} However, ONJ risk could not be definitively demonstrated, and further controlled studies with adequate sample sizes are required to verify such guidelines. An early morning specimen and overnight fasting prior to beta-CTX-1 testing minimizes changes subject to food intake and diurnal variability, but interpretation of beta-CTX-1 levels remains subject to other sources of variability such as season, age, sex hormone levels, intra-individual variability and renal function.⁶⁸

Given that the risk of ONJ in cancer correlates with duration of administration of IV bisphosphonates, and zoledronic acid in particular, a number of international and Australian guidelines have been established to reduce the cumulative dose of IV bisphosphonates received in multiple myeloma.^{61,62,64} In general, monthly IV NBPs are advised for disease with active osseous involvement, but after this initial treatment phase reassessment occurs (12–24 months), and alternatives such as complete NBP cessation, oral bisphosphonates or three-monthly IV NBPs are to be considered.

Treatment

A conservative approach to management of established ONJ is favoured. The ASBMR guidelines advise antimicrobial rinses (e.g. chlorhexidine 0.12%) and systemic antibiotics if there is evidence of infection.⁵⁶ Surgical treatment should be conservative or delayed and be limited to: (1) removal of sharp bony edges to prevent trauma to adjacent soft tissues; (2) removal of loose segments of bony sequestra without exposing uninvolved bone; and (3) segmental jaw resection for symptomatic patients with large segments of necrotic bone or pathological fracture.

The CCPG and AAOMS guidelines are similarly conservative in nature, the latter including culturing in

conjunction with systemic antibiotics, particularly for *Actinomyces* species.^{57,60}

There is no empirical evidence to inform the decision of whether to cease bisphosphonate therapy in the event of ONJ development. Accordingly, the ASBMR and AAOMS guidelines recommend that the indication for bisphosphonates therapy be considered and bisphosphonates only ceased if the systemic condition permits.^{56,57} Hence, management is interdisciplinary and involves ongoing close monitoring. The Myeloma Foundation of Australia (MFA) recommend ceasing bisphosphonate therapy for at least three months on ONJ development, except in the setting of difficult to control hypercalcaemia.⁶⁴ Recommencement of bisphosphonates is dependent on risk for SREs, but is best delayed until ONJ resolution. Recommencement of bisphosphonates should be with either oral non-NBPs or a reduced frequency of IV NBPs, clinical condition permitting.

CONCLUSIONS

Bisphosphonates have revolutionized osteoporosis treatment and confer considerable anti-fracture benefits that outweigh the small risk of ONJ. Whilst bisphosphonates have potential positive applications, in periodontology in particular, this is balanced against the risk of substantial risk of ONJ, a potentially debilitating condition, predominantly in patients receiving intravenous bisphosphonates for cancer. In the context of substantial uncertainty, the implications of bisphosphonate use in the dental clinical setting are still being determined. Nonetheless, numerous guidelines inform the clinician, both in regards to ONJ prevention, management and dosing schedules in cancer. Invasive dental procedures are certainly to be avoided wherever possible in patients with a history of bisphosphonate use, especially intravenous bisphosphonates for cancer. Cessation of oral and intravenous bisphosphonates is advised, both prior to invasive dental procedures and on development of ONJ, provided the systemic condition permits. Limited surgical debridement together with systemic and local antibiotics is the favoured management of ONJ, however, healing is not assured. More controlled clinical studies are recommended to justify the use of serum beta-CTX-1 in assessing ONJ risk. Dental and medical practitioners cannot be reticent about the risks associated with bisphosphonate use and have a duty of care to be fully informed regarding their combined management of patients on bisphosphonates.

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CONFLICT OF INTEREST STATEMENT

PRE declares that he has received commercial research funding from Amgen (Title: *Double blind multicentre randomized study to assess the effects of strontium ranelate and alendronate on bone histomorphometry in women with post-menopausal osteoporosis*) and Novartis (Title: *Zoledronic acid for prevention of bone loss after allogenic stem cell transplantation*).

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