Dental interventions in patients taking anti-resorptive medication for the treatment of osteoporosis and other bone disease: an audit of current practice in the Dublin Dental University Hospital

ABSTRACT

Medication-related osteonecrosis of the jaws (MRONJ) is a well-established complication of anti-resorptive and, more recently, anti-angiogenic therapy. The dental profession has a pivotal role to play in the prevention and management of this debilitating condition, and all dentists have a responsibility to remain cognisant of national and international best practice guidelines in the prevention of this disease process. The management of patients in the Dublin Dental University Hospital at risk of MRONJ when carrying out dental interventions was audited against nationally- and internationally-published guidelines. The results of the audit showed compliance with the national and international guidance in 5% and 0% of cases, respectively. The most common measures implemented in the management of patients at risk of MRONJ were: preoperative antibiotics in 49% of cases; preoperative chlorhexidine mouthwash in 76%; plain local anaesthetic in 51%; and, post-operative antibiotics in 80%.

In conclusion, we found a low level of absolute compliance to both guidelines included in this audit. This highlights a need to re-examine the evidence underpinning these guidelines to ensure best practice patient care. Early recommendations have been made based on the findings of this audit, which will help to maximise its impact on clinical care delivery and generate discussion to stimulate and support action planning. Guidelines that are not followed are indicative of differing clinical opinions, highlighting the need for clarification and guidance as our understanding of this pathological entity broadens.

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Introduction

Osteonecrosis of the jaw (ONJ) is a rare but serious disease of the maxilla and mandible.[1] As the name suggests (osteo = bone and necrosis = death), ONJ manifests as lesions of necrotic and exposed bone in the oral cavity that persist for at least eight weeks.[2] Other accompanying symptoms include pain, mucosal swelling, loose teeth, erythema, and/or infections.[1,3]

ONJ may be associated with different predisposing conditions, with its

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Table 1: Medications predisposing to medication-related osteonecrosis of the jaw+

Generic name	Trade name	Clinical indication
Oral BPs		
1. Alendronate* 2. Risedronate* 3. Etidronate 4. Ibandronate* 5. Clodronate 6. Tiludronate	Fosamax Actonel Didronel Bondronat, Bonviva Bonefos, Loron, Clasteon Skelid	Treatment of osteoporosis and corticosteroid-induced osteoporosis, Paget's disease of bone.
Intravenous BPs		
1. Pamidronate* 2. Zoledronate* 3. Clodronate 4. Ibandronate*	Aredia Zometa, Aclasta Bonefos, Loron, Clasteon Bondronat, Bonviva	Hypercalcaemia of malignancy, osteolytic lesions, Paget's disease of bone, skeletal metastases, osteoporosis (at lower frequency and dose).
Denosumab		
	Prolia, Xgeva	Bone metastases, and osteoporosis.
Antiangiogenic medications		
1. Sunitinib 2. Sorafenib 3. Bevacizumab 4. Sirolimus	Sutent Nexavar Avastin Rapamune	Treatment of neoplastic lesions and prevention of organ rejection.

+ *Adapted from Brock* et al.[45]
* *Nitrogen-containing, higher-potency bisphosphonates.*

pathophysiology varying depending on these predisposing factors.[4,5] One such predisposing factor is the manipulation of bone metabolism by therapeutically administered drugs.[2]

Bisphosphonates (BPs) (pyrophosphate analogues, which share a common phosphorous-carbon-phosphorous chemical core) are considered the archetypal drug predisposing to ONJ.[6] Their principal action is to inhibit resorption of bone, which results in an increase in the mineral density of bone and a reduction in serum calcium.[7] BPs are the most clinically important, and widely used, anti-resorptive medication for the treatment of conditions with increased bone resorption caused by osteoclastic activity including osteoporosis, Paget's disease of bone, multiple myeloma, and metastatic bone disease.[7] **Table 1** details the current medications associated with ONJ and the conditions which they are used to treat. Indeed, ONJ was first reported in this patient cohort and the term bisphosphonate-related osteonecrosis of the jaw (BRONJ) was introduced to the literature.[6]

Various other drug groups which promote ONJ (including RANK ligand inhibitors[8] and angiogenesis inhibitors) have been identified recently. This has prompted the American Association of Oral and Maxillofacial Surgeons (AAOMS) to update the term bisphosphonate-related osteonecrosis of the jaw (BRONJ) to anti-resorptive agent-related osteonecrosis of the jaw (ARONJ) and subsequently to medication-related osteonecrosis of the jaw (MRONJ).[2] The term MRONJ will be used for the purposes of this audit.

Although MRONJ has been reported for well over a decade, the precise pathophysiologic mechanisms of the disease remain unknown.[9] ONJ is most commonly associated with procedures that stimulate the alveolar bone, and has also been described to occur spontaneously. The condition is particularly associated with dental extractions,[10,11] implantology,[12,13] and oral and periodontal surgery, although non-interventional causes of bone stimulation such as periapical or periodontal infection may have the same effect.[14] This suggests that the development of ONJ may be strongly linked to local inflammation. The incidence of MRONJ, although a point of contention in the literature with conflicting evidence, is reported at 1:10,000 in patients receiving oral BPs for the treatment of osteoporosis[15,16] and 1:1,000 for those receiving intravenous BPs or denosumab for the treatment of metastatic cancer.[17,18]

Measures proposed to reduce the risk of MRONJ, where invasive dental treatment is necessary, in patients already taking anti-resorptive medication, range from the use of peri-operative antibiotics and chlorhexidine mouthwash[19-21] to advocating a drug holiday,[2,22,23] the rationale for the latter being the recovery of normal bone haemostasis to encourage healing following dento-alveolar surgery.[24] However, there is little evidence supporting any of these measures, and this topic remains shrouded in controversy throughout the literature.

The serum bone turnover marker C-telopeptide (CTX) level has also been suggested as a biomarker useful in predicting an individual's risk of developing MRONJ prior to dental interventions.[25-32] However, other publications have illustrated that serum CTX levels exhibit neither accuracy nor reliability in predicting the risk for MRONJ and advocate against routine testing.[33-35]

Aims and objectives

This audit compared standard practice in the Dublin Dental University Hospital (DDUH) for the management of patients currently (or with a history of) receiving anti-resorptive medications with that suggested by nationally- and internationally-published guidelines. The audit retrospectively considered a period of six months, July 1 to December 1, 2015.

A secondary objective was to formulate recommendations, based on the findings, to more closely align DDUH protocol with that of the most recent, most reliable, evidence-based practice.

Materials and methods

Guidelines representing national and international protocols were used for comparison with current DDUH practice:

- guidelines published in the *Journal of the Irish Dental Association (JIDA)* for treating patients taking BPs prior to dental extractions;[36] and,
- American Association of Oral and Maxillofacial Surgeons Position Paper on Medication-Related Osteonecrosis of the Jaws.[2]

A standard of 95% strict adherence to either one of the above protocols was considered acceptable. Strict adherence to the *JIDA* protocol was considered to be implementation of every measure other than placement of sutures and a vacuum-formed splint, as the guidelines suggest that these are not absolutely necessary. The audit proposal was approved by the DDUH Audit Committee.

An algorithmic search of the DDUH electronic dental records was conducted to identify all patients using anti-resorptive medications who underwent any surgical procedures involving the manipulation of mucosal and osseous tissues in the time period considered. The information detailed in **Table 2** was extracted manually by the authors from each patient's records. The data were recorded and analysed using Microsoft Excel 2016 MSO.

Results

A total of 40 patients were identified that met the inclusion criteria. This translated to 41 treatment appointments, as one patient attended on two

Table 2: Extracted clinical information

Patient demographic	*JIDA* guidelines	AAOMS guidelines
• Age • Procedure(s) completed • Operator experience (recorded as the most senior clinician present during the procedure) • Clinic • Medication: – Type – Route – Dosage – Duration • Steroid use • Diabetes • Smoking status • Denture wearer • Concomitant oral disease	**Preoperative** • OHI* • Antibiotics • Chlorhexidene rinse **Intra-operative** • Plain local anaesthetic • Sutures **Post-operative** • Antibiotics • Vacuum-formed splint • Chlorhexidene rinse • Soft diet	• Risk classification • OMFS* opinion for patients at high risk of developing MRONJ • Drug holiday and length

**OHI = oral hygiene instruction, OMFS = oral and maxillofacial surgery, MRONJ = medication-related osteonecrosis of the jaw*

occasions in the six-month period. The patients were aged from 13 to 91 years and the majority of the treatments were completed by specialists/consultants in a dental chair unit.

It was found that 20% of patients were current smokers at the time of the procedure. A further 39% wore dentures and 88% had concomitant oral disease (predominantly carious lesions and periodontal disease). The most common type of medication being used by patients were BPs, specifically alendronate. BPs were most often administered orally, although 10% of patients had received both oral and intravenous BPs. Some 7% of patients had a history of BP use, as well as alternative anti-resorptive agents. The duration of anti-resorptive therapy ranged from three months to 17 years. A further 12% of patients were simultaneously using steroids and 7% were diabetic. **Table 3** details the concomitant risk factors predisposing to MRONJ.

The preventive measures taken in the management of this patient cohort were analysed. **Table 4** details conformance to additional clinical measures to prevent MRONJ according to the AAOMS and *JIDA* guidelines. Preoperative chlorhexidine mouth-rinse, plain local anaesthetic, and pre- and post-operative antibiotics were the most frequently implemented at 49%, 51%, 76% and 80% of cases, respectively. Of the preoperative antibiotic prescriptions, 94% were as recommended by the *JIDA* guideline. Contrastingly, 30% of the post-operative antibiotic regimens complied with the guideline. Patients in 27% of cases received a drug holiday, ranging from one month to seven years' duration. Clinical recording of which measures were or were not applied varied from 100% to 49%.

During the six-month period of interest, absolute adherence to either standard was low. No clinicians (0%) implemented the AAOMS guidelines as recommended. The *JIDA* guidelines were strictly implemented, and properly documented, in 5% of cases. This translates to two of 41 cases. Of these two cases, one was carried out in a dental chair unit, the other in a day-theatre environment.

In 80% of cases reviewed, one case of MRONJ subsequently developing was reported – an incidence of 2%. This single case of MRONJ occurred in a 51-year-old female following extraction of a left mandibular second molar. The patient was receiving six-monthly subcutaneous injections of 60mg denosumab at the time of the procedure, and there was a history of oral BP use of five years' duration. There were no other concomitant risk factors for MRONJ development

Table 3: Patient risk factors

Parameter	Patient status		
	Yes	No	Not recorded
Current smoker	20%	76%	4%
Steroid use	12%	76%	12%
Denture wearer	39%	49%	12%
Concomitant oral disease	88%	12%	0%
Diabetes	7%	93%	0%

Table 4: Preventive measures

Preventive measure	Was it applied?		
	Yes	No	Not recorded (unknown)
Drug holiday	27%	63%	10%
OMFS opinion for patients at high risk of developing MRONJ	66%	0%	34%
Pre-op OHI	10%	39%	51%
Pre-op chlorhexidene	49%	24%	27%
Pre-op antibiotic	76% (5% incorrect regimens)	20%	4%
Plain local anaesthetic	51%	46%	3%
Sutures	49%	51%	0%
Post-op antibiotic	80% (56% incorrect regimens)	20%	0%
Splint	0%	100%	0%
Review appointment	80%	20%	0%

Discussion

Since the introduction of the *JIDA* guidelines in 2010,[36] and the AAOMS position paper in 2007[37] (updated in 2014[2]) no audit of this nature has been completed in the DDUH. This is the first audit of preventive measures taken prior to invasive dental procedures in patients at risk of MRONJ published in the scientific literature. A previous retrospective audit, published in 2016, assessed whether high-risk patients about to undergo intravenous BP therapy for metastatic disease were examined by the oral and maxillofacial surgery department.[38] The authors of this audit reported two cases of MRONJ occurring in patients who had not undergone a dental examination prior to commencing BP therapy.[38] The results of the current audit highlight a range of discussion points regarding the current clinical practice in the treatment of patients at risk of MRONJ.

The most significant issue detected in the undertaking of this audit was in the area of clinical record keeping. The results highlighted a lack of standardised clinical record keeping, when performing dental interventions on the patient

population at risk of MRONJ. This information is critical when planning dental interventions, as it plays a key role is classifying those at high risk of MRONJ. This is one of the key stipulations of the AAOMS guidelines, and is mirrored in other contemporary guidelines.

Given the retrospective nature of this audit, it is impossible to determine the precise actions taken during the procedures under consideration. Therefore, the authors rely on precise clinical records to measure compliance to the standard. When this detail is omitted, particularly surrounding clear clinical steps (e.g., was a preoperative chlorhexidine rinse dispensed) it must be assumed that no such precautionary measure was taken. However, it may also be possible that clinical practice was indeed more closely aligned to the standard, but the clinical recording of measures taken was insufficient and not representative of actual practice. This may amount to an inconsistency between the recorded and actual level of compliance.

As mentioned, overall compliance with accepted guidelines did not conform to the determined standard of 95%. Additionally, none of the individual clinical preventive measures reached the accepted standard in isolation. One possible explanation for the reduced compliance is a lack of awareness of the guidelines. Time constraints also render their strict implementation difficult. This may stem from widely-differing international guidelines regarding the prevention of MRONJ,[2,36,39,40] and indeed an overall poor understanding of the aetiopathogenesis of MRONJ and ways to prevent it following dental intervention.

Specifically, in relation to the AAOMS guidelines, a drug holiday and consultation with an oral and maxillofacial surgeon is only advocated for those patients deemed to be 'at risk' of developing MRONJ – not simply for those taking anti-resorptive medications. It highlights several factors other than medications that are thought to be related to risk of MRONJ, such as co-existing metastatic disease, concomitant steroid therapy, rheumatoid arthritis, diabetes and others.[41-43] As detailed above, there was no drug holiday in 63% of cases, which was considered to be non-compliance with the guidelines. However, if some of these were considered 'low risk' for developing MRONJ, a drug holiday would not be appropriate according to AAOMS guidance. This could be a significant confounding factor when assessing compliance to these guidelines. Currently, there is no facility to quantify or record 'MRONJ risk status' in the DDUH electronic record. This is an important observation. An assessment of risk could highlight the patient groups that would benefit most from additional measures and allow more cost- and time-efficient use of resources.

While 27% of patients did have a drug holiday prior to treatment, none were of the appropriate length – some being too long and some too short. The AAOMS guidelines advocate a drug holiday of two months prior to invasive dental treatment and four months post-operatively in high-risk patients.

The longest duration of BP therapy recorded in this audit was 17 years and this highlights an important point meriting further discussion. Current literature suggests that the therapeutic benefits of BPs in the treatment of osteoporosis potentially plateau at approximately three to five years.[44] In those patients deemed to be at low risk of fragility fractures, cessation of BP therapy after this time would theoretically reduce the risk of MRONJ.

Recommendations and conclusion

In conclusion, this audit highlighted a need to update and revisit the guidelines available when treating patients at risk of developing MRONJ following dental

APPENDIX: MRONJ CHECKLIST

Patient name:

Date of birth:

MRN:

Date of procedure:

Questions	YES	NO
PREOPERATIVE		
1. Is this patient at high risk of MRONJ?	☐	☐
▸ previous diagnosis of MRONJ	☐	☐
▸ taking a bisphosphonate as part of the management of a malignant condition	☐	☐
▸ other non-malignant systemic condition affecting bone (e.g., Paget's disease)	☐	☐
▸ under the care of a specialist for a rare medical condition (e.g., osteogenesis imperfecta)	☐	☐
▸ concurrent use of systemic corticosteroids or other immunosuppressants	☐	☐
▸ coagulopathy, chemotherapy or radiotherapy	☐	☐
2. If high risk, has a consultation from OMFS been obtained?	☐	☐
3. Has the patient undertaken a two-month drug holiday?	☐	☐
4. Has the patient received preoperative OHI, and one-week preoperative chlorhexidine rinse twice daily?	☐	☐
INTRA-OPERATIVE		
5. Has the patient been given a loading dose of 3g amoxicillin (600mg clindamycin if allergic) orally?	☐	☐
6. Was local anaesthetic without vasoconstrictor used?	☐	☐
7. Was the surgery atraumatic?	☐	☐
8. Were sutures placed?	☐	☐
If yes, were they placed without tension?	☐	☐
POST-OPERATIVE		
9. Was a soft diet advised?	☐	☐
10. Was the patient instructed to rinse twice daily with chlorhexidine and three times daily with saline until the socket heals?	☐	☐
11. Was the patient prescribed 500mg amoxicillin (or clindamycin 450mg QDS) TDS for seven days?	☐	☐
12. Was a pull-down splint constructed to protect the soft tissues?	☐	☐
13. Was a review appointment arranged to ensure mucosal healing?	☐	☐

extractions and other oral surgical procedures. It is clear that neither the *JIDA* nor the AAOMS guidelines have been strictly adhered to during the study period.

It would be instructive to consider the establishment of a specific committee that would examine the current evidence related to the prevention of MRONJ, and prepare revised guidelines for clinicians in this area. As international best practice is in a state of flux, robust, clear, and evidence-based policy will aid in the provision of care to patients susceptible to the development of MRONJ, both in hospital and community-based dental practice. Until such time as a policy is drafted, the authors propose the utilisation of the MRONJ checklist (**Appendix 1**) when treating patients at risk of developing this condition. This will improve compliance with current guidelines and will aid clinical audit of this nature in the future.

Recommendations

- In-depth review of current evidence-based practice in this area and subsequent preparation of a specific hospital protocol for the treatment of patients deemed to be at risk of MRONJ after dental interventions.
- Emphasis on this protocol during undergraduate and postgraduate training (achieved by inclusion within the relevant curricula, and highlighted at the beginning of each clinical year) and staff induction.
- Implementation of the MRONJ checklist, and attachment of this document to the patient's clinical record.
- Risk assessment of each patient susceptible to MRONJ and stratification according to the Scottish Dental Clinical Effectiveness Programme (SDCEP) criteria.[39] This would include precise records regarding the nature of anti-resorptive and anti-angiogenic therapeutic regimes:
  - underlying medical condition;
  - drug type, formulation, dosage, route of administration, and frequency; and,
  - date of commencing (and ceasing if relevant) treatment.
- Clear displaying of the accepted hospital protocol in all clinical areas.
- Re-audit the compliance of clinicians in this area, subject to a new hospital policy guideline to ensure sustained improvements in compliance with best practice.

MRONJ is a rare but devastating condition affecting the oral cavity, with a significant impact on patients' quality of life. It is imperative, as dental clinicians, that we remain informed on current best practice when treating patients at risk of MRONJ and act accordingly in line with contemporary evidence-based guidelines. It is hoped that the recommendations put forward in this audit will help to maximise impact on clinical care delivery, and generate discussion to stimulate and support action planning.

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