Letters to the Editor

Relevance of bisphosphonate therapy in osteoporosis and cancer - no cause for alarm in dentistry (Dent Update 2016; 43: 235–242)

We write to challenge some of the assertions made in this recent paper.

Sadly, the attention grabbing title is rather naïve and/or misleading for general dentists and others. There **is** cause for concern and possible alarm in dentistry if patients, who have had *multiple IV injections* of bisphosphonates, usually for cancer, subsequently need to have dental extractions, or other operations **involving the bone** in their mouth.

While feeling great sympathy for patients who suffer from osteoporosis, the emphasis in the title of this paper and some of the content ought to be challenged, particularly in relation to intravenous bisphosphonates for patients with cancer.

Oral bisphosphonates are reputedly very beneficial in cases of osteoporosis .The risks of Medicine Related OsteoNecrosis of the Jaw ('MRONJ') after surgery to the jaws with **oral** bisphosphonates are so low that they should not be an issue for over 99% of oral surgical interventions. If oral bisphosphonates are taken for very many years and/or if they are combined with other risks, such as a long history of steroids, then the risks of MRONJ following jaw bone surgery are increased, but they are still low.[1]

The authors make many sensible points about the frequency of occurrence and seriousness of osteoporosis but, sadly, they fail to draw attention to balancing points about how serious osteonecrosis of the jaw can be in altering patients' quality of life when it does occur (Figure 1).

Unfortunately, the emphatic title of the paper breezily glosses over the reported occurrence of MRONJ, especially in such cancer cases. One of the references they cited referred to this happening in from **1.6% to 15%** of cases. That is huge range and probably reflects reporting issues, or the presence of other risk factors, such as the number of years on the drugs, or whether patients were taking other drugs, or whether the patients have had **jaw bone surgery** in the mandible or in the maxilla. At the risk of stating the obvious, it is the **combination** of these more potent drug(s) and surgery to the jaw that produces the risk of MRONJ. Many patients who are on long-term bisphosphonate drugs along with steroids, or those being given IV bisphosphonates, may well *not* need extractions, or other surgical intervention to the jaw bone, thereby reducing the reported **percentages**. About 73% of cases occur in the mandible as opposed to the maxilla, which is rarer at 23%, with about 4% occurring in both.[1]

It is the *combination* of multiple IV bisphosphonate infusions and extractions that produces the main causes for concern about MRONJ, but there are also significant risks with some other drugs used for their anti- bone resorptive effects, such as RANKL inhibitors, eg Prolia® (denosumab).

No mention is made in that paper of the prescribing doctors giving patients appropriate detailed warnings of those real risks of MRONJ when multiple infusions of these powerful bisphosphonates, or other anti-resorptive alternatives, are about to be employed, **particularly in patients with seriously compromised dentitions.** That would seem to be prudent following the Montgomery 2015 Supreme Court judgement in relation to issues of consent. That failure to mention serious potential possibilities is probably because those authors clearly felt strongly that there is no real problem. In our opinion, that almost casual mention of potential problems, particularly in cancer cases, has to be challenged because it is at variance with the reported and emerging, possibly delayed or under–reporting, of the problems of MRONJ problems in patients **who subsequently need surgical procedures involving jaw bone.[2]**

Interestingly, there was no suggestion in this article of patients who are being advised to have elective annual intravenous bisphosphonate, rather than staying on their oral bisphosphonates, having careful dental assessment first if they have a compromised dentition in order to reduce the risks to them of leaving potentially infected teeth, which subsequently might need riskier extractions in the future. That seems to us to be an opportunity missed and the rather bland suggestion to 'go for dental check-ups' does not allow for detailed appropriate assessment of this group, and just an apparent routine check-up is unlikely to lead to the elimination of predictable future dental problems, particularly under the NHS UDA system. Furthermore, it does not allow for 'aggressive preventive' measures to be instituted for these vulnerable patients early on in order to prevent them having problems in the future.[1,2]

Increasingly cancer, even with metastases, has become a chronic disease.[2] Many patients now survive for many years having had, and continuing to have, intravenous bisphosphonate therapy, which can be a brilliant drug in many such cases. As a consequence of this increase in patient survival, it is more likely that many such survivors will present to general dental practitioners at some stage. Unfortunately, traditional medical questionnaires used in many general dental practices do not specifically alert dental teams to the possibilities that their patient has had IV bisphosphonate therapy in the past, nor that they continue to have IV infusions on an annual basis. This is because patients often forget to enter the fact that they have had annual infusions, or a series of infusions, on these routine medical questionnaires and, in most cases, the question is not specifically put to them.

It should be stressed that

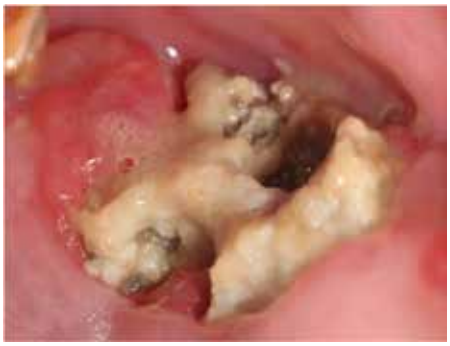

Figure 1. MRONJ: 5 months after extraction in a patient who had been off IV bisphophonates for six months and both dentist and patient had been reassured by the haematologist that there was no risk in extracting the tooth.

routine restorative treatment, including aggressive preventive treatment, is not a problem in such cases. However, some busy dentists, based on the scanning of the patient's completed medical questionnaire, may not realize that there is a real potential problem with *oral surgical procedures involving bone* and by doing, for example, an apparently routine surgical extraction, unintentionally cause MRONJ in that patient.

There is a joint Restorative/Oral Surgery Bisphosphonates Clinic at King's College Hospital, London. This clinic is staffed by a joint team with specialist restorative and oral surgery knowledge and skills in managing this patient group. This clinic screens patients who are at more serious risk of osteonecrosis of the jaw from IV bisphosphonate infusions, which are often combined with other drugs, or when alternative drugs to bisphosphonates are likely to be involved, such as RANKL inhibitors Prolia® (denosumab).

The aims of this clinic include giving individual patients neutral balanced information about their potential oral disease problems and to help them to get such problems treated early, thereby avoiding later complications, as well as working out more effective customized preventive strategies for these unfortunate patients. The essential point is that 'risk is individual' and is dependant on many relevant factors. A dogmatic, rather sweeping statement that there is *'no cause for alarm'* is worrying because such a headline is likely to be read as being 'gospel', rather than merely being one opinion. That is particularly the case when it appears in a peer reviewed journal but comes from authors whose interests are clearly more in research about osteoporosis, together with some oral surgeons at King's College Hospital who are not involved in that particular clinic.

Some points and emphasis in that article do **not** represent the rather more cautious and considered views of that King's College Hospital 'Bisphosphonate Clinic'. For many years there has been a dedicated osteonecrosis of the jaw clinic (ONJ) at Guy's Hospital. Neither of these clinics was put in place because there is not a problem of osteonecrosis of the jaw.

Rather simplistically oral surgery is the only thing that is mentioned in that article but there are other things, like decisions on periodontal surgery, or endodontic apical surgery, or prosthodontic planning which can be influenced by the presence, or absence, of a history of intravenous bisphosphonates or other potent anti-resorptive drugs. Individual assessment of patients' specific risks prior to them starting intravenous bisphosphonates should be encouraged rather than being casually dismissed by people with an understandable vested interest in osteoporosis, but who have, perhaps, rather less experience in the complicated dental risk planning aspects of these unfortunate cancer patients.

Interestingly, the article does not elaborate on the dilemma of patients taking very low risk oral alendronic acid, who are considering medical advice to move on to the somewhat higher risks of intravenous zoledronic acid. Curiously, their Table 1 refers to the reduction of over 50% of the spine fractures and about 50% of a hip fracture being achieved with oral alendronic acid with virtually no risk of MRONJ. Superficially, that would appear to be an attractive proposition relative to patients going on to intravenous zoledronic acid, with a reduction in hip fracture of only 41%. The authors do not comment on this apparent anomaly, ie why would patients want to take a greater risk of osteonecrosis of the jaw with an intravenous injection when they could get somewhat better results with less risk from taking oral alendronic acid? One suspects that patient compliance, or perhaps more cynically, the quiet influences of some drug companies' profits are just two of the possible explanations.

General dentists, to whom the article was addressed, might well ask the question 'Whose responsibility is it for MRONJ occurring in patients on intravenous bisphosphonates or in those patients who have had multiple years of oral bisphosphonate as well as steroids, who get osteonecrosis of the jaw after oral surgical procedures? Is it the treating dentist? Is it the prescribing doctor who did not give the patient appropriate warnings or a warning card, or a written note, to show to any future dentists? Is it the haemato-oncologist who, understandably, is probably more concerned with keeping the patient alive than about possible future MRONJ? Is it the rheumatologist, possibly influenced by a drug company anxious to promote its more profitable drugs? Is it the prescribing geriatrician possibly worried about the general frailty and memory of his/her patient? Who do MRONJ patients sue if they were to feel that they were given only some of the facts by a mono-focused specialist clinician, or one possibly influenced by pressures on their particular service, or by convenience issues, or subconsciously by some drug company presentation, when they now have a medicine-related osteonecrosis of the jaw problem that *might have been avoided?'*.

Interestingly, the article, perhaps inadvertently, could be now used as a defence by some dental practitioner by citing just this peer reviewed headline title of '***Bisphosphonate Therapy in Osteoporosis and Cancer - No Cause for Alarm in Dentistry'***. However, some of the views in the paper are in conflict with the advice cited in one of its own references,[1] as well as being at odds with other warnings about the increased likelihood of MRONJ problems developing with different emerging new cancer drugs. Sadly, it largely ignored advising the more careful and caring dentists about what they might be able to do to prevent future problems in these particularly unfortunate patients.[2]

A more balanced view of the real and imagined risks in this rapidly changing field could have been more helpful to the dental profession at large and such an article is now in preparation for *Dental Update*.

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Mark McGurk
London

Authors' response

We are writing in response to the letter from Martin Kelleher and Mark McGurk, received 20 June 2016 in response to our article.

On reflection, the title to the paper should not have included the

comment 'no cause for alarm in dentistry'.

The purpose of the paper was to explain to the dental team the main indications for prescription of anti-resorptive bone therapies and understand the potential risk to the patient of not taking medication prescribed. We chose this subject to educate dentists following reports from the Helpline Manager/Senior Osteoporosis Nurse for the National Osteoporosis Society[1] that many dentists are advising their patients to avoid anti-resorptive medication, causing stress and confusion to patients.

Whilst there are many articles, position papers and guidance notes available on the dental treatment of patients prescribed anti-resorptive medications, further analysis of that topic was not the purpose of our article.

Nowhere in the paper was it suggested that there is 'no problem with MRONJ', nor was it implied that MRONJ was not a potentially serious and problematic condition. Oral surgery was listed as one of several important risk factors; a detailed list of risk factors was not the remit of the paper.

We agree that the medicolegal issues are indeed complex and were not intended to be covered by this paper. The question as to 'Whose responsibility is it for MRONJ occurring in patients on intravenous bisphosphonates or in those patients who have had multiple years of oral bisphosphonate as well as steroids, who get osteonecrosis of the jaw after oral surgical procedure?' is important and we would suggest should be covered in a separate article.

Mr Kelleher and Professor McGurk raise important points with regard to the need for dental assessment and necessary preventive treatment, prior to starting and/or changes to anti-resorptive medication. We agree that this is particularly important for cancer patients who will face significantly higher doses of intravenous bisphosphonates and RANK-L inhibitors.

We trust that our article, together with their response, will allow dental teams to understand the treatment of patients prescribed anti-resorptive medications better and welcome further articles addressing these many issues which were not intended to be covered by our paper.

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A E Moore, Renton T, Taylor T, Popat S and Jasani MK
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EDTA – Factual disputes

Sir, I read with great interest the article entitled 'Modern Endodontic Principles Part 4: Irrigation' by Darcey J *et al*, which has been published in your esteemed journal (*Dent Update* 2016; **43**: 20–33). It was a good review article on the basic irrigating agents and devices used in endodontics. I want to share a few of my thoughts regarding this article. The use of ethylenediaminetetraacetic acid (EDTA) mentioned in that article as a root canal irrigant needs to be reconsidered. Even though EDTA is the most frequently used chelator in endodontics, it does not remove the smear layer effectively, especially in the apical third of the root canal system which is the vital area for disinfection.[1,2] In this regard, I would like to mention a novel chelating agent 'maleic acid', which has been studied extensively in endodontic literature. Maleic acid (7%) has been shown to remove the smear layer effectively when compared to 17% EDTA and various other chelators, especially in the apical third of the root canal system.[1,2,3] It is also less cytotoxic when compared to 17% EDTA[4] and has good antimicrobial properties when combined with auxiliary chemicals.[5] It has been shown to improve the bond strength of resin sealers when compared to 17% EDTA.[6,7,8] It has also been shown to produce increased surface roughness of the root canal walls when compared to EDTA, which might help in effective bonding of the resin-based materials to root canal dentine.[9] Hence, considering these drawbacks of EDTA, a clinician should rethink its use as a chelator in endodontic therapy.

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of human root canal dentin. *J Endod* 2010; **36**: 1385–1388.

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Authors' response

Thank you for the frank feedback of our paper: it is greatly appreciated. The authors are aware of the benefits of maleic acid and the growing evidence to suggest improved efficacy as an irrigant over EDTA. Our purpose with this publication was however to educate and inform dentists upon best clinical practice in irrigation at this current point in time. Maleic acid (7%) is not readily available in the UK and therefore it would seem irresponsible to advocate an irrigant that practitioners could not access. As such we took a pragmatic approach to education on this matter.

Nonetheless we appreciate that it would have been beneficial to readers to have referenced this agent and other possible agents to give a more comprehensive review of the literature and it was an oversight not to have included these in the series.

James Darcey *et al*
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A rare presentation of a primary diffuse large B-cell lymphoma of the oral cavity

I would like to share this case report of a primary diffuse large B-cell lymphoma of the oral cavity. It is essential for all general dental practitioners to be aware of this unusual presentation as early recognition, diagnosis and treatment can increase life expectancy of these patients. The prognosis is related to the disease staging.

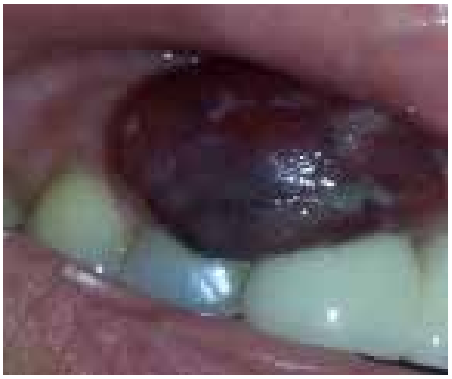

Figure 1. Growth on presentation.

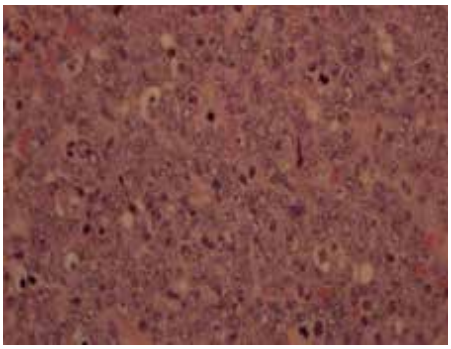

Figure 2. Histology (high power view) showing blastic-like cells with prominent nucleoli.

Figure 3. Histology (low power view) showing diffuse infiltrate of lymphoid blastic-like cells.

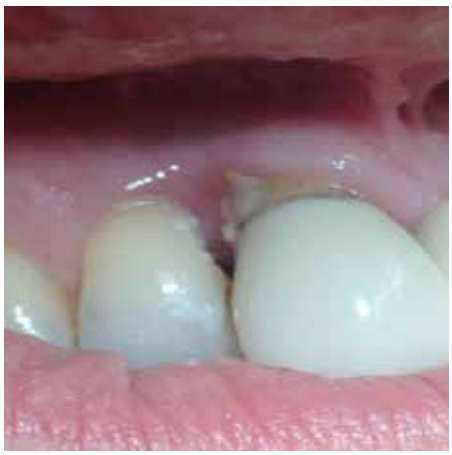

Figure 4. Following excision and completion of chemo- and radiotherapy.

Lymphomas are classified into Hodgkin's lymphomas and non-Hodgkin's lymphomas. Diffuse large B-cell lymphoma (DLBCLs) are non-Hodgkin's lymphomas and defined as neoplasms of large transformed B-cells with a nuclear diameter more than twice that of a normal lymphocyte. The prevalence of non-Hodgkin's lymphoma is 30–40%. Although NHLs of the oral cavity are rare (3–5%), the most frequent type of primary NHL of the oral cavity is DLBCL. DLBCL can be further classified prognostically into two subgroups, namely germinal centre B-cell like lymphomas (GCBs) and non-germinal centre B-cell like lymphoma (non-GBCs). GCB lymphomas have a better prognosis than non-GCB lymphomas.

A 68-year-old female patient was initially referred by her dentist to maxillofacial surgery in Kingston Hospital. She presented with a 3 months history of rapidly enlarging growth in her UR2 and UR3 labial gingivae. The upper right incisors and upper right canine were asymptomatic. Intra oral examination revealed a soft purple-coloured sessile lump attached to the gingivae of the upper right anteriors 1cm in diameter. There wasn't any discharge associated with this lump. Upper right anteriors were not mobile (Figure 1).

A periapical X-ray did not reveal any alveolar bone resorption in this region. The growth was excised completely under local anaesthesia and was sent for histopathological analysis. This showed diffuse infiltrate beneath a thin epithelium comprising blastic-like cells with prominent nucleoli and high mitotic activity. The cells were positive with CD20, CD45 and BC12 and showed some scattered small CD3 positive T lymphocytes interspersed (Figures 2 and 3). The cells also showed a high Ki67 proliferation rate. The appearances were of high grade B-cell non-Hodgkin's lymphoma non germinal centre type. Staging with CT scan and bone marrow biopsy showed no involvement. The patient was referred to haemato-oncologists for treatment involving 'R-CHOP x3' with cyclophosphamide, doxorubicin, vincristine and prednisone followed by field radiotherapy to the actual site of the lymphoma in the gums (Figure 4).

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Dental implications of novel oral anticoagulants

I read with interest the article

'Warfarin and Drug Interactions: Prescribing Vigilance' by Hook J *et al* (*Dent Update* 2016; **43**: 34–36) about warfarin and their drug interactions in dental management.[1]

Anticoagulation with low molecular weight heparin and vitamin K antagonists is the current standard of care for venous thrombo-embolism treatment and prevention. For the past decades, warfarin has been considered the mainstay of treatment, but its use is limited by a narrow therapeutic index that necessitates regular monitoring of the international normalized ratio (INR) and adjustments to the dose accordingly. Its use is also limited by drug interactions. Novel oral anticoagulants (dabigatran, rivaroxaban and apixaban) represent a new era in anticoagulation therapy. These novel oral anticoagulants have been developed and come in two categories: activated factor X inhibitors (rivaroxaban and apixaban) and a direct thrombin inhibitor (dabigatran). These new drugs do not require the INR to be monitored.[2]

There is little published in the current literature specific to professionals involved in oral health care. The degree of renal function, the complexity of the surgical procedure and the patient's risk of bleeding due to other concomitant causes are the most important factors to consider during surgical dental treatment of patients.[3,4]

As the number of patients taking these novel oral anticoagulants has been increasing, their use poses a number of challenges in dental management. The dentist must use caution and attention when treating patients taking dabigatran, rivaroxaban and apixaban. As healthcare professionals we should also be aware of how and when to report adverse drug reactions.

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An interesting development

A fit and well 28-year-old gentleman was referred to the Oral Surgery department at Ealing Hospital by his general dental practitioner for a specialist opinion regarding his upper 2nd and 3rd molar teeth. His GDP had taken periapical radiographs during the root canal treatment of the 1st permanent molars and noted that the 2nd molars were in fact unerupted.

At presentation the patient's only complaint was of mild generalized temperature sensitivity and, upon examination, no abnormalities were detected extra- or intra-orally. Upon review of an OPG radiograph (Figures 1 and 2) it was noted that both upper 2nd molar teeth are fully formed and completely unerupted. Both 3rd molar teeth are fully erupted and mesially angulated to such a degree that they contact the upper 1st molars.

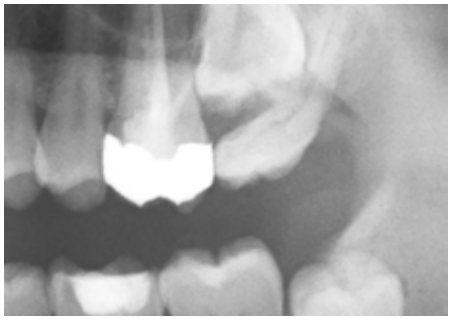

Figure 1.

A more focused clinical examination of the upper 3rd molars showed them to have good interproximal contacts with the upper 1st molars and good occlusal contacts with the lower 2nd molars by virtue of the selective attrition of the disto-occlusal surfaces, with exposed dentine, compensating for their mesial angulation. This wear, along with the wider than normal embrasures, were the only indication that the last standing molars were in fact 3rd molars.

Owing to the lack of any pathological or functional issues, the patient was keen to avoid treatment; the only treatment advised was topical fluoride preparations, desensitizing toothpastes and resin sealers to reduce the sensitivity of his exposed dentine. With regards to the elective extraction of his upper 3rd molars, the probability of spontaneous eruption of the upper 2nd molar teeth is very low; this is because of his age and the fact that the teeth are fully formed, which results in very little eruptive potential, but also because the most likely cause of their original absence, prior to their impaction against the upper 3rd molars, was primary failure of eruption.

It is important, upon the discovery of such an abnormality, that we remember always to act in our patient's best interests; however, with such an unusual presentation, seeking a second opinion about any possible intervention was appropriate.

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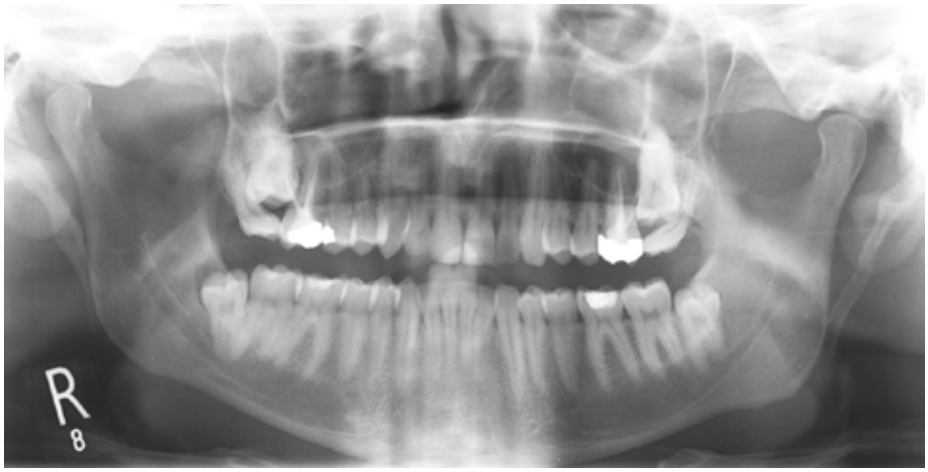

Figure 2.