Citation: IBMS BoneKEy **10**, Article number: 266 (2013) | doi:10.1038/bonekey.2012.266

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COMMENTARY

New insights into ONJ

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IBMS BoneKEy **10,** Article number: 266 (2013) | doi:10.1038/bonekey.2012.266; published online 23 January 2013

Commentary on: Aguirre JI, Akhter MP, Kimmel DB, Pingel JE, Williams A, Jorgensen M, Kesavalu L, Wronski TJ. Oncologic doses of zoledronic acid induce osteonecrosis of the jaw-like lesions in rice rats (*Oryzomys palustris*) with periodontitis. *J Bone Miner Res* 2012;**27**:2130–2143.

Osteonecrosis of the jaw (ONJ) presents as areas of exposed bone in the mouth, which fail to heal in spite of appropriate management over a period of 6–8 weeks.[1–3] It is almost a decade since the first description of this condition, which continues to be a major source of morbidity in cancer patients treated with high-dose anti-resorptive therapy (potent bisphosphonates or denosumab) for the prevention of skeletal-related events. It occurs in ~5% of cancer patients receiving these high-dose anti-resorptive therapies, and the development of a lesion is often precipitated by an extraction or other local trauma.[4] The lesions can be very resistant to therapy, and can be further complicated by progressive loss of the surrounding bone or by fistula formation. As a result, ONJ can be a major source of morbidity. Similar lesions have been described rarely in patients with osteoporosis receiving potent bisphosphonates or denosumab, but the infrequency of those events, and the fact that similar lesions occur in patients never treated with these drugs,[5,6] means that causality has not been established in this context.

We now have a number of descriptions of the morphology of these lesions. The exposure of bone in the mouth is almost always associated with local infection, almost invariably with the formation of microbial biofilms, within which *Actinomyces* is frequently a prominent species.[7–10] Biofilms are dense layers of mixed microorganisms embedded in a polysaccharide matrix, are resistant to local immune responses and to antibacterial agents. Local inflammation, necrotic bone, marked osteolysis both microscopically and macroscopically, though sometimes with elements of bone sclerosis on radiographs, are all commonly described. The paradox of local resorption of bone in a condition triggered by the use of potent anti-resorptives is notable.

Considerable effort has been put into studying the effects of bisphosphonates on bone cells in order to understand the development of ONJ. Bisphosphonates inhibit osteoclast activity through inhibiting farnesyl pyrophosphate synthase, a key enzyme in the pathway that leads to cholesterol synthesis. This pathway is key to the viability of most cells, suggesting that bisphosphonates could be toxic to many other cell types. Indeed, most cells incubated long-term in bisphosphonates in concentrations of 10^{-4}–10^{-6} M do show evidence of toxicity.[11] However, the very rapid uptake of bisphosphonates into bone means that most cells are never exposed to these toxic concentrations of drug, one exception being direct contact of bisphosphonate tablets with either the oral mucosa or the upper gastrointestinal tract. We postulated that bisphosphonate already attached to the surface of the mandible or maxilla was toxic to the overlying epithelium, or inhibited soft tissue healing following dental extractions. The toxicity of bone-bound bisphosphonate to a variety of cell types has now been demonstrated,[12] and would provide an adequate explanation of ONJ. However, recent clinical observations show that the non-bisphosphonate inhibitor of bone resorption, denosumab, is at least as big a cause of this problem as are the bisphosphonates.[13–15] Thus, any explanation that depends upon specific toxicities or actions of bisphosphonates is no longer viable. The common factor between bisphosphonates and denosumab is their potent inhibition of not just bone resorption, but global bone turnover, there being marked reduction in the presence of all cell types at treated bone surfaces. A pivotal role for bone turnover in the genesis of ONJ is supported by anecdotes of rapid clinical responses of ONJ lesions to teriparatide, an agent which globally increases bone turnover.[16]

A number of groups have attempted to develop animal models of ONJ, with a view both to understanding the pathology of the condition and providing a platform for assessing therapeutic interventions. Most recently, Aguirre *et al.*[17] have used a rat model prone to periodontitis, which they have treated either with alendronate or zoledronate in doses comparable to those used in osteoporosis management, or with very high doses of zoledronate, comparable to those used in oncology. They found that high doses of zoledronate induced ONJ-like lesions in the mandibles of these rats after 18–24 weeks of treatment. The lesions were characterised by exposed, necrotic bone, local increases in bone resorption, microbial biofilms with a predominant presence of *Actinomyces*, osteocyte death and reduced vascularity. Thus, this model reproduces lesions with many of the features characteristic of human ONJ, including the finding that high doses of bisphosphonates are required together with other local pathology (in this case periodontitis, though clinically it is frequently dental extraction) for its

genesis. The histological findings in this model emphasise the importance of microbial biofilms, and also demonstrate vigorous local osteolysis despite the presence of potent anti-resorptive therapy.

Does this model give us any greater certainty in our understanding of ONJ? To mirror the clinical situation, it would be important to see these lesions reproduced with high-dose denosumab, though the species specificity of that antibody make such experiments technically challenging. It would also be helpful to see that the lesions could be reproduced following the extractions, though there are other rodent models demonstrating ONJ-like lesions in rats treated with high-dose bisphosphonates who have undergone extractions. Finally, it would be of interest to determine which potential therapeutic interventions are effective in this context. Do teriparatide or other anabolic agents promote healing of these lesions? Are there local debridement procedures, antibiotic regimens or antiseptic mouth washes which promote healing? The principal benefit of such a model must be to provide a context for the assessment of individual therapeutic interventions, or their combinations.

What then, is the best current understanding of the genesis of ONJ? The fact that these lesions can be caused by either high-dose denosumab or bisphosphonates indicates that profound inhibition of bone turnover is central to the development of this problem. The second key element appears to be infection (introduced in the studies of Aguirre through pre-existing periodontitis), which leads to the formation of microbial biofilms on the acellular bone surface, just as they form on other acellular surfaces, such as indwelling catheters. These biofilms are resistant to local immune responses and to administered antiseptics and antibiotics, and so prove very difficult to treat. Microbial products directly stimulate osteoclastogenesis, which is also vigorously promoted by the products of the associated inflammatory response.[18–20] Thus, the scene is set for progressive bone necrosis, substantially driven by local infection. While the defining characteristic of ONJ has been taken as being exposed bone in the mouth, the initial exposure is usually the result of an invasive dental procedure (such as an extraction), but the perpetuation of this exposure and the associated bone destruction is probably predominantly infective in origin. Although bisphosphonates are toxic to a variety of cells (as discussed above), the fact that denosumab-induced ONJ is comparable in all respects, including in severity and persistence of lesions, makes it unlikely that the specific toxic effects of bisphosphonates to any of their potential targets are relevant to the development and persistence of these lesions. Our current understanding of the pathogenesis of ONJ is summarised in the **Figure 1**.

Although we are gradually moving towards a fuller understanding of the genesis of ONJ, its management remains empirical.[4] In patients starting on high-dose anti-resorptive therapies, completion of dental treatments before their initiation is important. Any invasive dental procedures should be accompanied by more vigorous measures to promote healing and prevent infection than are routinely used in patients without these co-morbidities, and once these lesions are established vigorous measures to eliminate what is essentially a chronic osteomyelitis are necessary. Anti-resorptive therapies can reduce the huge morbidity which comes from cancers metastatic to bone, and their value will be greatly enhanced if we are able to prevent and effectively manage the side effect of ONJ, which they too frequently produce.

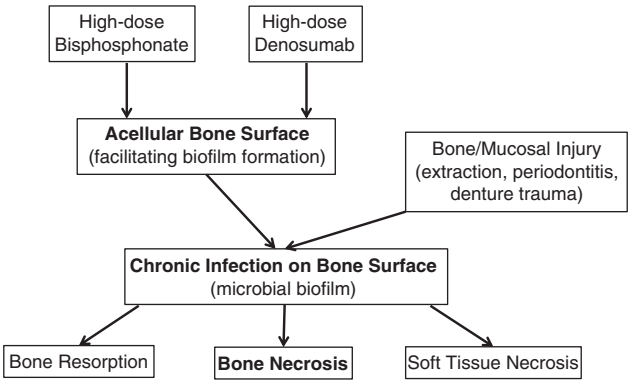

Figure 1 Pathogenesis of ONJ, based on currently available epidemiological, pathological and clinical data. Bolding indicates the central roles of very-low bone turnover, microbial biofilm formation and osteonecrosis in the development of this condition. Copyright IR Reid[4], used with permission.

Conflict of Interest

Dr Reid has received research grants or speaking/consulting fees from Merck, Amgen, Sanofi, Lilly and Novartis.

Acknowledgements

This work was supported by the Health Research Council of New Zealand.

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