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COMMENTARY

Osteonecrosis of the jaw associated with antiresorptives: more evidence on the role of infection

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Commentary on: Kalyan S, Quabius ES, Wiltfang J, Mönig H, Kabelitz D. Can peripheral blood γδ T cells predict osteonecrosis of the jaw? An immunological perspective on the adverse drug effects of aminobisphosphonate therapy. J Bone Miner Res 2013; **28**:728–735 and Bonnet N, Lesclous P, Saffar JL, Ferrari S. Zoledronate effects on systemic and jaw osteopenias in ovariectomized periostin-deficient mice. PLoS One 2013;**8**:e58726.

Antiresorptives have been the preferred agents in the treatment of osteoporosis. Over 40 years since their first oral clinical use[1] and 30 years since their application to IV preparations, primarily prescribed for patients with Paget's disease and metastatic bone cancer,[2] bisphosphonates (BPs) have recently been associated with a debilitating complication affecting the jaw, labeled as osteonecrosis of the jaw (ONJ) or as it has been described by some, 'osteomyelitis of the jaw'.[3] The oral lesions, especially those present in more advanced ONJ stages, brought back memories of the 'phossy jaw' described in workers of match-making factories when the use of white phosphorus in matches was a common practice in the 19th and early 20th century.[4] The complications described by nitrogen-containing BP (N-BP) users, however, are a separate entity, and 10 years after the first publication of ONJ cases, its association with N-BPs has been strengthened considerably to the extent that only a small minority still argue against it. However, a causal role of N-BPs in ONJ has yet to be established.

The described bone necrosis takes place almost exclusively in the jaw, with local infection touted as the hallmark of the ONJ. There is no consensus on which comes first.[5] Arguably, if necrosis came first, this would imply the absence of bone remodeling. Treatment with BPs could affect significantly the function of the osteoclasts, an effect that potentially could eliminate the resorption (and not the formation) phase of the bone remodeling cycle resulting in generalized osteopetrosis rather than osteonecrosis. If infection came first, then the local defense mechanism fighting infections should have been breached. Elimination/dysfunction of macrophages, a fundamental part of the defense mechanism, could be the first event in the development of the ONJ.[3] Macrophages are in a lot of ways osteoclast-like cells and could be reduced in numbers and/or become inactive after exposure to a BP, as is the case with the osteoclast.

The role of infection has been explored in the past as the oral cavity is home to a vast number of species of microorganisms/potential pathogen. Preexisting odontogenic infection (for example, periodontitis) and disruptions of mucosal integrity caused by oral trauma in general, including dento-alveolar surgery such as tooth extraction, have been recognized as the risk factors. Recent publications provide new insights on its central role and possible mechanisms involved. γδT cells that have critical roles in the early response to invasive pathogens and also constitute the major subset of resident T cells in mucosa and skin[6] were reduced significantly in the peripheral blood of naive or previous users of oral or IV N-BPs and osteoporotic patients treated with zoledronate.[7] Kalyan *et al.*[8] reported similar findings in patients treated with alendronate weekly (70 mg), 150 mg oral ibandronate monthly or 3 mg IV every 3 months and in cancer patients treated with zoledronate. They found a direct relationship between the major subpopulation of the γδT cells, the Vγ9Vδ2 cells, reduction and the potency of the systemic dose and the length of time on treatment. The route of administration also affected the rate of decline with the oral regimens requiring longer periods than 18–24 months observed in patients treated with IV N-BP preparations. They attributed this reduction to activation-induced cell death through the T-cell receptor resulting in apoptosis. This change in Vγ9Vδ2T-cell numbers, however, reflects rather general effects of N-BPs and does not discriminate between those who will eventually develop ONJ. Measurements in the peripheral blood of Vγ9Vδ2T-cell numbers/proportion therefore may not be a test of diagnostic value for assessing the risk of developing ONJ. Furthermore, participation of this subgroup of T cells is not vital in the process leading to ONJ because Vγ9Vδ2 cells could be found only in humans and higher primates and not in rodents, which may develop ONJ as well after administration of N-BPs.

Interestingly, N-BPs are not the only antiresorptives associated with ONJ. Patients treated with denosumab, a fully human monoclonal antibody inhibiting the RANK ligand (RANKL), develop ONJ at a similar incident rate to those treated with an N-BP.[3] Furthermore, in the Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months (FREEDOM) study, the serious adverse events of infections were most common in the denosumab-treated patients compared with those treated with placebo, although the pattern of the timing of administration or duration of exposure to denosumab was not indicative of a relationship.[9] Indeed, RANKL is a key factor in bone resorption and immune response/infection. RANKL is essential in osteoclastogenesis, function and survival of the osteoclasts. Furthermore, RANKL is expressed by the T helper cells and is a part of the regulation of T-cell-dependent immune response. Noticeably, the implication of denosumab in the development of ONJ has been completely ignored in the Kalyan *et al.*[8] study and not stressed enough in the accompanied editorial.[10] There are no studies on the number/proportion of Vγ9Vδ2 T cells in denosumab users. More importantly, however, the monocytes, the progenitors of macrophages and osteoclasts, express RANK on the cell surface, and the RANKL increases the production of pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin 1β, protects monocytes from apoptosis and induces migration. Blockade by a RANKL antibody such as denosumab could affect monocyte migration and function and decrease the survival and numbers of these cells. The significance of the finding in the Kalyan *et al.*[8] study of the apparently unaffected proportion of monocytes in the BP-treated patients remains unclear because their function and ability to migrate were not assessed.

In another interesting study, Bonnet *et al.*[11] provided evidence that the presence of severe inflammation is conditional to the development of ONJ. They used periostin-deficient mice ($Postn^{-/-}$), which develop generalized (including jaw) osteopenia after ovariectomy. Because of the traumatic mastication when they are fed with hard diet, they develop inflammatory infiltrates in the periodontal ligament. The soft diet, however, ameliorates significantly the severity of periodontal disease and partially prevents malnutrition. They administered oncologic concentrations of zoledronate weekly or monthly subcutaneously for 3 months in both $Postn^{+/+}$ and $Postn^{-/-}$ groups, which were fed with the same soft diet that was used in the sham-operated and vehicle-treated animals as well. When the $Postn^{-/-}$ animals were killed, there were no signs of prominent inflammatory infiltrates in periodontal tissues, mucosa and bone, and despite up to four times higher drug exposure after each injection than that achieved when administered monthly in cancer patients, no necrotic bone tissue was detected. These findings strongly support the central role of infection in the initiation of necrosis. However, the lack of controls on a hard diet, and thus lack of evidence that when this diet is used this animal model will develop ONJ, leaves the door on the debate on 'which comes first: bone necrosis or infection' ajar.

Conflict of Interest

MP is a consultant to the Alliance for Better Bone Health and Warner Chilcott.

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