Antiresorptive Drug–Related Osteonecrosis of the Jaw

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KEYWORDS

• Bisphosphonate • Denosumab • Osteonecrosis of the jaw • Zoledronate

KEY POINTS

- Nitrogen-containing and non–nitrogen-containing bisphosphonates have been implicated in the development of osteonecrosis of the jaw, a condition termed bisphosphonate-related osteonecrosis of the jaw.
- Other antiresorptive drugs have recently been implicated in the development of osteonecrosis of the jaw, hence the new term antiresorptive drug–related osteonecrosis of the jaw (ARONJ).
- Cofactors such as infection, diabetes, steroids, cancer, and chemotherapy may direct immune suppression and potentiate ARONJ development sooner.
- The risk of ARONJ is associated with the type of antiresorptive medication, route, and dosage.

INTRODUCTION

Osteonecrosis of the jaw (ONJ) is a debilitating bone disorder of the jaw and is defined by the advisory tasks forces from both the American Association of Oral and Maxillofacial Surgeon (AAOMS) and the American Society for Bone and Mineral Research (ASBMR) as the persistence of exposure of bone in the oral cavity for more than 8 weeks refractory to treatment, current or previous history of bisphosphonate (BP)

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use, no evidence of malignancy, and no prior radiotherapy to the affected region.[1–5] Antiresorptive drug–related ONJ (ARONJ) is a recent concept adapted and recommended by the 2008 American Dental Association (ADA) Council on Scientific Affairs. The ADA council recommended that all cases related to the administration of antiresorptive agents be termed antiresorptive agent–induced ONJ.[6] This recommendation encompasses all antiresorptive drugs that could cause development of ONJ. Many patients are being treated with antiresorptive or antiremodeling agents such as hormonal replacement therapy, selective estrogen receptor modulators, calcitonin (direct inhibitor of osteoclasts), BPs, or the monoclonal antibody (eg, denosumab).

At present, ARONJ development has been associated with the use of BPs and anti–receptor activated nuclear factor KB ligand (anti-RANKL) monoclonal antibody such as denosumab. It has been postulated that ARONJ results from reduced bone turnover caused by the antiresorptive drugs, by which denosumab seems to have an equal or greater extent of bone turnover suppression than BP. Besides BP and anti-RANKL drugs, other antiresorptive agents have a low risk of ARONJ, which may in part be because they do not suppress bone turnover by more than 50%.[7,8]

Antiresorptive Drugs Associated with ONJ

BP

BPs have been widely used as antiresorptive agents for management of skeletal-related events in neoplasia, hypercalcemia of malignancy, osteoporosis, Paget disease, osteogenesis imperfecta, and fibrous dysplasia.[9] BP has been linked to the development of ARONJ. The currently accepted theory for the development ARONJ is through direct and indirect effects on bone turnover via apoptosis of osteoclasts.[10] BP is the synthetic analogue of inorganic pyrophosphate, containing a phosphorus-carbon-phosphorus (PCP) backbone and a variable side chain (nitrogen or non-nitrogen) that determines the potency for inhibition of bone resorption.

BPs that lack a nitrogen functional group (etidronate, clodronate, tiludronate) condense to form the nonhydrolyzable analogue of ATP, which inhibits ATP-dependent intracellular enzyme, resulting in osteoclast cell death.[11,12] In contrast, the nitrogen-containing BP (pamidronate, ibandronate, zoledronate, risedronate, alendronate) inhibit the activity of farnesyl diphosphate synthase, which is a key enzyme in the mevalonate pathway. Inhibition of this enzyme creates an intracellular deficiency of geranylgeranyl diphosphate and farnesyl diphosphate, which are both required for prenylation of small signaling proteins with GTPase activity. This process results in dysfunctional osteoclasts and eventually apoptosis.[11,13] The nitrogen-containing BP has a higher potency and thus is effective in therapeutic management of skeletal-related events in cancer but also results in a higher risk ONJ. Zoledronic acid is the most potent BP (500–1000 times more potent than pamidronate) and was the first drug approved for use in all solid tumors with bone metastasis such as breast cancer, prostate, multiple myeloma, and lung cancer.[14] Intravenous (IV) BP exposure in the setting of managing malignancy remains the major risk factor for ARONJ, whereas treatment with oral BP therapy is at a considerably lower risk for ARONJ, possibly because IV administration of BP results in a higher skeletal accumulation caused by the high mineral-binding affinity and is also associated with earlier onset of ARONJ than oral BP.[15]

Anti-RANK ligand: denosumab

Denosumab is an antiresorptive agent that also inhibits osteoclast-mediated bone resorption. Denosumab has US Food and Drug Administration approval for the treatment of osteoporosis and skeletal-related events (SREs) in patients with cancer. Prolia