Medication-Related Osteonecrosis of the Jaw
Basic and Translational Science Updates

Matthew R. Allen, PhD

KEYWORDS

• Bisphosphonates • Denosumab • Antiremodeling agents • ONJ

KEY POINTS

- Basic science advancements in the field of medication-related osteonecrosis of the jaw (MRONJ) have been mainly in our understanding of how agents affect bone and oral epithelial cells.
- A greater understanding exists regarding bisphosphonate accumulation in bone and how this might affect cell function.
- Several animal models, both rodent and large animal, have been developed and have revealed important aspects of MRONJ.
- Basic questions that are essential to our understanding of MRONJ remain unanswered, and having a systemic approach to these questions would accelerate progress of the field.

INTRODUCTION

The clinical description of osteonecrosis of the jaw (ONJ) in 2003–2004,[1,2] along with the increasing reports in the years that followed, caused a significant jolt to those in the field of skeletal biology. Bisphosphonates, a class of antiosteoporotic agents that work by reducing osteoclast activity, were the clinical pillar of excellence in the field.[3] These agents were the most commonly prescribed class of drugs used for treating/preventing osteoporosis,[4] and this efficacy led to their use in numerous other metabolic bone diseases (ie, glucocorticoid-induced osteoporosis) as well as in cancer treatment for reducing skeletal-related events.[5] Significant preclinical and clinical study of bisphosphonates had occurred since the initial work to describe the mechanisms of action[6] and their effects on bone resorption.[7] Yet despite this extensive body of research on bisphosphonates, the clinical description of ONJ (now referred to as MRONJ[8]) made quite apparent the relative paucity of data describing how these agents affect the maxillofacial skeleton.

Over the past decade, progress has been made to understand MRONJ, although in many respects this progress has been faster in the clinical arena than in the basic science arena. It is interesting to think back, just a half dozen years or so, when it was clear that MRONJ was caused by high levels of bisphosphonate accumulation, leading to suppression of intracortical remodeling (which is high in the jaw) and accumulation of large regions of dead/apoptotic osteocytes, which constitute necrotic bone.[9–12] It is now known that nonskeletal accumulating drugs are linked to MRONJ and that MRONJ can be induced in species that do not undergo intracortical remodeling. Yet many questions still remain. The goal of this review is to highlight the key basic science and translational (animal) studies in the area of MRONJ and the needed areas of focus as the field moves forward into the next decade.

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Department of Anatomy and Cell Biology, Indiana University School of Medicine, 635 Barnhill Drive, MS-5035, Indianapolis, IN 46202, USA
E-mail address: matallen@iupui.edu

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MEDICATION-RELATED OSTEONECROSIS OF THE JAW AT THE CELL LEVEL—BISPHOSPHONATE ACTION ON CELLS AND TISSUE ACCUMULATION

Basic science studies aimed at understanding MRONJ have mainly focused on determining how agents linked to MRONJ affect cell characteristics in vitro. Most of this work has studied bisphosphonates because these were the first, and remain the most common, drug class linked to this condition. Another emerging and exciting area of work, again related to bisphosphonates, is localization of drug within the skeleton.

Years of work, using both in vitro and in vivo model systems, have documented the effects of bisphosphonates on osteoblasts, osteoclasts, and osteocytes.[3] Osteoclast effects depend on the type of bisphosphonate: either by altering ATP metabolism and inducing cell death or by altering the mevalonate pathway that disrupts formation of the small GTPases essential for resorption activity.[13] Osteoclast inhibition, the hallmark of bisphosphonate efficacy, has been confirmed repeatedly in numerous in vitro and in vivo models. Inhibition of osteoclast action seems to clearly be part of the MRONJ pathophysiology, because the agents most commonly linked to MRONJ, bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors (denosumab), both reduce bone resorption, albeit through different mechanisms. Yet the connection to suppression of osteoclasts is not entirely clear because (1) numerous antiresorptive drugs, including estrogen, selective estrogen receptor modulators, and odanacatib, have not been linked to MRONJ and (2) in numerous instances, there are a large number of osteoclasts and/or resorption pits associated with MRONJ lesions.[9,14] Various hypotheses have been presented regarding these 2 concepts, but definitive data explaining them have yet to be produced.

Necrotic bone is a central component of MRONJ, leading many investigators to focus on the osteocyte. Seminal work aimed at understanding the effects of bisphosphonates on osteocytes has shown that, both in vivo and in vitro, this class of drugs suppresses osteocyte and osteoblast apoptosis.[15] An interesting, and often not appreciated aspect of this work, is that the in vitro studies have repeatedly shown that antiapoptotic effects on osteocytes are dose dependent.[16,17] Although some differences exists among the specific bisphosphonates, concentrations around 10^{-8} M reduced osteocyte apoptosis, whereas those below 10^{-10} M or above 10^{-6} M do not have any effect (**Fig. 1**). In some instances, the highest doses have levels of apoptosis even above control, potentially suggesting a proapoptotic action at very high doses (above 10^{-5} M). Imaging studies have clearly shown that bisphosphonates can reach osteocyte lacunae,[18,19] yet the concentrations to which these cells are exposed in vivo remain unknown. Given the antiapoptotic effect observed in vivo,[15] it is assumed that they reach levels around 10^{-8} M, but neither has this been confirmed nor is it known whether it is possible, with prolonged or high-dose treatment, to achieve toxic doses.

In vitro assessment of other cells, specifically those of the oral cavity (oral epithelial cells [keratinocytes] and fibroblasts), has increased in the recent literature because of the potential relevance of soft tissue toxicity in MRONJ. In most cases, these studies have revealed that bisphosphonates reduce cell proliferation, induce apoptosis, and slow cell migration (as examples, see[20–23]). These studies typically involve using either primary cells

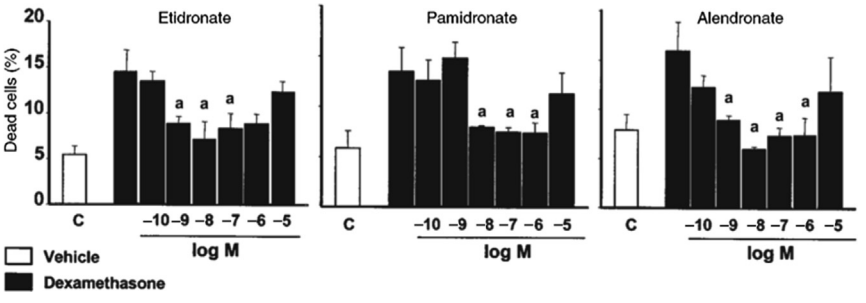

Fig. 1. Effects of bisphosphonates on osteocyte apoptosis are concentration dependent. Using an MLO-Y4 osteocytic cell apoptosis model, the ability of various concentrations of several bisphophonates to inhibit dexamethasone-induced cell death was assessed. The results show that at concentrations between 10^{-9} M and 10^{-6} M bisphophonates effectively prevent dexamethasone-induced apoptosis. Interestingly, at higher concentrations, the effect is lost and apoptosis is no different from that in untreated controls. [a] $P<.05$ versus dexamethasone treatment alone. (*Adapted from* Plotkin L, Weinstein R, Parfitt A, et al. Prevention of osteocyte and osteoblast apoptosis by bisphosphonates and calcitonin. J Clin Invest 1999;104(10):1363–74; with permission.)