SPECIAL COMMUNICATION

Task Force on Design and Analysis in Oral Health Research: Medication-Related Osteonecrosis of the Jaw

S. Ruggiero[1,2,3]*, D. Saxena[4]*, S. Tetradis[5]*, T. Aghaloo[6]*, and E. Ioannidou[7,8]

Knowledge Transfer Statement: *This article discusses the proceedings of the conference organized by the Task Force on Design and Analysis in Oral Health Research on the understanding of the translational evidence on the etiology and pathogenesis of medication-related osteonecrosis of the jaw as well as the clinical protocols on patient management.*

Keywords: microbiome, antiresorptive, bisphosphonates, MRONJ therapy, osteonecrosis of the jaws, MRONJ pathophysiology

Introduction

In its continued effort to foster evidence-based practices in oral health, the Task Force on Design and Analysis in Oral Health Research held a conference on November 14, 2017, in Newark, New Jersey, USA, on medication-related osteonecrosis of the jaw (MRONJ).

The conference, chaired by Dr. E. Ioannidou, focused on the multifactorial etiology and pathogenesis of MRONJ as well as the clinical findings that shaped the diagnosis and management. This article summarizes conference proceedings as presented by 4 exceptional scientists in bone biology, microbiology, and clinical science.

Current Concepts in MRONJ Management, by Dr. Salvatore Ruggiero

Dr. Ruggiero presented on the evolving diagnostic and treatment strategies for MRONJ. Antiresorptive agents, such as bisphosphonates and RANKL inhibitors, are widely used in the management of metastatic disease to the bone and in other diseases of altered bone turnover. Despite these benefits, MRONJ is a well-known complication that has afflicted a subset of patients receiving these drugs for the treatment of osteoporosis and metastatic bone cancer. The diagnosis of MRONJ can be established when exposed maxillary or mandibular bone is present for >8 wk in a patient who is receiving these medications but has not received radiotherapy to the head and neck region (Khan et al. 2015). More recently, certain antiangiogenic medications have been associated with MRONJ. The clinical risk factors in the development of MRONJ include

- Absorbed dose of the antiresorptive medication
- Duration of exposure or cumulative dose load of the drug
- Dentoalveolar trauma
- Preexisting oral inflammation/infection

Patients receiving antiresorptive medications on a monthly basis for the treatment of metastatic osteolytic disease have the highest risk of developing MRONJ following dentoalveolar surgery.

The current stage-specific management strategies provided a valid framework for the treatment of patients with MRONJ (Ruggiero et al. 2014). Nonoperative therapies, such as aggressive local hygiene and local

DOI: 10.1177/2380084418770662. [1]New York Center for Orthognathic and Maxillofacial Surgery, New York, NY, USA; [2]Stony Brook School of Dental Medicine, Stony Brook, NY, USA; [3]School of Medicine, Hofstra–Northwell Health, Hempstead, NY, USA; [4]Department of Basic Sciences and Craniofacial Biology College of Dentistry, New York University, New York, NY, USA; [5]School of Dentistry, University of California at Los Angeles, CA, USA; [6]Section of Oral and Maxillofacial Surgery, School of Dentistry, University of California at Los Angeles, CA, USA; [7]Division of Periodontology, UConn Health, Farmington, CT, USA; [8]Task Force on Design and Analysis in Oral Health Research, Princeton, NJ, USA. *Authors contributing equally to this article. Corresponding author: E. Ioannidou, Division of Periodontology, School of Dental Medicine, UConn Health, 263 Farmington Ave, Farmington, CT 06030-1710, USA. Email: ioannidou@uchc.edu

and systemic antimicrobial treatment, continue to play a major role in the management of all stages of MRONJ. Novel nonoperative therapies, including teriparatide (parathyroid hormone), were demonstrated to specifically enhance bone healing in several animal and few human models of MRONJ. The combination of systemically administered pentoxifylline and vitamin E has been used to effectively treat osseous necrosis associated with radiation therapy. This therapeutic approach is now being evaluated in a multi-institutional trial for the treatment of MRONJ lesions.

While major operative treatments were traditionally avoided for fear of creating larger and more recalcitrant bone wounds, more recent clinical studies validated the efficacy and safety of this approach for all stages of MRONJ. Long-term cure rates as high as 90% have been reported with surgery as the primary mode of therapy.

The importance of preventive strategies cannot be overstated. There is a robust and growing level of evidence demonstrating that increased dental surveillance and preventative dental care can significantly reduce the frequency of MRONJ for those patients at risk. A randomized open-label clinical trial conducted at 269 centers across the United States reported no difference in skeletal complications among patients with cancer receiving zoledronic acid every 12 wk as compared with the standard monthly dosing. More important, the frequency of jaw necrosis trended lower in the group receiving the reduced dose. This new treatment methodology, coupled with enhanced dental prevention strategies, will serve to significantly reduce the cumulative dose load of these drugs among patients with cancer. This information should serve to empower rather than dissuade the dental community to be more active in the care and treatment of these patients.

Microbiome Hypothesis in MRONJ, by Dr. Deepak Saxena

Dr. Saxena presented "the perfect storm" based on a paradigm shift that involves a unique interaction of the immune system, oral flora, and bone remodeling. He developed the microbiome hypothesis based on bacterial biofilms as potential critical triggers in the pathogenesis of MRONJ. Compared with other parts of the body, bone can easily be colonized by the abundant flora of bacteria and yeast in the oral cavity (including periodontal pockets and periapical abscesses) with the potential to cause biofilm-mediated disease.

Dr. Saxena and his team showed that bisphosphonate-related osteonecrosis of the jaw lesions were heavily colonized by oral bacteria (Pushalkar et al. 2014). Other groups indicated that long-term preoperative antibiotic treatment can lead to a complete healing in 70% to 87% of cases, in contrast to 35% to 53% with a short-term regime, thereby suggesting the role of bacteria in MRONJ. Using a culture-independent 16S rDNA molecular technique, his team compared the bacterial profile of subjects with MRONJ who were on systemic antibiotics with those were not on antibiotics and found no significant differences in bacterial diversity of MRONJ tissue samples, confirming that systemic antibiotics failed to restrict bacterial colonization after the onset of MRONJ.

Furthermore, he and his team examined the level of immunosuppression on patients with MRONJ and cancer. As compared with controls, patients with MRONJ demonstrated significantly lower levels of myeloperoxidase but moderately elevated levels of interleukin 6 and tumor necrosis factor alpha. Polymerase chain reaction array showed significant changes among patients with MRONJ with downregulation of host genes, such as nucleotide-binding oligomerization domain-containing protein 2, and cathepsin G—the key modulators for antibacterial response and upregulation of secretory leukocyte protease inhibitor, proteinase 3, and conserved helix-loop-helix ubiquitous kinase (Pushalkar et al. 2014). These results suggest that colonization of unique bacterial communities coupled with deficient innate immune response is likely to affect the pathogenesis of osteonecrosis of the jaw.

Their observations indicated that the MRONJ bone was colonized with unique bacterial phylotypes different from other bone infections in the oral cavity and not associated with bisphosphonate (BP) therapy. In the plausible basis for MRONJ development, the acidic environment created by the high abundance of aciduric bacteria, such as *Streptococcus* and other saccharolytic bacteria, may play a significant role in bone necrosis. This environment, coupled with other factors (e.g., dental infections, invasive procedures, and nitrogen-containing amino BPs), is speculated to act as an initiator of MRONJ. At this stage, it is not known whether bacteria colonize and promote the lesion or colonize after the lesion has developed. Identification of bacterial phylotypes will be highly significant for understanding the pathophysiology of MRONJ.

MRONJ: From Rodents to Humans, by Dr. Sotirios Tetradis

Dr. Tetradis stated that the detailed pathophysiologic mechanism of MRONJ still remains unidentified. Several hypotheses have been proposed, but none alone explains the full spectrum of MRONJ clinical, radiographic, and histologic features.

He emphasized that the inhibition of bone resorption plays a central role in the pathogenesis of MRONJ. BPs or denosumab (dmab) targets osteoclasts through distinct pharmacologic mechanisms. BPs interfere with osteoclast function and induce osteoclast apoptosis. Dmab, however, binds to RANKL and inhibits preosteoclast differentiation and osteoclast function. Yet, induction of MRONJ by both these agents is indistinguishable.

Furthermore, the altered immune response has been observed around MRONJ areas. Lower Treg and higher Th17 cell numbers, a lower Treg:Th17 ratio, low F4/80-positive VEGF-C-expressing macrophages, high levels of IL-36 and IL-8 proinflammatory cytokines, and altered γδ T-cell function and oral mucosal barrier immunity have been reported. However, the mechanisms

of this altered response and its link to MRONJ pathogenesis remain unclear.

Dr. Tetradis examined the microbial hypothesis of MRONJ pathogenesis, according to which the exposed necrotic bone is colonized by prominent biofilm formation and bacterial morphotypes. However, it is not clear whether bacteria are involved in the formation of the MRONJ lesions or whether the bone is colonized after is exposed.

He and his team reported the presence of MRONJ lesions in mice and rats treated with high doses of BPs or RANKL inhibitors in the absence of tooth extraction but in the presence of natural or experimental severe dental disease (de Molon et al. 2014). They observed that antiresorptive-mediated inhibition of osteoclasts allowed the persistence of necrotic bone around areas of periapical or periodontal disease that would otherwise have been resorbed. They also noted epithelial proliferation and migration along the necrotic bone, associated with bone exposure.

Dr. Tetradis and his team have consistently reported histologic osteonecrosis in 85% to 90% of the animals with bone exposure in only 30% to 35%, suggesting that bone necrosis occurs first, followed by bone exposure (Kang et al. 2013). They also found that withdrawal of zoledronic acid treatment for 6 or 10 wk did not change radiographic or histologic severity or incidence of osteonecrosis of the jaw. In contrast, RANKL inhibitor withdrawal quickly reversed features of osteonecrosis of the jaw and significantly decreased the osteonecrotic area and bone exposure. As these preclinical findings suggest that interruption of dmab, but not BPs, could reduce osteonecrotic bone and bone exposure, translational studies will facilitate the understanding of the disease at the human level.

In conclusion, MRONJ appears to be a multifactorial disease induced by the complex oral cavity environment, with participation of multiple cellular and molecular processes. During dental disease or dental trauma, inhibition of bone resorption results in exposure of bone to the noxious environment of inflammation, leading to bone necrosis and bacterial colonization. Subsequent tooth extraction expands the loss of soft tissue integrity, further compromises soft and osseous healing, and precipitates the full spectrum of MRONJ.

Clinical Evidence on MRONJ, by Dr. Tara Aghaloo

Dr. Aghaloo stressed the significance of MRONJ as a devastating complication of antiresorptive medications commonly prescribed for primary and metastatic bone cancer, osteoporosis, Paget's disease, rheumatoid arthritis, and osteoarthritis. They can be used alone or in combination with corticosteroids, antiangiogenics, and biologic anti-inflammatory agents.

Dr. Aghaloo highlighted the significant role that antiresorptives have played in the treatment of osteoporosis, offering extremely effective prevention of vertebral and hip fractures. Therefore, they became one of the most commonly prescribed medications between 2005 and 2009. However, in light of side effects associated with antiresorptives (including MRONJ), public concern has led patients to discontinue their use. With this recent development, Dr. Aghaloo offered to reexamine how side effects are presented to patients and how they will be managed if they occur.

MRONJ is not a common disease, with a prevalence of 0.8% to 12% in patients with cancer and 0.01% to 0.1% in osteoporosis. But this disease can significantly affect a patient's quality of life by causing pain, infection, paresthesia, tooth loss, intra-/extraoral fistulae, oroantral fistulae, and jaw fracture. Aghaloo et al. (2015) reviewed the published guidelines on MRONJ prevention and treatment, all focusing on preantiresorptive dental care, control of symptoms (e.g., pain and infection), and patient education. For stage 1, conservative therapy is recommended, which includes an antibacterial mouth rinse, patient education, and routine follow-up. For stage 2, treatment is escalated to include systemic antibiotics, pain control, and possible debridement of the necrotic bone. Stage 3 may also include more aggressive surgical debridement or resection. While surgery has been quite effective in recent years, as documented by several publications, patients may not be medically stable or psychologically willing to undergo aggressive surgery.

Recently, her team implemented a rigorous wound care protocol for patients with MRONJ, which involved aggressive mechanical debridement of exposed bone to remove the layers of plaque, debris, and biofilm with a cotton swab, toothbrush, or other hygiene aid to reduce inflammation and infection often associated with MRONJ lesions. Following this protocol, full mucosal epithelialization was seen in 71% of MRONJ lesions and was associated with sequestration of the necrotic bone. The ability to perform wound care without the presence of bleeding or plaque was significantly associated with complete healing. These data support locally aggressive wound care as first-line therapy for MRONJ, especially for patients in stages 1 and 2, but even in stage 3 for patients who are not surgical candidates. However, such a long healing time may not be acceptable for patients who desire faster disease resolution and should be considered in the discussion of treatment options.

Conclusions

Several hypotheses on the complex etiology and pathogenesis of MRONJ were presented. The speakers discussed the role of osteoclast inhibition, suppression of bone remodeling, increased drug toxicity leading to bone necrosis and poor wound healing, inhibition of angiogenesis, altered immune response, and bacterial colonization involvement during MRONJ pathogenesis. The task force acknowledged the importance of prevention prior to cancer or osteoporosis therapy. The speakers reviewed the conflicting data on drug holidays and the need for clinical research to test this question. Discussion

developed around future translational studies exploring the onset of bacterial colonization, identifying new therapeutic targets of bone remodeling and immune response, and understanding the role of the preexisting oral inflammatory diseases. There was a consensus on the leading role that the dental clinical and research community should play in the prevention and management of MRONJ.

Author Contributions

S. Ruggiero, contributed to conception and design, drafted and critically revised the manuscript; D. Saxena, contributed to conception and design, drafted and critically revised the manuscript; S. Tetradis, contributed to conception and design, drafted and critically revised the manuscript; T. Aghaloo, contributed to conception and design, drafted and critically revised the manuscript; E. Ioannidou, contributed to conception, design, and data acquisition, drafted and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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ORCID iD

E. Ioannidou https://orcid.org/0000-0003-1954-5900

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