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Osteonecrosis ONJ Session

## Summary of ASBMR Task Force on ONJ

**D.B. Burr**

Department of Anatomy and Cell Biology, Indiana University School of Medicine, Indianapolis, IN, USA

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The American Society for Bone and Mineral Research appointed a 24 member multi-disciplinary task force, co-chaired by Sundeep Khosla and Elizabeth Shane, to address six key areas important for the definition, understanding and study of bisphosphonate-related osteonecrosis of the jaw (BRONJ). The task force addressed issues related to the definition of BRONJ, epidemiology, risk factors, diagnostic imaging, clinical management and areas for future research. The Task Force Report will be published in the JBMR and should be online by late summer.

### Case definition

The Task Force separated the definition of confirmed and suspected cases of BRONJ. A confirmed case was defined as an area of exposed bone in the maxillofacial region that has not healed within 8 weeks after identification by a health care provider, in a patient who received bisphosphonate treatment and was not exposed to radiation therapy in the craniofacial region. A suspected case was defined as an area of exposed bone in the maxillofacial region that has been present for less than 8 weeks, in a patient who received bisphosphonate treatment and was not exposed to radiation therapy in the craniofacial region.

### Epidemiology

The risk of BRONJ was estimated to be ~1 in <100,000 patient-treatment years regardless of causality. The incidence in patients being treated for cancer is higher, probably

between 1-10%. Both dose and duration of bisphosphonate (BP) use is related to risk, with the mean time to onset of 18 months with zoledronic acid, but 39-72 months for patients treated with pamidronate. The odds ratio for i.v. BP use was estimated at 4.24, using insurance claims data.

### Diagnostic imaging techniques to characterize and diagnose BRONJ

Potentially useful imaging modalities were divided into those that image bone structure (panoramic radiography, computed tomography (CT), and cone beam computed tomography (CBCT)); those that image marrow and soft tissue (MRI); functional and physiological tests (scintigraphy with technetium and positron emission tomography (PET)); and those that are currently experimental but may have potential for development (optical coherence tomography (OCT)). Another more novel approach is to use sequential images to provide a temporal history of developing change. Some of the imaging approaches may also be enhanced by the contribution of contrast agents. While a number of imaging approaches could be used to possibly diagnose BRONJ at an early stage, considerable work needs to be done to define the most appropriate technique(s). The Task Force believes that the use of contrast agents combined with MRI, and the manipulation of different planes of image may be the most promising approach currently available for differential diagnosis. However, additional technological development of some relatively new approaches, such as OCT or CBCT, whose capabilities have not yet been fully explored, may prove to be valuable for detecting early stage disease.

### Recommendations for clinical management

The Task Force made a number of recommendations for clinical management, dividing them into general recommendations, as well as recommendations for patients with (a) osteoporosis or other non-malignant disease; (b) patients with malignancy; (c) patients with established BRONJ. In general, for those with

Dr. Burr has associations with P&G Pharmaceuticals, Merck, Eli Lilly and Co, and Amgen

*Corresponding author: David B. Burr, Ph.D., Department of Anatomy and Cell Biology, Indiana University School of Medicine, 635 Barnhill Dr., Indianapolis, IN 46202, USA  
E-mail: dburr@iupui.edu*

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established BRONJ, surgical treatment should be conservative or delayed. There are no data to suggest that stopping BP therapy will allow the ONJ to resolve, nor is there evidence that halting BP therapy prior to dental procedures is effective, because of the long half-life of BPs in the skeleton. The best management approach is still unclear and needs better definition.

### Future research

On the clinical/epidemiological side, it will be important to better define the true incidence of BRONJ, as well as to identify specific factors that put patients at risk. Because the risk of BRONJ is affected by the dose and duration of BP treatment, alternative dosing schedules could reduce the incidence of BRONJ while maintaining the benefits of BP therapy. Another area of future investigation should be to determine whether there are salivary or crevicular fluid markers that could be used as indicators of local bone metabolism. Outcome studies of those patients with dental implants or who have had routine dental therapy and also a history of current or past BP use should be defined. A number of basic or animal studies could be used to address these and other important questions. For example, the cellular and molecular mechanisms by which BPs predispose to the development of BRONJ need to be studied, as does the role of regional vascularization. Examination of the

bioavailability and distribution of the BPs in the skeleton, in relation to regional differences in bone metabolism and turnover, will be important. The roles of oral infection, trauma and inflammatory/immune processes in the pathogenesis of BRONJ are unclear. Development and validation of biomarkers for BRONJ will also provide important diagnostic information.

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### Reference

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#### Members of the Task Force:

\*Sundeep Khosla (Chair), David Burr, Jane Cauley, David W. Dempster, Peter Ebeling, Dieter Felsenberg, Robert F. Gagel, Vincente Gilsanz, Theresa Guise, Sreenivas Koka, Laurie K. McCauley, Joan McGowan, Marc D. McKee, Suresh Mohla, David G. Pendrys, Lawrence G. Raisz, Salvatore L. Ruggiero, David M. Shafer, Lillian Shum, Stuart L. Silverman, Catherine H. Van Poznak, Nelson Watts, Sook-Bin Woo and Elizabeth Shane.