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Review Article

Proceedings of the 2015 Santa Fe Bone Symposium: Clinical Applications of Scientific Advances in Osteoporosis and Metabolic Bone Disease

E. Michael Lewiecki,[*,1] *Roland Baron,*[2] *John P. Bilezikian,*[3] *Robert E. Gagel,*[4] *Mary B. Leonard,*[5] *William D. Leslie,*[6] *Michael R. McClung,*[7] *and Paul D. Miller*[8]

[1]New Mexico Clinical Research & Osteoporosis Center, Albuquerque, NM, USA; [2]Harvard Medical School and Massachusetts General Hospital, Harvard School of Dental Medicine, Boston, MA, USA; [3]Columbia University College of Physicians and Surgeons, New York City, NY, USA; [4]University of Texas, MD Anderson Cancer Center, Houston, TX, USA; [5]Stanford School of Medicine, Stanford, CA, USA; [6]Department of Internal Medicine, University of Manitoba, Winnipeg, Manitoba, Canada; [7]Oregon Osteoporosis Center, Portland, OR, USA; and [8]Colorado Center for Bone Research, Lakewood, CO, USA

Abstract

The 2015 Santa Fe Bone Symposium was a venue for healthcare professionals and clinical researchers to present and discuss the clinical relevance of recent advances in the science of skeletal disorders, with a focus on osteoporosis and metabolic bone disease. Symposium topics included new developments in the translation of basic bone science to improved patient care, osteoporosis treatment duration, pediatric bone disease, update of fracture risk assessment, cancer treatment-related bone loss, fracture liaison services, a review of the most significant studies of the past year, and the use of telementoring with Bone Health Extension for Community Healthcare Outcomes, a force multiplier to improve the care of osteoporosis in underserved communities.

Key Words: Bone Health ECHO; emerging; osteoporosis; Project ECHO; treatment.

Introduction

The 16th annual Santa Fe Bone Symposium was held on August 7–8, 2015, in Santa Fe, New Mexico, USA. The symposium is a 2-day multidisciplinary event that provides an opportunity for basic bone scientists, clinical researchers, physicians, and other healthcare professionals to review and discuss the clinical implications of recent

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*Address correspondence to: E. Michael Lewiecki, MD, New Mexico Clinical Research & Osteoporosis Center, 300 Oak St. NE, Albuquerque, New Mexico 87106, USA. E-mail: mlewiecki@gmail.com

advances in knowledge of skeletal health and disease. The focus of the presentations and discussions was the application of evidence-based medicine to clinical practice, recognizing that clinical decisions are often necessary despite limited scientific evidence. Proceedings of previous symposia have been published in peer-reviewed journals *(1–9)*.

Translation of Basic Bone Biology Into Improved Patient Care

Roland Baron, DDS, PhD

In the last 10–15 years, multiple discoveries have been made in the laboratory, most often as a consequence of the emergence of genetics and genomics, identifying novel mechanisms by which skeletal remodeling and homeostasis are ensured in both mice and humans. Some of these novel signaling pathways and/or potential therapeutic targets have been used to develop novel molecules to inhibit bone resorption (antiresorptives) or enhance bone formation (osteoanabolics) with the ultimate goal of restoring bone mass and microstructure in osteoporotic patients at risk of fragility fractures. This is a review of these therapeutic approaches and describes their mode of action.

A large part of skeletal homeostasis is accomplished through bone remodeling. This process is the result of crosstalk between 2 cellular lineages, the hematopoietic lineage, which gives rise to osteoclast precursors, and the mesenchymal lineage, which gives rise to osteoblast precursors *(10)*. Osteoclasts are responsible for resorption of bone; these cells also communicate with cells of the osteoblast lineage through the process of "coupling," thereby ensuring the recruitment of bone forming cells at the end of each resorption phase. In turn, cells of the osteoblast lineage (i.e., osteoblasts, osteocytes, and bone lining cells) are responsible for the activation of bone remodeling cycles by ensuring the differentiation of osteoclasts through the local secretion of receptor activator of nuclear factor kappa B ligand (RANKL) and for ensuring a balance between the amount of bone formed and the amount resorbed at each bone remodeling site. In the remodeling process, bone formation therefore occurs as a consequence of bone resorption *(10)*. Logically, a purely antiresorptive drug should therefore decrease not only resorption but also bone formation and ultimately bone turnover.

This link between resorption and formation is well illustrated by the results of the phase 2 and phase 3 clinical trials of denosumab, a fully human monoclonal antibody that prevents the osteoclastogenic action of RANKL *(11,12)*. In the phase 2 clinical trial, denosumab was compared with alendronate. Both treatments markedly decreased the bone resorption marker serum C-telopeptide and also, with a short lag in time, the bone formation marker serum procollagen type 1 N-terminal propeptide. The effect of denosumab on bone remodeling was confirmed in the phase 3 Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months trial, in which bone turnover markers (BTMs) and histomorphometric analysis of iliac crest biopsies were evaluated in a subset of patients *(11–13)*. Denosumab drastically reduced osteoclast numbers as well as bone formation and remodeling activity in trabecular bone. Despite these effects on bone remodeling, bone density at all measured skeletal sites increased significantly with long-term use. Denosumab treatment for up to 8 years was associated with persistent reductions of BTMs, continued bone mineral density (BMD) gains, and low fracture incidence *(14)*. The increase in bone density cannot be entirely explained by the very low remodeling-based bone formation. In monkeys, denosumab allows the continuation of another type of bone formation: modeling-based bone formation, perhaps explaining the continued gains in bone mass in humans *(15)*.

Attempts were then made to find novel antiresorptive drugs that could decrease resorption without having a negative impact on bone formation. The finding that deletion of cathepsin K (an osteoclast enzyme critical for bone resorption) blocks resorption but has a neutral or even positive effect on bone formation *(16)* opened the way. Mouse genetic studies have shown that, at least in part, this is due to an enhancement of the osteoclast-dependent coupling mechanism *(17)*. In preclinical and clinical studies *(16–18)* with small molecules inhibiting cathepsin K, markers of bone resorption are decreased to a level comparable to alendronate, but bone formation markers are maintained close to normal levels. In all these models, the decrease in bone resorption occurs despite a normal or even increased number of osteoclasts *(16–18)*, indicating that it does not affect osteoclast differentiation but rather decreases the resorbing activity of osteoclasts while maintaining the "coupling" activity *(17)*. The phase 2 and phase 3 Long-term Odanacatib Fracture Trial clinical trials with odanacatib have established the ability of these once-a-week oral compounds to increase bone density over several years *(19)* and to decrease the number of fractures *(20)*.

An alternative approach to increasing bone mass and strength is to increase bone formation with osteoanabolic drugs *(21)*. The prototype of this more recent class of osteoporosis drugs is teriparatide, the N-terminal 1–34 amino acids of parathyroid hormone (PTH 1–34). Unlike antiresorptive agents, this drug targets cells of the osteoblast lineage and induces an increase in their numbers and activity, increasing overall bone formation and bone mass, ultimately reducing the number of fractures *(22)*. A limitation of its use, however, is that PTH increases the local production of RANKL by osteoblasts and osteocytes and secondarily increases also osteoclast numbers and bone resorption, preventing further increases in bone density *(22)*. Two approaches have recently been proposed to limit this secondary increase in bone resorption. The first one uses an analog of PTH-related peptide (PTHrP [1–34]),