Osteoporosis
New Treatments and Updates

Stephen Honig, M.D., M.Sc.

The past year has been an interesting one for clinicians and researchers interested in osteoporosis. In a short review, such as this one, choosing which areas to highlight and which to omit is a challenge because of the many topics worthy of consideration in a 2011 update on osteoporosis. In this report, I have decided to focus on new and emerging pharmacologic therapies, recent findings exploring the relationship between serotonin and bone health, and to review the most recent information on bisphosphonate use and atypical femur fractures.

New and Emerging Treatments for Osteoporosis

Denosumab
The newest bone strengthening drug to win FDA approval is denosumab, a non-bisphosphonate anti-resorptive agent, which became available in June 2010. Denosumab is a fully humanized monoclonal antibody designed to target the receptor activator of nuclear factor-kappaβ ligand (RANKL), a soluble cytokine produced by osteoblasts. RANKL promotes osteoclast differentiation and activation, and denosumab prevents RANKL from engaging the RANK receptor on osteoclasts and osteoclast precursors thereby reducing osteoclast mediated bone resorption and increasing bone density. It is administered by subcutaneous injection (60 mg) every 6 months and rapidly reduces bone turnover with significant suppression of markers of bone resorption. In the FREEDOM trial, which involved 7,868 postmenopausal women who received either denosumab or placebo over 36 months, subjects receiving the active drug demonstrated a 68% relative reduction in morphometric vertebral fractures, a 40% relative reduction in hip fractures, and a 20% decrease in nonvertebral fractures compared to those women who received the placebo.1 Recently, 5-year data from the FREDOOM trial extension has shown continued bone density improvement and a low incidence of vertebral and nonvertebral fractures among those patients receiving denosumab.2 A subset of patients from the FREEDOM trial underwent iliac crest bone biopsies to assess the effects of denosumab on bone histomorphometry. Median eroded bone surface was reduced by more than 80%, and osteoclasts were absent from more than 50% of the biopsies in the denosumab group. Additionally, median bone formation rate was reduced by 97% in that group.3 Denosumab’s anti-resorptive effects are rapidly reversed once the drug is discontinued and bone density gains seen with its use are also lost if denosumab use is stopped. The side effect profile of denosumab includes rashes particularly eczema and infection but otherwise compared favorably to patients receiving placebo injections.1

Cathepsin K Inhibitors
Bone resorption by osteoclasts involves the breakdown of both the mineral and organic bone matrix of bone, the latter mainly involving type I collagen. The mineral component is degraded by acid secretion from osteoclasts on the surface of bone while the collagen is degraded primarily by cathepsin K. Cathepsin K is mainly produced by osteoclasts and inhibition of this protease has been targeted as a possible treatment for osteoporosis. Following below are brief descriptions of two cathepsin K inhibitors that are being evaluated for the treatment of postmenopausal osteoporosis.

Odanacatib
Odanacatib is an orally active selective inhibitor of cathepsin

Stephen Honig, M.D., M.Sc., is Clinical Associate Professor, New York University School of Medicine, within the Division of Rheumatology, Department of Medicine, and Director, Osteoporosis Center, NYU Hospital for Joint Diseases, NYU Langone Medical Center, New York, New York.

Correspondence: Stephen Honig, M.D., 301 East 17th Street, NYU Hospital for Joint Diseases, New York, New York 10003; stephen.honig@nyumc.org.
K that has been studied for the treatment of postmenopausal osteoporosis. It was shown to increase bone mineral density and reduce bone turnover markers in a 2-year dose-ranging study. After the 2-year study, 189 patients were re-randomized to Odanacatib 50 mg weekly or placebo for an additional year. The group of patients who received Odanacatib had continued, significant increases in bone mineral density at the lumbar spine and total hip while the subjects randomized to placebo (after 2 years of Odanacatib) rapidly lost bone at all sites with bone density scores approaching their baseline, pre-Odanacatib BMD values. Odanacatib appears to mainly suppress bone resorption with only a transient effect on bone formation and does not seem to impact osteoclast survival. These small studies were not powered to assess the fracture reduction properties of Odanacatib, but such a study with the 50 mg weekly dose of this drug has been initiated. The side effect profile of Odanacatib was similar to that seen with placebo, although there were a greater number of urinary tract infections seen in the one year extension among those subjects who continued on the active drug compared to those who were switched to the placebo.

ONO-5334
Another cathepsin K inhibitor, ONO-5334, was recently compared to alendronate (70 mg weekly) as a treatment for postmenopausal osteoporosis in a ONO-5334 dose-ranging (50 mg twice daily, 100 mg daily, and 300 mg daily) 12-month study conducted in six European countries. The effects on bone mineral density at the hip and spine were measured as were biochemical markers of bone turnover. All ONO-5334 doses and alendronate showed a significant increase in BMD for the lumbar spine, total hip (except ONO-5334 100 mg daily), and femoral neck BMD. There was little or no effect of ONO-5334 on bone formation markers compared with alendronate while the suppressive effects of bone resorption markers were similar with all doses of ONO-5334 and alendronate. There was no significant adverse effect data produced in this study. The 300 mg once daily dose of ONO-5334 and alendronate resulted in BMD gains of 5% at the lumbar spine at 12 months holding out promise that cathepsin K inhibitors may be effective treatment alternatives for osteoporosis.

Sclerostin Antibody
Sclerostin, a product of the SOST gene, is a glycoprotein produced mainly by osteocytes, the most abundant cell type of bone. Osteocytes are the mechanosensory cells of bone and have an extensive network of canaliculi well suited for this process. Sclerostin travels through these processes to the surface of bone where it binds to LRP5 and LRP6 and acts as an antagonist to Wnt signaling to reduce bone formation. Loss of function mutations in the SOST gene result in high bone mass phenotypes and recognition of this finding prompted the development of a monoclonal antibody to Sclerostin as a potential anabolic agent in the treatment of fractures and low bone mass states. In a rat closed femoral fracture model and in a fibular osteotomy model in cynomolgus monkeys, sclerostin antibody treatment significantly increased bone mass and bone strength at the site of fracture. Additionally, there were improvements in bone formation, bone mass and bone strength at both cortical and trabecular sites in non-fractured bone. In a phase I randomized placebo controlled study, 72 healthy subjects received either AMG 785, a sclerostin monoclonal antibody, or placebo (3:1). AMG 785 was administered at different dosage strengths by subcutaneous or intravenous injection. Dose-related increases in bone formation markers were seen as were dose-related decreases in the bone resorption marker serum C-telopeptide, suggesting a strong anabolic effect for AMG 785. Additionally, significant increases in bone mineral density at the lumbar spine and total hip were seen at day 85 in the treated group compared to those subjects who received the placebo. While these early results are preliminary and the safety of sclerostin antibody therapy has yet to be established, targeting sclerostin will likely be an ongoing strategy in the development of another anabolic agent for the treatment of osteoporosis and fracture non-unions.

Nitrates and Nitroglycerin
Nitric oxide can inhibit osteoclast activity and positively influence osteoblast and osteocyte function. More than a decade ago intermittent use of nitrates was shown to increase bone mineral density, and this finding has prompted a number of clinical studies investigating the relationship between nitrates and bone health and the feasibility of using nitric acid donors in the treatment of osteoporosis. Animal studies using nitric oxide donors such as nitroglycerin, isosorbide mononitrate, and dinitrate showed that these compounds can prevent bone loss associated with estrogen deficiency and glucocorticoid use. In a report involving subjects from the Canadian Multicentre Osteoporosis Study, nitrate use was associated with increased bone mineral density at the hip and spine in men and women when compared to subjects who did not use nitrates. The utility of nitroglycerin ointment as a bone strengthening agent was recently investigated in a placebo controlled 24-month study involving postmenopausal women with osteopenia. At 2 years, those women randomized to the nitroglycerin group had significantly greater gains in bone density and bone strength while decreasing bone resorption compared to those in the placebo group. This report lends further support to a possible role of nitrates as a treatment for osteoporosis.

The Role of Gut-Derived Serotonin and Bone Health
The hope for additional anabolic agents to treat low bone mass conditions now includes inhibition of gut-derived serotonin. Yadav and colleagues were the first to show that serotonin produced by the enterochromaffin cells of the duodenum inhibits bone formation and that targeting
tryptophan hydroxylase-1 (Tph-1), the rate-limiting enzyme in serotonin synthesis might be an effective strategy to promote new bone formation. In a mouse model, this group demonstrated that an oral inhibitor of Tph-1 blocks the synthesis of serotonin and prevents and reverses bone loss in ovariectomized mice. The effects on bone mass seen in this model were comparable to those seen with the use of teriparatide, the only currently approved anabolic agent used in the treatment of osteoporosis. This proof of concept study is an exciting development and holds promise for the emergence of a new approach to building bone. It also offers a possible explanation for the negative effects on bone seen with the use of serotonin uptake inhibitors.

Bisphosphonates and Atypical Fractures
In 1995, alendronate became the first bisphosphonate to be approved for the treatment of postmenopausal osteoporosis in the United States. This and other bone strengthening drugs reduce the incidence of fragility fractures in patients at increased fracture risk. The hip fracture rate in the United States is estimated to have decreased by 31% from 1996 to 2007, a result attributed in large part to the use of these drugs. However, several years ago, reports linking an association between subtrochanteric femur fractures (Fig. 1) and long-term bisphosphonate use began to appear. The cause of these fractures is not known, but markedly suppressed bone turnover has been advanced as a possible etiology. Epidemiologic data suggests that treatment with a bisphosphonate for more than 5 years is associated with an increased risk of subtrochanteric fractures, but the absolute risk of these atypical fractures is very low and that the risk of fracture decreases significantly after stopping the use of these drugs. It is important to remember that bisphosphonate drugs play an important role in fracture reduction and that atypical femur fractures are not common in long-term users of these drugs. It is estimated that for every 100 typical (femoral neck or intertrochanteric) fractures prevented by the use of bisphosphonate there is one atypical fracture that occurs. When prescribing these drugs to patients, they should be made aware of the increased risk of fracture. Drug holidays after 3 to 5 years of sustained use are recommended, particularly in younger postmenopausal women who may be at only moderately increased fracture risk.

Conclusions
This update has focused on clinically relevant information involving new and possibly future drug treatments for osteoporosis, discussed a newly emerging pathway influencing bone formation (gut derived serotonin), and outlined some of the data reporting the relationship between atypical femur fractures and bisphosphonate use. There are, of course, other areas that could have been included in this review, including advances in imaging with peripheral micro CT and high resolution MRI modalities, but space constraints naturally limit the subjects that could be covered. With the aging of the population, osteoporosis and other low bone mass conditions will be of increasing interest to both patients and health care planners alike and will be an area of continued interdisciplinary interest.

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