Novel Therapies for Postmenopausal Osteoporosis

Leonardo Bandeira, MD, John P. Bilezikian, MD*

KEYWORDS

• Osteoporosis • Postmenopausal • Antiresorptive • Osteoanabolic • Therapeutics

KEY POINTS

- Recently discovered mechanisms in the regulation of mineral metabolism have led to the development of new therapies for osteoporosis.
- These developments have led to new classes of drugs for the treatment of osteoporosis.
- Despite numerous advances over the past 2 decades, the search for newer therapies continues.

INTRODUCTION

Osteoporosis, the most common metabolic bone disorder, is characterized by low bone mass and microarchitectural deterioration, both of which lead to reduced bone strength and increased fracture risk.[1,2] With millions of postmenopausal women at risk for an osteoporotic fracture, osteoporosis is a major public health issue. Data from the National Health and Nutrition Examination Survey, 2005 to 2010, show a 15.4% prevalence of osteoporosis in women over 50 years old in the United States.[3]

Over the past 2 decades, an impressive array of pharmacologic therapies for postmenopausal osteoporosis has been introduced and shown to be efficacious. Nevertheless, the search for newer therapeutics continues for 3 reasons. First, none of the therapeutic classes available at this time eliminates osteoporotic fracture risk. Second, all classes of drugs have side effects, some of which, although rare, have engendered reluctance on the part of both practitioners and patients. Third, the perfect drug would be one that restores the microarchitectural deterioration that is characteristic of the disease. The latter continues to be an elusive goal.

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Department of Medicine, College of Physicians and Surgeons, Columbia University, 630 West 168th Street, PH8W-864, New York, NY 10032, USA
* Corresponding author.
E-mail address: jpb2@columbia.edu

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This review summarizes the data regarding therapies for osteoporosis that have recently been introduced or that are in development. Newly discovered mechanisms that form the basis for these new developments are focused on.

ANTIRESORPTIVE AGENTS

Denosumab

The drug denosumab has taken advantage of the discovery of a key activator of osteoclast function and development. Receptor activator of nuclear factor κB (RANK) ligand (RANKL) is a product of the osteocyte and a member of the tumor necrosis factor cytokine family. It binds to its cognate receptor, RANK, promoting both the activation of mature osteoclasts and the development of preosteoclasts. Recognition that RANKL has a natural inhibitor, known as osteoprotegerin, led to the development of the drug known as denosumab. This is a fully human antibody that binds to and inhibits RANKL's actions.[4–7]

The pivotal clinical trial leading to the approval of denosumab as a treatment of osteoporosis is known as Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM). In this study, 7868 postmenopausal women with osteoporosis were randomly assigned to receive denosumab, 60 mg, by subcutaneous injection, or placebo injection every 6 months for 3 years. In the denosumab group, there was a 68% reduction in risk of new vertebral fractures (VFs) ($P<.001$), a 40% reduction in risk of hip fractures ($P = .04$), and a 20% reduction in risk of nonvertebral fractures ($P = .01$) compared with placebo.[8]

The bone turnover markers (BTMs), C-telopeptide of type I collagen (CTX) and procollagen type 1 amino-terminal propeptide (P1NP), reflecting bone resorption and bone formation, respectively, showed similar and highly significant reductions of 72% and 76% ($P<.001$ for both). Denosumab was associated with a 9.2% gain at lumbar spine (LS) bone mineral density (BMD) and a 6% gain at total hip (TH) BMD ($P<.005$ for both compared with placebo). BMD also increased at the femoral neck (FN), trochanter, 1/3 radius, and total body ($P<.005$ for all compared with placebo).[8,9] In subjects who underwent quantitative CT (QCT), there was an increase in volumetric BMD (vBMD) at all sites in the denosumab group (21.8% at LS, 7.8% at TH, and 5.9% at FN; $P\leq.0001$ for all compared with placebo).[10]

The drug was shown to be safe and well tolerated. Because RANKL is also expressed in lymphocytes, infection risk was a theoretic concern. Superficial skin infections were a common adverse event (AE). In terms of serious AEs, 0.3% of patients in the denosumab group developed cellulitis compared with less than 0.1% in the placebo group ($P = .002$). The cellulitis was amenable to effective treatment. There were no cases of osteonecrosis of the jaw (ONJ) or atypical femur fracture (AFF).[8,11,12] Extension of this trial has not sustained the apparent imbalance in superficial skin infections that was seen in the first 3 years of the trial. Most experts have discounted the theoretic risk of infection as a major concern.[13]

In another multicenter phase 3 study, 1189 postmenopausal women with low bone mass were studied in a 1-year trial comparing denosumab and alendronate. In the denosumab group, there was a significantly greater increase in BMD compared with alendronate at all sites (3.5% vs 2.6% at TH, 2.4% vs 1.8% at FN, 5.3% vs 4.2% at LS, 1.1% vs 0.6% at 1/3 radius, and 4.5% vs 3.4% at trochanter; $P\leq.0001$ for all). BMD gains were greater for the denosumab group as early as month 6, the earliest time point measured. By the end of the trial, both groups showed major reductions in CTX (-74% denosumab vs -76% alendronate; $P = .52$), but the denosumab group had a greater reduction from month 1 to month 9 ($P\leq.0001$ compared with the