

New Antiresorptive Therapies for Postmenopausal Osteoporosis

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Osteoporosis is a systemic skeletal disease whose risk increases with age and it is common among postmenopausal women. Currently, almost all pharmacological agents for osteoporosis target the bone resorption component of bone remodeling activity. Current antiresorptive agents are effective, but the effectiveness of some agents is limited by real or perceived intolerance, long-term adverse events (AEs), coexisting comorbidities, and inadequate long-term adherence. New antiresorptive therapies that may expand options for the prevention and treatment of osteoporosis include denosumab, combination of conjugated estrogen/bazedoxifene and cathepsin K inhibitors. However, the long-term efficacy and AEs of these antiresorptive therapies need to be confirmed in studies with a longer follow-up period. (**J Menopausal Med 2015;21:1-11**)

Key Words: Bone density conservation agents, Fractures bone, Osteoporosis, Postmenopause

Introduction

Osteoporosis is a systemic skeletal disease whose risk increases with age and it is common among postmenopausal women. Because of reduced bone mineral density (BMD) and weakened bone structure, osteoporosis decreases bone resistance to low-energy trauma and increases bone fragility and fracture risk. The goal of osteoporosis treatment is to prevent fractures. Currently, almost all pharmacological agents for osteoporosis target the bone resorption component of bone remodeling activity. The only anabolic agent currently available is teriparatide. Current antiresorptive agents are effective, but the effectiveness of some agents is limited by real or perceived intolerance, long-term adverse events (AEs), coexisting comorbidities, and inadequate long-term adherence. This review aims at providing an overview of the shortly after available or investigated new antiresorptive agents for osteoporosis.

Receptor Activator of Nuclear Factor-Kappa B (RANK) Ligand (RANKL) Inhibitor, Denosumab

RANKL is a cytokine essential for osteoclast differentiation, activation and survival. RANKL accelerates osteoclastogenesis when it binds to its receptor, RANK on the osteoclast surface. These actions can be blocked by a decoy receptor, osteoprotegerin (OPG) which is produced by osteoblasts and stromal cells. Denosumab is a human monoclonal antibody that binds RANKL, which selectively inhibits osteoclastogenesis, being recently approved for the treatment of postmenopausal osteoporosis in women at a high or increased risk of fracture by the Food and Drug Administration (FDA) in the U.S and by the European Medicines Agency in Europe since June 2010.^{1,2} Denosumab is administered by subcutaneous (SC) injection and 60 mg once every 6 months and may be injected in the upper arm,

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upper thigh or the abdomen.³ Denosumab inhibits numerous aspects of osteoclast differentiation and function by inhibiting the intracellular signal pathways that are activated by the RANKL/RANK binding, which results in decreased fractures and increased BMD.⁴ RANKL presents ubiquitously throughout many tissues including cells of immune system such as activated T cells and B cells.⁵ Since denosumab specifically binds RANKL, however, it is less likely to affect the immune system or other regulatory systems. Moreover, denosumab does not have the potential for autoimmunization against vital regulatory proteins and is characterized by a longer half-life which permits less frequent dosing.⁶

1. Pharmacokinetics and metabolism

The pharmacokinetics of denosumab is nonlinear with dose.⁷ Studies with similar IgG antibodies showed that SC denosumab is absorbed by the lymphatic system with subsequent drainage into the vascular system. The bioavailability is about 50% to 100%. The clearance is probably by the reticuloendothelial system and no significant amount of denosumab seems to be filtered and excreted by the kidneys. SC administration is characterized by 3 stages: a prolonged absorption phase with the maximum serum concentration (at 5 to 21 days post-dose); a long duration phase with half-life of a maximum of 32 days; a rapid terminal phase when serum concentration is lower than 1000 ng/mL. The magnitude of the initial response was similar among the doses, although the duration of the effect was dose-dependent.⁶

2. Clinical studies on postmenopausal osteoporosis

1) Phase 3 studies

Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) randomized 7,668 postmenopausal women with osteoporosis into 2 groups: placebo or SC denosumab 60 mg/6 months.⁴ Primary endpoint was a reduction in the incidence of new vertebral fractures in a 3-years period. Secondary endpoints were reduction in hip and other nonvertebral fractures and changes in BMD and bone turnover markers (BTMs). Denosumab group presented a 68% reduction in new vertebral fracture risk compared to placebo group (2.3% vs.

7.2%, $P < 0.0001$), 40% reduction in the hip fracture (0.7% denosumab vs. 1.2% placebo; $P = 0.036$), and 20% reduction in the nonvertebral fracture risk (6.5% denosumab vs. 8.0% placebo; $P = 0.011$). Denosumab group showed a significantly increase in BMD at all sites including forearm. Over 3 years, the number needed to treat (NNT) to prevent one new vertebral and one hip fracture were 21 and 232, respectively. Absolute risk reduction was greater in women with multiple risk factors, such as prior fracture plus low baseline femoral neck BMD.⁸ This study was extended for 2 years with all patients ($n = 4,550$) switched to open-label denosumab. Data suggest that 5 years of treatment leads to continued protection from vertebral and non-vertebral fractures. There were additional gains in BMD at the lumbar spine and total hip, resulting in 5-year gains of 13.7% and 7%, respectively. In patients who crossed over to denosumab from the placebo group, findings at 2 years were similar to those in the group originally randomized to denosumab.⁹ A post-hoc analysis of data from the FREEDOM study revealed that 3 years of treatment of denosumab significantly reduced the risk of hip fractures in subjects aged 75 years.⁸ Similarly, a recent subgroup analysis of the same trial showed that the effect of denosumab treatment on reduction in risk of vertebral and nonvertebral fractures was similar in subjects older or younger than 75 years of age.¹⁰

2) Head-to-head comparison with alendronate

Determining Efficacy: Comparison of Initiating Denosumab vs. Alendronate (DECIDE) was a non-inferiority study to compare the effects of denosumab and alendronate on BMD and BTMs in naïve postmenopausal women ($n = 1,189$) with low BMD (T-score of lumbar spine or total hip less than -2.0).¹¹ BMD gains at all measured skeletal sites and BTMs reduction were significantly greater with the denosumab group (3.5% denosumab vs. 2.6% alendronate; $P < 0.0001$) compared to the alendronate group after 12 months of treatment.

3) Transitioning from alendronate to denosumab

Study of Transitioning from Alendronate to Denosumab (STAND), a study of postmenopausal women ($n = 504$) with low BMD (T-scores between -2.0 and -4.0) who had been receiving alendronate for at least 6 months

were randomized assigned to switch to denosumab or to continue alendronate.¹² At 12 months, there were small but significantly greater gains in BMD in the denosumab group at all skeletal sites measured, along with greater reduction in BTMs compared to the alendronate group.

4) Denosumab in patients with renal impairment

Phase 1 study was conducted to evaluate the pharmacokinetics, pharmacodynamics and safety of a single dose of 60 mg SC denosumab in 55 patients with different degree of renal function.¹³ Results showed that the renal impairment did not affect the pharmacokinetics and pharmacodynamics, and no dose adjustment is necessary in impaired renal function. However, about 30% of patients with severe renal function and hemodialysis showed symptomatic hypocalcemia.

5) Effects of discontinuing denosumab on BMD and levels of BTM

For 256 postmenopausal women, 60 mg denosumab or a placebo was administered every 6 months for 2 years, followed by 2 years of discontinued treatment.¹⁴ Denosumab discontinuation resulted in a decline in BMD at all sites during the first 12 month, followed by BMD stabilization during the next 12 months. After this 4-year period, the denosumab group maintained a higher BMD than the placebo group. Levels of BTMs were increased above baseline within 3 to 6 months of the initial 2-year treatment period. By the end of the 4-year period, the levels of the BTMs had returned to baseline. The effects of denosumab were fully reversible over this time span, with no deleterious effect on bone micro-structure.¹⁵

6) Patient-focused perspectives

Denosumab Adherence, Preference, Satisfaction (DAPS) study evaluated patient perspectives with SC denosumab 60 mg every 6 months compared with oral alendronate 70 mg weekly in 250 women with postmenopausal osteoporosis.¹⁶ Adherence was significantly greater with denosumab than alendronate (87,3% vs. 76,6%). Subject ratings for treatment preference and satisfaction were also significantly higher for denosumab than alendronate.

3. Safety

In osteoporosis clinical trials, denosumab was generally safe and well tolerated. Overall, there were no significant differences between subjects who received denosumab and those who received placebo in the total incidence of AEs, serious AEs, or discontinuation of treatment because of AEs. Safety concerns with denosumab use include infections, cancer, skin reactions, hypocalcemia, osteonecrosis of the jaw (ONJ), and atypical femur fractures.

1) Infections, cancer and skin reactions

The major safety concerns with denosumab have been the potential risks for infection and malignancy because of the ubiquitous presence of RANKL throughout many tissues, including cells of the immune system such as activated T lymphocytes and B cells.⁵ In the FREEDOM study, there was no increase in the overall risk of infection or cancer; however, serious AEs of cutaneous infections such as cellulitis and erysipelas, occurred more in the denosumab group (<0,1% vs. 0,3%, $P = 0,002$).⁴ Dermatological AEs such as dermatitis, eczema and rashes also occurred at a significantly higher rate (8,2% vs. 10,8%, $P < 0,0001$) in the denosumab group.⁴ In a post-hoc analysis of this study, serious AEs of infection such as skin, gastrointestinal, ear, urinary and cardiac valvular infection, were numerically higher in the denosumab group although the number of events was small and the differences between groups were not statistically significant.¹⁰ The heterogeneous and no clear clinical pattern suggests that a relationship to time or duration of exposure to denosumab arguing against a causal relationship.¹⁷ Finally, infectious events did not increase with long-term treatment of denosumab in the FREEDOM extension study.⁹

2) Hypocalcemia

The FDA label includes a caution about the possibility of hypocalcemia after denosumab administration. Also, there have been post-marketing reports of severe, symptomatic hypocalcemia after denosumab injection.¹⁸⁻²⁰ It is important to ensure that patients maintain an adequate calcium and vitamin D supplementation, especially with conditions that predispose to hypocalcemia, such as chronic kidney disease or malabsorption syndrome. Denosumab should not be

given to patients with preexisting hypocalcemia until it is corrected.

3) ONJ

The FREEDOM study reported no case of ONJ in either denosumab or placebo group.⁴ However, there have been eight adjudicated cases of ONJ in the FREEDOM extension study in the crossover and long-term groups.^{4,9} There has also been a low but similar incidence of ONJ in the oncology trials using monthly denosumab vs. monthly zoledronic acid (1.3% vs. 1.8% over 3 years).²¹ Good oral hygiene and regular dental visits should be recommended for everyone.

4) Atypical femur fractures

To date there have been two cases of atypical subtrochanteric femur fractures reported in the denosumab osteoporosis clinical trials as well as reports of unusual fractures with denosumab use.²² It is important to note that these fractures can occur in patients who are on no any antiresorptive treatment for osteoporosis, and further studies on long-term treatment are needed to evaluate the possible occurrence of atypical femur fractures with the use of denosumab.

5) Cardiovascular disease

The effect of denosumab on vascular calcification is controversial. Preclinical models suggest that OPG has a possible protective role in the process of arterial calcification.²³⁻²⁶ On the other hand, several studies in humans have suggested that OPG may be involved in the onset and progression of coronary artery disease and cardiovascular mortality.²⁶⁻²⁸ On the other hand, hypercholesterolemia was reported as an AE in 7.2% of patients on denosumab in the FREEDOM study (vs. 6.1% placebo, nasal spray [NS]) although this was not statistically significant. Ultimately, there was no increase in the overall risk of cardiovascular disease in the denosumab group in both the FREEDOM study and its extension study.^{4,9}

4. Differences between denosumab and the bisphosphonates (BPs)

Denosumab blocks osteoclasts formation, function and survival while BPs cause loss of resorptive function but

disabled osteoclast may persist. Denosumab exerts its effect from within the extracellular fluid and does not bind to bone tissues.²⁹ Denosumab induces more rapid and greater reduction in bone remodeling and has rapid and completely reversible offset of action at about 6 months.¹⁴ Denosumab shows greater increase in BMD and positive effects on both trabecular and cortical bone.³⁰

5. Indications

Denosumab is currently approved by the U.S. FDA for the treatment of postmenopausal women and men with osteoporosis as well as for treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer and for treatment to increase bone mass in men at high risk for receiving androgen deprivation therapy for non-metastatic prostate cancer.³

6. Contraindication, warning and precautions

Hypocalcemia, pregnancy and known hypersensitivity are all contraindications.³ Hypocalcemia must be corrected before initiating denosumab. ONJ and atypical femur fracture have been reported. Monitoring for symptoms of ONJ and evaluation of patients with thigh or groin pain are required. Serious infections including skin reactions may occur. Patients should be advised to seek prompt medical attention if they develop signs or symptoms of infection, including cellulitis, Dermatitis, rashes, eczema, and severe bone, joint and muscle pain have been reported. If severe symptoms develop, consider discontinuation of denosumab.

Tissue Selective Estrogen Complex (TSEC), Bazedoxifene (BZA)/ Conjugated Estrogen (CE)

Hormone therapy (HT) has been the standard of care for managing moderate to severe hot flashes and vulva-vaginal atrophy (VVA) associated with menopause. In postmenopausal women with a uterus, the inclusion of a progestin is necessary because unopposed estrogen therapy (ET) is associated with an unacceptably high rate of endometrial hyperplasia as well as endometrial cancer.

The Women's Health Initiative studies found an increased risk of invasive breast cancer and breast cancer-related mortality among estrogen/progestin therapy (EPT) users, in contrast to a protective effect against breast cancer among hysterectomized women using ET.^{31,32} A new strategy is the combination of a selective estrogen receptor modulator (SERM) with estrogen(s), TSEC, based on the simultaneous but differential effects of each compound on estrogen receptor activity. Also, this combination provides a progestin-free alternative to traditional HT for postmenopausal women with a uterus who has bothersome menopausal symptoms. BZA is a good candidate for investigation in combination with estrogens as part of a TSEC because BZA does not stimulate either breast or endometrium. In multiple investigations, BZA exhibited less agonist activity in the endometrium compared with raloxifene or lasofoxifene.³³⁻³⁵ The TSEC consisting of CE 0.45 mg and BZA 20 mg represents the newest option for the management of moderate to severe postmenopausal hot flashes and prevention of postmenopausal bone loss.

1. Endometrium and breast safety in clinical trials

In phase 2 studies, BZA 20 mg (but not BAZ 5 or 10 mg) provide adequate endometrial protection when combined with CE 0.3 or 0.625 mg and that combination of CE 0.625/BZA 20 mg (but not CE 0.3/BZA 20 mg) were effective in reducing hot flashes.³⁶ An ancillary retrospective study of Selective estrogens, Menopause, And Response to Therapy (SMART)-1 and a prospective substudy of SMART-5 both found that neither CE 0.45/BZA 20 mg nor CE 0.625/BZA 20 mg increased breast density compared with placebo.^{37,38} Also, CE/BZA offers a better breast tolerability profile than EPT which has been associated with breast pain and tenderness and increased breast density. Firm conclusions regarding CE/BZA and breast cancer risk are not yet drawn given the small number of breast cancer events in the SMART trials and the limited duration (up to 2 years) of these studies.

2. Effects of bone in clinical trials

1) SMART-1 trial

The SMART-1 trial included 2 osteoporosis prevention

substudies that evaluated CE/BZA in different subpopulations: subjects in substudy I were women more than 5 years postmenopause with lumbar spine or hip BMD T-scores between -1.0 and -2.5 plus 1 other osteoporosis risk factor (n = 1,454), and subjects in substudy II were 1 to 5 years postmenopause and had at least 1 osteoporosis risk factor (n = 861).³⁹ SMART-1 study subjects were randomized to 1 of 6 doses of CE/BZA (CE 0.45 or 0.625 mg in combination with BZA 10, 20, and 40 mg), raloxifene, or placebo. In both SMART-1 substudies, all doses of CE/BZA significantly increase the adjusted mean % change in BMD of the lumbar spine from baseline to month 24 compared with BMD decreases with placebo ($P > 0.001$). Similar results were seen for total hip BMD. Compared to raloxifene, all CE/BZA doses (except those containing BZA 40 mg) in substudy I produced significantly greater differences in lumbar spine BMD, and some doses (CE 0.625/BZA 20 mg in substudy I and CE 0.45/BZA 20 mg in substudy II) produce significantly greater increases in hip BMD as well. The median %change of BTMs was significantly greater than for placebo with all BZA/CE doses at all-time points. Median %change in these BTMs was also significantly greater than raloxifene for all doses of CE/BZA at nearly all-time points: the only exceptions were with doses containing BZA 40 mg. Thus CE/BZA was generally more effective than raloxifene in maintaining or increasing bone mass and reducing bone turnover in both substudy populations of SMART-1 throughout 2 years.

2) SMART-5 trial

The SMART-5 trial included an osteoporosis substudy in subjects who were 5 or less years of postmenopausal, had lumbar spine and total hip T-scores less than -2.5 at screening.⁴⁰ Subjects were randomized to CE 0.45/BZA 20 mg, CE 0.625/BZA 20 mg, BZA 20 mg, CE 0.45/medroxyprogesterone acetate (MPA) 1.5 mg, or placebo. Both doses of CE/BZA significantly increased lumbar spine and total hip BMD compared with decreased BMD in the placebo group over the 12-month. In addition, compared with placebo, both CE/BZA doses produced greater decreases from baseline to month 12 in BTMs. On the other hand, both doses of CE/BZA showed similar efficacy to CE/MPA and a superior bone effect as compared with BZA 20 mg. SMART-1 and SMART-5 demonstrated that treatment with

CE 0.45/BZA 20 mg and CE 0.625/BZA 20 mg effectively prevented loss of total hip BMD, having a comparable effect to that of raloxifene 60 mg and BZA 20 mg at all-time points evaluated.^{39,40} Also, CE 0.45/BZA 20 mg and CE 0.625/BZA 20 mg demonstrated a comparable effect to CE 0.45/MPA 1.5 mg in terms of effects on total hip BMD. Overall, the skeletal effects observed with CE/BZA treatment were clinically meaningful and greater than for raloxifene and BZA monotherapy and comparable with CE/MPA,

3. Other effects of BZA/CE

Clinical studies confirmed the efficacy of the selected doses for relieving vasomotor symptoms, VVA, and dyspareunia; and improving sexual function, menopause-specific quality of life and sleep in postmenopausal women.^{41–44}

4. Safety and tolerability

CE/BZA was well tolerated in the SMART studies. The overall incidence of treatment emergent AEs among women treated CE/BZA was similar to placebo in all of the trials. Rates of venous thromboembolism, ischemic stroke, and coronary heart disease event among women using CE 0.45/BZA 20 mg were comparable to placebo.^{40–42,45} There were no cases of pulmonary embolism in any of the SMART trials. Laboratory findings with CE/BZA have shown largely neutral or beneficial effects on lipids and coagulation markers.^{41,42} Cumulative amenorrhea rate and incidence of bleeding/spotting are similar to placebo.^{40,43,46}

5. Indications

To date, CE 0.45/BZA 20 mg was approved by the U.S. FDA for women who suffer from moderate to severe hot flashes associated with menopause and to prevent osteoporosis after menopause. CE/BZA is not approved to treat osteoporosis.⁴⁷ Alternative agents should be considered if osteoporosis prevention without moderate to severe vasomotor symptoms is the only indication. Also, CE/BZA is not approved for the treatment of VVA. Use in women over 75 years of age is not recommended because CE/BZA has not been studied in women over 75 years of age.

6. Contraindications

Contraindications of CE/BZA are similar to those of ET

or EPT. Undiagnosed abnormal uterine bleeding, known, suspected or past history of breast cancer, known or suspected estrogen-dependent neoplasm, active deep vein thrombosis, pulmonary embolism or history of these conditions, active arterial thromboembolic diseases (stroke, myocardial infarction, etc.) or history of these conditions are all contraindications of CE/BZA.⁴⁷

Cathepsin K Inhibitor, Odanacatib

Cathepsins are lysosomal proteases that belong to the papain-like cysteine protease family. Eleven different types have been described with cathepsin K being the most important with respect to bone remodeling. It is predominantly expressed in osteoclasts and is the most abundant cysteine protease in these cells, accumulating in specific subcellular compartments, lysosomal vesicles.⁴⁸ In actively resorbing osteoclasts, cathepsin K is localized at the ruffled border and discharged into the extracellular space when the lysosomal vesicles fuse with the cell membrane, to degrade the two main types of collagen, I and II within the acidic microenvironment of resorption lacunae.^{49,50} The expression of cathepsin K is down-regulated by estrogen and up-regulated by RANKL, tumor necrosis factor, and many other agents capable of increasing osteoclast formation and differentiation, such as vitamin D, parathyroid hormone (PTH), and interleukins.^{51,52} Cathepsin K inhibitors have to be delivered into the lysosomes. It is the concentration of these drugs in the resorption lacunae that is most relevant to their activity. Because cathepsin K and most other cathepsins are lysosomal enzymes, early inhibitors were designed to contain lipophilic and basic moieties to allow cell permeability and localization to lysosomes (lysosomotropism).⁵³ However, their increased accumulation in acidic lysosomes resulted in the inhibition of other cysteine proteases such as B and L, causing undesired effects.⁵³ The strategies subsequently shifted to the design of nonbasic inhibitors, which are non-lysosomotropic but still maintain their potency and selectivity against individual cathepsins and in vivo efficacy in animal studies.⁵⁴ Odanacatib is a nonbasic and non-lysosomotropic nitrile-based molecule displaying high potency for cathepsin K and increased selectivity versus cathepsins B, L, and S

when compared with balicatib and relacatib.⁵⁵ In preclinical studies, odanacatib presented good pharmacokinetic parameters such as minimal in vitro metabolism and long half-life, and oral bioavailability.

1. Effects of bone

1) Two-year results of phase 2 trial

This was a double-blind, randomized, placebo-controlled trial of 12 months duration with an extension period of 12 months to evaluate the safety and efficacy of weekly doses of placebo or 3, 10, 25, or 50 mg of odanacatib on BMD and BTMs.⁵⁶ Twenty-four months of treatment produced progressive dose-related increases in BMD. With the 50 mg dose of odanacatib, lumbar spine and total hip BMD increased 5.5% and 3.2% respectively, whereas BMD at these sites was unchanged with placebo. Resorption markers fell in a dose-dependent manner. The urinary N-terminal telopeptide (NTX)/Cr ratio decreased by 52%, while the B-cell-specific activator protein (BSAP) levels decreased initially but then recovered gradually from month 6 onward to reach -13% with the 50 mg dose at month 24. Significant difference from control for BSAP was observed only for the 50 mg group. The decrease in BSAP level associated with odanacatib treatment was less than what is typically seen with other antiresorptive agents, such as BPs.

2) Three-year results of phase 2 trial

At the end of 2 years of phase 2 trial, a 1-year extension study was carried out to further assess odanacatib efficacy, safety, and the effects of discontinuing therapy.⁵⁷ After 2 years, patients (n = 189) were re-randomized to odanacatib 50 mg weekly or placebo for another year in such a way that some participants received placebo for the entire 3 years (PLB/PLB), some were treated with odanacatib for the entire 3 years (ODN/ODN), and some received odanacatib 50 mg for 2 years followed by placebo (ODN/PLB) for 1 year. Women in the ODN/ODN group showed further improvement in BMD and the cumulative gain in BMD after 3 years of treatment with odanacatib 50 mg was 7.9% at the lumbar spine, 5.8% at the total hip, 5.0% at the femoral neck, and 7.4% at the trochanter. Urine NTX/Cr remained suppressed at year 3 (-50.5%) compared with a 17.5% decline for those

who received placebo for the 3-year period (PLB/PLB). Tartrate-resistant acid phosphatase 5b (TRAP5b) levels were not significantly different from the placebo group and bone formation markers returned to near baseline. In the ODN/PLB group, women who were previously treated with odanacatib 50 mg for 2 years showed significant bone loss in all sites and this was most rapid during the first 6 months after discontinuation of active treatment. BMD of all skeletal sites returned to baseline levels after 12 months off medication, although femoral neck BMD remained slightly increased (+2.3%).

3) Five-year results of phase 2 trial

At the end of 3 years, the Phase 2 trial was extended for a further 2 years.⁵⁷ After 5 years, women who received odanacatib 50 mg continuously from year 1 (n = 13), showed BMD increases from baseline of 11.9% at the lumbar spine, 9.8% at the femoral neck, 10.9% at the hip trochanter, and 8.5% at the total hip. Additionally, women treated continuously with odanacatib 50 mg maintained a low level of urine NTX/Cr (-67.4% from baseline) through 5 years of treatment; while levels of serum BSAP remained only slightly reduced relative to baseline (-15.3%).

4) Phase 3 trial

Long-Term Odanacatib Fracture Trial (LOFT) is a randomized, double-blind, placebo-controlled, event-driven trial, including a pre-planned, blinded placebo-controlled extension study.⁵⁸ The trial enrolled 16,713 women, 65 years of age or older, diagnosed with osteoporosis, who have been postmenopausal for five years or more. Patients were randomized to receive odanacatib 50 mg/week (n = 8,357) or placebo (n = 8,356). The results from this trial were presented at the 2014 American Society for Bone and Mineral Research (ASBMR) Annual Meeting in Houston, Texas. In LOFT, odanacatib significantly reduced the risk of three types of osteoporotic fractures compared to placebo in the primary efficacy analysis (54% relative risk reduction of new and worsening morphometric vertebral fractures; 47% relative risk reduction of clinical hip fractures; 23% relative risk reduction of clinical non-vertebral fractures; all $P < 0.001$) and also reduced the risk of the secondary endpoint of clinical vertebral fractures (72% relative risk reduction, P

< 0.001).

2. Safety data from LOFT

The rates of AEs overall in LOFT were generally balanced between patients taking odanacatib and placebo.⁵⁸ Adjudicated morphea-like skin lesions occurred more frequently on odanacatib: in 12 patients in the odanacatib group (0.1%) and 3 patients in the placebo group (< 0.1%). These skin lesions resolved or improved after discontinuation of the study drug. Adjudicated atypical femoral shaft fractures were reported for 5 patients in the odanacatib group (0.1%) and not reported in patients in the placebo group. No meaningful differences were observed in adjudicated events of systemic sclerosis, serious respiratory infections or delayed fractured unions between groups. There were no adjudicated cases of ONJ. Adjudicated major adverse cardiovascular events were generally balanced overall between the treatment groups. There were numerically more adjudicated stroke events with odanacatib than with placebo (hazard ratio [HR] = 1.28; 95% confidence interval [CI], 0.97–1.70).

3. Differences between odanacatib and other antiresorptive agents

Odanacatib has shown greater suppression of bone resorption than bone formation, suggesting dissociation between bone resorption and bone formation.^{56,57} The exact molecular mechanisms linking cathepsin K inhibition and bone formation remain largely unknown; however, they have been predicted to involve complex networks of cell to cell communications. Khosla⁵⁹ hypothesized that in the setting of odanacatib treatment, while the reduction in bone resorption would lead to a reduction in the release of growth factors from the bone matrix, direct communication between non-resorbing osteoclasts and osteoblasts through the ephrin 2-erythropoietin-producing human hepatocellular carcinoma receptor B4 (EphB4) system may not be affected. The same may be true of coupling factors, if they are also secreted by non-resorbing osteoclasts. Thus, the net effect of odanacatib on bone formation could depend on offsetting the effects of the loss of growth factor release from bone matrix with the ongoing, perhaps enhanced, effects of coupling factors from the increased numbers of relatively healthy osteoclasts. Furthermore, different remodeling or

modeling rates of specific bone surfaces could be linked to the compartment-specific action of odanacatib on bone formation. In trabecular bone, with its high remodeling rate, and where inhibition of bone resorption was associated with reduction in bone formation, the release of growth factors from the bone matrix may be particularly important.⁶⁰ On periosteal surfaces, however, where the remodeling rate is much lower and the activity is predominantly modeling, the direct stimulatory effects of osteoclasts on osteoblasts could be responsible for the increased periosteal bone formation and cortical thickness.⁶¹

Conclusion

New antiresorptive therapies that may expand the menu of options in the prevention and treatment of osteoporosis include the denosumab, combination of CE/BZA and cathepsin K inhibitors. The long-term efficacy and AEs of these antiresorptive therapies remains to be confirmed with studies that include longer follow-up periods. Also, it is to be hoped that future research will allow us to answer important questions regarding treatment duration and discontinuation. This is particularly relevant since postmenopausal women are increasingly experiencing a longer life expectancy. We can expect to see a transition from the twentieth-century medications that have had such a great impact on osteoporosis treatment to newer medications and new ways of using the old drugs.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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