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New Frontiers in Osteoporosis Therapy

Cheng Cheng,[1,2] Kelly Wentworth,[2,3] and Dolores M. Shoback[1,2]

[1]Endocrine Research Unit, Endocrine-Metabolism Section, Department of Medicine, San Francisco Veterans Affairs Medical Center, San Francisco, California 94121, USA; email: dolores.shoback@ucsf.edu

[2]Division of Endocrinology and Metabolism, Department of Medicine, University of California, San Francisco, California 94143, USA

[3]Zuckerberg San Francisco General Hospital and Trauma Center, San Francisco, California 94110, USA

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Abstract

Current osteoporosis medications reduce fractures significantly but have rare and serious adverse effects (osteonecrosis of the jaw, atypical femoral fractures) that may limit their safety for long-term use. Insights from basic bone biology and genetic disorders have led to recent advances in therapeutics for osteoporosis. New approaches now in clinical use include the antisclerostin monoclonal antibody romosozumab, as well as the parathyroid hormone–related peptide analog abaloparatide. Clinical trial data show significant antifracture benefits with recently approved romosozumab. Studies using abaloparatide build on our longstanding experience with teriparatide and the importance of consolidating the bone mineral density gains achieved from an anabolic agent by following it with an antiresorptive. Combination and sequential treatments using osteoporosis medications with different mechanisms of action have also been tested with promising results. On the horizon is the potential for cell-based therapies (e.g., mesenchymal stem cells) and drugs that target the elimination of senescent cells in the bone microenvironment.

INTRODUCTION

Osteoporosis is a worldwide epidemic characterized by low bone mass and weakened microarchitecture, which predispose affected patients to fragility fractures. It is projected that ~40% of women and ~14% of men over age 50 will suffer an osteoporotic fracture in their remaining lifetime (1). These figures are alarming because fractures, particularly of the hip, are associated with significant morbidity and mortality. This translates into an overwhelming financial burden for society; the medical cost of osteoporotic fractures in 2005 was estimated at ~$17 billion (2) and will only continue to rise as the population ages.

Substantial progress has been made toward developing drugs that treat osteoporosis. Early studies focused on drugs that target bone resorption, including bisphosphonates, calcitonin, selective estrogen response modulators (SERMs), and estrogen. The potent antiresorptive agent denosumab was developed more recently. All of these agents inhibit bone resorption, but due to the coupling between resorption and formation, they secondarily reduce formation. Concomitant efforts focused on strategies to enhance bone cell anabolic activity. The first approved agent to accomplish this was teriparatide. Teriparatide [recombinant human parathyroid hormone, PTH(1–34)] stimulates bone formation, but it eventually also increases bone resorption because the two processes remain coupled. Bone resorption is due to the well-known ability of PTH to stimulate production of RANKL (receptor activator of nuclear factor kappa B ligand) by cells of the osteoblast lineage (3).

A major concern with prolonged use of potent antiresorptive agents such as the bisphosphonates and denosumab is the rare incidence of osteonecrosis of the jaw and atypical femoral fracture. These occurrences have restrained the use of these agents for the long term. Considering these limitations and the need for more potent agents capable of restoring skeletal structure and integrity, efforts have been directed toward developing therapies that target anabolic pathways in bone and therapies that restore a population of bone-forming cells, osteoblasts and their precursors, capable of enhancing bone mass and/or healing fractures.

This review focuses on approved osteoporosis medications, two newer anabolic agents (abaloparatide and romosozumab), and promising combination and sequential treatment regimens. Treatment recommendations for osteoporosis also include increasing physical activity and weight-bearing exercise as well as nutritional approaches to maintain calcium and vitamin D adequacy. These are critical nonpharmacologic components of an effective regimen to preserve and augment bone mass and strength. This review also briefly discusses possible future therapeutic approaches and new molecular targets: neutralizing the Wnt inhibitor Dickkopf 1 (DKK1) and cell-targeted therapies such as the elimination of senescent cells in bone or transfer of mesenchymal stem cells (MSCs) to an osteoporotic host.

CURRENT OSTEOPOROSIS THERAPIES

Antiresorptive drugs are the most common therapies for treating osteoporosis (4). These agents are from several classes, including estrogen, SERMs, bisphosphonates, and monoclonal antibodies such as the RANKL inhibitor denosumab. While these medications inhibit bone resorption, they subsequently inhibit bone formation because the processes are coupled. Thus, effects on both aspects of bone remodeling will be the final outcome of antiresorptive therapy. Bisphosphonates are taken up by osteoclasts, induce apoptosis of mature osteoclasts, and inhibit the formation of the ruffled border, thus halting bone resorption. Denosumab neutralizes RANKL, a molecule produced by osteoblasts that interacts with RANK, a receptor expressed on the surface of cells

of the osteoclast lineage (4). Blockade of the RANKL–RANK interaction inhibits key steps in osteoclast-mediated bone resorption.

Clinical trials of bisphosphonates and denosumab have clearly shown substantial antifracture benefits with these medications. For example, annual intravenous zoledronic acid infusions for three years significantly reduced the risk of all clinical fractures and clinical vertebral, hip, and nonvertebral fractures by ~25% to 77% in the HORIZON trial, compared to placebo (5). In the FREEDOM trial, denosumab treatment for three years significantly reduced new radiographic vertebral, hip, and nonvertebral fractures by 68%, 40%, and 20%, respectively, compared to placebo (6). Estrogen, also an antiresorptive, reduces hip fractures by 34% versus placebo, based on findings from the Women's Health Initiative (7). However, serious cardiovascular and breast cancer adverse events limit the long-term use of estrogen (7). The SERMs raloxifene and bazodoxifene produce similar fracture risk reduction (RR) compared to placebo [vertebral fracture relative RR: 42% for raloxifene, 37–42% for bazodoxifene (20 or 40 mg)] (8, 9). In contrast, the nonvertebral fracture RR was nonsignificant for both raloxifene and either dose of bazodoxifene compared to placebo (8, 9). Although studies powered to examine fracture RR were done with bazodoxifene alone, the approved medication in the United States is a combination pill (bazodoxifene plus conjugated estrogen). Although certain SERMs have some procoagulant properties like estrogen, raloxifene confers a benefit to reduce breast cancer (10).

Currently available anabolic agents improve bone mass and reduce fractures through intermittent stimulation of the PTH receptor-1 on osteoblasts and their precursors by either PTH (i.e., teriparatide) or the PTH-related peptide analog abaloparatide (4). These agents produce greater bone anabolic versus catabolic activity. Teriparatide is the best-studied anabolic agent. In the pivotal phase III fracture trial, teriparatide (20 μg daily) produced a 65% RR in new vertebral fractures and 53% RR in nonvertebral fractures (11). A head-to-head study comparing teriparatide (20 μg daily) to risedronate (35 mg weekly) for 24 months demonstrated superiority of teriparatide in reducing both new vertebral (RR 0.44; $p < 0.0001$) and clinical fractures [hazard ratio (HR) 0.48; $p = 0.0009$] over risedronate (12).

Abaloparatide exerts its anabolic actions through the same receptor as PTH. Treatment with abaloparatide (80 μg daily) for 18 months in ACTIVE (the Abaloparatide Comparator Trial in Vertebral Endpoints) was shown to reduce fractures compared to placebo, including new morphometric vertebral fractures (RR 0.14; $p < 0.001$), nonvertebral fractures (HR 0.57; $p = 0.049$), major osteoporotic fractures (HR 0.45; $p = 0.03$), and clinical fractures (RR 0.30; $p < 0.001$) (13). When this study compared treatment with abaloparatide versus teriparatide, fracture rates did not differ between the two treatment groups except for the event rate for major osteoporosis fractures (including fractures of the wrist, upper arm, hip, and clinical spine), which showed a significantly lower HR (0.45; $p = 0.03$) for treatment with abaloparatide versus teriparatide (13).

The recently completed ACTIVExtend trial built upon data from the ACTIVE trial (14). In ACTIVExtend, patients who had been randomized to either placebo or abaloparatide (80 μg daily) for 18 months were subsequently treated with oral alendronate (70 mg weekly) for an additional 24 months. Over the entire 43-month treatment period, the patients on abaloparatide initially (followed by alendronate) had an 84% relative RR in new morphometric vertebral fractures compared to those on placebo initially (followed by alendronate) ($p < 0.001$). Incident rates for other osteoporotic fractures were also significantly lower in the abaloparatide/alendronate group compared to the placebo/alendronate group ($p < 0.05$) (14). The concern of possible osteosarcoma, observed in animal studies with teriparatide and abaloparatide, restricts their use to two years in a patient's lifetime.

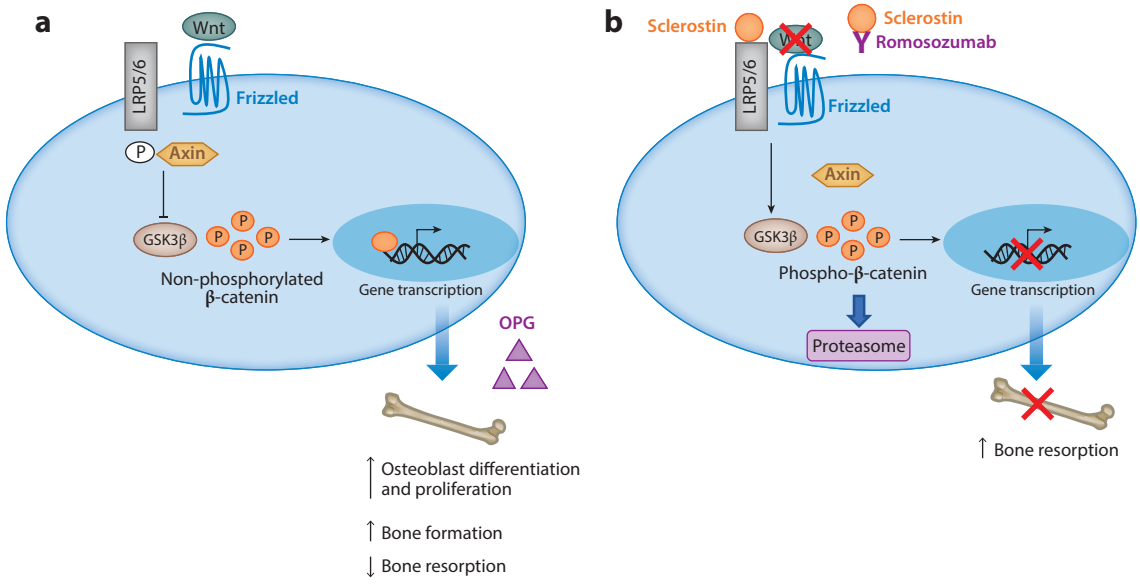

Figure 1

Wnt signaling pathway and its role in bone turnover. (*a*) Activation of the Wnt pathway. Wnt ligands bind to frizzled and coreceptor LRP5/6 and activate axin and GSK3β pathways. These steps increase non-phosphorylated β-catenin and allow its translocation to the nucleus, where it can activate gene transcription and promote osteoblast differentiation and proliferation, ultimately resulting in bone formation. OPG is also increased in response to Wnt signaling. (*b*) Inhibition of the Wnt pathway. Osteocytes secrete sclerostin, which binds LRP5/6 and prevents Wnt ligand from binding, thereby inhibiting canonical Wnt signaling. Romosozumab is an antisclerostin monoclonal antibody that prevents sclerostin from binding to LRP5/6. This in turn results in increased Wnt signaling. Abbreviations: GSK3β, glycogen synthase kinase 3β; LRP5/6, low-density lipoprotein receptor-related protein 5/6; OPG, osteoprotegerin. Figure and caption modified with permission from Dove Medical Press, Ltd. Shah AD, Shoback D, Lewiecki EM. 2015. Sclerostin inhibition: a novel therapeutic approach in the treatment of osteoporosis. *Int. J. Women's Health* 7:565–80.

NEW OSTEOPOROSIS AGENTS AND COMBINATION THERAPIES

Wnt Pathway Activation

Agents that stimulate signaling through the Wnt pathway are a new direction in anabolic therapy for osteoporosis (see **Figure 1**). One such medication recently approved by the US Food and Drug Administration (FDA) is romosozumab, a neutralizing antibody to sclerostin. Sclerostin is an endogenous inhibitor of the canonical Wnt pathway and is critically important in regulating osteoblast activity and bone formation. Antisclerostin antibody prevents the binding of sclerostin to the low-density lipoprotein receptor-related protein 5/6 (LRP5/6) by Wnt ligands (15). Under normal conditions, when the ligand Wnt binds to LRP5/6 and its coreceptor frizzled, there is inhibition of the activity of the glycogen synthase kinase 3β (GSK3β), which phosphorylates the transcription factor β-catenin in osteoblasts. That phosphorylation serves to enhance delivery of β-catenin to the proteasome of the cell for degradation (see **Figure 1**). When GSK3β activity is inhibited (by Wnt stimulation), non-phosphorylated β-catenin accumulates in the cytosol, translocates to the nucleus, and binds to DNA elements that promote multiple osteoblastic activities, ultimately leading to bone formation (15). The notion that sclerostin inhibition might be a successful pathway to stimulate bone formation was supported by reports that inactivating mutations of *SOST*, the gene encoding sclerostin, manifested as high-bone-mass phenotypes. Disorders caused by *SOST* inactivation include the rare genetic bone disorders sclerosteosis and Van

Buchem disease (16). A detailed investigation of sclerostin's actions by numerous laboratories led to the development of two antisclerostin antibodies, romosozumab and blosozumab. Both have been tested in clinical trials, and while blosozumab produced favorable skeletal findings in phase I and II trials (17, 18), only romosozumab progressed to phase III trials and is approved at this time.

Several trials (see **Table 1**) have shown that romosozumab is highly effective at increasing BMD and reducing new vertebral fractures, such as the FRAME (Fracture Study in Postmenopausal Women with Osteoporosis) trial. The ARCH (Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk) trial reported that fracture risk was reduced at vertebral and nonvertebral sites (19, 20). These were the two largest phase III trials of romosozumab in which an antiresorptive, either denosumab or alendronate, followed after a 12-month treatment phase with romosozumab. In the STRUCTURE (Open-Label Study to Evaluate the Effect of Treatment with Romosozumab or Teriparatide in Postmenopausal Women) trial, bone mass at the hip as measured by quantitative computed tomography and strength as measured by finite element analysis increased to a greater extent in women treated with romosozumab versus teriparatide for 12 months (21). All women in this study had been previously treated with bisphosphonate for at least three years (see **Table 1**).

It was expected that Wnt pathway activation would be purely anabolic and avoid the adverse events of osteonecrosis of the jaw and atypical femoral fracture associated with bisphosphonates and denosumab. Unexpectedly, small numbers of both adverse events have been reported in trials with romosozumab (19, 20). Pure activation of bone formation should not induce oversuppression of bone remodeling—a proposed mechanism for atypical femoral fracture. However, the decrease in bone resorption, reflected in the suppression of bone resorption markers by romosozumab, is best explained by the fact that stimulating Wnt signaling also increases osteoprotegerin (OPG) formation (see **Figure 1**). OPG is a natural inhibitor of RANKL (4). Thus, antagonizing sclerostin (and promoting Wnt pathway activation) also has antiresorptive effects. Importantly, physicians considering prescribing this agent should also be aware of an imbalance in the rate of adjudicated serious cardiovascular adverse events [50 patients (2.5%) in the romosozumab-treated group versus 38 (1.9%) in the alendronate-treated group] during the 12-month initial double-blind treatment period (20).

After completion of these phase III trials, romosozumab was approved in 2019 for the treatment of osteoporosis with high risk of fracture. The recommended duration of therapy is 12 months, and there is a boxed warning of possibly increased cardiovascular and cerebrovascular risk, which must be factored into choosing candidates for this new therapy (22).

DKK1 is another endogenous inhibitor of LRP5/6 binding to Wnt ligands, similar to sclerostin (see **Figure 1**). High levels of DKK1 block Wnt signaling, stimulate β-catenin phosphorylation and degradation, and suppress osteoblastic activity (23). DKK1 differs from sclerostin in important ways. DKK1 binds to different domains of LRP5/6 and produces a broader inhibition of Wnt signaling. DKK1 is expressed in multiple tissues, in contrast to the largely bone-specific expression of sclerostin, which underlies concerns about possible off-target effects of agents directed against DKK1 (23).

Monoclonal antibodies to DKK1 have been tested as potential agents to treat osteoporosis in preclinical studies, but the results have been disappointing. Variable levels of efficacy were demonstrated in ovariectomized rodent models, and only small improvements in BMD were shown in ovariectomized monkeys with the antibodies tested (24, 25). A bispecific antibody against both sclerostin and DKK1 was tested in a rodent fracture healing model. The effects of the bispecific antibody were greater than those of either monospecific antibody (i.e., to DKK1 or to sclerostin alone) in bone repair activity (26).

Table 1 Clinical trials assessing the efficacy of romosozumab in postmenopausal women with osteoporosis

Trial	Population characteristics	Design	Study outcomes
FRAME (Fracture Study in Postmenopausal Women with Osteoporosis) (NCT01575834) (19)	7,180 postmenopausal women with osteoporosis by BMD criteria with T-score of −2.5 to −3.5 at TH or FN	Phase III trial comparing two treatment arms: 12 months of romosozumab (210 mg monthly) or placebo by subcutaneous injections followed by 12 months of open-label denosumab (60 mg) every 6 months by subcutaneous injection	Primary endpoints: Incidence of new vertebral fractures at 12 months for romosozumab versus placebo (% of patients with fracture): 0.5% versus 1.8% (RR 0.27; $p < 0.001$] Incidence of new vertebral fractures at 24 months for romosozumab versus placebo (% of patients with fracture): 0.6% versus 2.5% (RR 0.25; $p < 0.001$) Secondary endpoints: Differences in clinical and nonvertebral fractures at 12 and 24 months of treatment with romosozumab followed by denosumab and placebo followed by denosumab did not reach statistical significance except for a modest reduction in all clinical fractures for the group treated with romosozumab for 12 months versus placebo (HR 0.64, $p = 0.008$)
ARCH (Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk) (NCT01631214) (20)	4,093 postmenopausal women with BMD < −2.5 at TH or FN plus either ≥1 moderate or severe vertebral fracture or ≥2 mild vertebral fractures or a BMD T-score ≤ −2 at TH or FN plus either ≥2 moderate or severe vertebral fractures or a fracture of the proximal femur 3 to 24 months before randomization	Phase III trial comparing 12 months treatment with romosozumab (210 mg) by monthly subcutaneous injections or alendronate (70 mg) orally followed by 12 months of open-label alendronate (70 mg) orally weekly for both groups	Primary endpoints: Cumulative incidence of new vertebral fractures at 24 months (% of women): 6.2% (romosozumab followed by alendronate) versus 11.9% (alendronate for 24 months) (RR 0.52; $p < 0.001$) Cumulative incidence of clinical (nonvertebral plus symptomatic vertebral) fractures at the time of primary analysis (% of women): 9.7% versus 13% (HR 0.73; $p < 0.001$) Secondary endpoints: Nonvertebral fractures at the time of primary analysis (% of women): 8.7% versus 10.6% (HR 0.81; $p = 0.04$) Hip fractures (% of women): 2.0% versus 3.2% (HR 0.62; $p = 0.02$)
STRUCTURE (Open-Label Study to Evaluate the Effect of Treatment with Romosozumab or Teriparatide in Postmenopausal Women) (NCT01796301) (21)	436 postmenopausal women with history of prior treatment with oral bisphosphonate for ≥3 years and alendronate during the year before screening and with history of nonvertebral fracture after age 50 or vertebral fracture and BMD T-score < −2.5 at the LS, TH, or FN	Randomized phase III open-label trial comparing romosozumab (210 mg) monthly by subcutaneous injection or teriparatide (20 μg) daily by subcutaneous injection for 12 months	Primary endpoint: % change in BMD at the TH from baseline through month 12 (mean of months 6 and 12) for women treated with romosozumab versus teriparatide: +2.6% versus −0.6% (p <0.0001) Secondary endpoints: % change in BMD from baseline to month 12 in romosozumab- versus teriparatide-treated women: TH (+2.9% versus −0.5%); FN (+3.2% versus −0.2%); LS (+9.8% versus +5.4%) ($p < 0.0001$ for all) % change in integral and cortical BMD by QCT of the hip was significantly greater in romosozumab-treated versus teriparatide-treated women ($p < 0.05$) % change in estimated hip strength by finite element analysis was significantly greater in romosozumab-treated versus teriparatide-treated women (+2.5% versus −0.7%) ($p < 0.0001$)

Abbreviations: BMD, bone mineral density; FN, femoral neck; HR, hazard ratio; LS, lumbar spine; QCT, quantitative computed tomography; RR, relative risk; TH, total hip.

Studies have not been done that confirm DKK1 inhibition as an effective means for treating osteoporosis. The application of DKK1 antibodies to the management of multiple myeloma–induced bone disease is based on high DKK1 expression in those bone lesions and has progressed to phase II clinical trials. At present, findings from two phase II studies of the anti-DKK1 antibody BHQ880, alone (NCT01302886) or in combination with intravenous bisphosphonate (NCT00741377), in multiple myeloma have not been reported.

Combination and Sequential Therapies

Combining or sequencing treatments with anabolic and resorptive agents have been studied for some time, in an effort to achieve synergism by capitalizing on distinct modes of action of different agents. Two clinical trials studying the combination of an oral bisphosphonate with PTH(1–84)—namely the PaTH (Parathyroid Hormone and Alendronate; NCT01631214) study and PICS (PTH and Ibandronate Combination Study; NCT00683163) (27, 28)—failed to demonstrate superior benefit of the combination treatments for BMD. Concomitant administration of zoledronic acid with teriparatide for 52 weeks (Efficacy Study of Zoledronic Acid and Teriparatide Combination Therapy in Women with Osteoporosis; NCT00439244) did show enhanced lumbar spine (LS) bone mineral density (BMD) gains versus zoledronic acid alone ($p < 0.001$) and greater total hip (TH) BMD gains versus teriparatide alone ($p < 0.01$), suggesting site-specific differences in responsiveness to combination therapy. The study, however, was short-term and not powered for fracture reduction endpoints (29).

Data are limited for the weaker antiresorptive therapies. Combined treatment with raloxifene and teriparatide for six months showed no differences in BMD at the LS or femoral neck (FN) versus teriparatide plus placebo. A modest difference in TH BMD in the combined treatment group versus teriparatide and placebo was seen ($p < 0.04$), but the study was too short for assessing durability of differences at the TH site and did not have fracture endpoints (30). In an early study, postmenopausal osteoporotic women who had been on at least two years of hormone replacement therapy (HRT) were randomized to receive teriparatide combined with HRT or HRT alone for three more years. BMD changes were greater at the LS and hip in the combined treatment group ($p < 0.05$). The study was underpowered for fracture endpoints (31).

The most recent combination study in postmenopausal osteoporosis was the DATA (Denosumab and Teriparatide Administration; NCT00926380) trial, which compared BMD responses to combined treatment with both denosumab (60 mg every 6 months) and teriparatide (20 μg daily) to either drug as monotherapy over 24 months (see **Table 2**) (32, 33). Significantly greater gains in LS, TH, and FN BMD were seen in the combination arm than in the denosumab alone or teriparatide alone treatment arms. At the one-third distal radius site, BMD responses to combination therapy and to denosumab alone were greater than those due to teriparatide over 24 months.

The DATA-Switch trial extended this study for an additional 24 months (33). Subjects were switched from both the combination and teriparatide monotherapy arms to denosumab, and subjects in the denosumab arm were switched to teriparatide. In all cases, 24 months of additional treatment were given (see **Table 2**). At 48 months, all three treatment groups showed continued increases in LS BMD compared to baseline, and there were no significant differences among the three groups. There were, however, modest differences in BMD responses at the hip and radius. At the TH, BMD responses were significantly greater in the combination → denosumab treatment group compared to either of the two other treatment groups (teriparatide → denosumab or denosumab → teriparatide). There were no significant differences in FN BMD responses in the combination → denosumab treatment group compared to the teriparatide → denosumab group, but these two treatment sequences both produced greater changes in FN BMD than did

Table 2 Bone mineral density (BMD) responses to combination and sequential therapy with teriparatide and denosumab:[a] DATA, DATA Extension and DATA-Switch studies

DATA and DATA Extension (32, 33): % change in BMD at 24 months versus 0 months, +/– standard deviation	DATA-Switch (33, 34): % change in BMD at 48 months versus 0 months, +/– standard deviation
Treatment with teriparatide alone for 24 months LS: +9.5 ± 5.9% TH: +2.0 ± 3.0% FN: +2.8 ± 3.9% One-third distal radius: −1.7 ± 4.6%	Treatment with denosumab alone for additional 24 months LS: +18.3 ± 8.5% TH: +6.6 ± 3.3%[h] FN: +8.3 ± 5.6%[i] One-third distal radius: 0 ± 2.9%
Treatment with denosumab alone for 24 months LS: +8.3 ± 3.4% TH: +3.2 ± 2.5% FN: +4.1 ± 3.8% One-third distal radius: +2.1 ± 3.1%	Treatment with teriparatide alone for additional 24 months LS: +14 ± 6.7% TH: +2.8 FN: +4.9 ± 6.0% One-third distal radius: −1.8 ± 5.9%
Treatment with teriparatide + denosumab (combination) for 24 months LS: +12.9 ± 5.0%[b,c] TH: +6.3 ± 2.6%[d] FN: +6.8 ± 3.6%[e,f] One-third distal radius: +2.2 ± 3.1%[g]	Treatment with denosumab alone for additional 24 months LS: +16.0 ± 4.1% TH: +8.6 ± 3%[j,k] FN: +9.1 ± 6.1%[i] One-third distal radius: +2.8 ± 3.2%[l]

[a]Treatment was with teriparatide 20 μg daily by subcutaneous injection and/or with denosumab 60 mg by subcutaneous injection every 6 months as specified in each arm of the trial and the extension. The DATA and DATA Extension studies (covering months 0–24) were followed by the DATA-Switch study (covering months 25–48). Statistical significance at 24 months is shown for comparisons of the changes in BMD at the sites noted.
[b]$p < 0.01$ for changes in lumbar spine (LS) BMD in the combination versus teriparatide group.
[c]$p < 0.008$ for changes in LS BMD in the combination versus denosumab group.
[d]$p < 0.001$ for changes in total hip (TH) BMD in the combination versus teriparatide or denosumab group.
[e]$p = 0.003$ for changes in femoral neck (FN) BMD in the combination versus teriparatide group.
[f]$p = 0.008$ for changes in FN BMD in the combination versus denosumab group.
[g]$p < 0.004$ for changes in radius BMD in the combination and denosumab groups versus teriparatide group. Statistical significance at 48 months is shown for the following comparisons of changes in BMD at the sites noted. At 48 months, there were no significant differences in LS BMD between groups.
[h]$p = 0.0002$ for changes in TH BMD in the group receiving 24 months of teriparatide → 24 months of denosumab compared to the group receiving 24 months of denosumab → 24 months of teriparatide.
[i]$p < 0.05$ for changes in FN BMD in the groups receiving 24 months of combination therapy → 24 months of denosumab or in the group receiving 24 months of teriparatide → 24 months of denosumab compared to the group receiving 24 months of denosumab → 24 months of teriparatide.
[j]$p = 0.04$ for changes in TH BMD in the group receiving 24 months of combination therapy → 24 months of denosumab compared to the group receiving teriparatide for 24 months → denosumab for 24 months.
[k]$p < 0.0001$ for changes in TH BMD in the group receiving 24 months of combination therapy → 24 months of denosumab compared to the group receiving denosumab for 24 months → teriparatide for 24 months.
[l]$p < 0.01$ for changes in radius BMD in the group receiving 24 months of combination therapy → 24 months of denosumab compared to the other two treatment groups.

the denosumab → teriparatide sequence (see **Table 2**) (33). At the one-third distal radius, combination therapy → denosumab showed a greater rise in BMD than the other two treatment groups. Thus, while BMD responses to combined treatment with the RANKL inhibitor denosumab and the anabolic agent teriparatide look promising in terms of achieving greater skeletal benefit, this study was not powered for fracture endpoints to confirm an improvement in this important clinical outcome.

NEW APPROACHES AND TARGETS TO TREAT OSTEOPOROSIS

There are several investigational approaches on the horizon for the treatment of osteoporosis. While current treatments are focused on the use of antiresorptive and anabolic agents that target

bone remodeling, future therapies could include stem cells, antisenescence agents, and drugs that target specific osteoblast pathways.

Stem Cell Therapies

Osteoporosis is thought to be caused in part by decreased numbers of MSCs and their preferential differentiation into adipocytes rather than osteoblasts in the aging skeleton. This could lead to decreased number and quality of osteoblasts in the bone of aging women and men and increased bone marrow fat (35). Age-related dysfunction of MSCs may result in decreased bone formation and compromised bone microarchitecture. These consequences could lead to increased fractures and reduced fracture healing. Thus, if aging MSCs could be augmented to increase their osteoblastic potential, or if healthy MSCs could be transplanted into osteoporotic bone and stimulated to differentiate into osteoblasts and synthesize new bone, such cell replacement could potentially be used to treat osteoporosis.

There have been significant advances in stem cell biology. Stem cells are ideal candidates in regenerative medicine due to their unique ability to self-renew and differentiate into multiple adult cell types. Bone marrow–derived MSCs (BM-MSCs) are of particular interest in bone diseases as they have the potential to differentiate into adipocytes, chondrocytes, and osteoblasts (36, 37). Their roles in fracture repair have been extensively studied preclinically, and the potential use of these cells as a therapy for osteoporosis is being explored in both preclinical studies and clinical trials.

Several preclinical studies have explored the role of autologous and allogeneic BM-MSC transplantation either locally or systemically in various animal models, including ovariectomized mouse and rabbit models of osteoporosis, glucocorticoid-induced osteoporosis mouse models, and senescence-accelerated osteoporosis models (38–44). Adipose-derived MSCs also have considerable appeal, as fat is a readily accessible source for cells (43–45). These studies are summarized in detail in recent reviews (35–37, 46, 47).

While preclinical studies of stem cell therapy in animal models of osteoporosis look promising, only two clinical trials exploring the use of stem cell therapy in humans (NCT02566655 and NCT01532076) were initiated. The former was terminated early because of slow recruitment. The second trial (intravenous infusion of fucosylated autologous BM-MSCs in patients with established osteoporosis and low impact fractures) is ongoing. No interim analyses are available.

Targeting Senescent Cells in Bone

Cellular senescence occurs in nearly all tissues and is characterized by irreversible cell cycle arrest without loss of cell viability. Senescent cells accumulate and secrete various factors that have both autocrine and paracrine effects on the microenvironment. This is referred to as the senescence-associated secretory phenotype (SASP) (48). Cellular senescence is thought to be the consequence of multiple stressors including telomere loss, oxidative damage, oncogene activation, and direct DNA damage (48). Cells in the bone microenvironment become senescent, which leads to decreased bone mass, increased bone marrow fat, and increased bone turnover. Since osteoporosis typically accompanies advancing age, it is hypothesized that the attendant bone loss might be arrested if these senescent cells and their secretory phenotype could be pharmacologically targeted.

Pharmacologic agents termed senolytics target and destroy senescent cells, while drugs termed senomorphs address the SASP and prevent release of senescence-related factors from these cells. Only preclinical studies have examined the effect of targeting senescence in bone as a potential treatment for osteoporosis (49). Farr et al. (49) investigated removal of senescent cells by genetically activating the so-called suicide transgene, *INK-ATTAC*, which results in caspase-8-directed

apoptotic pathway activation when treated with the drug AP20187 in senescent cells. Farr et al. examined whether this treatment improved age-related changes in bone parameters (mass and strength) in aging mice. The same group also assessed whether Janus kinase (JAK) inhibition in mice resulted in similar changes. Both approaches resulted in improved bone mass, strength, and microarchitecture compared to vehicle-treated mice. This is a promising potential therapeutic strategy. Similarly, in older mice treated with a combination of three senolytic drugs—dasatinib (a tyrosine kinase inhibitor), quercetin, and ruxolitinib (a JAK inhibitor)—the senescence phenotype was suppressed, and both trabecular and cortical bone microarchitecture improved (49). While still in very early stages, it is possible that senolytic and senomorphic therapies may one day be tested as potential treatments for osteoporosis.

CONCLUSIONS

Our review describes currently available osteoporosis agents, newly approved medications, and possible exciting new therapeutic strategies still in development. There is currently a wide range of medications available for the treatment of osteoporosis in postmenopausal women. Most clinical guidelines would support the use of a bisphosphonate as an initial course of therapy with denosumab given to those who are intolerant to or who have failed bisphosphonate therapy. Anabolic agents are often reserved for women with fractures or those who have failed other initial therapies. As for new therapies, the hope is that rapid progress in our understanding of bone biology will continue to yield drugs and approaches with improved efficacy and safety. The goals are not only gains in bone mass but also improvements in bone quality and reduced fracture rates with minimized skeletal and other adverse events.

DISCLOSURE STATEMENT

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