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LEADING ARTICLE

Modulating Bone Resorption and Bone Formation in Opposite Directions in the Treatment of Postmenopausal Osteoporosis

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Abstract Bone remodeling, the fundamental process for bone renewal, is targeted by treatments of osteoporosis to correct the imbalance between bone resorption and bone formation and reduce the risk of fractures and associated clinical consequences. Currently available therapeutics affect bone resorption and bone formation in the same direction and either decrease (inhibitors of bone resorption) or increase (parathyroid hormone [PTH] peptides) bone remodeling. Studies of patients with rare bone diseases and genetically modified animal models demonstrated that bone resorption and bone formation may not necessarily be coupled, leading to identification of molecular targets in bone cells for the development of novel agents for the treatment of osteoporosis. Application of such agents to the treatment of women with low bone mass confirmed that bone resorption and bone formation can be modulated in different directions and so far two new classes of therapeutics for osteoporosis have been defined with distinct mechanisms of action. Such treatments, if combined with a favorable safety profile, will offer new therapeutic options and will improve the management of patients with osteoporosis.

Key Points

In osteoporosis, there is an imbalance between bone resorption and bone formation leading to bone loss and structural decay of the skeleton.

Currently available therapeutics affect bone resorption and bone formation in the same direction and either decrease (inhibitors of bone resorption) or increase (PTH peptides) bone remodeling.

New classes of therapeutics for osteoporosis with different mechanisms of action are in clinical development.

Inhibitors of Cathepsin K reduce bone resorption while preserving bone formation and increase bone mineral density at the spine and the hip continuously for at least 5 years of treatment.

Inhibitors of sclerostin increase bone formation while reducing bone resorption and impressively increase bone mineral density at the spine and the hip.

1 Introduction

Osteoporosis is characterized by reduced bone mass and strength leading to increased risk of fractures. Pharmacological interventions aim to decrease this risk and the associated clinical consequences by correcting the imbalance between bone resorption and bone formation that constitutes the pathophysiological basis of the disease. Most currently available agents inhibit bone resorption and

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formation to varying degrees and decrease the risk of fractures but cannot replace already lost bone, and they only modestly decrease the risk of non-vertebral fractures, the most frequent osteoporotic fractures. Parathyroid hormone (PTH) peptides, the only approved bone-forming agents, stimulate bone formation but also bone resorption and have not been shown to reduce the risk of hip fractures, the most devastating clinical consequence of osteoporosis. These unmet needs have led to efforts for the development of new therapeutics for osteoporosis based on improved knowledge of the local regulation of bone remodeling arising mainly from the study of rare bone diseases and genetically modified animal models [1]. We review here the information that led to the rational design and clinical application of new agents for the pharmacological management of osteoporosis.

2 General Considerations

Bone remodeling occurs in an orderly fashion by the basic multicellular units (BMUs), temporary anatomical structures comprising a team of osteoclasts in the front and a team of osteoblasts in the back, supported by blood vessels, nerves, and connective tissue. Osteoclasts resorb bone by removing bone mineral and degrading the organic matrix, while osteoblasts move to the resorbed area and lay down new bone matrix that subsequently mineralizes, a process known as coupling. The mechanisms regulating this coupling are not entirely clear but it is thought that growth factors mobilized from the bone matrix during resorption might contribute to intercellular signaling and subsequent stimulation of bone formation. Alternatively or in addition, the osteoclasts produce factors that might contribute to generation and differentiation of osteoblast precursors [2, 3]. It is now generally accepted that osteocytes are the main regulators of bone remodeling due to their location in bone allowing them to sense mechanical signals and to respond to chemical signals regulating bone and mineral metabolism by secreting factors that can modulate the number and function of osteoblasts and osteoclasts [4–6].

An increased number and life span of osteoclasts and a decrease in the formation and life span of osteoblasts induce an imbalance between bone resorption and bone formation, the cellular basis of osteoporosis. This imbalance, in favor of resorption, results in bone loss and deterioration of bone architecture. The decline in the ability of osteoblasts to refill the resorption cavity leads to reduction of the thickness of the bone packets and thinning of the trabeculae. In addition, the enhanced osteoclastic resorption per unit time that occurs at the menopause results in perforation and removal of trabeculae and loss of their connectivity [7]. Cortical bone becomes wider in diameter and thinner, due to the move of the endosteal surface outwards at a greater pace than bone

placed in the periosteum, but also more porotic due to enhanced intracortical remodeling [8]. The net outcome of these changes is increased bone fragility and this provides the rationale for the development of agents for the pharmacological management of osteoporosis. It is clear from the described changes that reduction of bone resorption must be an essential component of any therapeutic approach for the maintenance or improvement of bone strength. However, this approach cannot replace already lost bone, which is required for better fracture protection in women with severe disease. For this, specific stimulation of bone formation is essential. Thus, in theory, optimal pharmacological management of osteoporosis should aim at decreasing bone resorption (endosteal and intracortical) and stimulating bone formation at all skeletal envelopes, including the periosteum. Such approach will not only prevent the structural decay of bone tissue but will also increase bone mass and may lead to improved reduction of the risk of non-vertebral fractures, which occur predominantly at cortical bone sites.
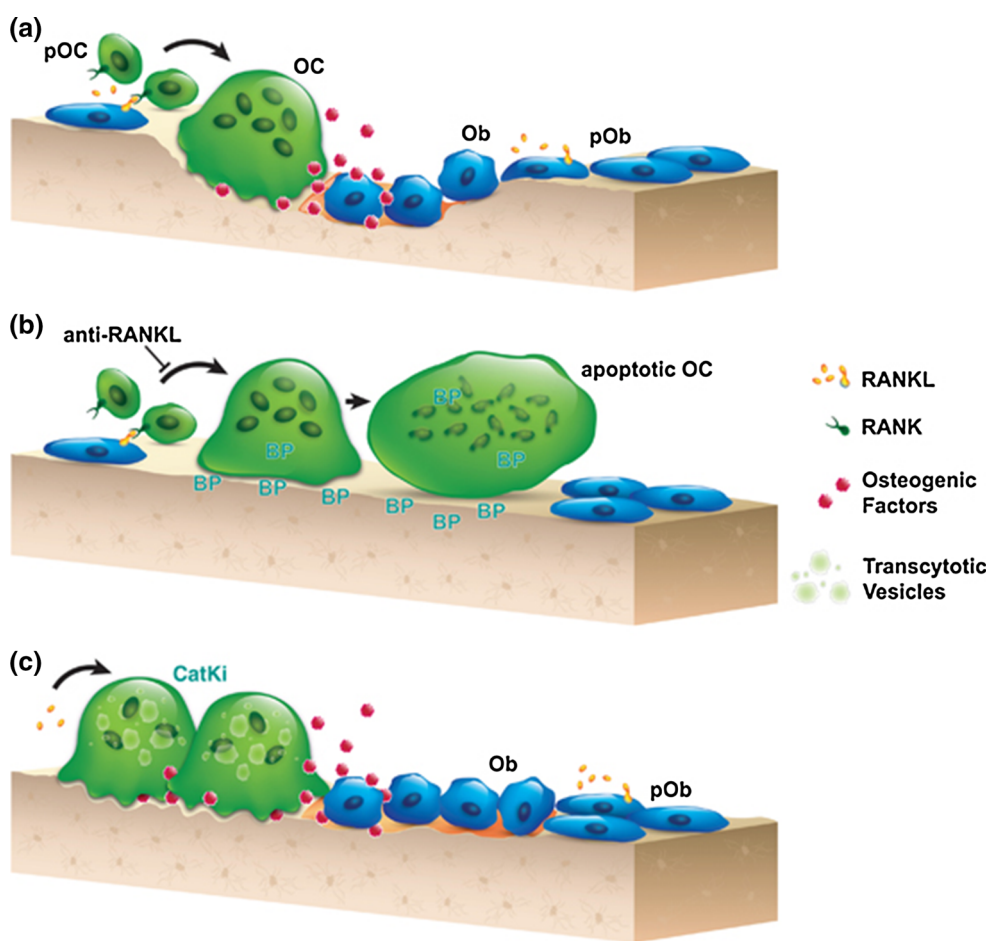
3 Inhibitors of Bone Resorption

Inhibitors of osteoclastic bone resorption, such as bisphosphonates, denosumab and selective estrogen receptor modulators (SERMs), reduce the rate of bone resorption to varying degrees by different mechanisms of action. The reduction of the rate of bone resorption is invariably followed by reduction of the rate of bone formation due to the coupling of the two processes. The final result is an overall decrease of the rate of bone turnover to a level that depends on the potency of the individual agent used and is maintained during the whole period of treatment. The introduction of the most potent inhibitor of bone resorption, denosumab, into clinical practice made any further development of this class of agents obsolete. However, studies of humans and animals with osteopetrosis indicated that reduction of bone resorption may not necessarily be coupled with reduced bone formation if the osteoclasts remain intact [9]. Loss of function of a number of molecules regulating removal of bone mineral or degradation of bone matrix were shown to be associated with a decrease of bone resorption without, however, affecting or even stimulating bone formation [10, 11]. Cathepsin K (CatK), a protease abundantly expressed in osteoclasts responsible for the degradation of the organic matrix of bone, is the most extensively studied molecule in preclinical and clinical studies.

3.1 Cathepsin K Inhibitors

CatK is a member of a family of cysteine proteases that is synthesized as a pro-enzyme before being transported to lysosomes where it is cleaved to produce the active enzyme that degrades collagen type I and other bone matrix proteins

within the acidic environment of resorption lacunae [12]. Congenital absence of CatK in patients with pycnodysostosis, a rare, autosomal, recessive osteochondrodysplasia, is characterized by increased bone density, bone deformities, and increased bone fragility, complications that are not present in heterozygotes [13]. CatK-deficient mice develop a high bone mass phenotype in the presence of fully differentiated osteoclasts, while mice over-expressing CatK had increased bone turnover and decreased trabecular bone volume [14, 15]. The discovery that loss of function of CatK decreases bone resorption with increased number of viable osteoclasts and the surprising finding of preservation or even increase in bone formation provided the rationale for the development of a new class of antiresorptive agents that

target this enzyme (Fig. 1) [16–18]. The mechanism responsible for the maintenance or increase in bone formation in the presence of reduced bone resorption by CatK inhibition may be due to stimulation of osteoblasts by osteoclast-derived factors (clastokines, such as sphingosine-1-phosphate) or matrix-derived growth factors (such as IGF-1) that are not degraded [19, 20]. Initial studies of CatK inhibitors showed off-target inhibition of other cathepsins due either to their lack of specificity for CatK or to their accumulation in lysosomes of cells other than osteoclasts and led to the design of new agents potentially devoid of such effects. Two CatK inhibitors are currently in clinical development for the treatment of osteoporosis, namely odanacatib (Merck & Co) and ONO-5334 (Ono Pharmaceutical

Fig. 1 Schematic representations of **a** the normal coupling process of bone resorption and formation during the remodeling process. RANKL promotes differentiation and activation of osteoclasts at remodeling sites. Coupling factors derived from the resorbed bone matrix or directly from the activated osteoclasts stimulate the recruitment and maturation of osteoblasts to initiate bone formation on the existing resorption surface. **b** Denosumab blocks osteoclastogenesis, and bisphosphonate induces the loss of ruffled border and eventual osteoclast apoptosis. These therapies lead to little-to-no resorption surface and fewer numbers of osteoclasts on bone. **c** Treatment with a CatK inhibitor reduces osteoclastic resorption efficiency and retards transcytotic trafficking of matrix removal. This does not prevent other osteoclast functions, such as the generation of a shallow resorption surface and the release of osteogenic factors; together, these functions initiate osteoblast bone formation. *BP* bisphosphonate, *CatKi* cathepsin K inhibitor, *Ob* osteoblast, *OC* osteoclast, *pOb* osteoblast progenitor, *pOC* osteoclast progenitor, *RANK* receptor activator of nuclear factor kappa-B, *RANKL* RANK ligand. Reproduced with permission from [17]

Company), which in phase II clinical trials had similar effects on bone turnover and bone mineral density (BMD) without any off-target effects. We will further discuss only odanacatib, as an example of pharmacological inhibition of CatK, because it is the only one tested so far in a phase III clinical study.

Odanacatib is a selective, orally administered CatK inhibitor [21]. Unlike basic CatK inhibitors, odanacatib is neutral and does not accumulate in the acidic environment of lysosomes which could lead to off-target inhibition of other cathepsins [16, 22]. Odanacatib is metabolized by CYP3A4 and its absorption is not impaired by food intake [17, 23]. In animal models, odanacatib reduced bone resorption while preserving bone formation in trabecular and endocortical surfaces. In addition, odanacatib reduced cortical remodeling and increased modeling-based bone formation, and improved the cortical area of the femur and its strength [24, 25]. Odanacatib was further superior to alendronate in increasing cortical thickness, possibly through increased periosteal bone formation, an action that was also observed during treatment with another CatK inhibitor [26, 27].

A 2-year (with a 3-year extension) phase IIb dose-finding clinical trial of postmenopausal women with low bone mass identified 50 mg once weekly as the optimal oral dose of odanacatib [28–30]. In this study, treatment with odanacatib 50 mg once weekly reduced biochemical markers of bone resorption by about 55 %, while markers of bone formation were mildly and transiently reduced, returning to baseline after about 2 years. Serum levels of the osteoclast marker TRAP5b increased with treatment, confirming osteoclast viability. These changes of bone markers were associated with continuous increases in BMD by 11.9 % at the spine and more importantly at the hip by 8.5 and 9.8 % at the total hip (TH) and femoral neck (FN), respectively, after 5 years. Different from bisphosphonates but similar to other antiresorptives, the effects of odanacatib on bone turnover and BMD were rapidly reversible upon discontinuation of treatment. Odanacatib treatment exhibited a generally favorable safety and tolerability profile, with incidence of adverse events similar to placebo.

In another 2-year, placebo-controlled study, the effects of odanacatib on the cortical and trabecular compartments and strength of bone were assessed by quantitative computed tomography (QCT) and high-resolution QCT (HR-QCT) in 214 postmenopausal women with low areal BMD [31, 32]. As in the phase II study, odanacatib decreased bone resorption, maintained bone formation, and increased areal BMD. In addition, it increased volumetric BMD and estimated bone strength of both the hip and the spine as well as cortical and trabecular density, cortical thickness, and estimated strength of the distal radius and distal tibia. In this study, adverse effects were also similar between placebo- and odanacatib-treated women.

The antifracture efficacy of odanacatib was examined in the Long-Term Odanacatib Fracture Trial (LOFT), the largest clinical trial in osteoporosis. LOFT is a phase III, event-driven clinical trial, with a preplanned extension, of women aged >65 years with osteoporosis [33]. Participants had either a prior radiographic vertebral fracture and BMD T-score ≤-1.5 at the FN or TH or no prior vertebral fracture and BMD T-score ≤-2.5 at the FN or TH. The trial was designed to test the hypothesis that treatment with odanacatib 50 mg once weekly reduces the risk of new morphometric vertebral, hip and non-vertebral fractures (all primary endpoints) in postmenopausal women with osteoporosis. Women were randomized in a 1:1 ratio to receive placebo or odanacatib 50 mg once weekly. All received weekly vitamin D3 (5600 IU) and daily calcium supplements to ensure a daily intake of approximately 1200 mg. In July 2012, an independent Data Monitoring Committee (DMC) recommended termination of the study since odanacatib displayed a favorable benefit/risk profile as well as efficacy relative to placebo. At the same time, the DMC suggested that additional safety data should be obtained in the preplanned blinded extension study.

The 16,071 women included in the study had a mean age of 72.8 years, 57 % were Caucasian and 46.5 % had prior vertebral fracture. Mean BMD T-scores were: LS -2.7, TH -2.4, and FN -2.7 and mean duration of follow-up was 34 months [34]. Compared with placebo, treatment with odanacatib decreased the incidence of new and worsening morphometric vertebral fractures by 54 %, of hip fractures by 47 %, of non-vertebral fractures by 23 % and of clinical fractures by 72 % (all $p < 0.0001$). Odanacatib treatment led to progressive increases over 5 years in BMD at LS and TH: 11.2 and 9.5 %, respectively, compared with placebo. Adverse events were generally well balanced between groups. Adjudicated morphea-like skin lesions occurred more frequently in odanacatib-treated patients (12) compared with placebo (3) and resolved/improved after study drug discontinuation. Adjudicated femoral shaft fractures with atypical features occurred only in odanacatib-treated patients (5), while no cases of ONJ were reported. No meaningful differences between groups were observed in adjudicated systemic sclerosis, respiratory infections, or delayed fracture union. Major cardiovascular events overall were generally balanced; however, there were numerically more adjudicated strokes with odanacatib than with placebo; final blinded adjudication of major cardiovascular events is ongoing [35].

4 Stimulators of Bone Formation

The only currently available bone forming agent, PTH, stimulates bone formation but also bone resorption. PTH binds to the PTH/PTHrP type 1 receptor and activates

several signaling pathways, including the canonical Wnt-signaling pathway, having both anabolic and catabolic effects on bone that are probably exerted via signaling in osteocytes [36]. Teriparatide, given by daily subcutaneous injections, increases cancellous and endocortical bone formation, mainly at sites undergoing active bone remodeling, but has limited effect on periosteal bone formation and increases cortical porosity [37]. PTHrP 1–36 and its analog abaloparatide, which bind to the PTH/PTHrP 1 receptor, also increase bone formation and bone resorption markers, but to a lesser extent than teriparatide, and improve hip BMD significantly more than teriparatide [38, 39].

Concurrent treatment of women with osteoporosis with teriparatide and the inhibitor of bone resorption, denosumab, increased BMD at all skeletal sites considerably more than either monotherapy alone after 2 years [40, 41]. The difference in response between teriparatide and teriparatide/denosumab treatment is probably due to inhibition of teriparatide-stimulated RANKL (receptor activator of nuclear factor kappa-B ligand) production by denosumab that reduced bone resorption and allowed teriparatide to exert a stimulatory effect only on bone formation. These results reinforce the hypothesis that for optimal therapeutic outcome, bone formation and bone resorption should be modulated in different directions. The results of the studies of CatK inhibitors illustrated that this may be feasible. CatK inhibitors, however, may preserve bone formation but are not anabolic agents, an important unmet need in the management of osteoporosis.

The design of a genuine anabolic treatment for osteoporosis must address the possibility of stimulating bone formation without concomitant stimulation of bone resorption and ensuring that formation is stimulated at quiescent bone surfaces. Human and animal genetics indicated that this may be feasible. In particular, the recognition of the pivotal role of the Wnt signaling pathway in bone formation provided a number of potential targets for the development of new pharmaceuticals. For clinical use, however, treatments should not only modify the expression of target molecules but need also to have bone specificity to avoid potential off-target effects [1, 42, 43]. One such target is sclerostin, a negative regulator of bone formation produced exclusively in the skeleton by osteocytes [44].

4.1 Sclerostin Inhibitors

The role of sclerostin in bone metabolism was identified in studies of patients with sclerosteosis and van Buchem disease, two rare sclerosing bone dysplasias with very similar phenotypes and high bone mass [45]. These diseases are characterized by progressive generalized overgrowth and thickening of bone that is resistant to fracture [46]. The two conditions are due to different defects of the

SOST gene which is located on chromosome 17q12–21 and encodes the protein sclerostin [47–50]. Both defects result in impaired production of sclerostin leading to a dramatic increase in bone mass in humans and mice, whereas mice overexpressing sclerostin are osteopenic [51, 52].

Osteocyte-produced sclerostin is transported to the bone surface through the osteocyte dendritic network where it inhibits the proliferation, differentiation, and survival of osteoblasts. Sclerostin also has an autocrine function and upregulates RANKL synthesis in osteocytes, thereby stimulating osteoclastogenesis [53] (Fig. 2). *SOST* has been identified in the kidney, liver, and heart, but sclerostin expression has not been identified in any of these tissues in humans [45, 47, 48]. Sclerostin decreases bone formation by antagonizing the canonical Wnt signaling pathway in osteoblasts. It binds to the first propeller domain of the LRP5/6 receptor, thereby disabling the formation of the co-receptor complex between LRP5/6 and Frizzled receptor, and inhibiting the Wnt pathway high up in the signaling cascade [54]. The exact mechanism by which sclerostin interacts with the LRP5/6 receptor remains to be established but it is thought that it requires a co-factor to inhibit the Wnt pathway similar to another Wnt antagonist, Dkk1, which needs Kremen to inhibit the pathway. LRP4, produced by osteoblasts and early osteocytes, was recently proposed as a facilitator of the inhibitory function of
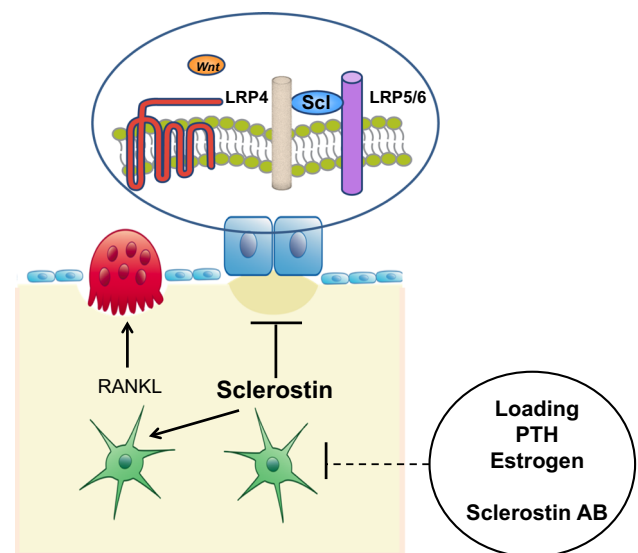
Fig. 2 Schematic representation of sclerostin actions. Osteocyte-produced sclerostin inhibits the proliferation, differentiation, and survival of osteoblasts and reduces bone formation; it also stimulates the production of RANKL by neighboring osteocytes and bone resorption. In osteoblasts, sclerostin binds to LRP5/6 and inhibits the Wnt signaling pathway, an action facilitated by LRP4. Production of sclerostin is decreased by mechanical loading, PTH, estrogens and other factors, and antisclerostin antibodies. *LRP* low-density lipoprotein receptor-related protein, *PTH* parathyroid hormone, *RANKL* receptor activator of nuclear factor kappa-B ligand

sclerostin on bone formation, and mutations in LRP4 were identified in patients with a phenotype closely resembling that of sclerosteosis [53]. In addition, inhibition of LRP4 by a specific antibody increased the rate of bone formation and bone mass in mice [55].

The restricted expression of sclerostin in the skeleton and the lack of abnormalities in organs other than the skeleton in patients and animals with sclerostin deficiency made this protein an attractive target for the development of a new bone-forming therapy for the management of osteoporosis. This approach was further supported by studies of heterozygous carriers of sclerosteosis who have increased serum levels of P1NP and high, normal, or increased BMD but no clinical symptoms, signs, or complications of sclerosteosis [46, 56]. Two inhibitors of sclerostin are currently being tested for the treatment of osteoporosis; romosozumab or AMG 785 (humanized monoclonal antibody, Amgen and UCB) and blosozumab (humanized monoclonal antibody, Eli Lilly). Romosozumab was used in most reported studies. In aged ovariectomized rats and nonhuman primates, romosozumab stimulated trabecular and cortical bone formation and increased bone mass and strength [57, 58]. Importantly, the majority of new bone formation induced by romosozumab was modeling-based, occurring at quiescent surfaces, demonstrating a clear anabolic response [59, 60]. The increased bone formation induced by romosozumab treatment was not associated with an increase in bone resorption. Instead, a decrease of osteoclast surface was observed, suggesting a functional uncoupling between bone formation and bone resorption, as also shown in the studies of *SOST* knock-out mice. The effect of sclerostin inhibition on bone formation markers decreased with prolongation of treatment and was reversible upon its discontinuation.

In phase I human studies, administration of single or multiple doses of romosozumab and blosozumab increased bone formation and decreased bone resorption markers associated with significant increases in BMD [61– 63]. In a placebo-controlled, dose-escalating study of 72 healthy men and postmenopausal women, it was shown that a single injection of romosozumab markedly increased bone formation markers and BMD and was well tolerated [62]. Serum levels of the bone formation marker P1NP reached a peak 14–25 days after the antibody administration and returned progressively to baseline after about 2 months. In contrast, serum levels of the bone resorption marker CTX decreased to a minimum about 14 days after the antibody injection and returned to baseline after about 2 months, in agreement with animal data.

Recker et al. recently reported the results of a dose-finding study of blosozumab given subcutaneously for 1 year to 120 postmenopausal women aged 45–85 years with BMD T-scores between −2.0 and −3.5 [64]. All women received calcium and vitamin D supplements and were randomized to receive placebo or blosozumab (180 mg every 4 weeks, 180 mg every 2 weeks, or 270 mg every 2 weeks). Blosozumab treatment induced dose-dependent increases in spine BMD by 8.4, 14.9, and 17.0 %, respectively; TH BMD by 2.1, 4.5, and 6.3 %, respectively; FN BMD by 2.7, 3.9, and 6.3 %, respectively; and total body bone mineral content by 1.7, 4.2, and 7.3 %, respectively, after 1 year; blosozumab treatment had no effect on BMD of the distal radius. Mild injection site reactions were more frequently observed with blosozumab than with placebo and neutralizing antibodies developed in one patient, which affected her response to treatment. Although the frequency of adverse events was similar among all groups, four women (all Japanese) were diagnosed with breast cancer between 3 months of initiating treatment to 1 year after the last dose of blosozumab; none of the investigators considered this adverse event to be related to blosozumab treatment.

Results of a phase II clinical trial of the efficacy and tolerability of romosozumab in postmenopausal women with low bone mass were also reported [65]. In this study, different doses and dosing intervals of subcutaneous injections of romosozumab were compared with placebo, oral alendronate 70 mg weekly, and subcutaneous teriparatide 20 µg daily. The primary efficacy point of the study was the change of spine BMD after 12 months. All doses of romosozumab induced significant increases in BMD. The highest dose of romosuzamab used, 210 mg once monthly, increased BMD at the spine (11.3 %), TH (4.1 %) and FN (3.7 %). These increases were significantly higher than those observed in women treated with either alendronate or teriparatide. For example, the corresponding increases at the spine were 4.1 % for alendronate and 7.1 % with teriparatide after 12 months. No significant differences in BMD of the distal third of the radius were observed at 12 months between any of the romosozumab groups and placebo, alendronate, or teriparatide groups. Adverse events were similar among all groups of studied women except for mild reactions at the injection sites of romosozumab. One patient treated with romosozumab was diagnosed during the trial with breast cancer that was not considered to be treatment-related.

Continuation of treatment for a second year was associated with further increases in LS and TH BMD to total gains of 15.7 and 6.0 %, respectively. Women who transitioned to denosumab after 2 years with romosozumab continued to accrue BMD at a rate similar to that of romosozumab during the second year, while in those who transitioned to placebo, BMD returned towards pretreatment levels; similar results were reported after discontinuation of blosozumab [66]. Serum P1NP and CTX levels remained below baseline values during the second year of romosozumab treatment [67].
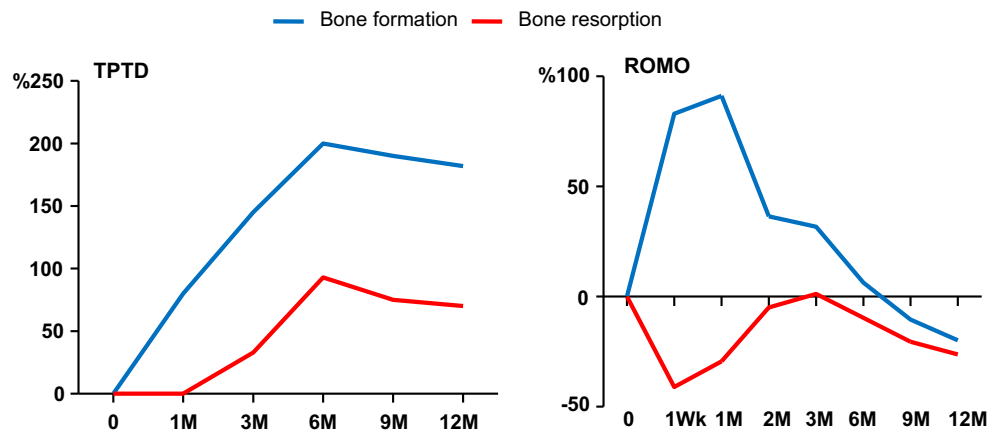
Fig. 3 Schematic representation of changes in the levels of biochemical markers of bone turnover during treatment with subcutaneous injections of either teriparatide (TPTD, 20 ug daily) or romosozumab (ROMO, 210 mg once monthly) for 1 year. Bone formation and bone resorption were assessed by measuring serum levels of procollagen type 1 aminoterminal propeptide (P1NP) and carboxy-terminal collagen crosslinking (CTX), respectively. Reproduced from [41]

Kinetics of biochemical markers of bone turnover in humans and histological data in animals during treatment with sclerostin inhibitors were different from those observed during treatment of patients with other antiosteoporotic agents (Fig. 3). There was an early rapid increase in bone formation markers followed by a progressive decline with time which was not due to the development of neutralizing antibodies. The effect of sclerostin inhibition on bone formation was further associated with a decrease of bone resorption, possibly through an inhibitory effect of the antibody on the production of RANKL by the osteocytes [68]. Treatment prolongation, however, appears to modestly reduce bone resorption but also bone turnover. It may, thus, be that while romosozumab acts as a pure anabolic agent in the beginning of treatment, its continued administration results in mild inhibition of bone resorption and reduction of the remodeling space. Phase III clinical studies are currently investigating the antifracture efficacy and tolerability of romosozumab and blosozumab in patients with osteoporosis (www.clinicaltrials.gov).

Positioning inhibitors of sclerostin in the management of patients with osteoporosis will depend not only on their efficacy in increasing bone mass and reducing the risk of fractures at all skeletal sites, but also on their safety profile. The observations that patients with sclerostin deficiency do not have complications from organs other than the skeleton, and that heterozygous carriers do not have any specific clinical phenotype, are reassuring. However, the number of these individuals is small and the Wnt-signaling pathway is involved in growth and differentiation of many cell types and its activation has been linked to tumorinogenesis, osteoarthritis, and cardiovascular calcification.

5 Conclusions

The two components of bone remodeling, resorption and formation, constitute the primary target of pharmacological interventions for the management of the disease. It is now clear that bone resorption and formation can be differently modulated by new classes of antiosteoporotic medications that provide a novel, personalized perspective for the management of patients in clinical practice.

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