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NEW TREATMENT MODALITIES IN OSTEOPOROSIS

Ernesto Canalis, MD

Department of Research, Saint Francis Hospital and Medical Center, Hartford, Connecticut, and University of Connecticut School of Medicine, Farmington, Connecticut

Abstract

Objective—To describe recently discovered agents for the management of osteoporosis.

Methods—A literature review (PubMed search) was conducted to identify agents at various stages of development for osteoporosis treatment. Agents under study or review for approval were included.

Results—In menopause, bone remodeling is increased, and agents that suppress bone resorption can stabilize bone mass. In contrast, agents that target the osteoblast can increase bone formation and bone mass. Novel antiresorptive agents can target the formation or the activity of osteoclasts. They include denosumab, an antibody to receptor activated nuclear factor κ B; new selective estrogen receptor modulators, such as bazedoxifene; and cathepsin K inhibitors, such as odanacatib. Src kinase inhibitors are in the early phases of development. Parathyroid hormone is the only approved anabolic agent for the treatment of osteoporosis. Novel anabolic therapies for osteoporosis may include the use of factors with anabolic properties for bone or the neutralization of growth factor antagonists. Recent discoveries have demonstrated that the Wnt/ β -catenin signaling pathway has a central role in osteoblastic cell differentiation. Antibodies to Wnt antagonists, such as sclerostin, are under development as new therapeutic approaches for osteoporosis. Anabolic therapies have the potential to enhance bone mass, but their long-term safety must be proven.

Conclusions—New developments in the treatment of osteoporosis include novel antiresorptive and anabolic agents. Their success will depend on their long-term effectiveness and safety profile.

INTRODUCTION

Bone remodeling is a tightly regulated process resulting in the coordinated resorption and formation of skeletal tissue performed in microscopic units, where osteoclasts resorb bone and osteoblasts fill the cavity with collagenous matrix, which is then mineralized (1). Osteoclasts are multinucleated cells derived from pluripotential hematopoietic cells, and osteoblasts are mononuclear cells derived from mesenchymal cells (2). Signals that determine the replication, differentiation, function, and death of cells of both lineages dictate the degree of bone remodeling, a process necessary to maintain calcium homeostasis and to remove and prevent the accumulation of aged or weakened bone. In the postmenopausal years, estrogen deficiency leads to excessive bone resorption, bone loss, and eventually osteoporosis. This disease is a major world-wide health problem and a cause of fragility fractures. These are the most important consequences of osteoporosis, and the goal of

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Address correspondence to Dr. Ernesto Canalis, Department of Research, Saint Francis Hospital and Medical Center, 114 Woodland St, Hartford, CT 06105-1299. ecanalis@stfranciscare.org.

DISCLOSURE

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therapeutic interventions is to reduce the incidence of fractures. This can be achieved by reducing bone resorption or by enhancing bone formation. The target cell of antiresorptive agents is the osteoclast or its precursors, whereas the target cell of anabolic agents is a cell of the osteoblastic lineage.

NOVEL ANTIRESORPTIVE AGENTS

Postmenopausal osteoporosis is characterized by a state of high bone remodeling leading to decreased bone mass (3). Agents that reduce bone resorption are effective in stabilizing bone architecture and reducing the incidence of fractures in osteoporosis. Consequently, antiresorptive therapy has a central role in the management of the disease. Antiresorptive agents target cells of the osteoclast lineage and can act by interfering with the formation or the activity of osteoclasts or can decrease the survival of mature osteoclasts.

Bisphosphonates are the most commonly used antiresorptive agents for the management of osteoporosis. They are effective, but their prolonged half-life and potential adverse effects are issues of concern, and novel therapies are being developed.

Receptor Activated Nuclear Factor κ B Neutralization

Receptor activated nuclear factor κ B neutralization (RANK-L) and macrophage colony-stimulating factor are factors derived from osteoblasts and are necessary for the formation of osteoclasts. RANK-L binds to its receptor, RANK, on osteoclasts and osteoclast precursors to induce osteoclastogenesis. Osteoprotegerin acts as a decoy receptor binding RANK-L and preventing its activity. Denosumab is a human monoclonal antibody directed against RANK-L and constitutes a new class of antiresorptive agents (Box 1). In contrast to bisphosphonates that inhibit osteoclast function and survival, denosumab acts by blocking RANK-L, decreasing the formation of osteoclasts. Denosumab, when administered subcutaneously at 60 mg every 6 months for 2 years, increases vertebral and hip bone mineral density (BMD) in postmenopausal women when compared with placebo (4). The effect was observed as early as 6 months after the first dose of denosumab and was sustained for the duration of the 2-year study. Denosumab also decreased biochemical markers of bone remodeling. A phase III trial demonstrated the fracture reduction efficacy of denosumab, 60 mg every 6 months, in 7868 postmenopausal women with osteoporosis (T scores ≤ -2.5 to -4.0 ; women with severe or multiple fractures excluded) (5). Compared with placebo, denosumab decreased the incidence of vertebral fractures by 68% after 3 years, and a significant as early as after 1 year of treatment. In addition, denosumab reduced fractures of the hip by 40% and reduced the cumulative incidence of nonvertebral fractures by 20% (5). The incidence of adverse events was not different between denosumab and placebo except for eczema, flatulence, cellulitis considered to be a serious adverse event, which occurred in 12 participants (0.3%) in the denosumab arm and in 1 participant ($<0.1\%$) in the placebo arm. A similar higher incidence of serious infections was reported for denosumab than for placebo in other trials (5,6). RANK-L and RANK are expressed by lymphoid cells, and RANK-L suppression in these cells may explain the increased incidence of serious infections. A concern regarding the long-term use of denosumab relates to its possible effects on the immune system. A preliminary study reporting the results of bone biopsies from the phase III pivotal fracture trial demonstrated absence of dual tetracycline labels in biopsies from patients receiving denosumab, a sign of markedly suppressed bone remodeling.

Box 1**Differences Between Denosumab and Bisphosphonates**

Denosumab	Bisphosphonates
<ul style="list-style-type: none"> • Biological • Inhibits receptor activated nuclear factor κB • Prevents osteoclast formation • Subcutaneous • Twice a year • Half-life short, not bound to skeleton • Efficacy reduces vertebral, nonvertebral, and hip fractures • Safety, possible increase in serious infections such as cellulitis • Suppression of bone remodeling marked but potentially reversible 	<ul style="list-style-type: none"> • Nonbiological • Inhibit mevalonate pathway • Decrease osteoclast function and survival • Oral, intravenous • Weekly, monthly, yearly • Prolonged half-life, accumulate in the skeleton • Efficacy on fracture reduction is agent dependent • Safety bone selective, oral bisphosphonates associated with gastrointestinal intolerance • Suppression of bone remodeling protracted

In the absence of head-to-head comparisons, it is not possible to define the fracture reduction efficacy of denosumab relative to other antiresorptive agents. However, in terms of magnitude, the fracture risk reduction efficacy of denosumab appears to be comparable to that reported for zoledronic acid (7). In terms of BMD, denosumab, 60 mg every 6 months, was shown to have a greater effect on BMD at multiple skeletal sites after 1 year than alendronate, 70 mg weekly (8). Potential advantages of denosumab over bisphosphonates could include increased adherence because it would be administered in a physician's office, it lacks skeletal accumulation, and it is not cleared by the kidneys, making it a possible alternative to bisphosphonates in individuals with impaired renal function (9) (Box 2). But, in the population of patients with impaired renal function, its efficacy and safety have not been documented. Denosumab was recently approved for use in the United States.

Box 2**Advantages and Disadvantages of Denosumab**

Advantages	Disadvantages
<ul style="list-style-type: none"> • Administered every 6 months • Does not accumulate in skeletal tissue • Not cleared by the kidneys • Possible increased adherence to regimen • Fracture reduction efficacy at multiple sites including spine, nonvertebral, and hip • Potentially reversible 	<ul style="list-style-type: none"> • Impact on the immune system, infections • Marked suppression of bone remodeling • Long-term safety and efficacy unknown

Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators (SERMs) bind to estrogen receptors, inducing different receptor conformational changes than estrogens, allowing for interactions with

distinct intranuclear proteins resulting in estrogenlike and estrogen-antagonistic effects. Currently, raloxifene is the only SERM approved by the US Food and Drug Administration (FDA) for the prevention and treatment of osteoporosis. A limitation of raloxifene is its effectiveness in reducing fractures of the spine, but not fractures of the hip or nonvertebral fractures. Because of their potential to prevent breast carcinoma, SERMs, such as arzoxifene, lasofoxifene, and bazedoxifene, were developed with the hope to achieve a greater impact on fracture reduction in osteoporosis and better tolerability than raloxifene (Box 3). Arzoxifene will not be pursued because its efficacy and safety profile are not different from those of raloxifene. Lasofoxifene was filed with the FDA and received approval conditional to the generation of additional cardiovascular safety data, and its future as a therapy for the management of osteoporosis is not clearly known. In a phase III trial, lasofoxifene was compared with raloxifene for its effect on fracture risk reduction in postmenopausal women with osteoporosis (10). After 3 years, lasofoxifene at dosages of 250 mcg and 500 mcg daily decreased the incidence of vertebral and nonvertebral fractures, but did not reduce the incidence of hip fractures. Lasofoxifene also decreased the incidence of breast carcinoma. However, increased vaginal discharge and hot flashes were reported with lasofoxifene, although the incidence of stroke and cardiovascular events was not increased (10). In another trial, lasofoxifene at a dosage of 250 mcg and 1 mg daily was more effective than placebo and raloxifene at a dosage of 60 mg daily for its effects on vertebral BMD in postmenopausal women, but its effect on hip BMD was comparable to that of raloxifene (11). The adverse event profiles of lasofoxifene and raloxifene were similar.

Box 3

Advantages and Disadvantages of Selective Estrogen Receptor Modulators

Advantages	Disadvantages
<ul style="list-style-type: none"> • Oral administration • Do not accumulate in skeletal tissue • Not cleared by the kidneys • Modest suppression of bone remodeling • Bone safe, no reports of osteonecrosis of the jaw or subtrochanteric fractures • Benefit of breast carcinoma prevention 	<ul style="list-style-type: none"> • Daily administration • Increased vascular symptoms • Higher incidence of thromboembolic and vascular events • Fracture reduction efficacy only proven at the spine • Long-term vascular safety may be problematic

Bazedoxifene has been studied singly and in combination with estrogens, the latter to reduce vasomotor symptoms, which are of similar frequency as that observed with raloxifene. Bazedoxifene, 20 mg and 40 mg daily, was compared with placebo and raloxifene, 60 mg daily, for its efficacy in reducing fractures in postmenopausal women with osteoporosis. At both dosages, bazedoxifene reduced the incidence of new vertebral fractures compared with placebo, and the effect was not different from that of raloxifene (12). The incidence of nonvertebral fractures was not different from placebo with either agent. In a post hoc analysis, bazedoxifene reduced nonvertebral fractures in a subgroup of individuals at high risk of fractures. The incidence of vasomotor symptoms, leg cramps, and venous thromboembolic events was higher in participants receiving bazedoxifene than in participants receiving placebo. There was no increased incidence of myocardial infarction or strokes at 3 years, and bazedoxifene was associated with a favorable endometrial, ovarian, and breast safety profile (13).

Tibolone is a synthetic steroid, and its metabolites have estrogenic, androgenic, and progesterone-like properties. Tibolone is not a SERM, and it is considered a selective tissue estrogenic activity regulator. In a recent trial, tibolone reduced the incidence of vertebral and nonvertebral fractures in older postmenopausal women (14). Tibolone increased the risk of stroke, for which the trial was interrupted, as well as the risk of endometrial thickness and vaginal bleeding. Tibolone is not approved by the FDA for the treatment of osteoporosis.

Cathepsin K Inhibitors

Cathepsin K is a lysosomal cysteine protease preferentially expressed by osteoclasts that degrades type I collagen. Loss-of-function mutations in the gene encoding cathepsin K (*CTSK*) cause pycnodysostosis, a rare disease characterized by osteosclerosis, short stature, and bone fragility (15–17). Osteoclasts from patients with pycnodysostosis contain large vacuoles of undigested collagen and defective bone resorption. The bone fragility observed is explained by an abnormal distribution of collagen fibrils and deterioration of bone architecture. Mouse models of *Ctsk* inactivation exhibit an increased number of dysfunctional osteoclasts and altered bone resorption. Although osteoblast number is not affected, skeletal parameters of osteoblastic function, such as the mineral apposition rate are increased, although the reason is not clear. *Ctsk* null mice exhibit increased trabecular and cortical bone volume. Despite this increase, studies of the biomechanical properties of *Ctsk* null mice have yielded controversial results and suggest that *Ctsk* inactivation, like pycnodysostosis, may cause bone fragility despite high bone mass (18–20).

Several cathepsin K inhibitors, including odanacatib, balicatib, and relacatib, have been developed; they reduce bone remodeling and have good oral bioavailability (21). Ideally, these inhibitors should be selective for cathepsin K and should not inhibit other cathepsins expressed at non-skeletal sites because lack of specificity of other cathepsins could lead to adverse effects. In this regard, it is important to note that cathepsin K itself is expressed in nonskeletal tissues including epithelial cells and fibroblasts or 50 mg once weekly for 2 years increased vertebral and hip BMD in postmenopausal women with osteoporosis (T scores ≤ -2.0 to -3.5) (24). Odanacatib caused a dose-related increase in BMD at the lumbar spine and hip; at the 50-mg dose, it increased vertebral BMD by 5.7% compared with that observed with placebo. Biochemical markers of bone resorption were suppressed, and adverse events were not different from those observed with placebo. Bone biopsies were obtained in a limited number of subjects, but they did not reveal any obvious abnormalities; activation frequency was decreased (24). Odanacatib is currently being tested for its fracture reduction efficacy in a phase III trial to be completed in 2012. In a phase II trial, balicatib increased vertebral and hip BMD in postmenopausal women with T scores of -2 or lower, but balicatib was discontinued because of its lack of skeletal selectivity and adverse effects (21). Relacatib reduces bone turnover in ovariectomized cynomolgus monkeys, and a phase I study to assess its effects in humans was completed, but knowledge of its efficacy in osteoporosis is unknown (25). Additional cathepsin K inhibitors are in early stages of development and may have potential advantages over current therapies (Box 4).

Box 4

Advantages and Disadvantages of Cathepsin K Inhibitors

Advantages	Disadvantages
<ul style="list-style-type: none"> • Oral bioavailability • Weekly administration • Do not accumulate in skeletal tissue 	<ul style="list-style-type: none"> • Potential targeting of nonskeletal cathepsins leading to adverse effects • Fracture reduction efficacy unknown • Long-term safety and efficacy unknown

Advantages	Disadvantages
<ul style="list-style-type: none"> • Good effect on bone mineral density • Biopsies suggest bone safety 	<ul style="list-style-type: none"> • Increased bone fragility in pycnodysostosis and cathepsin K null mouse models

Src Kinase Inhibitors

Src kinase is a nonreceptor tyrosine kinase and a member of the Src family of protein kinases. Src has a role in osteoclast survival and activity (26). *Src* inactivation in the mouse causes osteopetrosis, indicating that Src is an essential requirement for osteoclastic bone resorption (27). In *Src* null mutants, osteoclasts fail to form a ruffled border and do not resorb bone. Saracatinib is a novel, orally available competitive inhibitor of Src kinase shown to inhibit bone resorption in vitro. A recent phase I trial tested saracatinib, 60 to 250 mg, in healthy men (28). Saracatinib caused a dose-dependent decrease in bone resorption markers without significant adverse events. Saracatinib has the potential to become an agent for the treatment of osteoporosis, but appropriate phase II and phase III trials are necessary to assess its efficacy and safety.

NOVEL ANABOLIC THERAPIES

An increase in bone formation can be obtained by increasing the pool of bone-forming cells. An increase in osteoblastic cell number can be achieved by enhancing the replication or differentiation of preosteoblastic cells or by supporting the survival of the mature cell. An increase in the function of mature osteoblasts also can augment bone formation. Consequently, anabolic agents can target signals increasing the osteoblastic cellular pool or the function of the mature cell (29–31). Because of their potential to increase bone mass, novel anabolic agents are being investigated (Box 5). Currently, the only anabolic agent approved by the FDA for the treatment of osteoporosis in the United States is teriparatide, a 1–34 amino acid fragment of human parathyroid hormone (PTH[1–34]). In Europe, a full-length PTH (1–84) molecule also is approved for therapy. A limitation of PTH is the need for daily subcutaneous administration. Therefore, alternative delivery systems, such as oral, transdermal, and intranasal, have been tested. A recent study comparing the transdermal daily administration of teriparatide with its subcutaneous administration demonstrated good bioavailability and an increase in vertebral BMD comparable with subcutaneous teriparatide (32). Another approach is the stimulation of endogenous PTH secretion by agents that interfere with the calcium-sensing receptor on the parathyroid cell. Oral calcilytic agents stimulate endogenous PTH secretion in rodents, and they are being studied for their effects in humans (33). PTH-related peptide also is being examined for its potential anabolic effects in humans. Initial studies in postmenopausal women with osteoporosis suggested that PTH-related peptide increases vertebral BMD (34). A phase II trial comparing PTH-related peptide with PTH is listed in [clinicaltrials.gov](#), but recruitment has not started.

Box 5

Mechanisms to Increase Bone Mass

Increase the osteoblast cell pool

Enhance cell replication (ie, parathormone and analogues)

Inhibit cell death (ie, parathormone and analogues)

Induce osteoblast differentiation (ie, enhancing Wnt signaling by inhibiting Wnt antagonists)
 Increase osteoblast function (ie, insulinlike growth factor 1)

Enhancing Wnt Signaling in the Skeleton

Activation of the Wnt signaling pathway induces osteoblastic cell differentiation, and loss-of-function mutations of Wnt co-receptors cause profound bone loss, whereas gain-of-function mutations result in increased bone mass (35). In skeletal cells, Wnt uses the canonical Wnt/ β -catenin signaling pathway (35). In this pathway, when Wnt receptor binding interactions are absent, β -catenin is phosphorylated and degraded in the proteasome. Binding of Wnt to frizzled receptors and to the low-density lipoprotein receptor-related protein (LRP) 5 and 6 co-receptors leads to the stabilization of β -catenin and its translocation to the nucleus, where it associates with nuclear factors to regulate gene transcription. Because Wnt induces osteoblastogenesis and bone formation, and suppresses osteoclastogenesis and bone resorption, Wnt signaling is a suitable target for the development of new anabolic therapies (36,37). The activity of Wnt is modulated by extracellular antagonists that act by binding Wnt itself or by preventing its interactions with its receptor or coreceptors. Sclerostin and dickkopf 1 (Dkk-1) bind to LRP5 and LRP6, and mutations in *LRP5* and *LRP6*, preventing the association of sclerostin or Dkk-1 with LRP5, result in increased bone mass. Sclerostin is the product of the *SOST* gene, and *SOST* mutations resulting in absent expression of sclerostin cause sclerosteosis and van Buchem disease, both characterized by marked increases in bone mass (38,39). It is important to note that persons with these conditions live a fairly normal life, except for skeletal manifestations leading to nerve compression. These clinical findings indicate that inactivation or neutralization of sclerostin could be used as a reasonably safe approach to enhance Wnt signaling and to obtain an anabolic response in bone (40). Humanized monoclonal antibodies to sclerostin cause enhanced Wnt signaling and an increase in bone mass in rodents and non-human primates (41). A phase I study in humans demonstrated that the administration of sclerostin antibodies once resulted in an increase in BMD and biochemical markers of bone formation lasting 3 months.

Dkk-1 neutralization increases trabecular bone volume and bone formation in rodents, suggesting that Dkk-1 neutralization, like sclerostin, could be pursued as an anabolic approach in the treatment of osteoporosis, but no studies have been reported in humans (42). A small molecule inhibitor of secreted frizzled receptor-1, an antagonist that binds Wnt, also was reported to enhance Wnt signaling and bone formation, offering a nonbiologic approach to the development of bone anabolic agents (43).

Although the inactivation of Wnt antagonists is a plausible approach for the development of bone anabolic agents, it is not without potential problems. Indiscriminate Wnt activation could result in adverse effects and possible tumorigenicity in nonskeletal tissues (44). It is reassuring that patients with high-bone mass syndrome and sclerosteosis do not appear to have a higher incidence of malignancies. However, a recent report demonstrated that the Wnt antagonist, Wnt inhibitory factor, is hypermethylated and epigenetically silenced in osteosarcoma, causing increased Wnt signaling (45). Furthermore, the inactivation of *Wif* predisposes mice to the development of osteosarcoma. Findings from an experimental model of multiple myeloma revealed that the activation of Wnt signaling rescues the skeletal disease, but favors the invasion of soft tissue by myeloma cells (46). These observations are a concern, and this class of anabolic agents will probably be used for limited periods of time

to obtain a rapid increase in bone mass, which can then be stabilized by antiresorptive agents.

Regulating Activin Signaling

Activin is a member of the bone morphogenetic protein (BMP)/transforming growth factor β superfamily of polypeptides (29). Activin is constituted by homodimers and heterodimers of inhibin β_A and β_B subunits and stimulates the release of follicle-stimulating hormone by pituitary cells. In bone, activin enhances osteoclastogenesis and bone resorption, but its effects on bone formation are less clear, and both stimulatory and inhibitory effects have been reported (47,48). There are 4 activin receptors, 2 type I receptors (ActRIA or activin receptorlike kinase [ALK]-3 and ActRIB or ALK-6) and 2 type II receptors (ActRIIA and IIB). Activin receptors do not activate BMP signaling, but BMP-3, an inhibitor of bone formation, binds to activin receptors (49). A soluble activin receptor type II fused to IgG-Fc decreases bone resorption in ovariectomized mice and enhances bone formation in intact animals (50). The mechanism of the anabolic effect is not clear. It is possible that under certain circumstances activin has inhibitory activity on bone formation or that the soluble receptor binds BMP-3 and causes an anabolic response. The soluble ActII receptor administered twice a week to Rhesus monkeys increased bone mass and strength (51). The half-life of the soluble receptor in rhesus monkeys is 7 to 9 days. In a phase I trial in humans, it was well tolerated and increased markers of bone formation (52).

BMPs are used locally to treat nonunion fractures and to enhance the formation of spinal fusions, but there is no information regarding their value for osteoporosis treatment. Their systemic administration would be limited by their nonskeletal effects, mitogenicity, short half-life, and stimulatory effects on bone resorption. Proteasome inhibitors can enhance BMP-2 expression and bone formation, but their activity is not selective to the skeleton and these agents cause substantial cell toxicity (53,54).

Insulinlike Growth Factor 1

Insulinlike growth factor 1 (IGF-1) is a peptide synthesized in multiple tissues including bone. The synthesis of circulating IGF-1 is growth hormone dependent and occurs in the liver (55). In bone cells, the production of IGF-1 is primarily regulated by PTH (56). IGF-1 enhances the differentiated function of osteoblasts and bone formation. It is of interest that IGF-1 stabilizes β -catenin and can potentially enhance Wnt signaling (57). IGF-1 increases the synthesis of RANK-L by the osteoblast, and, as a consequence, it can enhance osteoclast recruitment and bone resorption (58). Circulating IGF-1 contributes to cortical bone integrity, whereas skeletal IGF-1 has a more important role in the maintenance of trabecular bone integrity (59–61). Growth hormone and IGF-1 have important roles in the acquisition of bone mass during adolescence and in the maintenance of skeletal architecture during adult life (55). A decline in growth hormone and IGF-1 levels occurs during aging and may have a role in the pathogenesis of osteoporosis, since IGF-1 levels correlate with BMD in postmenopausal women (62). Studies to define the effects of IGF-1 on bone turnover are limited. At high dosages, IGF-1 increases bone remodeling, whereas at low dosages, it increases bone formation without an effect on bone resorption (63). Administration of IGF-1 at dosages that normalize serum IGF-1, in combination with estrogen replacement therapy, increases BMD in anorexia nervosa (64). Notwithstanding these encouraging results, the long-term efficacy and safety of IGF-1 for the treatment of osteoporosis, in the context (or not) of anorexia nervosa, remain to be determined. The expense, the need for parental administration, the potential adverse effects, the lack of tissue specificity, and the possible role of IGF-1 in the development and propagation of malignancies are concerns that temper the enthusiasm for the development of IGF-1 as a therapeutic option for osteoporosis (65).

Another constraint is the need for careful monitoring of the dose administered to avoid an increase in bone resorption.

Strontium Ranelate

Strontium ranelate has anabolic and antiresorptive properties in vitro (66). Studies in humans have documented its antiresorptive properties, but bone biopsies from subjects treated with strontium ranelate do not reveal increased bone formation (67). Strontium ranelate at a dosage of 2 g daily for 3 years reduced vertebral fractures in postmenopausal women with osteoporosis by 41% (67). In a subsequent study, strontium ranelate reduced the risk of nonvertebral fractures (16%), but not the risk of hip fractures (68). The incidence of adverse events was balanced between strontium ranelate and placebo. Strontium ranelate is approved for the treatment of postmenopausal osteoporosis in Europe, but not in the United States.

CONCLUSION

During the past decade and a half, we have witnessed the appearance of a significant the treatment of osteoporosis. With the exception of teriparatide, all the agents currently available reduce bone resorption. Although emphasis is being placed in the development of new anabolic agents, new antiresorptive agents are being pursued with the hope to develop therapies with good efficacy, tolerability, and simplicity of administration. Anabolic agents will have a place in the management of severe osteoporosis and in specific forms of the disease characterized by decreased bone formation and remodeling, such as glucocorticoid-induced osteoporosis. The administration of systemic growth factors for the management of osteoporosis is limited by a lack of skeletal specificity and potential adverse effects. The discovery of the Wnt signaling pathway and its activity in bone tissue has led to the development of novel anabolic agents that, by targeting Wnt antagonists, can enhance Wnt signaling in skeletal cells. Efforts should target anabolic signals specifically in the skeletal environment as new therapeutic avenues for the treatment of osteoporosis emerge.

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Abbreviations

BMD	bone mineral density
BMP	bone morphogenetic protein
Dkk-1	dickkopf 1
FDA	US Food and Drug Administration
IGF-1	insulinlike growth factor 1
LRP	low-density lipoprotein receptor-related protein
PTH	parathyroid hormone
RANK-L	receptor activated nuclear factor κ B
SERM	selective estrogen receptor modulator

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