

MANAGEMENT OF ENDOCRINE DISEASE

Novel anabolic treatments for osteoporosis

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Skeletal anabolic agents enhance bone formation, which is determined by the number and function of osteoblasts. Signals that influence the differentiation and function of cells of the osteoblast lineage play a role in the mechanism of action of anabolic agents in the skeleton. Wnts induce the differentiation of mesenchymal stem cells toward osteoblasts, and insulin-like growth factor I (IGF-I) enhances the function of mature osteoblasts. The activity of Wnt and IGF-I is controlled by proteins that bind to the growth factor or to its receptors. Sclerostin is a Wnt antagonist that binds to Wnt co-receptors and prevents Wnt signal activation. Teriparatide, a 1–34 amino terminal fragment of parathyroid hormone (PTH), and abaloparatide, a modified 1–34 amino terminal fragment of PTH-related peptide (PTHrp), induce IGF-I, increase bone mineral density (BMD), reduce the incidence of vertebral and non-vertebral fractures and are approved for the treatment of postmenopausal osteoporosis. Romosozumab, a humanized anti-sclerostin antibody, increases bone formation, decreases bone resorption, increases BMD and reduces the incidence of vertebral fractures. An increased incidence of cardiovascular events has been associated with romosozumab, which is yet to be approved for the treatment of osteoporosis. In conclusion, cell and molecular studies have formed the foundation for the development of new anabolic therapies for osteoporosis with proven efficacy on the incidence of new fractures.

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(2018) **178**, R33–R44**Introduction**

Osteoporosis is a disease characterized by low bone mass, increased bone porosity and microarchitectural deterioration of the skeleton causing bone fragility and a predisposition to fractures. Osteoporosis is a major health problem, and it is considered that over 200 million individuals suffer from the disease and an estimated 9

million new osteoporotic fractures occur in a given year (1, 2). Consequently, treatments for osteoporosis are evaluated by their effectiveness in reducing the incidence of new fractures. Following the menopause, bone remodeling is increased and bone resorption exceeds the capacity of the skeleton to form new bone. As a result,

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there is a loss of cancellous and cortical bone. By targeting the generation, function and survival of bone resorbing osteoclasts, anti-resorptive therapy prevents the loss of skeletal structure and stabilizes the skeleton but fails to restore bone mass and architecture. Therefore, there has been a continued interest in the development of agents capable of increasing bone mass with the hope to restore skeletal architecture.

To have a better understanding of anabolic agents, this review addresses cellular events responsible for bone remodeling, signals and pathways known to enhance bone formation as well as current and newly developed anabolic therapies for osteoporosis.

Skeletal cells and bone remodeling

Bone remodeling is a highly regulated process that results in bone resorption coupled to the formation of skeletal tissue. Bone remodeling occurs in basic multicellular units, where osteoclasts resorb bone; and following a reversal period, osteoblasts fill the cavity with a collagenous matrix, which is then mineralized (3). Osteoclasts are multinucleated cells derived from the myeloid lineage, and osteoblasts are mononuclear cells derived from mesenchymal cells (4). Osteoblasts can differentiate into quiescent lining cells and into osteocytes, terminally differentiated osteoblasts that are embedded in the mineralized matrix. Osteocytes form a canalicular network to communicate their signals to osteoblasts and osteoclasts. As a consequence, osteocytes play a major role in skeletal remodeling. Osteocytes secrete receptor activator of nuclear factor kappa B ligand (RANKL); and through this mechanism, they control osteoclastogenesis and bone resorption. Osteocytes are a source of sclerostin, a Wnt antagonist, and through this mechanism, they control osteoblastogenesis and bone formation (5). Signals that determine the replication, differentiation, function and death of cells of the osteoblast and osteoclast lineages dictate bone remodeling. This is a process necessary for the maintenance of calcium homeostasis and the removal of bone preventing the accumulation of aged or weakened bone. In the postmenopausal years, estrogen deficiency leads to excessive bone resorption and bone loss, and a way to control the bone loss is to target cells of the osteoclast lineage and reduce bone resorption. Alternatively, in severe osteoporosis, bone formation can be enhanced by the use of an anabolic agent that can increase the number or the function of osteoblasts. An increase in osteoblast cell number can be obtained by an increase in

the replication or differentiation of pre-osteoblastic cells or by a decrease in the death of mature cells. An increase in the function of mature osteoblasts can be obtained by direct effects on the differentiated cells.

Signals controlling osteoblast differentiation and function and mechanisms of anabolic therapies in bone

The osteoblast cell pool is increased by growth factors with mitogenic activity for cells of the osteoblast lineage; however, whether or not the replicating cells differentiate into mature osteoblasts will determine an anabolic response. Factors that induce the differentiation of cells of the osteoblastic lineage into mature cells or factors that enhance the differentiated function of the osteoblast are necessary to achieve a bone-forming response (6, 7). Bone morphogenetic proteins (BMPs) and Wnts induce the differentiation of mesenchymal cells toward mature osteoblasts, whereas insulin-like growth factor (IGF)-I has a lesser effect on cell differentiation but enhances the differentiated function of the osteoblast (8, 9, 10, 11, 12). The activities of Wnt, BMPs and IGF-I are regulated at the level of their synthesis and receptor binding, as well as by specific extracellular and intracellular regulatory proteins that control their activity. Some act as carrier proteins, like IGF-I-binding proteins, others act as BMP or Wnt antagonists such as noggin and sclerostin (8, 11, 12). Approaches to obtain an anabolic response are diverse and include the enhancement of the synthesis or activity of a growth regulator or the targeting of a secreted growth factor antagonist (10, 13, 14). Intracellular proteins can potentiate or attenuate an anabolic signal but are difficult to target since this would require crossing the cell membrane and reaching inside the cell. Therefore, the development of agents targeting non-secreted proteins is not practical.

Wnt signaling and skeletal homeostasis

Wnts constitute a family of secreted glycoproteins that play a fundamental role in the biology of many cells. Wnt/ β -catenin signaling controls skeletal development and adult skeletal homeostasis (11, 15, 16). In the absence of Wnt, axin, adenomatous polyposis coli and β -catenin form a complex, leading to the phosphorylation of β -catenin by casein kinase 1 α and glycogen-synthase kinase 3 β (GSK3 β) (17). Phosphorylated β -catenin is degraded by ubiquitination (17). Following the binding

of Wnt to specific frizzled receptors and to the low-density lipoprotein receptor-related protein (LRP) co-receptors 5 and 6, GSK-3 β activity is inhibited and β -catenin is stabilized. β -catenin translocates to the nucleus where it associates with T-cell-specific transcription factor 4 or to lymphoid enhancer-binding factor 1 to regulate the transcription of target genes required for osteoblastogenesis (18, 19, 20, 21, 22, 23, 24, 25).

By inducing Runx-2 and osterix, which are required for osteoblastogenesis, Wnt can enhance bone formation (26, 27). In addition, Wnt suppresses adipogenesis (20). Wnt has a less recognized but important inhibitory role in osteoclastogenesis and bone resorption, and the constitutive activation of β -catenin in cells of the osteoblast or osteoclast lineage causes osteopetrosis (22, 28). The mechanism is a direct effect on cells of the osteoclast lineage and an indirect effect secondary to the induction of osteoprotegerin. The downregulation of β -catenin in osteocytes/osteoblasts and osteoclast precursors causes osteopenia due to a decrease in osteoprotegerin expression and a direct effect in osteoclast progenitors both resulting in an increase in osteoclast number and bone resorption (15, 16, 22, 24, 29).

Wnt antagonists

Wnt activity is modulated by secreted proteins that interact with Wnt or with its receptors to control the activity of Wnt. Wnt antagonists interacting with Wnt are Wnt inhibitory factor (WIF)1, secreted Frizzled-related proteins (sFRP) and Cerberus (11, 14, 30). Antagonists interacting with the Wnt co-receptors LRP5/6 are sclerostin, Dickkopf1 and Wnt modulator in surface ectoderm (WISE) also termed ectodin or sclerostin domain-containing 1 (11, 14, 30).

Sclerostin, the product of the *Sost* gene, is preferentially expressed by osteocytes and binds to the Wnt co-receptor LRP5/6, inhibiting Wnt signaling (31, 32, 33). As a consequence, sclerostin inhibits osteoblastogenesis and bone formation and enhances osteoclastogenesis and causes bone loss (34, 35). Conversely, the inactivation of *Sost* causes an increase in osteoblast number, bone formation and cortical and trabecular bone with enhanced biomechanical properties (36).

By downregulating the Wnt antagonist sclerostin, mechanical loading activates Wnt signaling suggesting that this mechanism is responsible for coupling mechanical forces to an anabolic response in the skeleton (37, 38, 39, 40). Conversely, sclerostin is upregulated in the unloaded skeleton causing enhanced bone resorption

and decreased formation, a mechanism playing a role in disuse osteoporosis (39). Parathyroid hormone (PTH) downregulates sclerostin expression, a mechanism proposed to contribute to the anabolic actions of PTH in the skeleton (41, 42, 43). It is important to note that serum levels of sclerostin do not correlate with changes in bone mineral density (BMD) in patients with osteoporosis and are of limited diagnostic value in this disease (44, 45, 46). This is because sclerostin acts locally in the bone microenvironment and serum levels of sclerostin do not reflect changes in sclerostin expression by the osteocyte (47).

The importance of the Wnt/ β -catenin canonical signaling pathway is underscored by the skeletal disorders associated with alterations in Wnt signaling. Mutations in the *SOST* gene resulting in the downregulation of the expression of sclerostin, such as sclerosteosis and van Buchem disease, are characterized by a marked increase in bone mass (34, 48, 49, 50, 51, 52, 53, 54). Similarly, activating and inactivating mutations of the Wnt co-receptors *LRP5/6* cause significant skeletal phenotypes. Activating mutations of the Wnt co-receptor *LRP5* result in increased bone mass, whereas inactivating mutations of this gene cause bone loss (21, 55, 56). High bone mass syndrome is secondary to missense mutations of *LRP5*, resulting in reduced affinity of Dkk1 or sclerostin for the co-receptor and consequent increased Wnt signaling (57, 58, 59, 60). Inactivating mutations of *LRP5* cause osteoporosis-pseudoglioma syndrome characterized by severe bone loss and fractures (23, 61). These findings, in conjunction with studies on the biology of Wnt signaling and its antagonists, have formed the foundation for the development of therapies targeting Wnt antagonists with the purpose of enhancing Wnt signaling.

Insulin-like growth factor I

IGF-I is a peptide that acts as a systemic and local regulator of skeletal growth. Circulating IGF-I is synthesized in the liver and is growth hormone (GH)-dependent and mediates the effects of GH on longitudinal bone growth (12). In bone cells, the synthesis of IGF-I is primarily dependent on PTH, and IGF-I is required to obtain an anabolic response to PTH in bone *in vitro* and *in vivo* (62, 63). Similarly, PTH-related peptide (PTHrp) increases IGF-I secretion by skeletal cells, and IGF-I mediates the effects of PTHrp on bone formation *in vitro* (12, 64). These observations have demonstrated that IGF-I plays an important role in the mechanism of PTH and PTHrp action in bone. Six IGF-binding proteins control IGF-I transport,

availability and activity (10). IGF-I signals through a transmembrane tyrosine receptor, which activates the insulin receptor substrates to initiate signaling, through either the phosphatidylinositol-3 kinase (PI-3K)-protein kinase B (PKB/Akt) or the MAP kinase pathway (65, 66). IGF-I enhances the differentiated function of the osteoblast and prevents osteoblast apoptosis. IGF-I can regulate osteoblast differentiation indirectly by stabilizing β -catenin and enhancing Wnt signaling (67). IGF-I is necessary for skeletal development and the maintenance of bone mass. Overexpression of IGF-I in osteoblasts enhances bone formation and increases cancellous bone volume documenting its anabolic effect (68). IGF-I also increases the synthesis of RANKL by the osteoblast; and as a consequence, it can enhance osteoclastogenesis, bone resorption and bone remodeling (69, 70). Circulating IGF-I contributes to cortical bone integrity, whereas locally produced skeletal IGF-I plays a more significant role in the maintenance of cancellous bone integrity (68, 71, 72). Targeted deletions of the IGF-1 receptor in osteoblasts or deletion of elements of the IGF-I signaling pathway cause impaired bone formation and osteopenia confirming that IGF-I is a critical factor in the control of bone formation and remodeling (72, 73).

GH and IGF-I play an important role in the acquisition of bone mass during adolescence and in the maintenance of skeletal architecture during adult life (12). A decline in GH and IGF-I secretion and in the cortical bone content of IGF-I occur during aging and may contribute to a role in the pathogenesis of osteoporosis in the elderly. There is a correlation between serum IGF-I levels and BMD in postmenopausal women (74). Human studies to define the effects of GH or IGF-I on bone turnover are limited. At high doses, IGF-I increases bone remodeling, whereas at low doses, it increases bone formation without an effect on bone resorption (75). These observations would suggest that at low doses IGF-I can increase osteoblast function without a deleterious bone resorptive effect. Indeed, experience in subjects with anorexia nervosa associated with osteopenia and decreased serum levels of IGF-I would suggest that this is the case. Administration of IGF-I at doses that normalize serum IGF-I, in combination with estrogen replacement therapy, increases BMD in osteopenic subjects with anorexia nervosa (76, 77). GH replacement therapy has beneficial effects on BMD in the GH deficient state, but there is no evidence for skeletal benefit in other clinical conditions (78, 79). In postmenopausal osteoporotic subjects, the effects of GH are inconsistent, and well-designed longitudinal studies

to demonstrate fracture risk reduction in this condition have not been reported (80).

Anabolic treatments for osteoporosis

Teriparatide

Teriparatide, the 1–34 amino terminal fragment of PTH, was the first anabolic agent to be approved for the treatment of osteoporosis. It is approved in postmenopausal women and in men who are at high risk for fracture, such as *T*-score on dual-energy x-ray absorptiometry that is very low, in the context or not of other significant risk factors for fractures such as a previous fragility fracture. Teriparatide is also approved for the treatment of glucocorticoid-induced osteoporosis (81).

The intermittent administration of PTH induces an anabolic response in the skeleton. PTH signals through the PTH 1 receptor, a G protein-coupled protein, which mediates most of the functions of PTH and of PTH-related peptide (PTHrP). PTH has mitogenic properties for cells of the osteoblast lineage and decreases osteoblast apoptosis (82). As a consequence, the number of bone-forming cells is increased. The anabolic actions of PTH are secondary to its direct effects on cells of the osteoblast lineage and indirect effects through the induction of IGF-I and the suppression of sclerostin with the consequent enhancement of Wnt signaling (83). PTH also suppresses Notch signaling, an inhibitor of osteoblast differentiation, in cells of the osteoblast lineage *in vitro* and *in vivo* (84). Through these mechanisms, PTH could enhance osteoblastogenesis and increase the osteoblast cell pool. It is unclear why intermittent, low-dose PTH administration is anabolic, whereas sustained PTH increases bone resorption. Although the induction of IGF-I could account for both effects, the anabolic effect of PTH appears to be limited to cancellous bone and not observed in cortical bone and also is congruent with the effects of locally synthesized IGF-I (85, 86).

The effects of teriparatide on the treatment of osteoporosis has been studied in postmenopausal women and in men, as well as in subjects with glucocorticoid-induced osteoporosis (81, 87). Teriparatide administered at a dose of 20 μ g daily subcutaneously increases vertebral and femoral BMD over a 21-month period and causes a 65% reduction in the incidence of vertebral fractures and a 54% reduction in non-vertebral fractures. The life-term exposure to teriparatide is limited to 2 years. The

relatively short duration of the treatment is because of safety concerns.

Adverse events with teriparatide include mild hypercalcemia, which has been reported in 1–3% of patients treated (87, 88). The Fischer 344 rat exposed to prolonged, high-dose teriparatide develops osteosarcoma (89, 90). However, it is not known whether teriparatide increases the risk of osteosarcoma in humans (91). Because of this potential risk, teriparatide is contraindicated in children and in persons at risk of developing osteosarcoma including those with active Paget's disease of bone, unexplained elevations in serum levels of alkaline phosphatase, open epiphyses, prior external beam or implant radiation to the skeleton, skeletal metastases or skeletal malignancies or hereditary disorders predisposing to osteosarcoma.

Discontinuation of teriparatide leads to a rapid decline in BMD (92). Consequently, it is prudent to administer an anti-resorptive agent after the completion of the treatment with teriparatide so that gains in BMD are sustained. Patients who are candidates for anabolic therapy with teriparatide are frequently treated previously with anti-resorptive agents and those with significant inhibitory activity on bone turnover temper the response to teriparatide on BMD (93, 94, 95). Because of these reasons, it is preferable to administer teriparatide prior to anti-resorptive therapy, although often teriparatide is prescribed following the failure to achieve an optimal therapeutic response with an anti-resorptive agent.

Studies on the simultaneous administration of alendronate and teriparatide or PTH 1–84 have not shown an obvious benefit of combining the two drugs as compared with the administration of either agent alone (95, 96). It is of interest that the simultaneous administration of zoledronic acid and teriparatide did not blunt the effect of teriparatide on lumbar spine BMD at 1 year, and combination therapy resulted in a greater increase in hip BMD than teriparatide alone (97). Concomitant therapy with denosumab and teriparatide for two years resulted in a substantial increase in BMD at the lumbar spine, hip and femoral neck that was greater than the one achieved with either agent alone (98, 99). Biochemical markers revealed that the increased bone turnover observed with teriparatide was suppressed by denosumab, and this effect might be mechanistically relevant to the greater response in BMD. In a pre-planned two-year extension study, it was demonstrated that subjects switching from teriparatide to denosumab continue to have an increase in BMD, whereas subjects switching from denosumab to teriparatide experience a decline in BMD at the radius and

hip. Subjects receiving teriparatide and denosumab for two years continued to gain BMD (100). These observations indicate that it is preferable not to administer teriparatide following potent anti-resorptive therapy, since it may result in a rapid decline in BMD.

Abaloparatide

Abaloparatide is a synthetic agonist of the PTH type I receptor that was recently approved for the treatment of postmenopausal women with osteoporosis at high risk for fracture. Abaloparatide is a synthetic 34 amino acid peptide and an analog of PTHrP 1–34 with which it shares 76% homology. Abaloparatide also shares 41% homology with PTH 1–34. Initial work on the actions of PTHrP demonstrated that when administered intermittently PTHrP has anabolic effects in bone analogous to those observed with PTH. PTHrP causes a dose-dependent increase in biochemical markers of bone formation, such as serum osteocalcin and procollagen 1 aminoterminal propeptide (P1NP) in humans with little effect on biochemical markers of bone resorption (101). Transient exposure of bones to PTHrP *in vitro* causes an increase in collagen and non-collagen protein synthesis as well as an increase in IGF-I levels. An IGF-I neutralizing antibody prevented the stimulatory effect of PTHrP on bone collagen synthesis, suggesting that the stimulatory effect of PTHrP on bone matrix synthesis is mediated at least in part by an enhancement in the local production of IGF-I (64). These effects are similar to those observed with PTH. Although abaloparatide and teriparatide bind to the PTH type I receptor, abaloparatide binds more efficiently to the RG over the RO conformation of the PTH receptor, and this may lead to a more transient effect of PTHrP and favorable anabolic action (102). Clinical studies have demonstrated a lesser effect of abaloparatide than teriparatide on biochemical markers of bone remodeling (103). This may suggest a tempered effect on bone resorption which might prove to be an advantage over teriparatide.

Treatment with abaloparatide increases BMD at the lumbar spine, femoral neck and total hip in a dose-dependent fashion (103, 104). The increase in BMD at the total hip is greater with abaloparatide at 80 µg daily, the recommended dose, than with teriparatide at 20 µg daily. Abaloparatide at a dose of 80 µg daily for an 18-month period was studied for its effects on fracture prevention in postmenopausal women with osteoporosis and compared to the effects of placebo and of open-label teriparatide at a dose of 20 µg daily. At baseline, 24% of patients had at least one vertebral fracture and 48% had at least one

prior non-vertebral fracture. The relative risk reduction of new vertebral fractures was 86% and in non-vertebral fractures was 43% for abaloparatide (104). Although abaloparatide had a greater effect on BMD than teriparatide, the rate reduction in vertebral and non-vertebral fractures was not significantly different. There was a greater reduction in major osteoporotic fractures, defined as fractures of the wrist, upper arm, hip and clinical fractures of the spine, in abaloparatide than in teriparatide-treated subjects. A *post hoc* analysis revealed that the effect of abaloparatide on fracture risk reduction is independent of baseline clinical risk factors or fracture probability estimated by FRAX (105). Participants in the abaloparatide and placebo groups of the trial were eligible to enter an extension trial, at the completion of the 18-month intervention, where they received alendronate 70mg once a week for 24 months starting 1 month following the completion of the parent trial. An interim analysis following 6 months of alendronate treatment revealed an 87% relative risk reduction in morphometric vertebral fractures in the abaloparatide-alendronate-treated population compared to the placebo-alendronate-treated individuals. The initial results indicate a persistent effect of abaloparatide followed by the administration of alendronate (106).

Although abaloparatide is considered an anabolic agent, bone biopsies obtained following a 12- to 18-month administration of abaloparatide at 80µg daily did not reveal an increase in either mineralizing surface or mineral apposition rate so that bone formation was not increased. In the same study, teriparatide at 20µg daily increased mineral apposition rate reflecting increased osteoblast activity (107). The reason for the lack of an effect of abaloparatide on histomorphometric parameters of bone formation is not immediately apparent. Eroded surface was decreased in cancellous bone, but cortical porosity was increased by abaloparatide. The histological appearance of iliac crest bone biopsies from subjects treated with abaloparatide was normal suggesting that the agent is safe from a skeletal point of view. The bone histomorphometric analysis findings in humans are in contrast with those in ovariectomized rats. Treatment of ovariectomized rats with abaloparatide for 12 months increased bone formation on trabecular, endocortical and periosteal surfaces without an increase in osteoclast number or eroded surface. Abaloparatide stimulated periosteal expansion and endocortical bone apposition leading to an increase in cortical bone volume (108). These effects were accompanied by an increase in cortical and trabecular bone mass and strength and improved

cortical geometry in ovariectomized rats treated with abaloparatide (108).

Adverse events with abaloparatide are limited to nausea, tachycardia and hypercalcemia in 3% of subjects. To determine the carcinogenic potential of abaloparatide, Fischer 344 rats were administered daily abaloparatide at 10–50µg/kg subcutaneously. There was a dose-dependent induction of osteosarcomas in rats treated with abaloparatide, and the effect was of a similar magnitude as the one observed with PTH 1–34 (109). It is not known whether or not abaloparatide causes osteosarcoma in humans, but its use is not recommended in patients at increased risk of osteosarcoma, as described for teriparatide. Because of the potential risk of osteosarcoma, the recommended cumulative use of abaloparatide, like teriparatide, is limited to 2 years during an individual's lifetime.

A transdermal formulation of abaloparatide to be administered via a microneedle patch is under development (110).

Romosozumab

Genetic disorders characterized by gain- and loss-of-function mutations of Wnt co-receptors and the *SOST* gene have demonstrated that Wnt signaling is enhanced when the antagonist is downregulated or its association with Wnt co-receptors is decreased. These observations formed the foundation for the development of neutralizing anti-dickkopf1 and anti-sclerostin antibodies, an approach to enhance Wnt signaling (111, 112). The latter were developed further for clinical applications. Romosozumab, a monoclonal humanized antibody to sclerostin, has been evaluated for its efficacy, but is not yet approved by regulatory agencies for the treatment of osteoporosis (113, 114). In accordance with the enhancement of bone formation and suppression of bone resorption by Wnt signaling, the administration of romosozumab causes a rapid increase in P1NP followed by a sustained decrease in carboxy terminal collagen crosslinks (CTX). The administration of romosozumab at a dose of 210mg once a month to postmenopausal women with low BMD results in an increase in BMD at vertebral sites and at the hip one year after the initiation of treatment. The increase in BMD is substantially greater than that achieved with either alendronate (70mg weekly) or teriparatide (20µg daily) (115). Analysis of the lumbar spine and hip by quantitative computed tomography (QCT) of subjects treated with romosozumab demonstrated an increase in trabecular and cortical volumetric BMD at vertebral sites

and an increase in trabecular volumetric BMD at the hip (116). Finite element analysis revealed greater increases in vertebral and hip strength in romosozumab-treated than in teriparatide-treated subjects (117). The positive effects of romosozumab on bone structure were attributed to a contribution of both cortical and trabecular bone compartments at the spine and hip. Romosozumab has a greater effect on areal and volumetric BMD by QCT at the hip than teriparatide in subjects previously treated with bisphosphonates for ≥ 3 years (118). Interestingly, there was loss of cortical volumetric hip BMD in teriparatide-, but not in romosozumab-treated subjects and this correlated with a greater increase in hip strength by romosozumab as estimated by Finite element analysis. The differences between the two drugs may be related to the dual anabolic and anti-resorptive action of romosozumab in relationship to an exclusive anabolic effect of teriparatide.

Two phase 3 clinical trials assessed the anti-fracture efficacy of romosozumab. One trial compared romosozumab 210 mg subcutaneously monthly to placebo for 12 months, with both arms followed by open-label denosumab 60 mg every 6 months for 12 months. The primary endpoint was incident vertebral fractures at 12 and 24 months in women with postmenopausal osteoporosis as defined by a *T*-score of -2.5 to -3.5 at the total hip or femoral neck. Following the initial 12-month period, romosozumab decreased the incidence of new vertebral fractures and clinical fractures by 73% and 36%, respectively (119). However, romosozumab did not reduce incident non-vertebral fractures significantly. After 24 months, 12 months after the transition to denosumab, subjects treated with romosozumab-denosumab had a 75% reduction in the incidence of new vertebral fractures and a non-significant reduction in non-vertebral fractures (119). Romosozumab caused a significant and substantial increase in BMD at 12 months at the lumbar spine, hip and femoral neck.

In a second pivotal trial, romosozumab 210 mg monthly administered subcutaneously was compared to alendronate 70 mg weekly for 12 months, and both arms were followed by open-label alendronate 70 mg weekly for 12 months in postmenopausal women with osteoporosis and fractures. Over the 24-month period, there was a 48% reduction in incident vertebral and a 19% reduction in non-vertebral fractures in subjects treated with romosozumab-alendronate than in the alendronate-alendronate-treated ones (120). The subjects who received romosozumab had greater gains in BMD at the lumbar spine and total hip. There was an early rise in the bone formation marker P1NP in the romosozumab group in

both trials followed by a return to baseline at 3 months and a suppression of the bone resorption marker CTX levels within the first month, and these remained suppressed during the 12 months of romosozumab administration.

Adverse events with romosozumab included hypersensitivity and development of anti-romosozumab antibodies although these did not seem to affect the efficacy of the agent (119, 120). Rare occurrences of osteonecrosis of the jaw, and a small number of atypical femoral fractures were observed in romosozumab-treated patients. Although no vascular events were noted when romosozumab was compared to placebo, there was a higher incidence of serious cardiovascular events in the trial comparing romosozumab to alendronate. In the first 12 months, there was a 2.5% incidence of cardiovascular events in romosozumab-treated subjects and 1.9% in the alendronate arm. Moreover, there was a 2.65-fold increase in the incidence of cerebrovascular events in romosozumab-treated subjects. A possible mechanism underlying these events is a role for sclerostin in vascular remodeling and homeostasis. It is not probable that alendronate had a vascular protective effect since in placebo-controlled trials alendronate was not shown to decrease vascular events (121). Although the neutralization of sclerostin continues to be a promising new approach in the management of osteoporosis and the overall number of vascular events found in the trial are small, the vascular signal for romosozumab is a source of concern.

Additional concerns regarding the enhancement of Wnt signaling is its tumorigenic potential (122, 123). Somatic mutations of the Wnt signaling pathway leading to the stabilization of β -catenin are associated with various malignancies. However, the risk of malignancy is minimized by the relatively specific expression of sclerostin by the osteocyte and the short duration of therapy in the skeleton. The Wnt antagonist WIF1 is epigenetically silenced in 75% of human osteosarcomas, and its inactivation in the mouse predisposes to an early appearance of radiation-induced osteosarcoma (124). However, there is no evidence for a predisposition to malignancies in patients with high bone mass syndrome, sclerosteosis or van Buchem disease suggesting that the absence of sclerostin or of its activity does not lead to an increased risk of malignancy. The carcinogenic potential of romosozumab has been assessed in rats treated with romosozumab at 3 mg/kg, 10 mg/kg and 50 mg/kg weekly. There was no neoplastic change that could be attributed to romosozumab in rats for up to 98 weeks of treatment, and the overall carcinogenic potential of romosozumab is considered low (125).

Conclusions

Advances in our understanding of cellular events and signals contributing to osteoblast differentiation and function coupled with genetic evidence for a role of these signals in human disorders have formed the foundation for new therapies for osteoporosis. At the center of the discoveries has been the demonstration of a fundamental role of Wnt signaling and IGF-I in osteoblast differentiation and function. Preclinical and clinical studies demonstrating that IGF-I expression can be enhanced by PTH and PTHrP and that Wnt signaling can be enhanced by targeting the Wnt antagonist sclerostin have been instrumental in the development of practical ways to achieve an anabolic response in bone. Currently approved anabolic agents for the treatment of osteoporosis include teriparatide and abaloparatide. There is hope for the future approval of additional agents, such as romosozumab, although the potential for vascular complications is a source of concern.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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