Efficient therapies are available for the treatment of osteoporosis, however, there are still unmet needs. Anti-resorptive therapies only increase bone mineral density to a certain extent and reduce the risk of non-vertebral fractures by 20%, only one anabolic option is available in most parts of the world –the effect of which levels off over time, and the evidence for combination therapy targeting both resorption and formation is limited. In addition, identification and treatment of patients with high and imminent fracture risk following a recent fracture and long-term adherence to treatment are 2 other very prominent challenges to the management of osteoporosis. The current review will focus on emerging osteoporosis treatments and optimized use of the existing treatments that may help overcome the currently unmet needs in the management of osteoporosis.

Key Words: Abaloparatide · Fracture · Osteoporosis · Romozosumab · Teriparatide

INTRODUCTION

Osteoporosis is a disease characterized by reduced bone mass, deteriorated bone microarchitecture, and fragility fractures [1] and affects more than 200 million patients worldwide.[2] Osteoporotic fractures are associated with morbidity, reduced quality of life, and increased mortality in the case of hip and spine fractures.[3,4] Bone is remodeled throughout life by a process of resorption of old bone by osteoclasts followed by new bone formation by osteoblasts.[5] Current available osteoporosis treatments are either anti-resorptive (inhibiting the osteoclasts) or bone-forming (stimulating the osteoblasts).[6] The anti-resorptive treatments are bisphosphonates, receptor activator of nuclear factor-κB ligand (RANKL) antibody, and selective estrogen receptor modulator (SERM) that either cause osteoclast apoptosis (bisphosphonates) or inhibit osteoclast recruitment (RANKL-antibodies and SERM). Teriparatide (parathyroid hormone [PTH] 1-34) and abaloparatide are bone-forming treatments of which abaloparatide currently is only available in the United States (US).[6]

The current treatments have one important feature in common; bone resorption and formation remain coupled.[7] This is both from a pharmacological and clinical point of view not optimal and results in unmet needs. First, anti-resorptive treatments can only increase bone mineral density (BMD) to a certain extent as the decrease in osteoclast number and release of substances from the bone ma-
trix subsequently impairs the recruitment of osteoblasts and de novo synthesis of new bone by the osteoblasts. Therefore, if the patient initially had very low bone mass, anti-resorptive treatments will not be able to improve BMD enough to optimally prevent future fractures. In addition, if the patient also had deteriorated bone architecture this will be improved, but not restored. Second, teriparatide stimulates osteoblasts and subsequently osteoclasts which limits the effect and some patients with very low bone mass or suboptimal response to teriparatide are left with very low BMD after treatment. Third, only few studies have examined if the coupling of bone resorption and formation can be overcome by combining the therapies and the unmet needs thereby may be improved. The current review will focus on emerging osteoporosis treatments and optimized use of the existing treatments that may help overcome the currently unmet needs in the treatment of osteoporosis.

SCLEROSTIN INHIBITION

The most important pathway for stimulation of bone formation by the osteoblasts is the canonical wnt-pathway. Here, lipoprotein related peptide (LRP) 5 and -6 binds to the frizzled receptor and activates the pathway and thereby gene transcription and bone formation.[8] The activity of both osteoclasts and osteoblasts are controlled by the osteocytes. The osteocytes are terminally differentiated osteoblasts that are imbedded within bone matrix. The osteocytes control bone formation by producing sclerostin that prevents the binding of LRPS and-6 to the frizzled receptor and thereby inhibits the wnt pathway and bone formation.[9]

Romosozumab is a humanized antibody against sclerostin and is administrated as monthly subcutaneous injections.[10] The effect of romosozumab on bone turn-over and BMD has been investigated in 419 postmenopausal women in a phase II trial. The women were randomized to treatment for 12 months with one of five different doses of romosozumab either monthly (70 mg, 140 mg, 210 mg) or 3-monthly (140 mg, 210 mg), alendronate 70 mg weekly, teriparatide 20 μg daily, or placebo.[11] Treatment with romosozumab 210 mg monthly increased serum procollagen type I N-terminal propeptide (s-PINP), a marker of bone formation, by 91% after 1 month but the increase leveled off over the following months and at the end of the treatment period s-PINP was 20% below baseline level. In addition, the bone resorption marker, C-terminal telopeptide of type 1 collagen decreased by 41% one week after administration of the first dose of romosozumab and then slowly returned towards baseline but remained 26% below baseline at 12 months. This study therefore suggested that romosozumab not only stimulates formation but also inhibits resorption. The fact that the effect on bone formation seemed to be temporary and that markers of bone formation were decreased below baseline level after 12 months of continued treatment is somewhat surprising but it has been suggested to be caused by depletion of osteoblast progenitors or a compensatory increase in other inhibitors of bone formation such as dickkopf.[12] The suppression of bone resorption was also initially a surprise, but it has now established that sclerostin in addition to inhibiting the wnt pathway and bone formation also stimulates the release of RANKL from the osteocytes. Therefore the suppression of bone resorption seen with romosozumab is most likely caused by a reduction in the osteocyte production of RANKL due to the lack of stimulation of its production by sclerostin.[13] Finally, romosozumab 210 mg monthly increased lumbar spine BMD 11.3% which was significantly more than teriparatide, alendronate, and placebo that increased lumbar spine BMD by 7.1%, 4.1%, and 0.1% respectively. A similar pattern was seen at the total hip where BMD changed by 4.1%, 1.3%, 1.9%, and -0.7% in women treated with romosozumab, teriparatide, alendronate, or placebo, respectively.[11]

Quantitative computed tomography (QCT) was performed in a subset of participants receiving placebo, teriparatide, or romosozumab.[14] Trabecular volumetric BMD (vBMD) increased similarly with romosozumab and teriparatide at the spine, however, at the hip trabecular vBMD increased 10.8% with romosozumab compared with 4.2% with teriparatide. Finally, cortical vBMD at the total hip increased with romosozumab (+1.1%) but decreased with teriparatide (-0.9%). Finite element analyses revealed that romosozumab increased vertebral and femoral neck strength more than teriparatide or placebo. At the vertebrae the increase was +27.3% in women treated with romosozumab compared to +18.5% and -3.9% in women treated with teriparatide and placebo, respectively. At the femoral neck the pattern was similar, although the changes were smaller;
+3.6%, -0.7%, and -0.1% in women treated with romosozumab, teriparatide and placebo, respectively. This shows that romosozumab increases BMD at both cortical and trabecular sites which distinguishes it from teriparatide that mainly increases BMD at trabecular sites.[15] An extension of the study lead to further increase in BMD (lumbar spine 15.7%, total hip 6.0%) in women treated with romosozumab 210 mg monthly for another 12 months.[16] After 2 years, the participants we re-randomized to placebo or denosumab 60 mg/6 month. Participants treated with denosumab during the third year had cumulative increases of 19.4% and 7.1% in BMD at the spine and total hip after 3 years, respectively. Women treated with placebo during the third year, lost bone and BMD returned towards pre-treatment levels.

The anti-fracture efficacy of romosozumab in women with osteoporosis was demonstrated in 2 phase 3 trials. In the FRActure study in postmenopausal woMen with ostEoporosis (FRAME) study 7,180 postmenopausal women with osteoporosis were randomized to romosozumab 210 mg monthly or placebo for 12 months followed by an open label extension during which all women received denosumab 60 mg every 6 months for 12 months.[17] Romosozumab increased BMD at the spine by 13.3% and at the total hip by 6.8% after 12 months compared to no changes in BMD at both regions in women treated with placebo. By 24 months BMD at the spine had increased by 17.6% and 5.0% in the romosozumab+denosumab and placebo+denosumab groups, respectively and at the total hip by 8.8% and 2.9%, respectively demonstrating that the absolute difference in BMD between the 2 groups was maintained during the extension.[17] During the first 12 months, romosozumab reduced the risk of vertebral fractures by 73%, the prevalence being 0.5% in the women treated with romosozumab compared to 1.8% in women treated with placebo. The risk of clinical fractures was reduced by 36%. The occurrence of non-vertebral fractures was non-significantly reduced by 25%. A significant interaction between geographical region and the effect of romosozumab on non-vertebral fractures was seen; there was no effect among women from Latin America but a 42% reduction in non-vertebral fractures among women from the rest of the world. The unexpected low rate of non-vertebral fractures among women from Latin America is in accordance with a post hoc estimation of fracture risk using fracture-risk assess-
Antibodies against romosozumab was found in 20% of the women treated with romosozumab in the clinical studies. A few percent were neutralizing in vitro but did not affect pharmacodynamics, pharmacokinetics, or the clinical response.[11,17] The clinical relevance of these antibodies in relation to long-term treatment is currently not known.

The adverse events in the FRAME,[17] ARCH,[18] and STRUTURE[19] studies were generally balanced between the treatment groups. There was a numeric imbalance in serious adverse events affecting the cardiovascular system during the first 12 months in the ARCH study; 2.5% of the women treated with romosozumab compared to 1.9% of the women treated with alendronate. The occurrences of cardiovascular serious adverse events were 6.5% and 6.1% after 24 months in women treated with romosozumab-alendronate and alendronate-alendronate, respectively.[18] Further adjudication of these events is ongoing. The incidences of death, adjudicated cardiovascular and serious cardiovascular events in the FRAME study were well balanced between the women treated with romosozumab and placebo.[17] Preclinical studies in rats have not demonstrated any increased risk of osteosarcoma with romosozumab, as is the case for long-term treatment with teriparatide and abaloparatide.[20]

Romosozumab is currently being evaluated by US Food and Drug Administration and the European Medicines Agency.

**ABALOPARATIDE**

Both PTH and PTH related peptide (PTHrP) exert their effects on bone by activating the PTH type 1 receptor (PTH1R).[21] The effect of activation depends on whether the activation is sustained or intermittent. Sustained activation predominantly increases bone resorption whereas intermittent activation predominantly increases bone formation.[22] Treatment with teriparatide (PTH 1-34) initially increases bone formation but subsequently also resorption, why the net bone forming response levels off over time, [12,23] despite continuing bone formation.[24] The PTH1R has 2 different high-affinity conformations termed R0 and RG and responses of prolonged duration are observed with ligands that bind efficiently to the R0 state whereas short duration responses are seen with ligands that bind more selectively to the RG state.[25,26] Abaloparatide is a PTHrP (1-34) analogue. Early studies showed that it induces bone formation without stimulating resorption and causing hypercalcemia[27] and it has been suggested that this effect may be owing to a lower affinity for the R0 conformation and thus a shorter activation period. The affinity to the RG conformation was shown to be similar between abaloparatide and teriparatide.[28]

In a phase II trial abaloparatide 20 μg, 40 μg, or 80 μg administered daily as subcutaneous injections was compared to teriparatide 20 μg daily or placebo for 24 weeks. Abaloparatide 80 μg increased lumbar spine BMD by 6.7% which was significantly more than placebo (1.6%) but not different from teriparatide (5.5%).[29] At the total hip abaloparatide 80 μg increased BMD by 2.6% which was significantly more than placebo (0.4%) and teriparatide (0.5%). The phase III trial enrolled 2,463 postmenopausal women who were randomized to abaloparatide 80 μg daily, teriparatide 20 μg daily or placebo for 18 months.[30] The teriparatide treatment was unblinded. Treatment with abaloparatide and teriparatide increased markers of bone formation and resorption, but the increases were less for abaloparatide throughout the study with the exception of the changes seen after 1 months. The differences in BMD at the lumbar spine and hip between women treated with abaloparatide and women treated with placebo were 8.7% and 3.5%, respectively, after 18 months. Compared with the women treated with teriparatide, BMD at the lumbar spine increased more rapidly, but without difference in BMD after 18 months. BMD at the hip sites increased approximated 0.5% more with abaloparatide than with teriparatide. Abaloparatide and teriparatide significantly reduced the risk of vertebral fractures by 80% to 85% without difference between the treatment groups. The risk of major osteoporotic fractures (upper arm, forearm including wrist, hip, shoulder, and spine) was reduced by 67% and 30% with abaloparatide and teriparatide compared with placebo, respectively. The fracture risk reduction seen with abaloparatide was significantly different from placebo and teriparatide, whereas the effect of teriparatide was not significantly different from placebo. The study was continued for an additional 24 months where women who received abaloparatide or placebo in the original study were continued on alendronate. An interim analysis performed after 6 months showed that the fracture risk reduction seen during the original study was maintained during these first 6 months of follow-up.[31] The occurrence of adverse events
was not compared between treatment groups with the exception of hypercalcemia. Hypercalcemia was more common in patients treated with abaloparatide compared to women treated with placebo but less common than among women treated with teriparatide. Dizziness, nausea and adverse events leading to discontinuation were numerically more common among women treated with abaloparatide compared to women treated with placebo or teriparatide.[30]

Abaloparatide is currently approved for the treatment of osteoporosis in the US only.

**COMBINATION TREATMENT**

Several treatments are available for osteoporosis and therefore an even larger number of combinations of therapies are possible. Additive or synergistic effects of different combinations have been investigated, but initially with disappointing results. The PTH and alendronate (PaTH) trial demonstrated that BMD in patients treated with a combination of teriparatide and alendronate did not increase more than with either treatment alone. In fact, alendronate appeared to impair the anabolic effect of teriparatide. [32,33] Similar results were found in a study investigating the combination of risedronate and teriparatide. [34] In accordance with these findings a rodent study showed that chronic exposure to a bisphosphonate blunted the response to teriparatide. [35] It was suggested that this was caused by the osteoblasts being expose to bisphosphonates while in the circulation. The clinical relevance of this was investigated in a study demonstrating that a single infusion of zoledronic acid, that is rapidly cleared from the circulation in combination with daily teriparatide for one year increased lumbar spine and total hip BMD by 7.5% and 2.3%, respectively, whereas zoledronic acid alone resulted in increases of 4.4% and 2.2%, respectively and teriparatide alone provided increases of 7.0% and 1.1% respectively.[36]

The DATA trial compared the effect of the combination of teriparatide 20 μg daily and denosumab 60 mg every 6 months with either treatment alone.[37] After 24 months, lumbar spine BMD had increased by 12.9%, 9.5%, and 8.3% and total hip BMD increased by 6.3%, 2.0%, and 3.2% in the combination, teriparatide, and denosumab groups, respectively. The increases were significantly higher with the combined treatments than with either treatment alone. Taken together the studies suggest that a combination of teriparatide and zoledronic acid provides “the best of both worlds” the significant increase in hip BMD seen with zoledronic acid combined with the significant increase in spine BMD seen with teriparatide, whereas the combination of denosumab and teriparatide appears to have additive effects. None of the studies, however, were powered to allow for conclusions regarding anti fracture efficacy.

**CAN OPTIMAL USE OF AVAILABLE AND EMERGING TREATMENTS OVERCOME THE CURRENTLY UNMET NEEDS?**

The currently unmet needs in the treatment and long-term management of osteoporosis are the treatment of severe osteoporosis, identification and treatment of the imminent fracture risk following a recent fracture and long-term adherence to treatment.

Patients with severe osteoporosis have very low bone mass or deteriorated bone architecture or a combination of the 2 conditions and often previous fractures. The goal of any osteoporosis treatment is to minimize the risk of future fractures and although all the approved treatments reduce the risk of fractures, the future risk of fracture may still be high despite treatment with anti-resorptives in some patients with severe osteoporosis. Two studies published in 2017 for the first time demonstrated that bone forming treatment in patients with severe osteoporosis is superior to treatment with anti-resorptives. The first study was the above-mentioned ARCH study comparing romosozumab with alendronate in treatment-naïve women and demonstrated that romosozumab reduced the risk of vertebral, non-vertebral and clinical fractures more than alendronate.[18] The other study is the VERtebral Fracture Treatment Comparisons in Osteoporotic Women (VERO) study. The VERO study compared the effects of teriparatide and risedronate on fracture risk on patients with severe osteoporosis of whom approximately 70% had previously been treated with anti-resorptives, most commonly bisphosphonates. The study demonstrated that teriparatide over a 2-year treatment period prevented vertebral and clinical fractures more strongly than risedronate.[38] These 2 studies investigating 2 different bone forming treatments against 2 different bisphosphonates suggest that treatment of pa-
tients with severe osteoporosis with a bone forming treatment may help overcome the unmet need in the treatment of severe osteoporosis.

Identification of patients with a high imminent risk of fracture relies predominantly on identification of patients with a recent fracture as it has been demonstrated that a recent fracture is associated with a high risk of a second fracture within the first years after the previous fracture. [39-41] Although the fracture patients usually present themselves at the emergency rooms or fracture clinics it has proven very difficult to organize a post fracture investigation for osteoporosis. There is strong evidence that the best way is to organize fracture liaison services,[42,43] however, the implementation of these services is only picking up very slowly around the world. Identification of the patients is a critical starting point but is not going to prevent the next fracture without initiation of treatment. The next question is therefore if we have treatments that very quickly reduce the risk of a new fracture. All the available treatments reduce the risk of new vertebral fractures very rapidly but it seems to take longer time to prevent non-vertebral fractures. The ARCH and the VERO studies demonstrated that bone forming treatments not only prevent fractures more strongly than anti-resorptives but also do so very rapidly. If there is room for combination therapy, for example teriparatide in combination with denosumab or zoledronic acid in the context of rapid reduction of a high imminent fracture risk remains to be demonstrated.

Improvement of the adherence to the treatment of osteoporosis is probably not going to come from new treatments alone. There are multiple obstacles to consider in relation to adherence to treatment, but confidence of the patient and the physician that the treatment is going to improve the situation for the patient by reducing the risk of future fractures seems to be crucial. Currently the treatment strategy for the individual patient is very much driven by strict reimbursement criteria that in most cases leave very little room for a personalized approach to the long-term management of osteoporosis. Physicians know that one drug is not the optimal choice for all patients and the patients know that as well. This is a major challenge to the confidence in the treatment plan of both the physician and the patient. With the existing very strong anti-resorptives with their different modes of administration and the well-known and emerging bone forming treatments we have a very strong platform for considering a more personalized approach to osteoporosis management where osteoporosis severity, the age and comorbidities of the patient and perhaps even patient preference could be taken into account both when deciding on the initial treatment and the long-term management plan.

CONCLUSIONS

There are still a number of unmet needs in the management of osteoporosis, including treatment of severe osteoporosis, treatment of imminent fracture risk and long-term adherence to the treatment. The emerging bone forming treatments, abaloparatide and romosozumab may help address these unmet needs. Two clinical trials have demonstrated superiority of bone forming treatments over anti-resorptives in patients with severe osteoporosis suggesting that a more personalized approach to the management of osteoporosis with access to the use of bone forming treatment in patients with severe osteoporosis may help address the currently unmet needs.

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