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Review article

Romosozumab for the treatment of osteoporosis

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ABSTRACT

Romosozumab, a specific inhibitor of sclerostin, is a unique approach to therapy for postmenopausal osteoporosis and related disorders. The elucidation of sclerostin deficiency as the molecular defect of syndromes of high bone mass with normal quality, and the pivotal role of sclerostin as a mediator of osteoblastic activity and bone formation, provided the platform for the evaluation of inhibitors of sclerostin to activate bone formation. An extensive preclinical program and 2 large fracture endpoint trials with romosozumab, a sclerostin-binding antibody, have been completed. This review will highlight the results of those studies and describe the current status of romosozumab as a potential therapy for osteoporosis.

1. Introduction

Osteoporosis is a disorder of increased fracture risk characterized by low bone mass and microarchitectural deterioration of the trabecular and cortical skeletal envelopes [1]. To restore the damaged and disconnected trabecular architecture will require strategies to stimulate new bone formation. The most commonly used treatments for osteoporosis, however, are antiremodeling drugs that decrease bone formation as well as bone resorption, precluding their ability to restore skeletal architecture or to cure osteoporosis. Parathyroid hormone analogues do increase bone formation but also activate bone resorption, limiting the anabolic or bone forming response.

The discovery of sclerostin as a key inhibitor of bone formation was made by groups evaluating patients with 2 rare autosomal recessive syndromes associated with high bone mass [2]. Sclerostiosis is a disorder characterized by very high bone mass due to inactivating mutations of the *SOST* gene on chromosome 17q21, the gene that codes for sclerostin. Excess bone growth during childhood results in frontal bossing, cranial and basilar stenosis, cranial nerve entrapment, and mandibular hypertrophy. Patients with Van Buchem disease, a somewhat less severe disorder, have a separate noncoding deletion of a gene required for normal transcription of the *SOST* gene. Heterozygous cases of both disorders have moderately high bone mass without other phenotypic or clinical features. Sclerostin is most highly expressed in osteocytes. Binding of sclerostin to low-density lipoprotein receptor-related proteins 5 and 6 (LRP5 and LRP6) prevents activation of canonical Wnt signaling in bone, resulting in decreased bone formation. These findings stimulated interest in exploring the potential of antisclerostin therapy as a strategy to increase bone formation and to restore skeletal architecture in patients with osteoporosis.

2. Preclinical studies

Genetic deficiency of sclerostin in rodents is associated with high bone mass, increased bone formation in both trabecular and cortical bone, normal bone quality and increased bone strength, recapitulating the high bone mass syndrome of sclerostiosis [3]. The mineralization of the bone matrix in sclerostin-deficient animals is normal or reduced, accounting for the lack of bone brittleness seen in patients with osteopetrosis due to osteoclast deficiency or dysfunction.

Inhibition of sclerostin by monoclonal antibodies in rats and monkeys resulted robust anabolic responses on trabecular, endocortical, intracortical and periosteal bone surfaces [4]. In aged, ovariectomized rats, antisclerostin therapy increased trabecular and cortical bone thickness and reduced cortical porosity. After 5 weeks of treatment, the skeletal abnormalities induced by ovariectomy were corrected, and bone mass and bone strength exceeded

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the sham-operated control animals. In gonad-intact female Cynomolgus monkeys, treatment with a humanized antisclerostin antibody for 2 months transiently increased markers of bone formation and induced anabolic responses on all skeletal surfaces. Bone mineral density (BMD) in the lumbar spine (LS), femoral neck, proximal tibia, and distal radius increased significantly, correlated with a substantial increase in LS and femoral diaphyseal bone strength occurred [5].

The skeletal response to antisclerostin therapy in old mice was similar to that observed in younger animals, important since osteoporosis is primarily a disorder of older men and women [4]. The anabolic response to antisclerostin therapy was restored upon retreatment following a short treatment free interval. Following antisclerostin therapy with an inhibitor of rank ligand, a potent antiremodeling agent, preserved or amplified the gain in bone mass achieved with the antisclerostin therapy. The skeletal response to antisclerostin therapy was not blunted in animals pre-treated with bisphosphonates.

3. Clinical studies

Single and multiple does phase 1 studies (ClinicalTrials.gov Identifiers: NCT01059435 and NCT01825785) with romosozumab (originally known as AMG 785/CDP7851) in healthy men and women demonstrated a brisk increase in biochemical indices of bone formation accompanied by a decrease in markers of bone resorption [6,7]. These divergent effects of romosozumab on bone formation and bone resorption are very distinct from the reductions in both resorption and formation by antiremodeling agents and the increases in both components of the remodeling cycle by teriparatide and abaloparatide [8]. BMD values, measured by dual-energy X-ray absorptiometry in the LS and total hip (TH), increased by 5.2% and 1.1%, respectively, when measured 85 days after the single-dose. Similar results were observed in the ascending multiple dose study [6]. Romosozumab was administered by subcutaneous (SQ) injections of 1 or 2 mg/kg every 2 weeks (Q2W) or 2 or 3 mg/kg every 4 weeks for 3 months. The biochemical marker responses to the injections were maintained during the first 2 months of dosing but were somewhat blunted following the final dose compared to the initial dose. Pharmacokinetics of romosozumab were similar in men and women.

In a placebo-controlled phase 1b study (ClinicalTrials.gov Identifier: NCT01825785), the effects of romosozumab on volumetric BMD (vBMD) and bone structure were assessed by high resolution quantitative computed tomography (HR-QCT) scans of the LS in 48 subjects (32 women, 16 men) with low bone mass who received active treatment with doses ranging from 1–3 mg/kg Q2W for 3 months, followed by no therapy for an additional 3 months [9]. At 3 months, HR-QCT assessments of trabecular BMD and stiffness increased by 9.5% and 26.9%, respectively, and were significantly greater than the changes in the placebo group (−3.0% and −2.7%, respectively). These improvements were maintained during the 3-month off-treatment follow-up period.

An international phase 2 dose-ranging study (ClinicalTrials.gov Identifier: NCT00896532) assessed responses to romosozumab treatment in 419 postmenopausal women with low bone mass [10]. The patients, ages 55–85, were randomly assigned to receive monthly SQ doses of romosozumab (70, 140, or 210 mg) or doses of 140 mg or 210 mg every 3 months, or placebo injections [10]. Other patients were randomly assigned to receive open label alendronate 70 mg once weekly (QW) or teriparatide 20 μg SQ daily. As seen in the phase 1 studies, romosozumab therapy resulted in rapid and substantial increases in serum bone formation markers (serum P1NP and alkaline phosphatase [AP]) but a decrease in the bone resorption marker serum β-CTX. Serum P1NP values peaked at 4 weeks, returned to baseline between 3 and 6 months and were below baseline for the remainder of the treatment interval. All doses of romosozumab increased BMD at both the spine and proximal femur. The largest increases at 12 months were observed with the romosozumab 210 mg once monthly (QM), the dose chosen for phase 3 studies. BMD in the LS and TH had increased by 11.3% and 4.1%, respectively, and these gains were significantly greater than with teriparatide or alendronate. During the second year of the study, markers of bone formation and resorption remained below baseline in women who continued romosozumab (McClung MR et al. J Bone Miner Res, 2014;29[Supp. 1] oral presentation 1152). Consistent with the lack of anabolic effect demonstrated by bone markers during the second year of romosozumab therapy, smaller increases in BMD occurred than had occurred during the first year. After 2 years, romosozumab therapy was discontinued. In patients randomly switched to placebo for 12 months, BMD values in the spine and hip returned to or toward baseline values. Serum β-CTX values rose above baseline before returning toward pretreatment values while markers of bone formation gradually returned to baseline values. In patients who were switched to denosumab 60 mg SQ every 6 months (Q6M), BMD increased in a fashion similar to the increases during the second year of romosozumab therapy.

In a similar phase 2 study, 252 postmenopausal Japanese women with osteoporosis received romosozumab in doses of 70, 140, and 210 mg QM or placebo (ClinicalTrials.gov Identifier: NCT01101061) [11]. All doses resulted in significant gains in BMD at the LS and proximal femur compared to baseline and to placebo. At 12 months with the 210 mg QM dose, the average gains were 16.9% and 4.7% in the LS and TH, respectively. Changes in serum markers of bone turnover were similar to those observed in the international phase 2 study.

In a subset of patients from the International phase 2 study, areal and vBMD of the LS and TH was assessed by quantitative computed tomography (QCT) in patients who received placebo (n = 27), teriparatide 20 μg daily (n = 31) or romosozumab 210 mg QM (n = 24) for 12 months [12] (Table 1). DXA BMD increased 12.3% in the LS and 3.9% in TH with romosozumab compared to 6.9% and 0.8%, respectively, with teriparatide. Gains in both vBMD and estimated strength, assessed by finite element analysis, of the hip and spine were significantly greater with romosozumab than with teriparatide [13]. The skeletal effects of romosozumab have also been compared with teriparatide in a randomized but open label phase 3 study (ClinicalTrials.gov Identifier: NCT01796301) in 436 postmenopausal women with osteoporosis who had previously taken bisphosphonates for at least three years (mean duration what is 5.6 years) [14]. After 12 months of therapy, TH areal BMD by DXA increased by 2.6% (95% confidence interval [CI], 2.2–3.0) in the

Table 1
Comparison of changes in areal and volumetric BMD and in estimated bone strength over 12 months of therapy with romosozumab and teriparatide.

	Reference	Romosozumab 210 mg QM	Teriparatide 20 μg/d
Areal BMD (DXA)			
Lumbar spine	[12]	12.3%[a]	6.9%
Total hip		3.9%[a]	0.8%
Integral volumetric BMD (QCT)			
Lumbar spine	[12]	17.7%[a]	12.9%
Total hip		4.1%[a]	1.2%
Estimated bone strength (FEA by QCT)			
Lumbar spine	[13]	27.3%[a]	18.5%
Total hip		3.6%[a]	−0.7%

BMD, bone mineral density; QM, once monthly; DXA, dual-energy X-ray absorptiometry; QCT, quantitative computed tomography; FEA, finite element analysis.
[a] $p \leq 0.05$ vs. teriparatide.

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