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Romosozumab: New anti-osteoporosis agent approved by food and drug administration of the United States

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Romosozumab, an anti-sclerostin monoclonal antibody, is the recently-approved anti-osteoporosis agent by the US Food and Drug Administration since April 2019. It is recommended to treat osteoporosis in postmenopausal women, anyone at high risk fracture and history of failed osteopenic treatment, with monthly dose of 210 mg subcutaneously-injected route to optimize the best benefit. The superior performance of romosozumab is different from other drugs. It increases bone formation while decreases bone resorption. Clinical studies have shown that romosozumab could promote bone mineral density in lumbar spine, total hip, and femoral neck in postmenopausal osteoporosis. Patients with osteoporosis might have invasive dental treatment which probably leads to a complication due to their medication. For that reason, dentists should basically know about this new drug. This article describes mechanism of action, clinical studies, pharmacological properties, and safety of romosozumab. Furthermore, the suggestion for dental consideration of patients with romosozumab is provided.

Keywords: anti-sclerostin, dental treatment, osteoporosis, romosozumab

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Introduction

Osteoporosis is a common silent disorder characterized by low bone mineral density (BMD) and defective micro-architecture which predisposes bone fragility and fracture. [1] There are many risk factors associated with osteoporosis; aging, hormonal change, calcium and vitamin D deficiency, leading to imbalance bone resorption and formation. Its consequences are considered serious conditions including chronic pain, deformities, dysfunction, and increased morbidity and mortality. Postmenopausal women are the most affected population by the osteoporosis while men are found less. Non-pharmacological therapy is individually recommended to every patients in terms of exercise, diet control and avoiding alcohol and smoking. [1, 2] Bisphosphonates are widely prescribed as a medication of choice for osteoporosis treatment with long history of outcome studies. Other medications are selective estrogen receptor modulators: SERM (raloxifene), RANKL inhibitor monoclonal antibody (denosumab), anabolic parathyroid hormone analogues (PTH (1-34) teriparatide, abaloparatide). Most drugs reduce bone resorption but fail to restore bone density and architecture. [1-3]

Bone remodeling is a complex process with an involvement of different cells, proteins and pathways. Ordinarily, bone resorption and formation remains coupled. [4] It is probably explained for the relatively limited effect of drugs on prevention of further fractures. Moreover, understanding of bone remodeling has proven to new drug that conquers the limitation of the existing treatments. Current studies have found BMD gain with romosozumab, a sclerostin inhibitor, which has been recently approved by the US FDA in this April.

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[5] Although it is initially available in some developed countries, it might be prescribed more prevailingly in the near future. This article describes general properties of romosozumab and dental consideration as the basic understanding for general dentists.

Wnt signaling pathway

Wnt is a glycoprotein defined by canonical and non-canonical pathway mediators. It regulates embryogenesis, neurogenesis, and cortical development. Non-canonical pathway is involved in tissue formation during development, stem cell maintenance, and tumor repression. Canonical Wnt signaling in differentiated osteoblasts stabilizes intracellular β-catenin via Wnt ligand binder; the Frizzled co-receptor, lipoprotein-related protein 5 and 6 (LRP5/6) and allows permitting scaffold axin to be the receptor complex. This conducts inhibition of glycogen synthase kinase-3 (GSK-3) which prevents degradation of β-catenin and then nuclear translocation occurs. [6, 7]

As the β-catenin is a nuclear transcriptional regulator, increased β-catenin induces transcription of bone-related genes, for examples; *RUNX 2, OCN (osteocalcin)*. This mechanism thus increases bone mass. (Figure 1A) Furthermore, it increases expression of osteoprotegerin (OPG) that binds to receptor activator of nuclear factor kappa-B ligand (RANKL), causing RANK cannot bind RANKL. Therefore, osteoclastogenesis and bone resorption are reduced. As a result of Wnt- β-catenin pathway activation, it should be primarily beneficial in osteoporosis treatment. [6-9]

Sclerostin

Sclerostin is a glycoprotein secreted by osteocytes, and encoded by *SOST* gene while there is smaller amount of sclerostin produced by chondrocytes. Two rare genetic disorders associated with high level BMD and bone mass; sclerosteosis and van Buchem disease, are the result of *SOST* gene mutation. Although there are some anatomical abnormalities in these individuals, they present low risk fracture because of increased bone mass. [10, 11] Sclerostin antagonizes the canonical Wnt signaling pathway in form of binding to LRP5/6, therefore, Wnt, LRP5/6, and the Frizzled family cannot bind together. [8] The consequence of this action is inhibition of GSK-3, phosphorylation of β-catenin causing subsequent degradation. Finally, bone formation is inactivated. (Figure 1B) In addition, it promotes bone resorption by increasing RANKL. This mechanism highlights an important role of sclerostin inhibition in osteoporsis treatment modality. [7, 8, 12, 13]

Anti-sclerostin monoclonal antibody was introduced in animal models. In ovariectomized rats with estrogen deficiency-induced bone loss, were treated with murine sclerostin neutralizing monoclonal antibody (Scl-AbII). This leaded to elevated bone formation on trabecular, endocortical, intracortical bone surfaces. [14]

A study conducted in gonad-intact cynomolgus monkeys with humanized sclerostin-neutralizing monoclonal antibody showed increased BMD and bone strength. Different types of formation and resorption suggested an uncoupling action of bone formation and resorption. [15] This finding corresponded to another study that this antibody in ovariectomized rats and male cynomolgus monkeys showed increase in bone volume. In term of bone repair, a ratized sclerostin antibody also enhances bone formation during metaphyseal repair in untraumatized rat bone. [16]

One of the most interesting announcements of anti-sclerostin was that romosozumab-aqqg (EVENITY™, Amgen, USA) has been recently granted by the US FDA on 9 April 2019. The following information indicates basic pharmacological profiles and dental consideration in patients taking romosozumab.

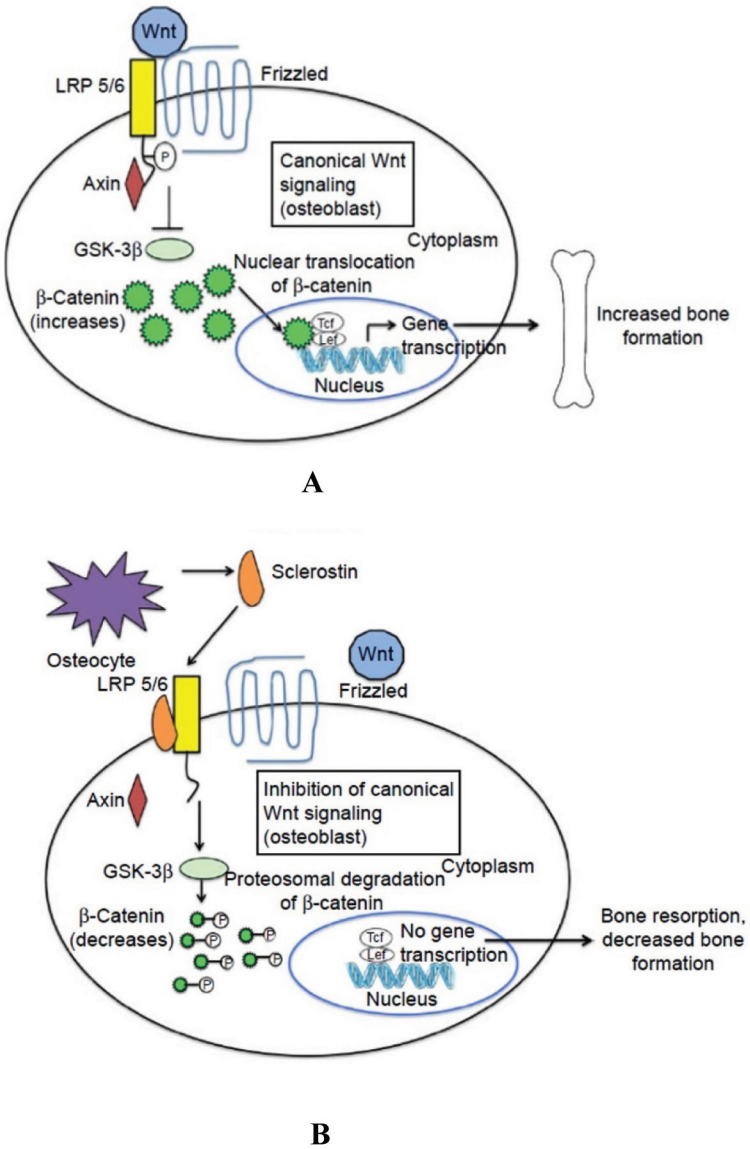

Figure 1 The canonical Wnt signaling pathways and the inhibition role of sclerostin. **(A)** Wnt binds to LRP 5/6 and Frizzled co-receptor. This results in phosphorylation of the cytoplasmic tail of LRP 5/6, which then allows axin to bind the receptor complex. It leads to inhibition of GSK-3β, which functions to target β-catenin for degradation. As a consequence, β-catenin levels increase and are translocated to the nucleus to bind to DNA binding proteins and activate target gene promoters. This action results in osteoblast differentiation, proliferation and increases bone formation. **(B)** When sclerostin binds to LRP 5/6, it prevents Wnt from binding to LRP 5/6 and its co-receptor. Therefore, Wnt signaling is inhibited and results in decreased bone formation and increased bone resorption. Copyright ©2015. Dove Medical Press. Shah AD, Shoback D, Lewiecki EM. Sclerostin inhibition: a novel therapeutic approach in the treatment of osteoporosis. ***Int J Womens Health*** 2015; 7: 565–80

Romosozumab

Romosozumab is a humanized monoclonal antibody against sclerostin. It is indicated in postmenopausal women, anyone at high risk fracture and history of failed osteopenic treatment. [17] Many clinical studies support the advantages and safety of romosozumab though major adverse cardiovascular events are in concerned.

Clinical studies

Phase I, II, III clinical trials of anti-sclerostin therapy were widely studied. This article performs some interesting clinical trials of romosozumab in brief (Table1).

The first-in human phase I single dose study of romosozumab demonstrated increase in BMD at lumbar spine (LS) and total hip (TH). [18] Followed the first trial, the multiple dose study receiving subcutaneous romosozumab at different doses, intervals, and duration, it increased LS bone density. [19] According to both studies, they showed non-linear pharmacokinetics, increased procollagen type 1 N propeptide (P1NP) bone formation marker, and decreased serum collagen type 1 cross-linked C-telopeptide (β-CTX) bone resorption marker. Neutralizing antibodies in some subjects were observed but not disturbed the study procedure and outcome. [18, 19]

Followed the previous trials, a phase II multicenter, international randomized controlled trial showed higher level of BMD with 12-month 210 mg romosozumab compared with placebo, alendronate and teriparatide. Increase in bone formation markers were transitory, noted 1 week after the initial dose was administered and were greatest at month 1. While the levels of serum

β-CTX fell from baseline and remained below the initial values at month 12. [20]

Table 1 Summary of Clinical Trials of Romosozumab

Study name	No. of participants	Intervention	Primary endpoint	Key results	Conclusion
Phase I					
Single-Dose, Placebo-Controlled, Randomized Study of AMG 785, a Sclerostin Monoclonal Antibody [18]	72 healthy people, 45-59 y, with AMG 785 (romosozumab) or placebo (3:1 ratio)	0.1, 0.3, 1, 3, 5, or 10 mg/kg SC , 1 or 5 mg/kg IV of romosozumab and placebo F/U duration; 0.1, 0.3 mg/kg for 29 d 1, 3 mg/kg for 57 d 5, 10 mg/kg for 85 d	Safety and tolerability of treatment (emergent adverse events & clinically significant changes)	- Tolerated and effective bone anabolic agent. - No deaths or study discontinuations - Non-linear PK with dose. - Increased P1NP, BAP and osteocalcin. - Decreased serum β-CTX - Marked increases in BMD at the LS and the TH compared with placebo	AMG 785 was a well-tolerated and effective bone anabolic agent which could benefit from an increase in bone formation such as osteoporosis.

Table 1 Summary of Clinical Trials of Romosozumab (continued)

Study name	No. of participants	Intervention	Primary endpoint	Key results	Conclusion
				- 2 subjects with neutralizing antibodies in - No discernible effect of neutralizing antibodies on PK or PD	
Multiple Doses of Sclerostin Antibody Romosozumab in Healthy Men and Post menopausal Women with Low Bone Mass: A Randomized, Double-Blind, Placebo-Controlled Study [19]	32 postmenopausal women and 16 healthy men, 45-80 y, with low bone mass	Female patients; - 6 doses of 1 or 2 mg/kg Q2W or - 3 doses of 2 or 3 mg/kg Q4W or - Placebo Male patients; - 1 mg/kg Q2W or - 3 mg/kg Q4W or - Placebo Treatment period: 12 w F/U period: 12 w	Safety and tolerability of treatment (emergent adverse events & clinically significant changes)	- Well tolerated with multiple doses of romosozumab - Increased serum PINP - Decreased serum β-CTX - Increased BMD in LS - 2 subjects with serious adverse events, but not considered to be related to study treatment - 2 subjects with neutralizing antibodies without discernable effects on PK, PD, or safety - Balanced adverse event rates between groups without any significant safety findings	Multiple doses of romosozumab were well tolerated, increased bone formation, decreased bone resorption, rapid and marked increases in BMD.

Table 1 Summary of Clinical Trials of Romosozumab (continued)

Study name	No. of participants	Intervention	Primary endpoint	Key results	Conclusion
Phase II					
Romosozumab in Post menopausal Women with Low Bone Mineral Density. [20]	419 postmenopausal women, 55 to 85 y, with low BMD	**Romosozumab group** - 70, 140, or 210 mg SC QM or - 140, or 210 mg SC Q3M **One of two open-label active comparators group** - 70 mg of oral alendronate weekly or - 20 µg of SC teriparatide **Placebo group** - injections either monthly or Q3M Treatment period: 12 m	Percentage change from baseline in BMD at the LS at 12 m	- With 210 mg monthly dose; significant increased BMD at the LS, TH, and FN shown - Decreased BMD with placebo - Increased BMD with alendronate and teriparatide - Transitory increase in bone-formation markers - Sustained decrease in a bone-resorption marker	Romosozumab leaded to an increase in BMD in the spine and hip regions greater than the placebo, alendronate, or teriparatide.
Romosozumab Increases Bone Mineral Density in Post menopausal Japanese Women with Osteoporosis: A phase 2 study [21]	252 women, 55-85 y	**Romosozumab group** - 70, 140, 210 mg SC QM for 12 m **Placebo group** - SC QM for 12 m	Percentage change from baseline in LS BMD at 12 m	- All romosozumab doses significantly increased LS BMD at month 12 compared with placebo - 210 mg regimen achieved the largest gain from baseline in LS, TH, and FN - P1NP increased and β-CTX decreased proportionally to the dose	Romosozumab leaded to significant gain in BMD. Romosozumab 210 mg was the most efficacious dose and was well tolerated.

Table 1 Summary of Clinical Trials of Romosozumab (continued)

Study name	No. of participants	Intervention	Primary endpoint	Key results	Conclusion
				- Vertebral, rib, radius, wrist, foot fractures reported at the different dose - No ONJ or atypical femoral fracture occurred - Anti-romosozumab antibodies developed without discernible effect on efficacy or adverse events	
Phase III					
The Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) [22]	7,180 postmenopausal women, 55-90 y	Romosozumab group; - 210 mg SC monthly for 12 m with daily calcium and vitamin D Placebo group; - SC monthly for 12 m with daily calcium and vitamin D All participants then received SC 60 mg denosumab Q6M for additional 12 m Total treatment period; 24 m	Incidence of vertebral fractures at 12 and 24 m	12-month efficacy - Less incidence of vertebral fracture in the romosozumab group compared to the placebo group - Lower risk of new vertebral fracture compared to the placebo 24-month efficacy - Less developed new vertebral fracture in the originally received romosozumab group compared to the placebo	- Romosozumab lowered risk of vertebral fracture at 12 m and, after the transition to denosumab at 24 m. - The lower risk of clinical fracture at 1 year seen with romosozumab.

Table 1 Summary of Clinical Trials of Romosozumab (continued)

Study name	No. of participants	Intervention	Primary endpoint	Key results	Conclusion
				- Lower risk of new vertebral fracture in the romosozumab group - 2 cases of ONJ developed after 12-m administration - 1 case of atypical femoral fracture observed after 3.5 m of romosozumab administration - Balanced adverse events in the two groups	
Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis, Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH) [23]	4,093 postmenopausal women with osteoporosis and a fragility fracture, 55-90 y		Cumulative incidence of new vertebral fracture at 24 m and the cumulative incidence of clinical fracture (non-vertebral and symptomatic vertebral fracture) at the time of the primary analysis	- Romosozumab followed by alendronate resulted in a lower risk of new vertebral fractures than alendronate alone - The cumulative incidence of clinical fracture in the romosozumab-to-alendronate group was lower compared to the alendronate-to-alendronate group.	Treating with romosozumab for 12 m followed by alendronate resulted in a significant lower risk of fracture than alendronate alone.

Table 1 Summary of Clinical Trials of Romosozumab (continued)

Study name	No. of participants	Intervention	Primary endpoint	Key results	Conclusion
			Along with 1:1 ratio in each group; **Romosozumab group;** - 210 mg SC every month with daily calcium and vitamin D for 12 m **Oral alendronate group;** - 70 mg weekly with daily calcium and vitamin D for 12 m All patients were followed by open-label 70 mg oral alendronate weekly until the time of primary analysis (up to 36 m).	- Overall adverse events were balanced between the two groups - During 1st year, adjudicated serious cardiovascular events observed more often with romosozumab - During the following alendronate period, adjudicated events of ONJ (1 event each in the romosozumab-to-alendronate and alendronate-to-alendronate groups) and atypical femoral fracture occurred. (2 events in romosozumab-to-alendronate group and 4 events in alendronate-to-alendronate group, respectively)	

Table 1 Summary of Clinical Trials of Romosozumab (continued)

Study name	No. of participants	Intervention	Primary endpoint	Key results	Conclusion
Romosozumab (Sclerostin Monoclonal Antibody) versus Teriparatide in Postmenopausal Women with Osteoporosis Transitioning from Oral Bisphosphonate Therapy: A Randomised, Open-label, Phase 3 Trial (STRUCTURE) [24]	436 osteoporotic women, 55-90 y, received oral BP therapy for at least 3 y, and oral alendronate (70 mg weekly or equivalent) the year immediately before screening.	Along with 1:1 ratio in each group; **Romosozumab group;** - 210 mg SC once monthly **Teriparatide group;** - 20 µg SC once daily Treatment period : 12 m	Percentage change from baseline in a real BMD at the TH through month 12 (mean of months 6 and 12)	- Mean percentage change from baseline in TH areal BMD was higher in the romosozumab group compared to the teriparatide group; difference 3.2% - The most frequently reported adverse events were nasopharyngitis followed by hypercalcaemia, and arthralgia. - Serious adverse events were reported in 8 % on romosozumab and in 11 % on teriparatide; none were judged treatment related.	Romosozumab offered an increased hip BMD to patients with postmenopausal osteoporosis who are transitioning from BP therapy.

Table 1 Summary of Clinical Trials of Romosozumab (continued)

Study name	No. of participants	Intervention	Primary endpoint	Key results	Conclusion
A Phase III Randomized Placebo-Controlled Trial to Evaluate Efficacy and Safety of Romosozumab in Men with Osteoporosis (BRIDGE) [25]	245 men, 55 – 90 y, 2:1 to receive romosozumab and placebo	**Romosozumab group;** - 210 mg SC QM for 12 months **Placebo group** - for12 months All subjects received calcium and vitamin D daily. Additional 3 months for F/U	Effect of treatment with romosozumab for 12 m compared with placebo on percentage change from baseline in the LS BMD	- Romosozumab performed a significant increase from baseline in the LS BMD compared with the placebo - Numerical imbalance in the positively adjudicated CV serious adverse events such as cardiac ischemic events, cerebrovascular events, heart failure, were higher in the romosozumab group compared to the placebo. - No positively adjudicated cases of atypical femoral fracture or ONJ	Romosozumab was well tolerated in men with osteoporosis. 210 mg SC QM increased the spine and hip BMD compared with placebo.

Abbreviations;

AMG 785: the original name of romosozumab, **BAP**: *bone alkaline phosphatase,* **BMD**: bone mineral density, **BP**: bisphosphonate, **CTX**: C-telopeptide, **CV**: cardiovascular, **FN**: femoral neck, **F/U**: follow up, **IV**: intravenous, **LS**: lumbar spine, **m**: month, **ONJ**: osteonecrosis of the jaw, **PD**: pharmacodynamics, **PK**: pharmacokinetics, **P1NP**: procollagen type 1 N propeptide, **QM**: every month, **Q2W**: every 2 weeks, **Q3M**: every 3 months, **Q4W**: every 4 weeks, **Q6M**: every 6 months, **SC**: subcutaneous, **TH**: total hip, **w**: week, **y** : year

As for a similar phase II study in postmenopausal Japanese women with 12-month various doses of romosozumab, it demonstrated that all romosozumab significantly increased LS BMD at month 12 compared with placebo. 210 mg regimen achieved the largest gain from baseline (16.9% LS, 4.7% TH, 3.8% femoral neck (FN)). Bone formation marker was increased whereas bone resorption marker was decreased. Nevertheless, new fractures at different sites were reported. No osteonecrosis of the jaw (ONJ) or atypical femoral fracture occurred. Incidences of adverse events and serious adverse events were generally comparable among the treatment groups. [21]

The international phase III study, The Fracture Study in Postmenopausal Women with Osteoporosis: FRAME, compared efficacy of romosozumab with placebo at month 12 and followed by denosumab in both groups at month 24. It revealed that romosozumab reduced new vertebral fracture for 73 % and 75 % at month 12 and 24 respectively. The levels of P1NP increased rapidly in the romosozumab group with maximum peak on day 14 and returned to baseline levels by 9 months. β-CTX went down early during treatment with maximum decline on day 14 and remained below the levels in the placebo group at 12 months. The lower risk of clinical fracture was evident at 1 year seen with romosozumab. [22]

The Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk: ARCH compared treatment efficacy between romosozumab and oral alendronate, respectively. It was found a 48% and 19 % lower risk of new vertebral fractures and non-vertebral fracture in the romosozumab-to-alendronate group comparing with the alendronate-to-alendronate group. Patients receiving romosozumab achieved greater gains in BMD from baseline at all measured sites and at all time points than patients receiving alendronate alone. Romosozumab increased P1NP level and decreased β-CTX level within 12 months. After transitioning to alendronate, levels of P1NP and β-CTX decreased and remained below baseline levels at 36 months. During open-label period, atypical femoral fracture was found in 2 romosozumab-to-alendronate patients and 4 patients in another group. 2 cases of ONJ was reported; 1 case in romosozumab-to-alendronate group and another 1 patient in alendronate-to-alendronate group. [23]

Another large randomized controlled trial, The Romosozumab (sclerostin monoclonal antibody) versus Teriparatide in Postmenopausal Women with Osteoporosis Transitioning from Oral Bisphosphonate Therapy: a randomized, open-label, phase 3 trial: STRUCTURE showed that the mean percentage change from baseline in TH areal BMD was 2.6% in the romosozumab group and –0.6% in the teriparatide group. P1NP rose lively after the first dose in the romosozumab group, peaked in the first month and then gradually returned towards baseline values during the 12 months of treatment. β-CTX declined rapidly after the first dose of romosozumab and returned to baseline by month 3, with concentrations remaining near baseline up to month 12.

Adverse events were generally balanced between the groups. Atrial fibrillation and death were reported but not considered as treatment sequele. No cases of ONJ or atypical femoral fracture were reported in either group. [24]

Not only women are the target of treatment, men are in concerned. A Phase III Randomized Placebo-Controlled Trial to Evaluate Efficacy and Safety of Romosozumab in Men with Osteoporosis: BRIDGE indicated 12.1 % increase in LH BMD of the test group compared to 1.2% of placebo. With bone biopsy study, histomorphometric analyses at 12 months observed a reduction in bone resorption consistent. Some subjects developed anti-romosozumab antibodies and one had neutralizing antibodies. It pointed out that treatment with romosozumab for 12 months increased the spine and hip BMD compared with placebo and was well tolerated in men with osteoporosis. [25]

Pharmacodynamics

Romosozumab is subcutaneously injected humanized monoclonal antibody which inhibits sclerostin; resulting in activation Wnt signaling pathway and inhibition RANK-RANKL binding. [6-9, 17] The net benefit is increased bone mass. (Figure 2) In a placebo-controlled phase I study in healthy postmenopausal women and male people, single subcutaneous doses of romosozumab 0.1–10 mg/kg or single IV doses of romosozumab 1 or 5 mg/kg related to increases in the levels of the bone-formation markers; P1NP; bone-specific alkaline phosphatase (BAP), and osteocalcin, and also a dose-related decrease in levels of serum β-CTX marker. Serum levels of bone formation markers increased transiently. It arose to the peak level around the first month and then gradually diminish to the baseline at months 9-12. Therefore, bone formation effect wanes after month 12. [18, 19]

Pharmacokinetics

Similar to other monoclonal antibodies, romosozumab is absorbed by lymphatic vessels and hepatic and renal function in elimination is less involved. [26] In phase I single doses of 210 mg romosozumab study showed exhibition of non-linear pharmacokinetic profile following subcutaneous administration mostly marked between 1 and 3 mg/kg. Peak serum concentrations were observed within the first week injection. Mean serum concentration discernibly declined in a biphasic manner after maximum concentration with beta and gamma half-lifes of 11-18 days and 6-7 days, respectively. Exposures in the 1 and 5 mg/kg subcutaneous dose groups were approximately 50% and 70%, respectively, of the corresponding

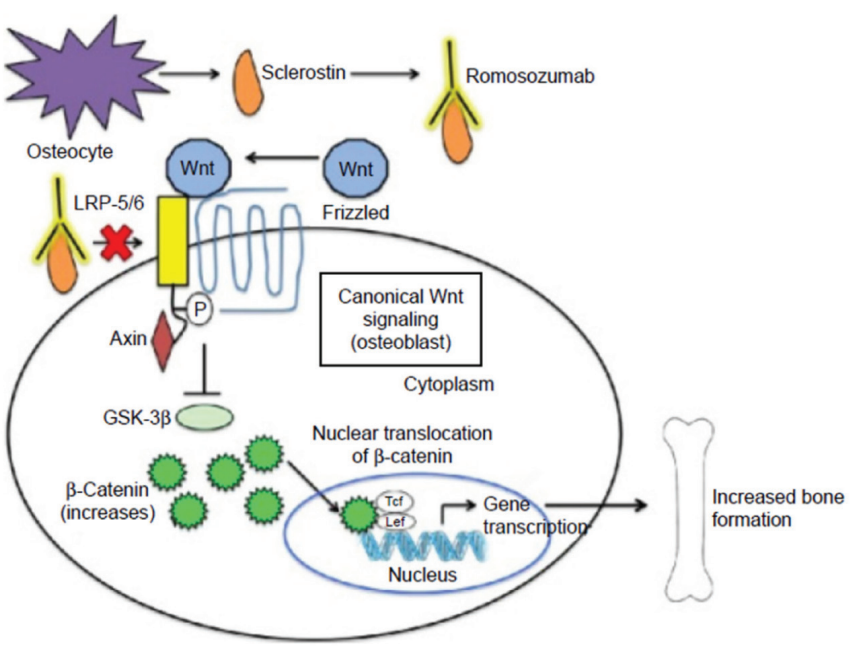

Figure 2 Mechanism of action of romosozumab. When romosozumab acts as sclerostin inhibitor, it binds to sclerostin which allow Wnt signaling pathway returns to normal function. Thus, bone formation is increased. Copyright ©2015. Dove Medical Press. Shah AD, Shoback D, Lewiecki EM. Sclerostin inhibition: a novel therapeutic approach in the treatment of osteoporosis. *Int J Womens Health* 2015; 7: 565–80

Safety

In clinical trials, romosozumab was generally well tolerated. However, arthralgia, nasopharyngitis, injection-site reaction and hypersensitivity were frequently observed than placebos, without apparent relationship between dose and adverse events. In addition, theoretically, sclerostin inhibition could be associated with cardiovascular risk. It is constitutively expressed in the aorta, up-regulated in foci of vascular and valvular calcification, but animal studies show no strong evidences. [23]

Arthralgia was mostly found as an adverse event in the FRAME trial followed by nasopharyngitis and back pain in patients receiving romosozumab. Serious adverse events of hypersensitivity occurred in 7 out of 242 patients in the romosozumab group during the first year. Hypocalcemia was observed about 0.1-0.2 % in all groups except the placebo during the first period. In the romosozumab group, 1 patient experienced atypical femoral fracture after 3.5 months with a history of prodromal pain at the site of fracture beginning before the enrollment. Additionally, other 2 participants developed ONJ. During the first 15 months of the study, anti-romosozumab antibodies and neutralizing antibodies developed in the romosozumab group without discernable effect on efficacy or safety. [22]

According to the ARCH trial, back pain was observed as one of major events. There was no atypical femoral fracture and ONJ report in the 12-month double-blind period. Nevertheless, in the 12-month open-label period, there were 1 patient with ONJ and 2 patients with atypical femoral fracture in the romosozumab-to-alendronate group while there were 1 patient with ONJ and 4 patients with atypical femoral fracture in the alendronate-to-alendronate group. Adjudicated serious cardiovascular adverse events were imbalance between 2 groups during the double-blind period. They were cardiac ischemic event, cerebrovascular event, heart failure, noncoronary revascularization, peripheral vascular ischemia not requiring revascularization, or even death. Anti-romosozumab antibodies during the first 18 months of the trial occurred without detectable effect on relevant efficacy or safety. Higher incidence of cardiovascular events were observed in romosozumab receivers but no increase in events after adding alendronate and lower incidence of the events after pretreatment with bisphosphonate. [23]

The STRUCTURE trial included 3 major adverse events; nasopharyngitis, arthralgia, and injection-site reaction. 6 patients (3%) in the romosozumab group and 12 patients (6%) in the teriparatide group had adverse events leading to discontinuation of study. Serious adverse events were observed in 17 patients (8%) on romosozumab and in 23 patients (11%) on teriparatide; none were judged to be treatment-related. Serious adverse events reported by more than one participant in either treatment group were atrial fibrillation in the romosozumab group and pneumonia and abdominal pain in the teriparatide group. There was one death in each treatment group. One death occurred in each treatment group with neither considered as treatment-related. [24]

The incidence rate of treatment-emergent adverse events was 75.5% in the romosozumab group and 80.2% in the placebo group in the BRIDGE trial. Injection-site reaction, hypersensitivity, osteoarthritis, incidence fracture and malignancy were noted found. On the other hand, no positively adjudicated cases of atypical femoral fracture or ONJ were reported. [25]

Carcinogenicity has been also concerned when treating patients with romosozumab. A review of scientific weight-of-evidence and findings in a rat lifetime pharmacology study showed no increase in the incidence of tumors in rats and might predict in human with the same result. [27]

Caution

Overall, 210 mg of subcutaneous injection romosozumab monthly shows superior benefit of boosting bone formation to other medications. In addition, patients should be supplemented with calcium and vitamin D during treatment with romosozumab. Anyone with hypocalcemia is treated with caution. Known severe hypersensitivity is contraindicated. Risk and benefit in patients with cardiovascular risk factors should be weighted. It should not be initiated in patients with recent myocardial infarction or stroke within the preceding year.

Dental consideration

Bisphosphonates and RANKL inhibitors are generally associated with ONJ. It is non-healing exposed jaw bone more than 8 weeks in patients receiving some medications without head and neck radiotherapy which usually due to invasive dentoalveolar surgery, depending on route of administration, dose, and duration. [28] Unlike this, romosozumab acts not only bone resorption interference but also bone formation promotion. In FRAME trial, 1 patient developed ONJ after 12 months of romosozumab therapy because of ill-fitting denture and another patient was owing to a tooth extraction and subsequent jaw osteomyelitis after 12 months of romosozumab treatment and 1 dose of denosumab. [22] Similar to ARCH trial, 1 patient established ONJ after receiving romosozumab-to-alendronate therapy while another 1 patient developed the same circumstance after receiving the alendronate-to-alendronate regimen. [23]

Concomitant administration of drugs associated with ONJ; chemotherapy, bisphosphonates, denosumab, angiogenesis inhibitors, and corticosteroids may increase risk of ONJ. Other risk factors are cancer, radiotherapy, poor oral hygiene, pre-existing dental disease or infection, anemia, and coagulopathy. To prevent ONJ, a routine oral examination and definitive treatment plan should be performed prior to initiating romosozumab. Patients requiring invasive dental procedures while taking romosozumab must be judged by physicians depending on benefit-risk assessment. Patients who are suspected or who develop ONJ while taking romosozumab should contact a dentist or an oral surgeon for a proper management. [17]

Conclusion

Romosozumab is a sclerostin inhibitor which could increase bone mass. Patients have been reported increased BMD and bone formation marker levels along with decreased bone resorption marker levels after receiving romosozumab. On the other hand, anabolic effect wanes after 12 monthly dose. Generally, it is well-tolerated with mild to moderate adverse reactions but may relate to major cardiovascular events. ONJ and atypical femoral fracture may be found in a small number of patients treated with romosozumab. According to dental view, to prevent ONJ, comprehensive oral examination, planned dental extraction or bony-related surgery should be offered to anyone before starting romosozumab. For patients being treated with romosozumab and planned to undergo dentoalveolar procedures, discontinuation should be weighted in risk and benefit circumstance. Like bisphosphonate therapy, the simplest way to prevent ONJ is to maintain good oral hygiene.

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