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Current Concepts

Clinical Studies On Romosozumab: An Alternative For Individuals With A High Risk Of Osteoporotic Fractures: A Current Concepts Review (Part I)

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Osteoporosis, a widespread skeletal disorder with a substantial economic burden, is characterized by reduced bone density, resulting in increased fracture risk. Sclerotin inhibition with romosozumab (ROMO) represents a new therapeutic paradigm for the treatment of postmenopausal osteoporosis. We conducted a narrative review of the literature on ROMO's role in osteoporosis treatment. ROMO has a unique dual effect of increasing bone formation (anabolic action) and decreasing bone resorption. It is a humanized monoclonal antibody injected monthly (210 mg subcutaneously once every four weeks for 12 months) that significantly increases lumbar spine, total hip, and femoral neck bone mineral density (BMD) compared with placebo, alendronate, and teriparatide at 6 and 12 months.

INTRODUCTION

According to Rauner et al., osteoporosis is characterized by diminished bone mass and disruption of bone architecture, leading to an augmented risk of fragility fractures and substantial long-term disability. In 2021, Rauner et al. claimed that although anti-resorptive and osteoanabolic treatments such as parathyroid hormone analogs were effective for fracture prevention, they had limitations due to a lack of compliance or contraindications to these medications. Therefore, there was a need for new potent drugs, especially for those at high fracture risk. Romosozumab (ROMO) is a monoclonal antibody against sclerostin with a dual mode of action. It increases bone formation while suppressing bone resorption, leading to a longer anabolic window.[1]

According to Tanaka and Matsumoto, skeletal integrity is sustained by a careful and precise equilibrium between bone resorption and bone formation. Recent publications have shown the fundamental role of canonical Wnt signaling pathways in maintaining skeletal homeostasis. The SOST gene, which encodes sclerostin, a member of the DAN family of glycoproteins, was initially recognized as the gene accountable for two sclerosing bone dysplasias: sclerosteosis and van Buchem disease. Sclerostin is highly expressed by osteocytes, negatively controls canonical Wnt signaling pathways by joining low-density lipoprotein receptor-related protein 5/6, and restrains osteoblast differentiation and/or function. ROMO, a specific anti-sclerostin antibody, curbs sclerostin-LRP5/6 interactions and indirectly triggers canonical Wnt signaling pathways and osseous formation.[2] ROMO's mechanism of action has been described by Aditya and Rattan **(FIGURE 1).**[3]

Because of its unique dual effect of increasing bone formation (anabolic action) and decreasing bone resorption, the United States Food and Drug Administration (FDA) approved ROMO (210 mg subcutaneous injection every four weeks for 12 months) for the treatment of postmenopausal osteoporosis.[3] The purpose of this article is to conduct a narrative review of the literature on the role of ROMO in the treatment of osteoporosis. The goal of this study was to review the current status on the efficacy of ROMO in the treatment of osteoporosis to prevent bone fragility fractures.

The rationale for conducting this study was to analyze the indications, efficacy, and possible side effects of ROMO in the prevention of osteoporotic fractures and to compare them with those of other drugs already used in the treat-

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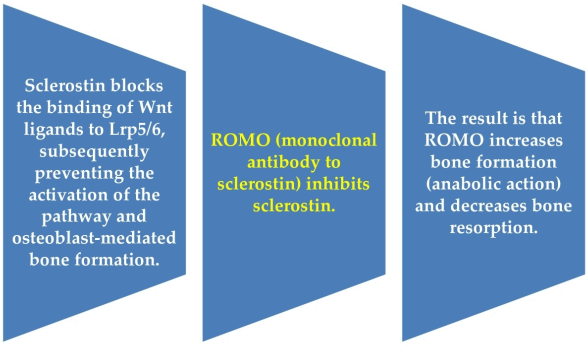

Figure 1. Mechanism of action of romosozumab (ROMO).[3]

Lrp5/6= low-density lipoprotein receptor-related proteins 5 and 6; sclerostin = a glycoprotein produced by osteocytes, an extracellular Wnt antagonist.

ment of osteoporosis. The basic questions we have asked ourselves are: when should ROMO be used; when should it be contraindicated; is ROMO more effective than the other existing anti-osteoporosis drugs; and is it more effective than other anti-osteoporosis drugs?

A literature search was conducted in PubMed (only articles published during the years 2019, 2020, 2021 and 2022 were analyzed), Web of Science, and Google Scholar. Using "romosozumab" as a keyword, 6280 articles were found (322 in PubMed, 958 in Web of Science, 5000 in Google Scholar), of which 30 were ultimately analyzed. The inclusion criteria were based on our subjective opinion regarding the relevance of the article content in relation to the title of this article. The criterion for exclusion of articles was that we subjectively considered that these articles were not relevant to the subject of our manuscript.

RESULTS: CLINICAL STUDIES

SAFETY AND EFFICACY OF ROMO

A randomized clinical trial (RCT) published in 2016 by Cosman et al. showed that in postmenopausal women with osteoporosis, ROMO was associated with a lower risk of vertebral fracture than placebo at one year and, after the transition to denosumab (DENO), at two years. The low risk of clinical fracture observed with ROMO was evident at one year.[4]

In 2017 Saag et al. observed that in postmenopausal women with osteoporosis who were at high risk for fracture, ROMO treatment for 12 months followed by alendronate resulted in a significantly lower risk of fracture than alendronate alone.[5]

In 2019, ROMO was approved for the treatment of osteoporosis in patients at high fracture risk.[6] The same year, Lewiecki et al. stated that in postmenopausal women with osteoporosis, 12 months of ROMO led to persistent fracture reduction and ongoing BMD gains, followed by 24 months of denosumab (DENO).[7] In the ARCH trial published in 2021 by Brown et al., it was found that ROMO considerably improved bone mass and bone strength parameters at the lumbar spine compared with alendronate.[8] In a meta-analysis describing several anti-osteoporotic drugs' effects in reducing fracture risk, Simpson et al. determined the clinical effectiveness of DENO, raloxifene, ROMO, and teriparatide. The four non-bisphosphonate interventions studied were all statistically significantly clinically effective for reducing vertebral fractures and were beneficial for change in femoral neck BMD compared with placebo. All the interventions reduced hip fractures in a statistically significant manner for teriparatide, ROMO, followed by alendronate, and DENO.[9] Geusens et al. observed that ROMO treatment for 12 months was associated with rapid and large reductions in clinical vertebral fracture risk versus placebo,[10] while Hernandez et al. reported that abaloparatide, ROMO, and teriparatide were the best treatments, respectively, to diminish vertebral/non-vertebral fractures, augment BMD, and increase bone formation.[11] Kendler et al. stated that after 12 months off-treatment, a second ROMO course led to rapid and large BMD gains. Following DENO, BMD gains with ROMO were smaller than initial treatment.[12] Bovijn et al. reported that ROMO could increase cardiovascular risk, warranting a rigorous evaluation of ROMO's cardiovascular safety.[13] Fuggle et al. reported that ROMO had been demonstrated to have a possible cardiovascular signal, and therefore post-market surveillance of this drug will be vital.[14] Paik and Scott stated that ROMO extended the treatment alternatives in postmenopausal women with osteoporosis who have a high risk of fracture and those who have failed or are intolerant to other available osteoporosis treatments.[15]

Migliorini et al. investigated the efficacy and safety of the most commonly used drugs in managing postmenopausal osteoporosis in a Bayesian network meta-analysis of randomized controlled trials of level 1 evidence. ROMO and ibandronate were the most effective in preventing vertebral and hip fractures, respectively. Adverse events leading to study discontinuation were less frequent in the ROMO and DENO groups, whereas overall, raloxifene and alendronate showed a lower incidence of serious adverse events.[16]

One study found that the incidence of new vertebral fractures was dramatically reduced in the group administered ROMO for 12 months compared with the placebo and active bisphosphonate control groups in patients with postmenopausal osteoporosis. However, it was stated that until more real-world evidence is available, ROMO should not be employed for patients with a recent cardiovascular event and should be used with caution in patients at high cardiovascular risk. Severe postmenopausal osteoporosis in patients with low cardiovascular risk appears to be its main indication.[17]

The results of the Vestergaard Kvist et al. study supported the safety warnings from the FDA and the European Medicines Agency to avoid administering ROMO in patients with high cardiovascular risk.[18] A 6-month study published by Tominaga et al. demonstrated that ROMO was safe and effective for preventing fractures and helped increase spine BMD. It was especially effective in patients with low spine BMD.[19]

Table 1. Efficacy and safety of romosozumab (ROMO) in the literature.

AUTHORS [REFERENCE]	YEAR	EFFICACY	SAFETY	CONCLUSION
Cosman et al[4]	2016	The Fracture Study in Postmenopausal Women with Osteoporosis (FRAME), an international, randomized, double-blind, placebo-controlled, parallel-group trial demonstrated that in postmenopausal women with osteoporosis, ROMO was associated with a lower risk of vertebral fracture than placebo at 12 months and, after the transition to DENO, at 24 months. The lower risk of clinical fracture that was seen with ROMO was evident at 1 year.	NA	Women were randomly assigned, in a 1:1 ratio, with the use of an interactive voice-response system, to receive ROMO in a blinded fashion at a dose of 210 mg or placebo. Randomization was stratified according to age (<75 years vs. ≥75 years) and prevalent vertebral fracture (yes vs. no). ROMO or placebo was administered subcutaneously once monthly for 12 months, followed by open-label DENO at a dose of 60 mg (Prolia, Amgen), which was administered subcutaneously every 6 months for an additional 12 months.
Saag et al[5]	2017	This phase 3, multicenter, international, randomized, double-blind trial demonstrated that in postmenopausal women with osteoporosis who were at high risk for fracture, ROMO treatment for 12 months followed by alendronate resulted in a significantly lower risk of fracture than alendronate alone.	NA	Women were randomly assigned, in a 1:1 ratio to receive monthly subcutaneous ROMO (210 mg) or weekly oral alendronate (Merck; 70 mg) for 12 months.
Markham[6]	2019	NA	NA	This article summarized the milestones in the development of ROMO leading to its first approval for the treatment of osteoporosis in individuals at high risk of fracture.
Lewiecki et al[7]	2019	12 months of ROMO led to persistent fracture reduction and ongoing BMD gains	NA	Results of the FRAME (FRActure study in postmenopausal woMen with osteoporosis) Extension Study showed that in postmenopausal women with osteoporosis, 12 months of ROMO led to persistent fracture reduction and ongoing BMD gains when followed by 24 months of DENO.
Geusens et al[10]	2019	ROMO was efficacious	NA	Results of the FRAME Study showed that ROMO treatment for 12 months was associated with rapid and large reductions in clinical vertebral fracture risk versus placebo.
Hernandez et al[11]	2019	ROMO was efficacious	NA	A systematic review and network meta-analysis of ranzomized controlled trials (RCTs) showed that abaloparatide, ROMO, and teriparatide were the best treatments, respectively, to diminish vertebral/non-vertebral fractures,

				augment BMD, and increase bone formation
Kendler et al[12]	2019	After 12 months off-treatment, a second ROMO course again led to rapid and large BMD gains.		In this phase 2, dose-finding study it was found that following DENO, BMD gains with ROMO were smaller than with initial treatment
Bovijn et al[13]	2020	NA	ROMO could elevate cardiovascular risk	Evidence from meta-analysis of clinical trials and human genetics advised a rigorous evaluation of the cardiovascular safety of ROMO.
Fuggle et al[14]	2020	NA	ROMO had been demonstrated to have a possible cardiovascular signal	In this narrative review of the literature it was stated that post-market surveillance of this drug will be vital
Paik and Scott[15]	2020	ROMO was efficacious	NA	This review article stated that ROMO could extend the treatment alternatives in postmenopausal women with osteoporosis who have a high risk of fracture and in those who have failed or are intolerant to other available osteoporosis treatment.
Simpson et al[9]	2020	This systematic review and network meta-analysis analyzed the clinical effectiveness of DENO, raloxifene, ROMO, and teriparatide for the prevention of osteoporotic fragility fractures. The four non-bisphosphonate interventions studied were all statistically significantly clinically effective for reducing vertebral fractures when compared to placebo, and were beneficial for change in femoral neck BMD compared to placebo.	NA	The four non-bisphosphonate interventions reduced hip fractures, and this was statistically significant for teriparatide, ROMO followed by alendronate, and DENO.
Rauner et al[1]	2021	NA	In this narrative review ROMO appeared to be a safe and well-tolerated medication.	ROMO should not be utilized in individuals with a myocardial infarction or stroke in the year previous to therapy or while on therapy, and the benefits and risks should be carefully outweighed in individuals at high risk of cardiovascular events.
Tanaka and Matsumoto[2]	2021	ROMO was effective	NA	This review summarized clinical studies that demonstrated the efficacy of ROMO to increase BMD and reduce osteoporotic fractures.
Aditya and Rattan[3]	2021	The efficacy of ROMO has been established in trials.	The safety of ROMO has been established in trials	These authors screened all the journal articles published from 2015 to 2020 that discussed the relevant clinical studies of ROMO.
Brown et al[8]	2021	ROMO improved lumbar spine bone mass and bone strength parameters relative to alendronate in postmenopausal women.	NA	The Active-Controlled Fracture Study in Postmenopausal Women With Osteoporosis at High

				Risk (ARCH) trial demonstrated the efficacy of ROMO.
Migliorini et al[16]	2021	DENO was associated with the lowest rate of non-vertebral fractures; ROMO with the lowest rate of vertebral fractures; and ibandronate with the lowest rate of hip fractures. DENO was more effective in reducing the occurrence of non-vertebral fractures. ROMO and ibandronate were the best to prevent vertebral fractures and hip fractures, respectively.	Adverse events leading to study discontinuation were less frequent in the ROMO and deno groups, while raloxifene and alendronate showed a lower incidence of serious adverse events overall.	This level I evidence-based-expert opinion concluded that ROMO and ibandronate were the best options for the prevention of vertebral fractures and hip fractures, respectively.
Fixen and Tunoa[17]	2021	Incidence of new vertebral fracture was dramatically reduced with 12 months of ROMO use compared with the placebo and active bisphosphonate control groups in patients with postmenopausal osteoporosis. Significant non-vertebral anti-fracture benefit was also demonstrated in patients with more severe osteoporosis. ROMO had impressive anti-fracture effects in postmenopausal women with high risk of fragility fracture.	Numerical increases in cardiovascular events call into question the safety of ROMO use, particularly in patients with cardiovascular history or at high cardiovascular risk. Despite no significant differences in baseline cardiovascular risk factors between groups, a numerical increase in serious cardiovascular adverse events was demonstrated with ROMO in randomized trials, with no discernable etiology.	This review article concluded that until more real-world evidence is available, ROMO should not be used in patients with a recent cardiovascular event and should be used cautiously in patients with high cardiovascular risk. ROMO's place in therapy appears to be in patients with severe postmenopausal osteoporosis and low cardiovascular risk.
Vestergaard Kvist et al[18]	2021	NA	This pharmacovigilance analysis of the US Food and Drug Administration Adverse Event Reporting System (FAERS) identified a potential signal for elevated major cardiovascular events, particularly in Japan.	The results of this study supported the safety warnings from the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to avoid use in high-risk individuals.
Tominaga et al[19]	2021	This 6-month study showed that ROMO is effective in preventing fractures and useful for increasing the spine BMD.	ROMO was relatively safe to use.	ROMO was especially effective in individuals with low baseline spine BMD, high 5b (TRACP-5b), and high iP1NP).
Baek et al[20]	2021	This phase 3 study evaluated the efficacy and safety of 6-month treatment with ROMO in postmenopausal women with osteoporosis. After treatment with ROMO, the percent change from baseline in procollagen type 1 N-	No events of cancer, hypocalcemia, injection site reaction, positively adjudicated	This randomized, double blind, placebo-controlled efficacy and safety study (phase 3) found that treatment with ROMO for 6 months was well tolerated and significantly increased

		terminal propeptide transiently increased at months 1 and 3, whereas that in the C-terminal telopeptide of type 1 collagen showed a sustained decrease. At month 9, 17.6% and 2.9% of patients in the ROMO group developed binding and neutralizing antibodies, respectively.	atypical femoral fracture or osteonecrosis of the jaw, or positively adjudicated serious cardiovascular adverse events were observed.	lumbar spine, total hip, and femoral neck BMD compared with placebo in postmenopausal women with osteoporosis.
Nealy and Harris[21]	2021	ROMO increased BMD at the lumbar spine, femoral neck, and total hip in patients with osteoporosis. After 12 months, ROMO provided greater BMD gains at the lumbar spine and hip than teriparatide. However, teriparatide was likely to further increase BMD if continued for up to 24 months. In postmenopausal women with a high fracture risk, 1 year of ROMO followed by 1 year of alendronate resulted in lower vertebral, nonvertebral, clinical, and hip fractures than alendronate alone for 2 years.	Although absolute event rates were low, serious cardiovascular and cerebrovascular events were numerically higher in 2 clinical trials compared with alendronate (2.5% vs 1.9%, respectively) and placebo (4.9% vs 2.5%, respectively).	In this study, PubMed, MEDLINE, and ClinicalTrials.gov searches (1966 to July 2020) were conducted using the keywords romosozumab and osteoporosis. It was concluded that ROMO offered an alternative for patients with a high risk of osteoporotic fractures. Clinicians should avoid ROMO in patients with a history of myocardial infarction or stroke in the past 12 months.
Langdahl et al[22]	2021	NA	ROMO should be used for the treatment of postmenopausal women with osteoporosis at high risk of fracture after careful consideration of the cardiovascular risk and the balance between benefits and risks.	Regarding the cardiovascular risk of ROMO, this review article stated that the evidence from the large clinical trials in postmenopausal women is conflicting.
Takeuchi[23]	2021	NA	There remains a concern for increased adverse cardiovascular events. Further relevant investigations are essential to understand whether ROMO is actually involved in the development of cardiovascular events.	This article briefly reviewed concerns about cardiovascular safety in ROMO obtained from prospective RCTs and presented real-world clinical data for its safety, especially in Japan. The conclusion was that more robust evidence to establish an appropriate and reasonable guide to prescribe ROMO in clinical practice is required.
McCloskey et al[24]	2021	Compared with placebo, ROMO reduced the incidence of all fracture outcomes in the first year (range: 32% reduction in major osteoporotic fracture [MOF] to 80% reduction in clinical vertebral fractures). Significant interactions were observed between efficacy and the baseline Fracture Risk Assessment Tool (FRAX) probability for composite outcomes of clinical fractures, osteoporotic fractures, and MOF, but not vertebral fractures. For example, ROMO decreased all clinical fractures by 22% at the 25th percentile	NA	A post hoc analysis of the first year of the FRAME study showed that the efficacy of ROMO on clinical fracture, osteoporotic fracture, and MOF was significantly greater in patients at high baseline fracture risk compared with placebo.

		of FRAX probability, but the reduction was 41% at the 75th percentile. Exclusion of vertebral fractures from each composite fracture outcome (i.e., only nonvertebral fractures) showed even stronger interactions with baseline FRAX probability.		
Tominaga et al[25]	2021	Percent changes from baseline in the spine and total hip BMD after 12 months of ROMO treatment were 10.67% and 2.04%, respectively. ROMO had better effects in cases of severe osteoporosis with low spine BMD, high TRACP-5b, and high iP1NP at the start of ROMO treatment. The percent change in the spine BMD at 12 months was significantly lower in the group transitioning from bisphosphonate than in the group not previously treated with other anti-osteoporosis medications.	There were 5 cases of new fractures during 1-year ROMO treatment. There were no fatal adverse events.	This study was an observational study designed as a pre-post study in 262 patients. It was concluded that ROMO was an effective treatment for spine osteoporosis because it significantly increased the percentage of change in the spine BMD at 12 months. This change was higher in patients not previously treated with other anti-osteoporosis medications.
Singh et al[26]	2022	ROMO significantly reduced the incidence of vertebral fractures, nonvertebral fractures, and clinical fractures (all high quality of evidence) at 24 months. Significant reduction in incidence risk of falls (high quality) was observed with ROMO. BMD was significantly increased in the ROMO-treated groups in the lumbar spine (high quality), total hip (moderate quality), and femoral neck (moderate quality) at 12 months.	The total adverse events (moderate quality) and serious adverse events (moderate quality) with ROMO were comparable to the control group.	This systematic review and meta-analysis of efficacy and safety of ROMO in postmenopausal osteoporosis advised ROMO treatment for postmenopausal osteoporosis.
Shen et al[27]	2022	ROMO (92.1%) was the most effective in reducing the risk for all fractures, with the best therapeutic effects on vertebral fracture (97.2%) and non-vertebral fracture (88%). ROMO (92.5%) provided better therapeutic effects for the reduction of hip fracture. The best treatment agents for improving whole-body BMD (100%), spine BMD (95.7%), hip BMD (92.4%), femoral neck BMD (86.7%), and trochanter BMD (95.5%) were alendronate, strontium ranelate, ibandronate, risedronate, and ibandronate, respectively.	The use of bazedoxifene was associated with the highest incidence of any upper-gastrointestinal event, nasopharyngitis, and back pain, whereas risedronate was associated with higher incidence of abdominal pain and dyspepsia.	This Bayesian Network Meta-analysis found that ROMO yielded the best effects for reducing fracture risk, while abaloparatide was the most effective in reducing the risk of vertebral fracture and non-vertebral fracture.
Poutoglidou et al[28]	2022	ROMO significantly increased lumbar spine, total hip, and femoral neck BMD compared with placebo, alendronate, and teriparatide at both 6 and 12 months.	Adverse events were comparable between ROMO and other treatments, except for the incidence of injection-site reactions, which were higher in the anti-sclerostin antibody groups.	This meta-analysis and systematic review stated that ROMO represents a valid therapeutic option for osteoporosis treatment.
Miller et al[29]	2022	ROMO reduced the relative risk of new vertebral fractures at month 12 among patients with estimated glomerular filtration rates of 30-59, 60-89, and ≥90 mL/min by 72%, 70%, and 84%, respectively, versus placebo, in the Fracture Study in Postmenopausal Women with Osteoporosis; and by 51%, 19%, and 57%, respectively, versus	Incidences of adverse events, asymptomatic decreases in serum calcium, and evolution of kidney function during the studies were similar	This post hoc analysis of two randomized, multicenter, phase 3 clinical trials-FRAME and Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH)-investigated the efficacy and safety of

		alendronate, in the Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk.	across all baseline kidney function groups.	ROMO in postmenopausal women with osteoporosis and mild-to-moderate chronic kidney disease. It was concluded that ROMO was an effective treatment option for postmenopausal women with osteoporosis and mild-to-moderate reduction in kidney function, with a similar safety profile across various levels of kidney function.
Miyauchi et al[30]	2022	Compared with placebo, ROMO increased lumbar spine BMD by 14.8% and 15.2% in the estimated glomerular filtration rate <90 and ≥90 mL/min/1.73 m^2 subgroups, total hip BMD by 4.6% and 5.5%, and femoral neck BMD by 4% and 5.5% at 12 months, respectively.	The incidence of adverse events was similar between subgroups. New vertebral fracture incidence was numerically lower with ROMO than placebo at 12 months in both estimated glomerular filtration rate subgroups.	This post hoc analysis of the placebo-controlled phase 3 FRAME study assessed the efficacy and safety of ROMO in a subpopulation of Japanese postmenopausal women with osteoporosis and chronic kidney disease. It was shown that ROMO for 12 months was an effective and well-tolerated treatment option for Japanese patients with osteoporosis and mild-to-moderate chronic kidney disease.

NA = not available; BMD = bone mineral density; DENO = denosumab; TRACP-5b = tartrate-resistant acid phosphatase 5b; iP1NP = intact type I procollagen N-terminal propeptide.

A phase 3 clinical trial published by Baek et al. showed that treatment with ROMO for six months was well tolerated and significantly increased BMD of the lumbar spine, total hip, and femoral neck compared with placebo in postmenopausal Korean women with osteoporosis.[20]

Nealy and Harris observed that ROMO increased BMD in the lumbar spine (12.1%-13.3%), femoral neck (2.2%-5.9%), and total hip (2.5%-6.9%) in patients with osteoporosis. After 12 months, ROMO provided greater BMD gains in the lumbar spine and hip than teriparatide, offering an alternative for patients at high risk of osteoporotic fractures. However, they advised that its use should be avoided in patients with a history of myocardial infarction or stroke in the past 12 months.[21]

According to Langdahl et al., ROMO should be used to treat postmenopausal women with osteoporosis and high fracture risk after carefully considering their cardiovascular risk and weighing the risk/benefit balance.[22]

Takeuchi has stated that ROMO is a potent pharmacological tool for preventing fractures in patients with osteoporosis. Its efficacy in the prevention of osteoporotic fractures is remarkable. However, given that concern remains about the increase in adverse cardiovascular effects, further research is essential to understand whether ROMO is actually involved in their development.[23]

McCloskey et al. studied the interaction between the baseline Fracture Risk Assessment Tool-determined fracture probability and ROMO's efficacy. Its efficacy on clinical fractures, osteoporotic fractures, and major osteoporotic fractures was significantly higher in patients at high baseline fracture risk than in the placebo group.[24]

Tominaga et al. reported that ROMO was an effective treatment for spine osteoporosis because it significantly increased the percent change in spine BMD at 12 months. This change was higher in patients not previously treated with other anti-osteoporosis drugs.[25]

Singh et al. performed a systematic review and meta-analysis to illustrate the effect of ROMO in patients with postmenopausal osteoporosis.[26] ROMO significantly reduced the incidence of vertebral fractures, non-vertebral fractures, and clinical fractures at 24 months, all with high-quality evidence. A significant reduction in the risk of fall incidence (high quality) was observed with ROMO. BMD was significantly increased in the ROMO-treated groups at the lumbar spine (high quality), total hip (moderate quality), and femoral neck (moderate quality) at 12 months. Total adverse events (moderate quality) and serious adverse events (moderate quality) with ROMO were comparable to those in the control group. Considering the study's results, Singh et al. recommended ROMO treatment in patients with postmenopausal osteoporosis.[26]

Many randomized controlled trials have evaluated the various pharmacological treatments available for osteoporosis. Shen et al. compared the efficacy and safety of pharmacological treatments in patients with osteoporosis, finding that ROMO was the most effective in reducing the risk for all fractures.[27] In a systematic review and meta-analysis, Poutoglidou et al. evaluated the efficacy and safety of ROMO compared with placebo and conventional treatments (alendronate and teriparatide) in the management of osteoporosis. ROMO significantly increased the lumbar spine, total hip, and femoral neck BMD compared

with placebo, alendronate, and teriparatide at 6 and 12 months.[28] According to Miller et al., patients with osteoporosis and chronic kidney disease have an increased risk of fracture and associated negative outcomes, including increased mortality. They stated that ROMO is an effective treatment option for postmenopausal women with osteoporosis and mild-to-moderate reduction in kidney function, with a similar safety profile across various levels of kidney function.[29]

In a *post hoc* analysis of phase 3, a placebo-controlled fracture study in postmenopausal women with osteoporosis (FRAME), Miyauchi et al. observed that ROMO for 12 months was an effective and well-tolerated therapeutic option for Japanese patients with osteoporosis and mild to moderate chronic kidney disease.[30] **TABLE 1** summarizes the efficacy and safety of ROMO.

CONCLUSIONS

ROMO is the first agent to inhibit bone resorption and stimulate bone formation. It is a human monoclonal antibody that inhibits the action of sclerostin and has been shown to significantly increase BMD and decrease vertebral and hip fractures in postmenopausal women with osteoporosis. However, ROMO should not be used in women with a history or high risk of cardiovascular disease because it can produce significant adverse cardiac effects. Arthralgia, headache, and injection site reactions have also been described. ROMO (210 mg) is administered subcutaneously once every four weeks for 12 months, and it can significantly increase BMD independent of the addition of an active vitamin D analog.

The limitations of this article are threefold: Only three search engines were used (Google Scholar, Web of Science and PubMed); only articles published during the years 2019, 2020, 2021 and 2022 in PubMed were analyzed; and the decision to include (or exclude) an article was made based on a subjective criterion. The aforementioned limitations of our article could hurt the conclusions reached, as it is likely that some (or many) important articles have not been considered relevant by us. The problem is that the bibliography is so immense (6280 articles) that in one way or another something of importance can always be left out. Logically we have honestly chosen those articles that we considered to be of greatest importance.

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REFERENCES

1. Rauner M, Taipaleenmäki H, Tsourdi E, Winter EM. Osteoporosis treatment with anti-sclerostin antibodies-mechanisms of action and clinical application. *J Clin Med*. 2021;10(4):787. doi:10.3390/jcm10040787

2. Tanaka S, Matsumoto T. Sclerostin: from bench to bedside. *J Bone Miner Metab*. 2021;39(3):332-340. doi:10.1007/s00774-020-01176-0

3. Aditya S, Rattan A. Sclerostin inhibition: a novel target for the treatment of postmenopausal osteoporosis. *J Midlife Health*. 2021;12(4):267-275. doi:10.4103/jmh.jmh_106_20

4. Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med*. 2016;375(16):1532-1543. doi:10.1056/nejmoa1607948

5. Saag KG, Petersen J, Brandi ML, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *N Engl J Med*. 2017;377(15):1417-1427. doi:10.1056/nejmoa1708322

6. Markham A. Romosozumab: first global approval. *Drugs*. 2019;79(4):471-476. doi:10.1007/s40265-019-01072-6

7. Lewiecki EM, Dinavahi RV, Lazaretti-Castro M, et al. One year of romosozumab followed by two years of denosumab maintains fracture risk reductions: results of the FRAME extension study. *J Bone Miner Res*. 2019;34(3):419-428. doi:10.1002/jbmr.3622

8. Brown JP, Engelke K, Keaveny TM, et al. Romosozumab improves lumbar spine bone mass and bone strength parameters relative to alendronate in postmenopausal women: results from the Active-Controlled Fracture Study in Postmenopausal Women With Osteoporosis at High Risk (ARCH) trial. *J Bone Miner Res*. 2021;36(11):2139-2152. doi:10.1002/jbmr.4409

9. Simpson EL, Martyn-St James M, Hamilton J, et al. Clinical effectiveness of denosumab, raloxifene, romosozumab, and teriparatide for the prevention of osteoporotic fragility fractures: A systematic review and network meta-analysis. *Bone*. 2020;130:115081. doi:10.1016/j.bone.2019.115081

10. Geusens P, Oates M, Miyauchi A, et al. The effect of 1 year of romosozumab on the incidence of clinical vertebral fractures in postmenopausal women with osteoporosis: results from the FRAME study. *JBMR Plus*. 2019;3(10):e10211. doi:10.1002/jbm4.10211

11. Hernandez AV, Pérez-López FR, Piscoya A, et al. Comparative efficacy of bone anabolic therapies in women with postmenopausal osteoporosis: a systematic review and network meta-analysis of randomized controlled trials. *Maturitas*. 2019;129:12-22. doi:10.1016/j.maturitas.2019.08.003

12. Kendler DL, Bone HG, Massari F, et al. Bone mineral density gains with a second 12-month course of romosozumab therapy following placebo or denosumab. *Osteoporos Int*. 2019;30(12):2437-2448. doi:10.1007/s00198-019-05146-9

13. Bovijn J, Krebs K, Chen CY, et al. Evaluating the cardiovascular safety of sclerostin inhibition using evidence from meta-analysis of clinical trials and human genetics. *Sci Transl Med*. 2020;12(549):eaay6570. doi:10.1126/scitranslmed.aay6570

14. Fuggle NR, Cooper C, Harvey NC, et al. Assessment of cardiovascular safety of anti-osteoporosis drugs. *Drugs*. 2020;80(15):1537-1552. doi:10.1007/s40265-020-01364-2

15. Paik J, Scott LJ. Romosozumab: a review in postmenopausal osteoporosis. *Drugs Aging*. 2020;37(11):845-855. doi:10.1007/s40266-020-00793-8

16. Migliorini F, Colarossi G, Baroncini A, Eschweiler J, Tingart M, Maffulli N. Pharmacological management of postmenopausal osteoporosis: a level I evidence based - expert opinion. *Expert Rev Clin Pharmacol*. 2021;14(1):105-119. doi:10.1080/17512433.2021.1851192

17. Fixen C, Tunoa J. Romosozumab: a review of efficacy, safety, and cardiovascular risk. *Curr Osteoporos Rep*. 2021;19(1):15-22. doi:10.1007/s11914-020-00652-w

18. Vestergaard Kvist A, Faruque J, Vallejo-Yagüe E, Weiler S, Winter EM, Burden AM. Cardiovascular safety profile of romosozumab: a pharmacovigilance analysis of the US Food and Drug Administration Adverse Event Reporting System (FAERS). *J Clin Med*. 2021;10(8):1660. doi:10.3390/jcm10081660

19. Tominaga A, Wada K, Kato Y, Nishi H, Terayama Y, Okazaki K. Early clinical effects, safety, and appropriate selection of bone markers in romosozumab treatment for osteoporosis patients: a 6-month study. *Osteoporos Int*. 2021;32(4):653-661. doi:10.1007/s00198-020-05639-y

20. Baek KH, Chung YS, Koh JM, et al. Romosozumab in postmenopausal Korean women with osteoporosis: a randomized, double-blind, placebo-controlled efficacy and safety study. *Endocrinol Metab (Seoul)*. 2021;36(1):60-69. doi:10.3803/enm.2020.848

21. Nealy KL, Harris KB. Romosozumab: a novel injectable sclerostin inhibitor with anabolic and antiresorptive effects for osteoporosis. *Ann Pharmacother*. 2021;55(5):677-686. doi:10.1177/1060028020952764

22. Langdahl BL, Hofbauer LC, Forfar JC. Cardiovascular safety and sclerostin inhibition. *J Clin Endocrinol Metab*. 2021;106(7):1845-1853. doi:10.1210/clinem/dgab193

23. Takeuchi Y. Romosozumab and cardiovascular safety in Japan. *Osteoporos Sarcopenia*. 2021;7(3):89-91. doi:10.1016/j.afos.2021.09.002

24. McCloskey EV, Johansson H, Harvey NC, Lorentzon M, Shi Y, Kanis JA. Romosozumab efficacy on fracture outcomes is greater in patients at high baseline fracture risk: a post hoc analysis of the first year of the frame study. *Osteoporos Int*. 2021;32(8):1601-1608. doi:10.1007/s00198-020-05815-0

25. Tominaga A, Wada K, Okazaki K, Nishi H, Terayama Y, Kato Y. Early clinical effects, safety, and predictors of the effects of romosozumab treatment in osteoporosis patients: one-year study. *Osteoporos Int*. 2021;32(10):1999-2009. doi:10.1007/s00198-021-05925-3

26. Singh S, Dutta S, Khasbage S, et al. A systematic review and meta-analysis of efficacy and safety of Romosozumab in postmenopausal osteoporosis. *Osteoporos Int*. 2022;33(1):1-12. doi:10.1007/s00198-021-06095-y

27. Shen J, Ke Z, Dong S, et al. Pharmacological therapies for osteoporosis: a Bayesian network meta-analysis. *Med Sci Monit*. 2022;28:e935491. doi:10.12659/msm.935491

28. Poutoglidou F, Samoladas E, Raikos N, Kouvelas D. Efficacy and safety of anti-sclerostin antibodies in the treatment of osteoporosis: A meta-analysis and systematic review. *J Clin Densitom*. 2022;25(3):401-415. doi:10.1016/j.jocd.2021.11.005

29. Miller PD, Adachi JD, Albergaria BH, et al. Efficacy and safety of romosozumab among postmenopausal women with osteoporosis and mild-to-moderate chronic kidney disease. *J Bone Miner Res*. 2022;37(8):1437-1445. doi:10.1002/jbmr.4563

30. Miyauchi A, Hamaya E, Nishi K, Tolman C, Shimauchi J. Efficacy and safety of romosozumab among Japanese postmenopausal women with osteoporosis and mild-to-moderate chronic kidney disease. *J Bone Miner Metab*. 2022;40(4):677-687. doi:10.1007/s00774-022-01332-8