



Effects of romosozumab on low bone mineral density or osteoporosis in postmenopausal women: a systematic review

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Abstract: Osteoporosis is characterized by induced bone mass and deterioration of the skeletal microstructural, which weakens bone strength and adds the risk of fracture. Patients with osteoporosis treated with romosozumab has been indicated to be effective in postmenopausal women. This study aimed to systematically review the effect of romosozumab in postmenopausal women with low bone mineral density (BMD) or osteoporosis. PubMed, Cochrane library, and EMBASE databases were searched from the inception dates till March 12, 2019, using the keywords romosozumab, postmenopausal women, and osteoporosis to identify published RCTs meeting inclusion criteria. A narrative synthesis was conducted under specific headings according to the framework by the Economic Social and Research Council. Eight studies meeting the inclusion criteria were included. It was found that romosozumab significantly increased BMD from baseline compared with placebo. Almost all studies included showed that the bone resorption marker CTX decreased from baseline early. The BMD at the lumbar spine, femoral neck and total hip was increased in both romosozumab group and teriparatide at month 6 and 12. Common adverse events mainly involved neutralizing antibodies developed and injection site reactions. Compared with alendronate, teriparatide, and placebo, romosozumab enhanced BMD greater. In addition, romosozumab markedly increased the level of bone formation markers and sustainedly decreased the level of bone resorption markers. However, the cardiovascular effect was seriously adverse events for romosozumab and the incidence of adverse events with treatment of romosozumab was a bit higher than that with treatment of alendronate or teriparatide.

Keywords: Romosozumab; postmenopausal women; low bone mineral density (BMD); systematic review

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Introduction

Osteoporosis is characterized by reduced bone mass and deterioration of the skeletal microstructural (1). It is predicted that about 14 million American people aged 50 years or older will be with osteoporosis by 2020 (2). As shown in the investigating, nearly 13 million Japanese women have osteoporosis (3). Despite all this, most people do not receive regular anti-osteoporosis therapy around the globe. Even suffering fracture, more than 75% of patients are absent from

pharmacologic treatment for osteoporosis (4).

Sclerostin, encoded by the gene SOST, inhibits the Wnt and bone morphogenetic protein signaling pathways, thereby decreases bone formation to regulate bone turnover (5,6). Some investigators found that a genetic deficiency of sclerostin would increase bone mass and bone strength (7). Moreover, mice with the sclerostin gene deleted increases bone formation compared with controls (8). Animal study has demonstrated that administration of an antibody to sclerostin caused enhanced bone mass (9). Romosozumab binding

sclerostin results in elevated bone formation and decreased bone resorption. As romosozumab blocks sclerostin activity, it results in allowing for increased Wnt signaling (10,11).

Alendronate can inhibit bone resorption and is used as first-line drug treating osteoporosis. In a trial, postmenopausal women treated with alendronate had less risk of fractures than those treated with placebo (12). To be different from alendronate, bone-forming therapy increases bone mass by stimulating bone formation. Teriparatide is one of bone-forming agents and works by improving remodeling activity (13). Despite teriparatide boosts trabecular bone mineral density (BMD), the promoting in bone resorption during up to 24 months of therapy has an association with a reduce in volumetric BMD (vBMD) of the cortical bone at the hip (14).

In the past several years, many studies about the effect of romosozumab on osteoporosis were published. Postmenopausal women with osteoporosis using romosozumab therapy for 12 months followed by alendronate caused a significantly decreased risk of fracture compared with that with treatment of alendronate alone (15). It was found that vertebral and femoral strength enhanced more with treatment of romosozumab than that with treatment of teriparatide at month 12 (16). Moreover, in women with postmenopausal osteoporosis, romosozumab resulted in gains in hip BMD which was not observed with treatment of teriparatide (17). Thus, we systematically review the effect of romosozumab in postmenopausal women with low BMD or osteoporosis.

Methods

Search trials

We searched the PubMed, Cochrane library, and EMBASE databases from the inception dates till March 12, 2019, using the keywords romosozumab, postmenopausal women, and osteoporosis to identify published RCTs meeting inclusion criteria. Only studies restricted to English with the full text available were included.

Inclusion criteria

Studies were selected according to the following inclusion criteria: (I) RCTs comparing romosozumab, romosozumab + alendronate, or romosozumab + denosumab with placebo, alendronate, teriparatide, or placebo + denosumab; (II) trials enrolling postmenopausal women with low BMD or osteoporosis; (III) trials providing data of BMD or

bone formation marker PINP and bone resorption marker CTX. Exclusion criteria were (I) randomized trials without a placebo or treatment group; (II) a history of vertebral fracture or a fracture of the wrist, humerus, hip; (III) a history of metabolic bone disease; (IV) current hypercalcemia, hypocalcemia, hyperparathyroidism or hypoparathyroidism; (V) participants if they had recent use of a medication affecting bone metabolism.

Risk-of-bias assessments

The methodological quality for the included RCTs was evaluated independently by 2 researchers on the basis of Cochrane risk-of-bias criteria, and each quality item was graded as low risk, high risk, or unclear risk. The 7 items used to assess bias in each study included the randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.

Data extraction

Country of researches, publish year, number of subjects, intervening measure, mean age, outcome (BMD, bone formation marker PINP and bone resorption marker CTX, adverse events), time of follow-up were comprised. Two researchers independently extracted the information by using a data extraction form from each study. Disagreements were resolved by discussion with another researcher until a consensus was reached.

Synthesis of results

A narrative synthesis was conducted under specific headings according to the framework by the Economic Social and Research Council. The narrative synthesis process was exploring relationships within and between the extracted data to find out how different studies contributed to the specific headings. Accurate findings from included studies were grouped together and reported by using appropriate descriptive statistics.

Results

Studies retrieved and characteristics

Initially, the search strategy identified 500 titles and abstracts. After excluding duplicates, 48 titles and abstracts were screened. Ultimately, 8 studies met the inclusion criteria and were included in *Figure 1*. Among these studies,

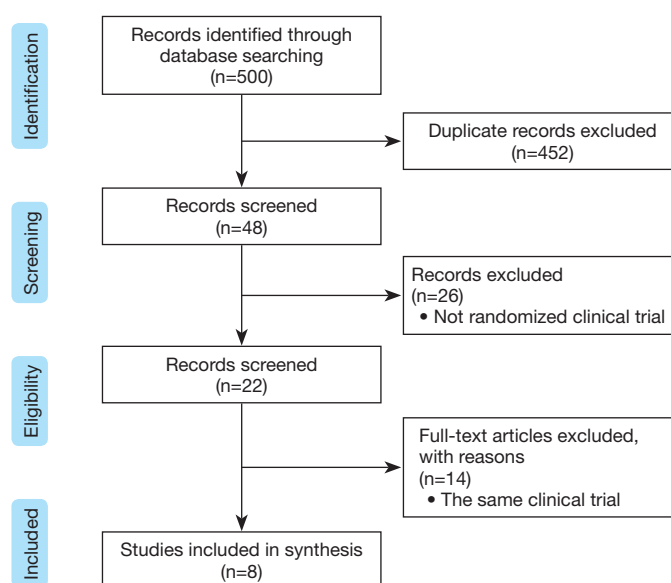


Figure 1 Flow diagram of study selection.

six trials included were romosozumab compared with placebo, three trials included were romosozumab compared with teriparatide and one trial included was romosozumab compared with alendronate (*Table 1*). Overall, all included studies were randomized, controlled trial and were judged to be of good quality.

Romosozumab compared with placebo

BMD

It was shown that romosozumab significantly increased BMD from baseline compared with placebo (18). Particularly, several studies have suggested that BMD of the lumbar spine was increased from baseline in comparison with placebo (2,11,16,19,20). McClung *et al.* (19) found that the results had statistical difference whether dose frequency (monthly or every 3 months) or dose level (140 or 210 mg). Ishibashi *et al.* (20) discovered that dose-dependent effect of romosozumab on BMD were existed in postmenopausal Japanese women with osteoporosis. It was also observed that BMD of the total hip and femoral neck was increased compared with placebo group in varying degrees (11,16,19). However, in another study, no significant difference was found in the risk of nonvertebral fracture at 24 months in both romosozumab group and placebo group (11).

Bone turnover marker

Padhi *et al.* (2) found that the serum level of the bone-

formation marker PINP was increased from baseline at all romosozumab doses. Moreover, serum concentration of PINP of the subjects using romosozumab was significantly higher than that in the placebo group. McClung *et al.* and Cosman *et al.* (11,19) discovered that the level of P1NP increased rapidly in the early time (month 1 or day 14), then declined to baseline level (between months 2 and 6 or at 12 months). Almost all studies (2,11,19,20) included on this topic showed that the level of the bone-resorption marker CTX decreased from baseline early, remaining below placebo and below baseline through the whole follow-up period, while it was an exception for women with dose of 1 mg/kg Q2W (2).

Romosozumab compared with teriparatide

BMD

The researchers (16-18) found that the BMD of the lumbar spine, femoral neck and total hip was increased in both romosozumab group and teriparatide group at month 6 and 12. These changes were more for romosozumab group than that for teriparatide group.

Bone turnover marker

Langdahl *et al.* (17) discovered that the level of P1NP increased rapidly in the romosozumab group, with an initial rise that was significantly higher than that in the teriparatide group, while the level of P1NP was significantly lower in patients in

Table 1 Characteristics of included studies

Study	Country	Year	Group	Number	Age (years, mean $\pm$ SD)	Study types	Outcome	Follow-up (months)
Genant	America	2017	Romosozumab	24	64.3 $\pm$ 4.7	Randomized, controlled trial	BMD, Aes	12
			Teriparatide	31	65.8 $\pm$ 5.7			
			Placebo	27	66.1 $\pm$ 5.8			
Padhi	America	2014	Romosozumab 1 mg/kg Q2W	6	56.8 $\pm$ 7.8	Randomized, controlled trial	BMD, BTM, Aes	3
			Romosozumab 2 mg/kg Q4W	6	57.3 $\pm$ 6.6			
			Romosozumab 2 mg/kg Q4W	6	62.5 $\pm$ 8.0			
			Romosozumab 3 mg/kg Q4W	6	54.3 $\pm$ 7.8			
			Romosozumab 1 mg/kg Q2W	6	61.2 $\pm$ 9.0			
			Romosozumab 3 mg/kg Q4W	6	59.3 $\pm$ 12.7			
			Placebo	12	59.1 $\pm$ 5.6			
McClung	America	2014	Romosozumab	261	66.7 $\pm$ 6.6	Randomized, controlled trial	BMD, BTM, Aes	12
			Teriparatide	55	66.8 $\pm$ 5.7			
			Alendronate	51	67.1 $\pm$ 5.8			
			Pooled Placebo	52	67.0 $\pm$ 6.5			
Ishibashi	Japan	2017	Romosozumab 70 mg QM	63	66.5 $\pm$ 6.3	Randomized, controlled trial	BMD, BTM, Aes	12
			Romosozumab 140 mg QM	63	68.4 $\pm$ 6.0			
			Romosozumab 210 mg QM	63	68.3 $\pm$ 5.9			
			Placebo	63	67.8 $\pm$ 7.2			
Saag	America	2017	Romosozumab	2,046	74.4 $\pm$ 7.5	Randomized, controlled trial	BMD, BTM, Aes	24
			Alendronate	2,047	74.2 $\pm$ 7.5			
Cosman	America	2016	Romosozumab	3,321	70.9 $\pm$ 7.0	Randomized, controlled trial	BMD, BTM, Aes	12, 24
			Placebo	3,322	70.8 $\pm$ 6.9			
Langdahl	Denmark	2017	Romosozumab	218	71.8 $\pm$ 7.4	Randomized, controlled trial	BMD, BTM, Aes	12
			Teriparatide	218	71.2 $\pm$ 7.7			
Keaveny	America	2017	Romosozumab 210 mg QM	24	64.3 $\pm$ 4.7	Randomized, controlled trial	BMD, Aes	12
			Teriparatide 20 mg QD	31	65.8 $\pm$ 5.7			
			Placebo	27	66.1 $\pm$ 5.8			

BMD, bone mineral density; Aes, adverse events and safety; BTM, bone turnover marker.

the romosozumab group than that in the teriparatide group measured between months 3 and 12. CTX decreased rapidly in the initial time, then increased to baseline by month 3, with the level remaining near baseline at month 12. Similarly, the concentration of CTX was significantly lower in patients in the romosozumab group than that in the teriparatide group

measured between months 3 and 12.

Romosozumab compared with alendronate

BMD

Patients using romosozumab had greater gains in BMD

from baseline measured at all the time points than patients who received alendronate alone. Therapy with romosozumab followed by alendronate resulted in lower risk of new vertebral fractures and nonvertebral fracture than alendronate alone over a period of 24 months (15).

Bone turnover marker

Romosozumab increased the level of P1NP and decreased the level of CTX within 12 months. After the transition to alendronate, the level of P1NP and β -CTX declined and remained below baseline level at 36 months. The level of P1NP and β -CTX of patients using alendronate alone decreased within 1 month and remained below baseline at 36 months (15).

Adverse events and safety

Among the 36 subjects using romosozumab, two subjects developed neutralizing antibodies during the study (18). Injection-site reactions were detected in several studies. Injection-site reactions (mostly mild in severity) were observed more frequently with romosozumab than with placebo, but no dose-response relationship was observed (2). Likewise, it was reported in 187 patients (5.2%) using romosozumab and in 104 (2.9%) using placebo over the 12-month period (15). In the first 12 months, injection-site reactions were reported in more patients using romosozumab [90 of 2,040 patients (4.4%)] than in those using alendronate [53 of 2,014 patients (2.6%)] (20). Otherwise, injection site reactions were reported by 17 (8%) patients with romosozumab and 6 (3%) patients with teriparatide (11). Many adverse events, involving hematochezia, acute blood loss anemia, severe coronary artery disease was not regarded to be associated with study treatment (18,19). Serious adverse events were reported in 14% in patients with placebo (7 of 50), 8% in patients with alendronate (4 of 51), 9% in patients with teriparatide (5 of 54), and 7% in patients with romosozumab (17 of 255) (2).

Discussion

It was found that romosozumab significantly improved BMD by using DXA from baseline and decreased the risk of fracture compared with placebo (2,11,16,18,19,20). In the patients with romosozumab, the level of bone turnover marker PINP increased from baseline, while the level of CTX declined from baseline compared with placebo (2,11,19,20). The changes of BMD from baseline were

greater for romosozumab than those for teriparatide (16-18). Both the level of PINP and CTX were significantly increased in patients in the teriparatide group than those in the romosozumab group at months 3 and 12. The level of PINP was higher than the baseline at all the time points and the level of CTX was nearly equivalent to the baseline (17). Patients who received alendronate alone had less gains in BMD from baseline than patients who received romosozumab plus alendronate at all measured sites (15). Romosozumab increased the concentrations of PINP, whereas alendronate reduced the level of PINP. Both romosozumab and alendronate resulted in the decreased level of CTX from baseline (15). No fatal adverse event was found in the studies of therapy with romosozumab. Seriously adverse of hypersensitivity took place in 7 patients in the romosozumab group in the first 12 months (20). Common adverse events mainly involved neutralizing antibodies developed, injection site reactions.

From the results of the included studies, we knew that alendronate and teriparatide could be good drugs for treatment of osteoporosis. However, alendronate may decrease the level of PINP when it inhibits bone resorption and teriparatide may increase CTX when it promotes bone formation. Romosozumab increased bone formation and reduced bone resorption, the effect of which was also superior to alendronate and teriparatide. In animal test, some researchers (21) examined the effect of romosozumab on bone quality in ovariectomized cynomolgus monkeys. In accordance with the included studies, the result showed that it was increased in bone mass, architecture, and bone strength. In general, the occurrence rate of adverse events was rare with the treatment of romosozumab. Otherwise, the study of Chouinard *et al.* (22) suggested that romosozumab would not generate a carcinogenic risk to humans. Nevertheless, serious cardiovascular events using romosozumab were a little more than those using alendronate and teriparatide. And this disadvantage will influence physicians to prescribe romosozumab and may remain obstacles to accept the new therapy for patients (23).

Our review firstly systematically showed the effect of romosozumab on osteoporosis and preventing fractures compared with various kinds of drugs or placebo. Compared with the study of Liu *et al.* (24), our review had more advantages such as the enlarged the enrolled subjects. Because the increased participants would improve the reliability of treatment effect of romosozumab. Except evaluating the changes of BMD, we also paid attention to the variation of bone turnover markers involved PINP and CTX. In addition,

assessment of adverse events and safety could not be ignored for any drugs, therefore we review all the descriptive adverse events and safety in the included studies.

There are several limitations of our systematic review. Firstly, we have not analyzed quantitatively the outcome by different doses of romosozumab compared with different drugs at various time points as the studies were still lack. Secondly, most of the included studies derived from Europe and the United States, which resulted in some bias of research participants. Thirdly, due to the short space, we did not present all results of every study and showed the main information in each paper.

Conclusions

Romosozumab increased BMD greater compared with alendronate, teriparatide, or placebo. In addition, romosozumab markedly increased bone formation markers and continually decreased bone resorption markers. However, the cardiovascular effects were main adverse events for romosozumab and the incidence was a bit higher than that with treatment of alendronate or teriparatide. It requires more researches of romosozumab as a therapy for patients with osteoporosis to validate the treatment outcome.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/aoj.2019.12.07>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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