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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 II)

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Romosumab (ROMO) should be used to treat postmenopausal women with osteoporosis at high fracture risk after carefully considering the cardiovascular status and the risk/benefit balance. Clinicians should avoid ROMO for patients with a history of myocardial infarction or stroke in the past 12 months. Although ROMO offers an alternative for patients with a high risk of osteoporotic fractures, it is affected by previous osteoporosis treatment: using denosumab (DENO) and oral bisphosphonates for over one year attenuates its effect. An additional 12 months of DENO appears to be more effective than ibandronate for the enhancement of bone mineral density (BMD) as a sequential agent after 12 months of ROMO, with few severe adverse events. However, it is important to emphasize that ROMO is not a first-choice medication. It is only indicated when bisphosphonates cannot help, and its clinical use has demonstrated cardiovascular risks. The cost and availability could also make its use problematic in clinical practice. Therefore, although ROMO represents an important advance in the treatment of osteoporosis, it is by no means a solution for osteoporosis.

INTRODUCTION

Kobayakawa et al. investigated the therapeutic and adverse effects of romosozumab (ROMO) in treating osteoporosis in clinical practice. Treatment with ROMO for 12 months significantly improved bone mineral density (BMD) of the lumbar spine, total hip, and femoral neck, according to real-world data.[1] In 2022, Iniose et al. demonstrated the efficacy of 12 months of ROMO treatment for osteoporosis with high fracture risk; the TRACP-5b value before ROMO administration was a significant predictor of the increase in lumbar spine BMD.[2]

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 treatment 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?

METHODS

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 40 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 the exclusion of articles was that we subjectively considered that these articles were not relevant to the subject of our manuscript.

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RESULTS

TIME-COURSE CHANGES IN BONE METABOLISM MARKERS AND DENSITY IN PATIENTS WITH OSTEOPOROSIS TREATED WITH ROMO

In the study by Inage et al., a significant increase in BMD was only observed in the lumbar spine. ROMO also improved BMD from the initial phase after administration, although the result was only observed in the lumbar spine. Significant improvements in bone metabolism markers (TRACP 5b and P1NP) levels were seen before and 1-2 months following ROMO administration.[3]

COMPARATIVE CLINICAL STUDIES

IMPACT OF ROMO ON TRABECULAR BONE SCORE COMPARED WITH ANTI-RESORPTIVE AGENTS IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS

According to Jeong et al., ROMO has shown significant BMD improvement in previously performed trials. However, BMD only reflects bone strength and does not provide information on bone microarchitecture.[4] The trabecular bone score (TBS) is a noninvasive tool to assess bone microarchitecture.[4] In the study of Jeong et al., the primary outcome was the percentage change in the TBS from baseline to post-treatment. Postmenopausal osteoporosis individuals were followed up for 6 and 12 months after ROMO (210 mg monthly, N =10) and denosumab (DENO) (60 mg every six months, N=21) or ibandronate (150 mg monthly, N=24) treatments, respectively. If the washout period was sufficient, individuals who had previously utilized osteoporosis drugs were included. The percentage change in TBS from baseline to post-treatment was 2.53±2.98% (6 months, N=10; P=0.04), 0.59%±3.26% (12 months, N=21; P=0.48), and -0.45±3.66% (12 months, N=24; P=0.51) in the ROMO, DENO, and ibandronate groups, respectively. ROMO showed a noticeable increase in TBS, although it did not reach the least significant change (5.8%) in TBS. This study concluded that ROMO improved the TBS in postmenopausal women with osteoporosis. TBS might be potentially useful for monitoring ROMO treatment.[4]

ROMO VERSUS TERIPARATIDE FOR THE TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS

Tian et al. published a systematic review on the efficacy and safety of ROMO and teriparatide for the treatment of postmenopausal osteoporosis. The study results indicated that ROMO showed better improvements in the lumbar spine, total hip, and femoral neck BMD. Also, injection site reactions were less frequent, but there was no significant difference in the incidence of serious adverse events and death. Based on these results, Tian et al. demonstrated that ROMO was better than teriparatide in terms of both efficacy and adverse effects.[5]

ROMO IMPROVES LUMBAR SPINE BONE MASS AND BONE STRENGTH PARAMETERS RELATIVE TO ALENDRONATE IN POSTMENOPAUSAL WOMEN

Brown et al. demonstrated the positive effect of ROMO on bone structural parameters evaluated by quantitative CT in a subset of patients included in the Active-Controlled Fracture Study in Postmenopausal Women With Osteoporosis at High Risk (ARCH) trial.[6]

ROMO VERSUS DENO FOR POSTMENOPAUSAL OSTEOPOROSIS TREATMENT

In a retrospective observational registry study, Kobayakawa et al. compared the efficacy of treatment with DENO or ROMO for 12 months in patients with postmenopausal osteoporosis. ROMO showed greater potential for BMD improvement than DENO.[7]

EFFECTIVENESS OF ROMO IN PATIENTS WITH OSTEOPOROSIS ON MAINTENANCE HEMODIALYSIS

Sato et al. evaluated the efficacy of ROMO in osteoporotic hemodialysis patients at high fracture risk in a 1-year single-center study of Japanese hemodialysis patients. There was no apparent increase in cardovascular disease (CVD) events during the study, which suggested that ROMO was a promising agent for hemodialysis patients with severe osteoporosis.[8]

IMPACT OF PREVIOUS OSTEOPOROSIS TREATMENT ON 12-MONTH ROMO TREATMENT RESPONSE IN PATIENTS WITH POSTMENOPAUSAL OSTEOPOROSIS

Ebina et al. reported that the significant predictors of BMD changes at 12 months were pretreatment difference and P1NP (N-terminal type I procollagen propeptide) value at one month for the lumbar spine, and pretreatment difference and percent change in TRACP-5b (isoform 5b of tartrate-resistant acid phosphatase) at one month for the total hip. The primary difference significantly affected the early effects of ROMO on increasing the lumbar spine and total hip BMD at 12 months.[9]

MODELING-BASED BONE FORMATION AFTER TWO MONTHS OF ROMO TREATMENT

According to Eriksen et al., the highest bone formation markers in human patients treated with ROMO are observed within the first two months. Histomorphometric analysis of bone biopsies from the phase 3 FRActure study in postmenopausal woMen with ostEoporosis (FRAME) trial showed an early and significant increase in bone formation with a concomitant decrease in resorption. Thus, the stimulation of bone formation in the first two months of treatment with ROMO in postmenopausal women with osteoporosis is predominantly due to increased modeling-based bone formation on endocortical and cancellous surfaces.[10]

ROMO DIMINISHES THE INCIDENCE OF NEW VERTEBRAL FRACTURES ACROSS SEVERITY GRADES AMONG POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS

Vertebral fractures are the most common type of osteoporotic fracture, and their prevalence and severity are key risk factors for future fragility fractures.[11] Geusens et al. evaluated the effect of ROMO treatment on the incidence of new vertebral fractures according to Genant severity grades (mild, moderate, and severe). Over 12 months, consistent reductions in new moderate or severe vertebral fractures were observed regardless of prevalent (FRAME; $p = 0.18$) or severe (ARCH; $p = 0.52$) vertebral fractures at baseline. These reductions were sustained for 24 months after the transition from ROMO to DENO or alendronate, regardless of their prevalence or severity at baseline. No significant interactions were observed between the incidence of new moderate or severe vertebral fractures and the presence of prevalent (FRAME; $p = 0.81$) or severe (ARCH; $p = 0.99$) vertebral fractures at baseline.[11]

ROMO IMPROVES VERTEBRAL BONE STRUCTURE IN WOMEN WITH LOW BMD

In one study, Poole et al. collected lumbar computed tomography spine scans at enrollment and 12 months after treatment with ROMO (210 mg subcutaneously monthly, n = 17), daily open teriparatide (20 µg subcutaneously, n = 19), or placebo (subcutaneously monthly, n = 20). For 56 women, cortical thickness, endocortical thickness, cortical BMD, cancellous BMD, and cortical mass surface density were measured on the first lumbar vertebral surface. This study confirmed widespread vertebral bone accretion with ROMO or teriparatide treatment. It provided new insights into how rapidly preventing vertebral fractures is achieved in women with osteoporosis using these anabolic agents.[12]

IMPACT OF ROMO WITH AND WITHOUT ACTIVE VITAMIN D ANALOG SUPPLEMENTATION FOR POSTMENOPAUSAL OSTEOPOROSIS

Kobayakawa et al. conducted a prospective cohort investigation in which they compared the effects of 12-month ROMO treatment for increasing BMD in postmenopausal osteoporosis to observe the influence of combined vitamin D supplementation. ROMO significantly increased BMD independent of adding an active vitamin D analog.[13]

IMPACT OF PRIOR OSTEOPOROSIS TREATMENT DURATION ON THE EFFECT OF ROMO TREATMENT

Tominaga et al. showed that the duration of prior treatment affected ROMO's efficacy; denosumab and bisphosphonates for more than one year attenuated its effect.[14]

SEQUENTIAL THERAPY

SKELETAL RESPONSES TO ROMO AFTER ONE YEAR OF DENO

McClung et al. reported that transition to ROMO after 12 months of DENO appeared to improve lumbar spine BMD and maintain total hip BMD while possibly preventing the rapid increase in bone turnover marker levels above baseline values expected after discontinuation of DENO.[15]

ROMO, FOLLOWED BY ANTIRESORPTIVE TREATMENT, INCREASES THE LIKELIHOOD OF ACCOMPLISHING BMD TREATMENT GOALS

The results of a study published by Cosman et al. suggest that baseline BMD and the probability of achieving target BMD T-score goals are factors to consider when selecting initial treatment for patients with osteoporosis. As the baseline T-score falls below -2.7 (total hip) and -3 (lumbar spine), alendronate has a <50% probability of achieving a BMD target above the osteoporosis range, whereas these probabilities remain relatively high for regimens starting with ROMO.[16]

IMPACT OF PREVIOUS OSTEOPOROSIS TREATMENT ON THE ROMO TREATMENT RESPONSE FOLLOWED BY DENO IN PATIENTS WITH POSTMENOPAUSAL OSTEOPOROSIS

Ebina et al. showed that in patients with postmenopausal osteoporosis, osteoporosis pretreatment affected the increase in BMD of subsequent treatment with 12 months of ROMO. Still, it did not affect the subsequent treatment with 12 months of DENO after ROMO.[17]

EFFECTS AFTER BEGINNING OR SWITCHING FROM A BISPHOSPHONATE TO ROMO OR DENO IN POSTMENOPAUSAL PATIENTS

Shimizu et al. observed that ROMO continuously augmented BMD over 12 months and performed better than DENO. Besides, the impact of ROMO in patients previously treated with bisphosphonate on the femoral neck and total hip BMD was nearly equal to those of DENO.[18]

ROMO FOLLOWED BY DENO IN WOMEN WITH HIGH FRACTURE RISK

A study showed that ROMO/DENO administration substantially increased BMD and a lower vertebral fracture rate versus placebo/DENO at all measured time points.[19]

EFFICACY AND SAFETY OF IBANDRONATE OR DENO FOR POSTMENOPAUSAL OSTEOPOROSIS AFTER 12-MONTH TREATMENT WITH ROMO AS SEQUENTIAL THERAPY

Kobayakawa et al. stated that ROMO is a potent drug for the treatment of postmenopausal osteoporosis but has a dosing period limited to 12 months. BMD decreases shortly after discontinuation of ROMO, underscoring the importance of adequate sequential treatment.[20] In the VICTOR ran-

domized controlled study, these authors compared the efficacy of ibandronate and DENO as sequential treatment options after 12-month ROMO treatment. This study revealed that DENO could be considered more effective than ibandronate, with few adverse events, for improving BMD as a sequential agent after ROMO in postmenopausal patients with osteoporosis.[20]

RHEUMATOID ARTHRITIS AND OSTEOPOROSIS

Mochizuki et al. have investigated the effects of ROMO treatment on disease activity and BMD in patients with rheumatoid arthritis (RA) and severe osteoporosis compared with the impact of DENO treatment. This study revealed that ROMO treatment was more effective than Deno treatment in increasing lumbar spine BMD at three months. The study also suggested that ROMO treatment does not affect disease activity in patients with RA and severe osteoporosis at six months.[21] In another study, ROMO showed comparable effectiveness to DENO for increasing BMD in patients with RA treated with glucocorticoids.[22] Mochizuki et al. investigated the effect of treatment with ROMO versus DENO on BMD in patients with RA. ROMO treatment was more effective for augmenting lumbar spine BMD than DENO.[23]

BONE LOSS SECONDARY TO PYOGENIC SPONDYLODISCITIS

Ohnishi et al. reported the case of a patient with osteoporosis due to pyogenic spondylodiscitis who was successfully treated with ROMO (bone formation was increased).[24]

COST-EFFECTIVENESS STUDIES

One study indicated that sequential ROMO-to-alendronate could be a cost-effective treatment option for postmenopausal women with severe osteoporosis at high risk of fracture. Base case results demonstrated that, compared with teriparatide/alendronate, ROMO/alendronate diminished costs by $5134 per patient and yielded 0.045 additional quality-adjusted life years. This study showed that ROMO/alendronate produces greater health benefits at a lower total cost than teriparatide/alendronate.[25] Another study assessed the cost-effectiveness of 1 year of ROMO followed by alendronate treatment versus oral bisphosphonates alone for women in Canada with postmenopausal osteoporosis at very high risk for fracture. The results demonstrated that ROMO followed by alendronate, was a cost-effective treatment alternative, superior to alendronate and risedronate alone.[26] In 2020, Davis et al. assessed the clinical efficacy, safety, and cost-effectiveness of non-bisphosphonates (DENO, ROMO, and teriparatide) compared with each other, bisphosphonates, or no treatment, for the prevention of fragility fracture. Although non-bisphosphonates were efficacious for preventing fragility fractures, the incremental cost-effectiveness ratios were generally greater than the commonly applied threshold of £20,000-£30,000 per quality-adjusted life year.[27]

CASE REPORTS

Uemura et al. published the case of a 61-year-old heavy smoker with a nonunion of the distal radius. Combining treatment with ROMO and spanning distraction plate fixation with bone graft substitutes achieved a satisfactory bone union.[28] Lee et al. presented the case of a 67-year-old woman with humerus shaft fracture nonunion, in whom bone union could not be achieved after 11 months of conservative treatment; however, adequate bone healing was attained after the administration of ROMO once a month for six months.[29] According to Crow et al., bone disease is a known complication of cystic fibrosis. They published the case of a 46-year-old premenopausal woman with cystic fibrosis-related bone disease and multiple fractures who were treated with ROMO. After one year of ROMO treatment, the medication was well tolerated, and BMD improved significantly. Of the currently available antiresorptive or anabolic osteoporosis drugs, only bisphosphonates have been studied in people with cystic fibrosis.[30] Suzuki et al. presented the case of a 42-year-old man with chronic kidney disease on hemodialysis who developed severe osteoporosis. Serum calcium levels were extremely high, bone metabolic markers were abnormal, and the patient had pathological fractures. Bone biopsy indicated a bone metabolism disorder and increased bone turnover. ROMO was administered once a month as an intervention for the bone disorder. Throughout the ten months of use, bone metabolic markers and the reduction in BMD improved.[31]

DISCUSSION

According to Yu et al., sclerostin (a protein secreted by osteocytes) negatively regulates the Wnt signaling pathway by binding to the LRP5/6 co-receptors, as well as inhibiting bone formation and promoting bone resorption.[32] Sclerostin contributes to musculoskeletal-related diseases, making it a promising therapeutic target for treating Wnt-related bone diseases. New evidence indicates that sclerostin also contributes to the development of certain types of cancer, obesity, and diabetes, suggesting that it could be a promising therapeutic target for these diseases. In particular, some cardiovascular diseases are related to the protective role of sclerostin. Three distinct types of inhibitors targeting sclerostin have been developed: monoclonal antibodies, aptamers, and small-molecule inhibitors. The monoclonal antibody ROMO, the first sclerostin inhibitor approved by the US FDA, has demonstrated excellent efficacy in the treatment of postmenopausal osteoporosis; however, in clinical trials, it has conferred a high cardiovascular risk. In addition, ROMO can only be administered by subcutaneous injection, which could cause compliance problems for patients who prefer oral therapy.[32]

The goal of osteoporosis treatment is to prevent fractures.[33] Several pharmacological agents are available to reduce fracture risk by reducing bone resorption or stimulating bone formation. Bisphosphonates are the most widely used anti-resorptive because they reduce bone turnover markers to low premenopausal concentrations and decrease

fracture rates (vertebral by 50%-70%, non-vertebral by 20%-30%, and hip by ~40%). Bisphosphonates bind avidly to bone minerals and have a compensatory effect measured over months to years. Long-term, continued use of oral bisphosphonates is typically interspersed with drug rest periods of 1-2 years to minimize the risk of atypical femoral fractures. DENO is a monoclonal antibody against RANKL that potently inhibits osteoclast development and activity, administered by subcutaneous injection every six months. The anti-fracture effects of DENO are similar to those of bisphosphonates. Still, there is a pronounced loss of the antiresorptive effect from 7 months after the last injection, which can result in clusters of rebound vertebral fractures. Two classes of anabolic drugs are currently available to stimulate bone formation: teriparatide and abaloparatide. Both target the parathyroid hormone-1 receptor and are administered daily subcutaneous injections for up to 2 years. ROMO is a monoclonal antibody against sclerostin that stimulates bone formation and inhibits bone resorption, administered as monthly subcutaneous injections for one year. Comparative studies suggest that anabolic agents have greater efficacy against fractures and produce greater increases in BMD than anti-resorptive drugs. The effects of anabolic agents are transient; thus, a transition to anti-resorptive medications is necessary. The optimal strategy for cycling anabolics, anti-resorptive, and treatment-free periods is yet to be determined. The efficacy and safety of ROMO have been established in trials. However, it should not be prescribed to patients at high risk for cardiovascular or cerebrovascular events.[33]

According to Lim et al., comprehension of the Wnt signaling pathway has resulted in the appearance of ROMO, one of the most potent osteoanabolic drugs to date for the management of osteoporosis.[34] The pivotal ARCH and FRAME reports determined ROMO's fracture reduction effectiveness. In the ARCH report, it was better than alendronate in fracture decrease and BMD rise; however, ROMO treatment must be followed consecutively with a powerful antiresorptive drug. The anti-fracture effectiveness obtained from ROMO is sustained or ameliorated after shifting to an antiresorptive drug. As one of the most potent osteoanabolic medications, establishing ROMO has substantially augmented our capacity to manage osteoporosis. Reports have rendered significant data on employing ROMO with other osteoporosis agents to optimize osteoporosis management. ROMO administered before antiresorptive drugs is related to more substantial BMD increases than when an antiresorptive medication is used before ROMO. ROMO is advised for osteoporosis management in individuals at very elevated risk for fracture with small cardiovascular risk. It is usually well tolerated, with 4%-5% of individuals having injection area adverse events. However, the ARCH study demonstrated a higher risk of cardiovascular complications in individuals taking ROMO. ROMO has a black-box warning stating that it must not be started in individuals who have had myocardial infarction or stroke in the previous year. Although ROMO has shown substantial osteoanabolic impact and anti-fracture effectiveness and can help those with high fracture risk, additional research is required to determine its cardiovascular safety.[34]

In 2022, McConnell et al. stated that polypharmacy and osteoporosis commonly co-occur in older adults.[35] Polypharmacy is increasingly acknowledged as a risk factor for hip and fall-connected fractures. Medications for osteoporosis include antiresorptive (alendronate, risedronate, zoledronic acid, ibandronate, DENO) and osteoanabolic (teriparatide, abaloparatide, ROMO) drugs. Given that polypharmacy is related to poorer adherence to pharmacologic treatment, the election of osteoporosis treatment must be personalized and based on several elements, including underlying fracture risk (elevated versus very elevated risk), medical comorbidities, treatment burden, fracture risk decrease types, manners of administration, and complications of management alternatives.[35]

In a recently published *post hoc* analysis, Langdahl et al. evaluated ROMO effectiveness and safety in European individuals recruited for the FRAME study. ROMO management for one year, followed by denosumab for a further two years, led to an early and maintained risk decrease for main fracture types, combined with a substantial BMD rise.[36]

According to Reid et al., drugs available for diminishing fracture risk act to either restrain bone resorption or promote bone formation.[37] ROMO is unique in that it has both actions. Bisphosphonates are the most commonly employed drugs because of their effectiveness, safety, and low cost. However, persistent utilization of oral bisphosphonates for >5 years increases the risk of atypical femoral fractures; thus, it is commonly punctuated with drug holidays of 6-24 months. DENO is a further powerful anti-resorptive medication given as 6-monthly subcutaneous injections. It is equivalent to the bisphosphonates in effectiveness and safety but has a rapid offset of impact following discontinuation. Thus, it must be followed by an alternate agent, commonly bisphosphonate. Teriparatide spurs both bone formation and resorption, significantly increases spine density, and diminishes vertebral and non-vertebral fracture percentages, though information for hip fractures is scarce. Management is commonly limited to 18-24 months, then shifting to an anti-resorptive. ROMO is given monthly subcutaneous injections for 12 months, followed by an antiresorptive. This succession averts more fractures than antiresorptive therapy alone. Because of the cost, anabolic agents are commonly used in patients at very high fracture risk. Levels of 25-hydroxyvitamin D must be sustained above 30 nmol/L, utilizing supplements if sunlight exposure is inadequate. Calcium intake has little impact on BMD and fracture risk but must be maintained above 500 mg/day, employing alimentary sources.[37]

Appelman-Dijkstra et al. reported that after discontinuation of DENO and ROMO, BMD rapidly returns to baseline. In the case of DENO, discontinuation can cause rebound bone loss and the appearance of vertebral fractures. Consequently, sequential antiresorptive treatment to maintain bone mass increases, and anti-fracture effectiveness is of paramount significance.[38]

Chen et al. explored ROMO's adverse events using the FDA Adverse Event Reporting System. A total of 4,413,695

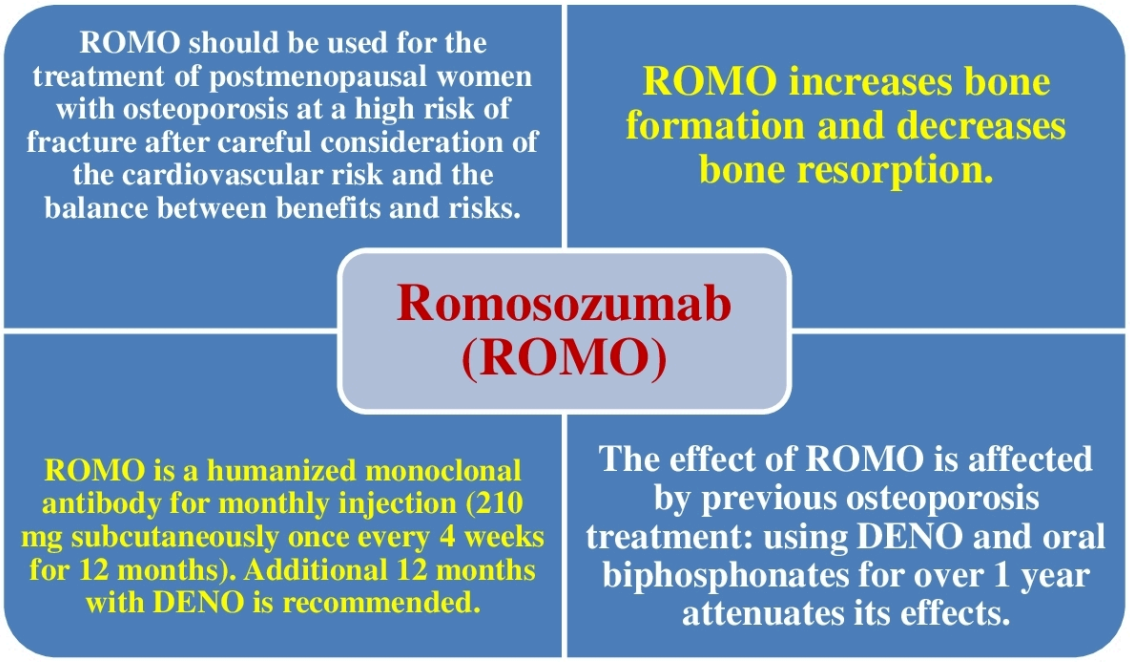

Figure 1. Summary of the main current data on the role of romosozumab (ROMO) in treating postmenopausal osteoporosis.

DENO = Denosumab.

adverse events were collected. There were 1948 adverse events related to ROMO. Injection area pain, cardiac failure, renal problems, pneumonia, and augmented blood alkaline phosphatase were potential adverse events following ROMO use. This report rendered an adverse reaction warning for the clinical use of ROMO.[39]

In 2022, Luo et al. reported a microsimulation Markov model comparing the cost-efficacy of 5 treatment approaches, including zoledronate, DENO, abaloparatide, teriparatide, and ROMO in patients with postmenopausal osteoporosis with a recent fracture. Zoledronate was the least expensive approach, and DENO was the most cost-effective choice among these five approaches.[40]

Since drug pricing is an important aspect of its usage capacity, the high cost of ROMO could be a problem in some countries, as well as its reported cardiovascular risks, possibly limiting its use in patients with cardiovascular problems. **FIGURE 1** summarizes the main current data on the potential role and risks of ROMO in the treatment of osteoporosis.

TABLE 1 summarizes the articles reviewed in this paper on the role of ROMO in the treatment of osteoporosis.

CONCLUSIONS

The effect of ROMO is affected by prior osteoporosis treatment; oral DENO and bisphosphonate attenuate its impact for more than one year. Finally, it is paramount to state that ROMO is not a first-choice drug, given that it is only indicated when bisphosphonates are unsuccessful. Additionally, its cost and availability can make its utilization problematic in clinical practice. Thus, even though ROMO represents an important advance in the management of osteoporosis, it is by no means a solution to the problem.

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 limitations mentioned above in 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 something of importance can always be left out in one way or another. Logically, we have chosen articles that we consider of the greatest importance.

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Table 1. Studies on the role of romosozumab (ROMO) in the treatment of osteoporosis.

AUTHORS [REFERENCE]	YEAR	TYPE OF STUDY	LoE	CONCLUSION
Davis et al.[27]	2020	A systematic review and economic evaluation.	NA	Non-bisphosphonates are effective in preventing fragility fractures, but the incremental cost-effectiveness ratios are generally greater than the commonly applied threshold of £20,000-30,000 per quality-adjusted life-year.
Kobayakawa et al.[1]	2021	Prospective multicenter cohort study.	NA	According to real-world data, ROMO treatment for 12 months significantly improved lumbar spine, total hip, and femoral neck BMD.
Inage et al.[3]	2021	Multicenter retrospective observational study.	NA	ROMO demonstrated improvement in bone density from the early phase after the administration, though the result was only seen in the lumbar spine.
Jeong et al.[4]	2021	Retrospective observational cohort study.	NA	ROMO improved the trabecular bone score (TBS) in postmenopausal women with osteoporosis. TBS may be potentially useful for monitoring ROMO treatment.
Tian et al.[5]	2021	Systematic review and meta-analysis through a grade analysis of evidence.	NA	This study demonstrated that ROMO was better than teriparatide both in terms of efficacy and side effects.
Brown et al.[6]	2021	The Active-Controlled Fracture Study in Postmenopausal Women With Osteoporosis at High Risk (ARCH) trial (NCT01631214; https://clinicaltrials.gov/ct2/show/NCT01631214).	NA	The ARCH trial showed that ROMO for one year, followed by alendronate, led to larger areal bone mineral density (aBMD) gains and superior fracture risk reduction versus alendronate alone.
Kobayakawa et al[7]	2021	This retrospective observational registry study compared the efficacy of 12-month DENO or ROMO treatment in postmenopausal osteoporosis patients.	NA	ROMO showed a higher potential for improving BMD than DENO in this clinical study of postmenopausal osteoporosis patient treatment.
Sato et al.[8]	2021	This was a single-center 1-year study in Japanese hemodialysis patients.	NA	BMD was increased significantly during ROMO treatment at the lumbar spine and the femoral neck, respectively, at one year in hemodialysis patients. Hypocalcemia occurred but without any intolerable event. There was no apparent increase in cardiovascular disease (CVD) events during one year of study, suggesting ROMO is a promising agent for hemodialysis patients with severe osteoporosis.
Ebina et al.[9]	2021	In this prospective, observational, and multicenter study, treatment naïve patients (Naïve; n=50) or patients previously treated with bisphosphonates (n=37) or DENO (n=45) or teriparatide (n=16) (mean age, 75.0 years; T-scores of the lumbar spine [LS] -3.2 and total hip [TH] -2.6) were switched to ROMO due to insufficient effects of prior treatment.	NA	The early effects of ROMO on LS and TH BMD increase at 12 months were significantly affected by the difference of prior treatment and are predicted by the early change in bone turnover markers.
McClung et al.[15]	2021	This phase 2 trial (NCT00896532) enrolled postmenopausal women with a lumbar spine, total hip, or femoral neck *T*-score ≤ -2.0 and ≥ -3.5. Individuals were randomized to placebo or various ROMO dosing regimens from baseline to month 24, were re-randomized to 12 months of DENO or placebo (months 24-36), and then all received ROMO 210 mg monthly for 12 months (months 36-48).	NA	Transitioning to ROMO after 12 months of DENO appeared to improve lumbar spine BMD and maintain total hip BMD while possibly preventing the rapid increase in bone turnover markers above baseline expected upon DENO discontinuation.

Cosman et al[16]	2021	This study compared the probability of achieving a *T*-score of > -2.5 over three years at the total hip (TH) or lumbar spine (LS) in women with osteoporosis, ≥55 years of age, after the following treatment sequences: 1-year ROMO followed by two years DENO [FRAME (FRActure study in postmenopausal woMen with ostEoporosis) and FRAME extension trials], one-year ROMO followed by two years alendronate, or alendronate-only for three years (ARCH trial).	NA	The findings of this study suggested baseline BMD and the probability of achieving BMD *T*-score goals are factors to consider when selecting initial treatment for patients with osteoporosis. As the baseline *T*-score falls below -2.7 (TH) and -3.0 (LS), alendronate has <50% likelihood of achieving a BMD goal above the osteoporosis range, whereas these probabilities remain relatively high for regimens beginning with ROMO.
Shimizu et al[18]	2021	Postmenopausal osteoporosis patients with a high risk of fracture-154 were recruited; their therapies were switched to ROMO or DENO from biphosphonates (BP)/naïve or vitamin D. Longitudinal changes in BMD were evaluated.	NA	ROMO continuously increased BMD for 12 months and performed better than DENO. On the other hand, the effects of ROMO switched from BP on BMD of the femoral neck and total hip were almost the same with DENO.
Miyauchi et al[19]	2021	This post hoc analysis of the FRAME study investigated the long-term efficacy and safety of ROMO followed by DENO in postmenopausal Japanese women with osteoporosis at high fracture risk.	NA	ROMO/DENO in Japanese subjects at high risk of fracture resulted in significant BMD gains and numerically lower vertebral fracture rate vs. placebo/DENO at all time points measured.
Mochizuki et al[21]	2021	Open-label, randomized, pilot study on patients with rheumatoid arthritis (RA).	NA	ROMO treatment was more effective than DENO treatment in increasing BMD of the lumbar spine at three months. Furthermore, the present study suggested that ROMO treatment has no effects on the disease activity of RA in patients with RA and severe osteoporosis for six months.
Ohnishi et al.[24]	2021	Case report (pyogenic spondylodiscitis).	NA	Considering the underlying characteristics of bone loss in pyogenic spondylodiscitis and the relatively older population of patients with this condition, the use of anabolic medications may be desirable in these patients, given the potential advantages reported in previous studies.
Söreskog et al[25]	2021	A microsimulation model with a Markov structure was used to simulate fractures, costs, and quality-adjusted life years (QALYs), for women treated with romo-to-alendronate or alendronate alone.	NA	The results of this study indicate that sequential ROMO-to-alendronate can be a cost-effective treatment option for postmenopausal women with severe osteoporosis at high risk of fracture.
Uemura et al[28]	2021	Case report	NA	A combination of systemic ROMO administration and grafting β-tricalcium phosphate with bridge plating provides an effective treatment option for difficult cases of comminuted distal radius nonunion with risk factors such as smoking, diabetes, and fragility.
Lee et al[29]	2021	Case report	NA	To our knowledge, this is the first case reporting the successful use of ROMO for treating established nonunion (humerus shaft fracture).
Inose et al.[2]	2022	Multicenter retrospective study	NA	This study demonstrated the effectiveness of the 12-month ROMO treatment for osteoporosis with a high risk of fractures.
Eriksen et al[10]	2022	These authors analyzed bone biopsies from FRAME to assess the effect of 2 months of ROMO versus placebo on the surface extent of modeling-based bone formation (MBBF) and remodeling-based bone formation (RBBF).	NA	This study showed that stimulation of bone formation in the first two months of ROMO treatment in postmenopausal women with osteoporosis is predominately due to increased MBBF on endocortical and cancellous surfaces.

Geusens et al[11]	2022	Data were reported from two phases 3 clinical studies for patients who received ROMO versus placebo through 12 months, followed by DENO through 24 months (FRAME: NCT01575834), and for patients who received ROMO through 12 months, followed by alendronate through 24 months, versus alendronate only through 24 months (ARCH: NCT01631214).	NA	Reductions in the incidence of new moderate and severe vertebral fractures (VFs) were sustained through 24 months after the transition from ROMO to DENO or alendronate, independent of baseline VF prevalence or severity; no significant interactions were observed between the incidence of new moderate-or-severe VFs and the presence of prevalent (FRAME; p = 0.81) or severe (ARCH; p = 0.99) VFs at baseline.
Poole et al.[12]	2022	These authors analyzed the data from a study collecting lumbar computed tomography (CT) spine scans at enrollment and 12 months post-treatment with ROMO (210 mg sc monthly, n = 17), open-label daily teriparatide (20 µg sc, n = 19), or placebo (sc monthly, n = 20).	NA	For all these measurements, the differences between ROMO and teriparatide were statistically significant ($p < 0.05$). There was no significant difference between the ROMO-associated BMD gains of 22.2% versus 18.1% for teriparatide, but both were significantly greater compared with the change in the placebo group (-4.6%, $p < 0.05$).
Kobayakawa et al[13]	2022	This prospective cohort investigation compared the effects of 12-month ROMO treatment to increase BMD for postmenopausal osteoporosis to observe the influence of combined vitamin D supplementation.	NA	ROMO may significantly increase BMD regardless of the addition of an active vitamin D analog.
Tominaga et al.[14]	2022	In total, 259 osteoporosis patients received subcutaneous injections of ROMO (210 mg) every four weeks during 2019 and 2020. This study was designed as a pre-post comparison. The endpoints were the percent changes in BMD after 12 months of ROMO treatment.	NA	The duration of the previous treatment affected the effectiveness of ROMO. Using DENO and oral biphosphonate for more than one year attenuated the effect of ROMO.
Ebina et al[17]	2022	In this prospective, observational, multicenter study, treatment-naïve patients (Naïve; n = 55) or patients previously treated with bisphosphonates (n = 37), DENO (n = 45), or teriparatide (n = 17) (mean age, 74.6 years; T-scores of the lumbar spine [LS] - 3.2 and total hip [TH] - 2.6) were switched to ROMO for 12 months, followed by DENO for 12 months.	NA	Previous treatment affected the BMD increase following treatment with ROMO, although it did not affect the following treatment with DENO after ROMO.
Kobayakawa et al[20]	2022	Prospective VICTOR study.	NA	The VICTOR study revealed that denosumab could be considered more effective than ibandronate, with few severe adverse events, for the enhancement of BMD as a sequential agent after ROMO in postmenopausal osteoporosis patients.
Kobayakawa et al[22]	2022	This retrospective observational registry study compared the efficacy of the 12-month treatment of DENO and ROMO in rheumatoid arthritis (RA) patients under the influence of glucocorticoid intake.	NA	ROMO exhibited comparable efficacy to DENO for increasing BMD even under the influence of glucocorticoids for treating RA. Both drugs may be, therefore, suitable for managing osteoporosis in patients with RA and glucocorticoid intake.
Mochizuki et al.[23]	2022	A randomized clinical pilot study	NA	ROMO treatment was more effective in increasing the BMD at the lumbar spine than DENO and may be selected for patients who require a significant increase in the lumbar spine BMD. Moreover, ROMO might not affect disease activity and joint damage in patients with RA.

Goeree et al[26]	2022	A Markov model followed a hypothetical cohort of postmenopausal osteoporotic women at very high risk for future fractures to estimate the cost-effectiveness of ROMO and alendronate compared to oral bisphosphonates alone.	NA	ROMO/alendronate was associated with reduced costs and greater benefits than other comparators. Probabilistic, deterministic, and scenario analyses indicate that ROMO/alendronate represents the best value for money; the uncertainty analyses are robust, and therefore ROMO should be considered for reimbursement by public drug plans in Canada.
Crow et al.[30]	2022	Case report (cystic fibrosis-related osteoporosis).	NA	This report highlighted that ROMO might be an effective alternative treatment modality in selected patients with cystic fibrosis at high risk for fractures.
Suzuki et al[31]	2022	Case report (autosomal dominant polycystic kidney disease undergoing hemodialysis–related osteoporosis).	NA	Through the 10-month usage of ROMO, bone metabolic markers improved, and the decrease in bone mineral density was ameliorated.
Yu et al[32]	2022	Review article.	NA	ROMO demonstrated excellent effectiveness in treating postmenopausal osteoporosis; however, it conferred high cardiovascular risk in clinical trials. Furthermore, ROMO could only be administered by injection, which may cause compliance issues for patients who prefer oral therapy.
Reid et al.[33]	2022	Review article.	NA	ROMO is given as monthly subcutaneous injections for one year. Head-to-head studies suggested that anabolic agents have greater anti-fracture efficacy and increase BMD more than anti-resorptive drugs. The effects of anabolic agents are transient, so a transition to anti-resorptive medications is required. The optimal strategy for cycling anabolics, anti-resorptive, and off-treatment periods remains to be determined.
Lim[34]	2022	Review article.	NA	The risk of cardiovascular disease with ROMO is unclear. While ROMO has demonstrated significant osteoanabolic effects and anti-fracture efficacy and will benefit high fracture-risk patients, further studies are needed to investigate the cardiovascular safety of ROMO.
McConnell and Shieh[35]	2022	Review article.	NA	Treatments for osteoporosis include antiresorptive (alendronate, risedronate, zoledronic acid, ibandronate, DENO) and osteoanabolic (teriparatide, abaloparatide, ROMO) agents. The selection of osteoporosis treatment should be individualized and based on various factors, including underlying fracture risk (high vs. very high risk), medical comorbidities, medication burden, fracture risk reduction profiles, modes of administration, and side effects of treatment options.
Langdahl et al[36]	2022	This post hoc analysis assessed ROMO efficacy and safety in European patients enrolled in FRAME.	NA	Among European patients in FRAME, ROMO resulted in early and sustained risk reduction for all major fracture categories, associated with large BMD gains that continued after the transition to DENO.

Reid[37]	2022	Review article.	NA	Because of cost, ROMO is usually reserved for those at very high fracture risk. 25-hydroxyvitamin D levels should be maintained above 30 nmol/L, using supplements if sunlight exposure is limited. Calcium intake has little effect on BMD and fracture risk but should be maintained above 500 mg/day using dietary sources.
Appelman-Dijkstra et al[38]	2022	Review article.	NA	Sequential antiresorptive therapy is of utmost importance to maintain bone mass gains and anti-fracture efficacy.
Chen et al.[39]	2022	This is a pharmacovigilance analysis of FDA adverse event reporting system events for ROMO.	NA	This study provided an adverse reaction warning for the clinical application of ROMO and provided real-world disproportionality analysis data support for the possible adverse events of ROMO.
Luo et al.[40]	2022	A microsimulation Markov model was created to compare the cost-effectiveness of five treatment strategies, including zoledronate, DENO, abaloparatide, teriparatide, and ROMO in postmenopausal osteoporosis patients with a recent fracture from the healthcare perspective of the USA.		Among postmenopausal osteoporosis patients with very high fracture risk in the USA, zoledronate is the cheapest strategy, and DENO is the most cost-effective choice among these five strategies.

LoE = level of evidence; NA = not available; BMD = bone mineral density; DENO = denosumab; FAD = Food and Drug Administration.

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