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Romsozumab (sclerostin monoclonal antibody) for the treatment of osteoporosis in postmenopausal women: A review

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ABSTRACT

Romsozumab (ROMO) is a recently approved monoclonal antibody (approved by the U.S. Food and Drug Administration [FDA] in April 2019 and Health Canada in June 2019) for the treatment of osteoporosis in postmenopausal women. ROMO works by selectively inhibiting sclerostin—a glycoprotein that inhibits osteoblasts and further promotes bone resorption. The authors reviewed three phase III clinical trials (Fracture Study in Postmenopausal Women with Osteoporosis [FRAME], Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk [ARCH], and Study evaluating the effect of Romsozumab Compared with Teriparatide in postmenopausal women with osteoporosis at high risk for fracture previously treated with bisphosphonate therapy [STRUCTURE]) that demonstrated ROMO's ability to increase bone mineral density (BMD) at the lumbar spine and hip and the risk of vertebral and clinical fractures. Additionally, clinical trials demonstrated the risk for serious cardiovascular events among patients that received ROMO, and these severe adverse reactions deserve further investigation. Although ROMO presents as a potentially exciting therapeutic with serious clinical implications, the authors recommend further analysis using real-world evidence (RWE) studies to fully elucidate the cardiovascular event risk associated with ROMO administration.

Keywords: *osteoporosis; romsozumab; sclerostin; review*

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INTRODUCTION

Osteoporosis is a skeletal disease that is clinically identified by low bone mass and microarchitectural deterioration, which eventually leads to decreased bone strength and higher probability for bone fractures.¹ Osteoporosis is the most common skeletal disorder, with the highest prevalence being in females (the female-to-male ratio is between 4 and 7.5).^{2,3} Census data from the United States show osteoporosis having a prevalence of 15.4% among women over 50 years old.⁴ It is estimated that most patients living with osteoporosis, clinically defined by T-score ≤ -2.5 , are not treated.³

To date, there are multiple classes of drugs available for the management of postmenopausal osteoporosis. These drug classes include hormone replacement therapy (HRT), selective estrogen modulators, calcitonin, bisphosphonates (BPs), teriparatide (TPTD) (fragment of parathyroid hormone), and denosumab (DMAB) (an antiRANK ligand monoclonal antibody).³ Romosozumab (ROMO) is a monoclonal antibody jointly developed by Amgen and UCB for the treatment of osteoporosis and is recently approved by the U.S. FDA in April 2019 and by Health Canada in June 2019.^{5,6}

The main purpose of this mini-review is to summarize the three randomized clinical trials that contributed to the approval of ROMO for the treatment of osteoporosis in post-menopausal women at high risk of fracture in the United States and Canada. After reporting information on ROMO's mechanism of action and drug disposition, we focused on evidence from randomized clinical trials about efficacy and safety concerns.

We searched for ROMO randomized clinical trials in MEDLINE/PubMed, EMBASE, and Cochrane Library from inception until June 2019. In addition, we hand-searched references from the retrieved articles and explored a number of related web sites.

BACKGROUND—PHARMACODYNAMICS AND PHARMACOKINETICS OF ROMO

Pharmacodynamics

When the canonical Wnt pathway is activated within osteoblasts, a series of intracellular events eventually lead to the translocation of β -catenin to the nucleus of these cells. This subsequently leads to gene transcription and upregulation of genes that stimulate osteoblast differentiation, proliferation and survival, in turn increasing bone formation.⁷

However, when the glycoprotein sclerostin, encoded by the SOST gene, binds to the osteoblast surface through the low-density lipoprotein receptor protein 5 and 6 (LRP5/6) and frizzled coreceptors, the canonical Wnt pathway is inhibited.^{8,9} Accordingly, sclerostin inhibits bone formation by inhibiting the osteoblasts. Further research has shown that sclerostin is able to increase bone resorption by increasing the production of receptor activator of nuclear factor kappa- β ligand (RANKL) by the osteocytes.¹⁰

The consequences of sclerostin downregulation have been delineated by two autosomal recessive disorders. Sclerosteosis and Van Buchem disease are two autosomal recessive disorders that lead to a loss of function mutation in the SOST gene and in the regulatory region of SOST, respectively.^{11–14} Both these patient groups have been shown to have increased bone mineral density (BMD) and a very low risk of fractures.

Recognition of the clinical effects of sclerostin motivated the development of sclerostin inhibitors as a potential treatment for osteoporosis. Thus, ROMO is a monoclonal antibody against sclerostin which leads to the stimulation of bone formation and the inhibition of bone resorption.

The pharmacodynamics of ROMO was examined in a placebo-controlled phase I study in male volunteers and healthy postmenopausal females ($n = 72$). A single subcutaneous dose (SC) of ROMO (doses used: 0.1–10 mg/kg) produced a

dose-dependent increase across all dosage cohorts in markers of bone formation, procollagen type 1 N-propeptide (s-P1NP), bone-specific alkaline phosphatase (s-BAP), and osteocalcin, 85 days after administration of ROMO (5.3 and 2.8% increase in lumbar spine and total hip, respectively, $p < 0.01$ vs. placebo).¹⁵ Thus, pharmacodynamic studies of ROMO in humans appear to have a dual action, stimulating bone formation and, at the same time, inhibiting bone resorption.

Pharmacokinetics

Generally, ROMO is administered subcutaneously (SC) with an absorption of 50–70% and a half-life of 6–7 days, as shown in the phase I study mentioned above.^{15,16} In the clinical trial, a single SC dose of ROMO administered to healthy postmenopausal female and male volunteers was associated with a dose proportional increase in serum concentrations, with clearance decreasing with increasing dose.¹⁷

ROMO has been shown to have a nonlinear pharmacokinetic profile, which was most prevalent in the dosage cohorts between 1 and 3 mg/kg SC. Peak ROMO serum concentrations were observed within the first week after SC administration, and declines were observed in a biphasic manner in the highest SC doses that were given, with a half-life of 6–7 days.

Exposure (area under the curve, 0–inf) in subjects administered SC ROMO (1 and 5 mg/kg) was about 50 and 70%, compared to subjects administered IV ROMO.¹⁵ Bioavailability was determined to be 81% after SC ROMO (210 mg) was administered once/month in healthy volunteers, patients with low bone mass, and those with postmenopausal osteoporosis.¹⁸ Clearance of ROMO from the body is decreased in patients with impaired renal function. The product monograph warns that caution is required in patients with severe renal impairment (glomerular filtration rate [eGFR] < 30 mL/min/1.73 m²) or undergoing dialysis.¹⁹

EVIDENCE FOR ROMO EFFICACY—THE PHASE III CLINICAL TRIALS

The antifracture efficacy of ROMO in women with osteoporosis (target population) was demonstrated in three different phase III clinical trials: FRAME (Fracture Study in Postmenopausal Women with Osteoporosis, NCT01575834), ARCH (Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk, NCT01631214), and STRUCTURE (STudy evaluating effect of RomosozUmab Compared with Teriparatide in postmenopausal women with osteoporosis at high risk for fracture previously treated with bisphosphonate therapy, NCT01796301).^{20–22}

The FRAME study randomized 7,180 postmenopausal women with osteoporosis to ROMO (210 mg/monthly) or placebo, followed by a continuation during which all patients received DMAB (60 mg) every 6 months for 12 months.²⁰ Results indicate that during the first 12 months of the study, ROMO reduced vertebral fracture risk by 73% and clinical fractures by 36%. During the extension of the trial (after 12 months of ROMO or placebo), the risk reduction for fracture was maintained, although this was only significant for vertebral fractures. ROMO also increased BMD at the total hip by 6.8% and spine by 13.3% after 12 months compared with 0.0% at both regions in postmenopausal women treated with placebo. During the extension, BMD was also increased in both the ROMO + DMAB and placebo + DMAB groups. By 24 months, BMD at the spine had increased by 17.6 and 5.0% in the ROMO + DMAB and placebo + DMAB groups, respectively, and at the total hip by 8.8 and 2.9%, respectively, meaning that the absolute difference in BMD between the two groups was maintained during the extension period of the study.²⁰

The ARCH study randomized 4,093 women with severe osteoporosis (T score ≤ -2.5 and a prevalent vertebral fracture) to ROMO (210 mg/month)

or alendronate (ALN) (70 mg/week) for 12 months followed by ALN (70 mg/week) for all patients.²¹ By 24 months, the risk of new vertebral fractures, nonvertebral fractures, clinical fractures, and hip fractures was reduced by 48, 19, 27, and 38%, respectively, in the ROMO–ALN group compared with the ALN–ALN group. Another finding by 24 months was that BMD increased by 7.1% at the total hip and 15.2% at the lumbar spine in women treated with ROMO–ALN compared with 3.4 and 7.1%, respectively, in women treated with ALN–ALN.

The aim of the STRUCTURE study was to compare the effects of ROMO with TPTD in postmenopausal women that were previously treated with BPs²²; 436 postmenopausal women were enrolled in the study who had been treated with BPs for 3 years or more. These women were randomized to 12-month treatment with either ROMO (210 mg/month) or TPTD (20 µg/daily). Results indicated that BMD increased significantly more with ROMO than with TPTD at both the total hip and lumbar spine.²² In addition, bone strength was increased by 2.5% in women treated with ROMO compared with a decrease of –0.7% in women treated with TPTD.

ADVERSE EVENTS—DRUG SAFETY CONCERNS THAT OCCURRED IN PHASE III CLINICAL TRIALS

Adverse events associated with ROMO were reported in 16.4% of patients receiving the drug in phase III clinical trials. The most common adverse events that were listed include nasopharyngitis (1.0%), injection site erythema (1.1%), injection site pain (1.3%), and joint pain (1.9%).²³

The initial 12-month component of the double-blinded FRAME trial included adverse events such as arthralgia (occurring in 13% of ROMO recipients and 12% of placebo recipient), nasopharyngitis (occurring in 12.8% of ROMO recipients and 12.2% of placebo recipients), back pain (occurring in 10.5% of ROMO recipients and

10.6% of placebo recipients), hypersensitivity (occurring in 6.8% of ROMO recipients and 6.9% of placebo recipients), injection-site reaction (occurring in 5.2% of ROMO recipients and 2.9% of placebo recipients), osteoarthritis (occurring in 7.8% of ROMO recipients and 8.8% of placebo recipients), and atypical femoral fracture (occurring in <0.1% of ROMO recipients and 0% of placebo recipients). Serious adverse events occurred as well, with 1.2% of ROMO patients and 1.1% of placebo recipients, respectively, experiencing a serious cardiovascular event, of which 0.5% of ROMO-treated and 0.4% placebo-treated patients died. About 18% of patients in the ROMO group (646 patients) developed anti-ROMO antibodies during the first 15 months of the FRAME trial, and neutralizing antibodies were detected in 0.7% of patients in the same group (25 patients).²⁰

The initial 12-month component of the double-blinded ARCH trial included adverse events such as back pain (occurring in 9.1% of ROMO recipients and 11.3% of ALN recipients), nasopharyngitis (occurring in 10.4% of ROMO recipients and 10.8% of ALN recipients), osteoarthritis (occurring in 6.8% of ROMO recipients and 7.2% of ALN recipients), hypersensitivity (occurring in 6% of ROMO recipients and 5.9% of ALN recipients), injection-site reaction (occurring in 4.4% of ROMO recipients and 2.6% of ALN recipients), and hypocalcaemia (occurring in <0.1% of ROMO recipients and <0.1% of ALN recipients). Serious adverse events were observed as well, with 2.5% of ROMO recipients and 1.9% of ALN recipients experiencing a serious cardiovascular event, of which 0.8% in the ROMO group and 0.6% in the ALN group died. About 15.3% of patients in the ROMO treatment group (310 patients) developed anti-ROMO antibodies during the first 18 months of the ARCH trial, and neutralizing antibodies were detected in 0.6% of patient in the same group (12 patients).²¹

In the STRUCTURE trial, adverse drug events were detected and included nasopharyngitis (occurring in 13% of ROMO recipients and 10% of TPTD recipients), arthralgia (occurring in 10% of ROMO recipients and 6% of TPTD recipients), injection-site reaction (occurring in 8% of ROMO recipients and 3% of TPTD recipients), hypercalcemia (occurring in <1% of ROMO recipients and 10% of TPTD recipients), and hypocalcemia (occurring in 1% of ROMO recipients and 0% of TPTD recipients). Serious adverse events were observed as well, with 8% of ROMO recipients and 11% TPTD recipients, respectively. About 17% (37 patients) in the ROMO group developed anti-ROMO antibodies; however, neutralizing antibodies were not detected in ROMO recipients during the study.²²

DISCUSSION

Now approved for the treatment of osteoporosis in the United States (April 2019) and Canada (June 2019), ROMO will be a new therapy for postmenopausal women living with severe osteoporosis. As the trials have shown, the goal is to increase BMD, restore bone quality, improve bone strength, and reduce fracture risks. Based on the clinical trials conducted to date, ROMO has been approved for a treatment duration of 12 months.¹⁹ Since the treatment effects of ROMO are reversible, it will be important for patients to continue with antiresorptive treatment thereafter.

The serious adverse events observed in the ARCH study (2.5% of ROMO recipients experiencing serious cardiovascular event) are of great concern and worthy of discussion. There have been possible explanations for the increased risk of cardiovascular events in ROMO recipients compared with ALN recipients. One explanation for the difference between the treatment groups is not caused by ROMO, but by ALN reducing the risk of cardiovascular events. Yet, current meta-analyses of clinical trials investigating ALN reducing cardiovascular risk failed to confirm its

cardio-protective role.²⁴ Another explanation is that sclerostin plays a physiological role in the cardiovascular system.²⁵ Sclerostin has been found in aortic vascular smooth muscle. Thus, inhibition of sclerostin via ROMO could potentially affect the Wnt pathway and thereby, vascular remodeling. Lastly, the difference in cardiovascular risk could be attributed to a chance finding, as the number of events is small.²⁶

Now that ROMO has been approved for general use, it is important to start conducting observational studies on its effectiveness and safety in the “real world.” To date, only randomized controlled trials (RCTs) have provided the efficacy and safety information about ROMO. However, RCTs usually have restrictive inclusion and exclusion criteria for enrolling patients, thus not being fully representative of the real-world population that is going to use ROMO.²⁷ It is important to conduct real-world evidence (RWE) studies as they include patient populations that are far more representative than those of RCTs by utilizing a wide range of research methodologies and data sources from patient registries, claims database studies, patient surveys, and electronic health record studies.²⁸ We believe ROMO RWE studies can complement the findings from the above listed RCTs by providing valuable information on treatment practices and patient characteristics among unselected patients that will use this newly approved medication. As the RWE studies accumulate over time, systematic reviews and meta-analysis should be conducted to further build on current findings and ultimately provide better care for patients.

CONCLUSION

In conclusion, the clinical potential for ROMO is noteworthy. ROMO is an osteoporosis treatment with dual action: (1) it stimulates bone formation and modeling and (2) inhibits bone resorption. This leads to increases in bone mass and bone strength, and reductions in the risk of

fractures among postmenopausal women. Strong evidence from clinical trials has demonstrated that fracture risk reductions are more prominent among ROMO recipients than the reductions seen with the commonly used BPs. Adverse events, particularly cardiovascular risk among ROMO users, are not well defined and not well studied. Once in the market, RWE studies will provide valuable information on the effectiveness and safety of ROMO in the real world.

AUTHORS' CONTRIBUTIONS

A. Shakeri and C. Adanty initiated the project, assembled the team, extracted relevant papers for the review, and wrote the manuscript. C. Adanty contributed topic area expertise to the manuscript draft. Both authors reviewed the drafts and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare that no potential conflicts of interest exist with respect to the research, authorship, and/or publication of this article.

DATA AVAILABILITY STATEMENT

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COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any studies with human participants or animals performed by any of the authors.

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