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# Comparing Romosozumab and Alendronate in the Treatment of Osteoporosis in Postmenopausal Women

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## Abstract

The purpose of this literature review is to determine if there is a statistical difference in the safety and efficacy between romosozumab, the prototypical drug in the new drug class sclerostin inhibitors, versus alendronate, the prototypical bisphosphonate, in the treatment of postmenopausal osteoporosis. A comprehensive literature review was performed searching PubMed, EMBASE, and Access Medicine from the last five years. Works chosen for review were limited to articles published in English, full-text articles, clinical trials, randomized control trials, systematic reviews, and meta-analyses. Items were excluded after reviewing abstracts due to material not directly comparing the treatment modalities. The research presented shows beneficial evidence of bone formation and retention of bone density with treating postmenopausal women with osteoporosis with romosozumab for two years, followed by bisphosphonate therapy. However, the risks and benefits of this treatment regimen must be taken into consideration for each patient. Providers should take extra caution in starting romosozumab treatment in patients with cardiovascular health issues. Healthcare providers must take a thorough medical history and decide in collaboration with the patient about their treatment for osteoporosis. Current research on romosozumab does show promise in the treatment of osteoporosis. However, studies do show potential cardiovascular risk in starting romosozumab. Therefore, providers must take cation in starting this medication in patients with pervious cardiovascular co-morbidities.

*Keywords:* romosozumab, alendronate, postmenopausal, female, human, safety, efficacy

## Introduction

Romosozumab is the prototypical drug in a new class of medication, sclerostin inhibitors, which have been found to decrease fractures in postmenopausal women with osteoporosis. Alternatively, Alendronate, the prototypical drug for bisphosphonates, has been around since the 1960s for the treatment of osteoporosis in postmenopausal women (Blume and Curtis, 2011). Osteoporosis in postmenopausal women is an essential issue because 10 million Americans have osteoporosis, and 80% of them are postmenopausal women (National Osteoporosis Foundation, 2019). This is a crucial issue because the annual medical cost spent on osteoporosis-related fractures in the United States is $16 billion (Blume & Curtis, 2011). Some patients with minimal health problems experience falls that cause devastating fractures due to their osteoporosis, which can leave them with significant medical bills and debilitating injuries.

## Statement of the Problem

- Osteoporosis in postmenopausal women is a very pressing issue in healthcare throughout the United States, as it affects numerous current patients and will continue to affect patients in the future.
- There are many different approaches to the treatment of postmenopausal osteoporosis. Alendronate has been considered the “tried and true” treatment.
- Romosozumab, the prototypical medication in the new class of drugs, sclerostin inhibitors, is now Food and Drug Administration (FDA) approved in the treatment of osteoporosis in postmenopausal women.
- A comparison of efficacy and adverse effects will determine which medication is preferred for the treatment of osteoporosis in postmenopausal women.

## Research Question

- Is there a statistical difference in safety and efficacy between romosozumab, the prototypical drug in the new drug class sclerostin inhibitors, versus alendronate, the prototypical bisphosphonate, in the treatment of postmenopausal osteoporosis?

## Literature Review

**Safety of Romosozumab**

- The most common side effects related to romosozumab in the phase III trials were dose-related to 210 mg injection and include arthralgia, nasopharyngitis, and back pain (Bandeira et al., 2017).
- Serious side effects of romosozumab included 6.8% experiencing hypersensitivity reaction, < 0.1% osteonecrosis of the jaw (ONJ), and < 0.1% atypical femur fracture (Bandeira et al., 2017).
- There is no significant difference in the incidence of adverse events in patients treated with romosozumab compared to placebo (95% CI, p = 0.93) and alendronate (95% CI, p = 0.02) (Liu et al., 2018).
- Cardiovascular events occurred in 2.5% of patients receiving romosozumab compared to 1.9% receiving alendronate (Khosla, 2017).

**Safety of Alendronate**

- The most common adverse effect of oral bisphosphonate treatment is gastrointestinal symptoms, including reflux, esophagitis, gastritis, and diarrhea (Milat & Ebeling, 2016).
- Atypical femoral fractures are more frequent (113 in 1000,000 patients per year) in patients who have been exposed to long-term bisphosphonate therapy (7 to 8 years) (Milat & Ebeling, 2016).
- There were minimal alterations in bone material properties when comparing five-year and ten-year alendronate therapy (Hassler et al., 2014). This suggests that prolonged reduction in bone turnover with ten years of alendronate therapy is unlikely associated with adverse effects on bone material.
- The risk of ONJ in patients taking oral bisphosphonates is 1 in 10,000 to 1 in 100,000 patients per year (Milat & Ebeling, 2016).

**Efficacy of Romosozumab**

- After one year, romosozumab showed a 73% reduction in new vertebral fractures compared to placebo (p < 0.001), shown in figure 1 (Bandeira et al., 2017).
- There was also a 36% decrease in clinical fractures (p = 0.008), as shown in figure 2 (Bandeira et al., 2017).

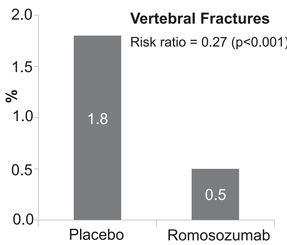


Figure 1. New vertebral fractures after 1 year. Romosozumab with a 73% reduction in new vertebral fractures compared to placebo.

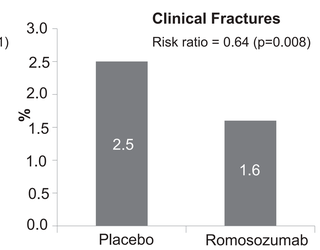


Figure 2. New clinical fractures after 1 year. Romosozumab with a 35% reduction in new clinical fractures compared to placebo.

Figures 1 and 2 From “Romosozumab for the treatment of osteoporosis,” by L. Bandeira, M. Lewiecki, and P. Bilezikian, 2017, Expert Opinion on Biological Therapy, volume 17, p. 259. Copyright 2017 Taylor & Francis Group.

**Efficacy of Alendronate**

- After 12 months, BMD increased from baseline at the lumbar spine, femoral neck, and total hip with alendronate (p= 0.001). The largest increase being 4.7% at lumbar spine (Cesareo et al., 2014).
- Bone turnover markers (BTM) significantly decreased in the treatment group compared to the control group at three months and six months (p < 0.001) (Casareo et al., 2014).

**Direct Comparison**

- Romosozumab significantly increased BMD of lumbar spine with a weighted mean difference (WMD) of 8.70 compared to alendronate (CI 95%, p < 0.00001), total hip WMD of 3.40 (95% CI, p < 0.00001), and femoral neck WMD 3.20 (5% CI, p < 0.00001) (Liu et al., 2018)

## Discussion

**Safety of Romosozumab**

- There does not appear to be a statistically significant difference in adverse effects of romosozumab compared to placebo groups.
- There is not enough evidence to conclude the cardiovascular events of romosozumab compared to placebo groups. This is something that should be further researched to draw a definite conclusion.

**Safety of Alendronate**

- Gastrointestinal symptoms are the most common adverse effects of alendronate therapy but are not statistically significant compared to placebo therapy.
- There is inconclusive evidence of whether the prolonged reduction of bone turnover being the mechanism for rare adverse events such as ONJ and atypical fractures and this should be the focus of future research.

**Efficacy of Romosozumab**

- Romosozumab significantly increased bone formation and substantially decreased bone resorption markers, along with significantly increasing BMD.
- There is also evidence that treatment with bisphosphonates after the use of romosozumab helps to maintain the increase in bone density that occurred with romosozumab treatment and that combination therapy might be the key to treating osteoporosis

**Efficacy of Alendronate**

- There is statistically significant data that alendronate plus vitamin D is superior in increasing BMD than the conservative treatment of vitamin D alone.
- There is also evidence that alendronate therapy continues to increase cancellous and cortical bone even during an extended length of therapy.

**Direct Comparison**

- It is unsure if romosozumab increases cardiovascular adverse events or if alendronate is cardioprotective.
- Women in the ARCH trial were less healthy than women in the FRAME trial. Even with this information, it is still believed that romosozumab slightly increases the risk of cardiovascular events in women with multiple co-morbidities (Khosla, 2017).
- Further research needs to be conducted on the effect romosozumab has on Wnt signaling, and its role in cardiovascular remodeling and sclerostin levels increased at sites of vascular calcification.
- There is clear evidence that romosozumab is superior to alendronate in increasing BMD, increasing bone forming markers, decreasing bone resorption markers, and decreasing fractures rates in postmenopausal women with osteoporosis.

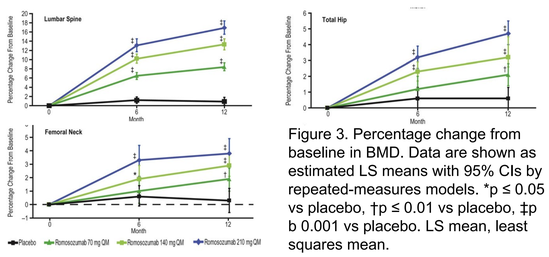


Figure 3. Percentage change from baseline in BMD. Data are shown as estimated LS means with 95% CIs by repeated-measures models. *p ≤ 0.05 vs placebo, †p ≤ 0.01 vs placebo, ‡p b 0.001 vs placebo. LS mean, least squares mean.

Figure 3 From “Romosozumab increases bone mineral density in postmenopausal Japanese women with osteoporosis: A phase 2 study,” by Ishibashi, H., Crittenden, B., Miyauchi, A., Libanati, C., Maddox, J., Fan, M., … Grauer, A. Bone, volume 103, p. 213. Copyright 2017 Elsevier

## Applicability to Clinical Practice

- Whether it is primary care or emergency medicine, osteoporosis will likely be seen daily by most providers due to the number of Americans affected by this disease.
- Because USPSTF recommendation of bone density scans in females 65 and older, many patients will have the diagnosis of osteoporosis.
- The population of the United States continues to grow, and the baby boomer generation is starting to move into the 65 and older category, osteoporosis will start to become even more prevalent in everyday healthcare.
- The Center for Disease Control states that by 2030 older adults, classified as 65 plus, will account for 20% of the United States population (CDC, 2013).
- Hip fractures are especially a topic of concern, as hip fractures are associated with a significant financial burden, increased risk of mortality, and loss of independence. In general, if a patient experiences a hip fracture, they will lose one level of independence (if they were previously using a cane, they would now need a walker, then wheelchair, etc.).
- It is crucial that we, medical professionals, provide the best evidence-based medicine for patients with osteoporosis because of the increasing elderly population of the baby boomers and because of how detrimental a fracture can be to a patient and their family.
- There really is no “perfect” solution in treating postmenopausal osteoporosis.
- I believe that treating postmenopausal women with osteoporosis with romosozumab for two years, followed by bisphosphonate therapy, shows the best evidence for both bone formation and retention of bone density.
- Providers must weigh the risks and benefits of this treatment regimen, being extra cautious at looking into cardiovascular health issues for patients.
- It is imperative that we, as healthcare providers, take a thorough medical history and consider patient preference and decide in collaboration with the patient about their treatment for osteoporosis.

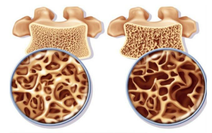


Figure 4. Normal versus osteoporosis diseased vertebral bone

*Figure 4. TCM Treatments for Osteoporosis- Pacific College*. From https://www.pacificcollege.edu/news/blog/2014/12/08/tcm-treatments-osteoporosis

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