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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 three databases, including 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. Taking 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 sclerostin inhibitors does show promise in the treatment of osteoporosis. However, more research still needs to be done to determine safety in patients with cardiovascular health issues.

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. Romosozumab was approved by the Federal Drug Administration (FDA) in April 2019 (Food and Drug Administration, 2019). Romosozumab, a monoclonal antibody, inhibits sclerostin, and rapidly increases BMD by increasing bone formation and decreasing bone resorption (Ishibashi et al., 2017). 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). Alendronate works by inhibiting osteoclast-mediated bone resorption (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.

The purpose of this scholarly project is to answer the question of whether romosozumab, the prototypical sclerostin inhibitor; or alendronate, the prototypical bisphosphonate, is more effective in decreasing fractures in the treatment of osteoporosis in postmenopausal women, along with a comparison of the adverse effect profile of each medication in this population.

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. However, romosozumab, the prototypical medication in the new class of drugs, sclerostin inhibitors, is now 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?

Methods

A comprehensive literature review was performed of PubMed, EMBASE, and Access Medicine. Keywords, MESH terms, and filters were used to define a set of literature discussing the efficacy and adverse effects of romosozumab and alendronate in the treatment of osteoporosis in postmenopausal women. Articles for theme one and three were found by using "romosozumab postmenopausal" as search terms; this resulted in 70 articles. The search was narrowed by limiting the search to the last five years, full text, "female," and "English" articles along with the MESH term "humans." Results for theme one was completed by adding "safety" to the search terms. After review of the articles, two were excluded due to the information not being relevant, resulting in four articles. Results for theme three were achieved by adding "efficacy" to the search terms. After review of the articles, three articles were excluded due to the information not being relevant, resulting in six articles.

Articles for theme two and four were found by using “alendronate postmenopausal” as search terms, this resulted in 1,675 articles. The search was narrowed by limiting the search to the last five years, full text, “female,” “English,” and “clinical trial article” filters. The MESH term “humans” was added to the search resulting in 160 articles. Results for theme two were completed by adding “safety” to the search terms. After reviewing the articles, five articles were excluded due to not being relevant, and two articles were added from other themes because the content fits better with theme two, resulting in four final articles. Results for theme four were completed by adding “efficacy” to the search term. After reviewing the articles, seven articles were excluded due to them not being relevant, and one article was added from a different theme because the content fits better in theme four, resulting in three final articles.

Articles for theme five were found by using “romosozumab alendronate” as search terms, resulting in 28 articles. The search was narrowed by filtering to “last five years,” “English,” “female,” and “journal article” to the filters. The search was further narrowed by adding “humans” as a MESH term. After reviewing the articles, one article was excluded due to the content not being relevant, and one article was added from another theme due to the content being more fitting with theme five, resulting in six final articles. In total, there were 16 articles found for this literature review, with some articles used in multiple themes.

Literature Review

A review of the literature shows that both romosozumab and alendronate have been extensively researched and determined to be safe and efficient in the treatment of postmenopausal females with osteoporosis. A review of the research shows that treatment with romosozumab or alendronate reduces fracture risk and increases bone mineral density (BMD). However, with different mechanisms of action, one may be statistically superior in safety and

efficacy. Studies are limited to those published within the last five years to incorporate the newest research on this topic.

Safety of Romosozumab, Prototypical Sclerostin Inhibitor, in Postmenopausal Women

A meta-analysis by Bandeira, Lewiecki, and Bilezikian (2017) investigates the efficacy and side effects of romosozumab. Amongst the studies, some patients developed anti-romosozumab antibodies with a higher incidence in higher doses. There were no clinical side effects in patients who developed antibodies (Bandeira et al., 2017). Mild side effects reported by participants were similar between the romosozumab and placebo groups. The most common side effects related to romosozumab in the phase III trial were dose-related to 210 mg injection and include arthralgia, nasopharyngitis, and back pain (Bandeira et al., 2017). Injection site reactions were also observed more frequently than with the placebo. Serious side effects of romosozumab included 6.8% participants experiencing hypersensitivity reaction, < 0.1% osteonecrosis of the jaw (ONJ), and < 0.1% atypical femur fracture (Bandeira et al., 2017). Since romosozumab is a bone-forming agent, there was concern about cancer formation. However, there was no difference between the romosozumab and placebo groups. Limitations include having limited data on the occurrence of adverse effects.

A phase II study conducted by Ishibashi et al., (2017) compared osteoporosis treatment with romosozumab 70 mg, 140 mg, and 210 mg once-monthly injections, along with a placebo group for 12 months. The study included postmenopausal Japanese women with osteoporosis. Requirements included having a lumbar spine, total hip, or femoral neck dual-energy X-ray absorptiometry (DEXA) T-score ≤ -2.5. Participants were excluded if they had any previous osteoporosis treatment or underlying metabolic disease. The study was double-blind, placebo-controlled, and dose-ranging. Patients in each treatment group also received ≥ 500 mg calcium

and ≥ 600 IU vitamin D. DEXA scans were completed at 6 and 12 months to determine percent change from baseline BMD. Bone turnover markers in the serum include procollagen type 1 N-terminal propeptide (P1NP) and C-terminal telopeptide of type 1 collagen (βCTX); these were tested at multiple visits. The placebo group reported 6.3% serious adverse events, and romosozumab reported 5.3% serious side effects; 9.5% in the 70 mg group, 3.2% in the 140 mg group, and 3.2% in the 210 mg group (Ishibashi et al., 2017). The placebo group experienced 68.3% mild adverse events and romosozumab experienced 74.6% mild adverse events; 77.8% romosozumab 70 mg, 71.4% romosozumab 140 mg, and 74.6% romosozumab 210 mg (Ishibashi et al., 2017). According to Ishibashi et al., no fatal adverse events were reported for any of the groups. However, three participants had to discontinue the study due to adverse events (Ishibashi et al., 2017). Two of these participants were in the romosozumab 70 mg monthly group, and experienced dizziness and subarachnoid hemorrhage, and one was in the romosozumab 210 mg monthly group and experienced hypochondriasis (Ishibashi et al., 2017). Ishibashi et al. reported that one member of each group experienced a fracture of the rib, radius, foot, or wrist. There were no events of ONJ or femur fractures (Ishibashi et al., 2017). Participants in the romosozumab groups did experience antibody development in 31% of the 70 mg group, 36.5% in the 140 mg group, and 23.8% in the 210 mg group (Ishibashi et al., 2017). Only two of the patients tested positive for antibodies one year after the last dose of romosozumab was given, and there were no adverse effects related to the antibodies (Ishibashi et al., 2017). The strengths of the study include eliminating pre-disposing health issues that would skew results. The limitations of this study are that it only included Japanese women, and the dose of calcium and vitamin D was not consistent between participants. Both of these factors could have significantly

skewed the results of the study as genetics, as well as calcium and vitamin D supplementation, play an important role in osteoporosis.

A systematic review and meta-analysis performed by Liu et al., (2018) of randomized control trials evaluate the safety and efficacy of romosozumab in the treatment of postmenopausal women with osteoporosis. According to Liu et al., there is not a 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, $p = 0.02$). A limitation of this study is that the follow-up time was short, only 12 months; the safety of romosozumab needs a longer duration of follow up to confirm the results of adverse events.

A meta-analysis by Romosozumab (Evenity) for Postmenopausal Osteoporosis (2019) looked at studies comparing romosozumab to other therapies, including placebo and alendronate. Arthralgia and headaches were the most reported adverse effects with romosozumab (Romosozumab (Evenity) for Postmenopausal Osteoporosis, 2019). Romosozumab was associated with three occurrences of ONJ and three occurrences of atypical femoral fractures. It was found by Romosozumab (Evenity) for Postmenopausal Osteoporosis that romosozumab may increase the risk of myocardial infarctions, stroke, or cardiovascular death and, therefore, should not be used in patients who have had a myocardial infarction or stroke within the previous year. According to Romosozumab (Evenity) for Postmenopausal Osteoporosis, clinical trials showed an increase of cardiovascular adverse effects with romosozumab compared to alendronate but similar events when comparing romosozumab to placebo. Neutralizing antibodies to romosozumab did develop, but it was not determined if the antibodies reduced efficacy or not (Romosozumab (Evenity) for Postmenopausal Osteoporosis, 2019). A limitation of this article

that should be addressed with future research is if anti-romosozumab antibodies change the effectiveness of romosozumab or not.

Safety of Alendronate, Prototypical Bisphosphonate, in Postmenopausal Women

A study by Hassler, Gamsjaeger, Hofstetter, Brozek, Klaushofer, and Paschalis (2014) compared the micro-spectroscopic analysis of iliac crests biopsies from postmenopausal osteoporosis patients that were treated with alendronate for ten years compared to five years. It revealed that 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. However, the continued bone turnover reduction has been proposed to be a possible mechanism of rare adverse effects of bisphosphonates, such as ONJ and atypical femoral fractures. A limitation of this study includes not having a placebo group for either of the five-year or ten-year alendronate groups, which makes the evidence less convincing since there is not a fair treatment comparison.

An article by Iwamoto et al. (2015) outlines a six-month, cluster-randomized, open-label, multicenter, crossover trial. This study compared monthly bisphosphonate therapy versus weekly bisphosphonate therapy in Japanese patients with osteoporosis. Upper gastrointestinal tract effects were the most common side effects noted, with 7.4% participants from the monthly injections and 10.7% participants from the weekly injections (Iwamoto et al., 2015). Iwamoto et al. concluded that there is a strong preference for the monthly injections versus weekly injections with no statistical difference in adverse effects. The limitations of this study are that the sample size may not have been sufficient to draw accurate conclusions and that the number of patients in

each group differed. Another limitation is that different types and doses of bisphosphonates were used in the weekly and monthly regimens.

Milat and Ebeling (2016) performed a narrative review of postmenopausal osteoporosis treatment options. Treatment with alendronate reduces vertebral fracture risk by 48% compared with the placebo (Milat & Ebeling, 2016). The most common adverse effect of oral bisphosphonate treatment is gastrointestinal symptoms, including reflux, esophagitis, gastritis, and diarrhea (Milat & Ebeling, 2016). Oral bisphosphonates should not be avoided in patients with active upper gastrointestinal disease, dysphagia, or achalasia. According to Milat and Ebeling, the most common adverse effect of intravenous bisphosphonates is flu-like symptoms such as fever, myalgia, headache, and arthralgia. Bisphosphonates can also lower serum calcium but are uncommon without underlying vitamin D deficiency (Milat & Ebeling, 2016). Milat and Ebeling found that bisphosphonates should not be recommended in patients with a creatinine clearance below 35 mL/min. ONJ and atypical femoral fractures have occurred but are less frequent (Milat & Ebeling, 2016). 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). It was also found by Milat and Ebeling that over suppression of bone remodeling could lead to microdamage accumulation, which could lead to increased fragility. Atypical femoral fractures appear to be more frequent (113 in 100,000 patients per year) in patients who have been exposed to long-term bisphosphonate therapy (seven to eight years) (Milat & Ebeling, 2016). However, the risk of sequential atypical femoral fracture reduced 12 months after cessation of bisphosphonate treatment (Milat & Ebeling, 2016). Limitations of this article include only studying participants of Australian ethnicity, which can significantly skew the results as genetics play an essential role in the pathogenesis of osteoporosis.

Zhang et al. (2015) performed a randomized, open-label, active comparator-controlled study of Chinese postmenopausal women with osteoporosis. The study compared the efficacy of alendronate/vitamin D5600 weekly infusions and calcitriol oral daily intake. The alendronate/vitamin D5600 group had 14% reported adverse events, and the calcitriol group had 7.4% reported adverse events (Zhang et al., 2015). The most frequently reported adverse event was upper abdominal pain (Zhang et al., 2015). According to Zhang et al., drug-related adverse events that lead to discontinuation of therapy occurred in 2.8% of the participants in the alendronate/vitamin D5600 and 0% of the participants in the calcitriol group. Zhang et al. reported that hypercalciuria after 12 months of treatment was 8.4% in the alendronate/vitamin D5600 versus 13.9% in the calcitriol group but was not statistically significant ($p > 0.05$). A limitation of this study was that it was an open-label design that allowed participants to know what medication they were taking.

Efficacy of Romosozumab, Prototypical Sclerostin Inhibitor, in Postmenopausal Women

A meta-analysis by Bandeira et al. compares romosozumab's efficacy and side effects compared to older medications and placebo groups. Bisphosphonates are the most common treatment for osteoporosis; this medication class is effective in reducing fracture risk, has low cost, and higher availability than newer medications such as romosozumab (Bandeira et al., 2017). In one study, Bandeira et al. found that romosozumab had a significant increase in bone formation markers, procollagen type 1 amino-terminal propeptide (P1NP), bone alkaline phosphatase (BAP), and osteocalcin along with a decrease in bone resorption marker, C-telopeptide of type I collagen (βCTX-I). Bandeira et al. reported that the changes seen with the biochemical markers were dose-dependent, and βCTX-1 decreased by 50% ($p < 0.01$) compared to placebo. In another study by McClung et al., an increase of 100% P1NP after one month of

210 mg romosozumab monthly subcutaneous injections ($p < 0.04$) compared to placebo but did return to baseline between two and nine months after discontinuation. A decrease of 50% βCTX-I occurred within the first week after 210 mg subcutaneous dose of romosozumab ($p < 0.04$) compared to placebo but did remain below baseline after one year with monthly doses (Bandeira et al., 2017). A phase III study showed an increase of 150% P1NP after monthly injections of 210 mg romosozumab ($p < 0.001$) compared to placebo, with the return to baseline at nine months (Bandeira et al., 2017). According to Bandeira et al., this study also showed evidence that βCTX-I decreased 50% and remained below baseline at 12 months ($p < 0.001$) compared to placebo. Bandeira et al. report that phase I studies showed a dose-dependent increase in BMD of 5.3% at the lumbar spine and 2.8% at the total hip after administration of 10 mg/kg romosozumab ($p < 0.01$) for both compared to placebo. Bandeira et al. found that in phase II studies, romosozumab showed a significant increase in BMD at the lumbar spine, femoral neck, and total hip ($p < 0.001$ compared to placebo, alendronate, and teriparatide). In a phase III postmenopausal study, women with osteoporosis were randomized into two groups, one to receive romosozumab 210 mg monthly injections and placebo (Bandeira et al., 2017). The first year each received either romosozumab or placebo injections; after one year, both groups were switched to denosumab 60 mg subcutaneous injections every six months (Bandeira et al., 2017). 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).

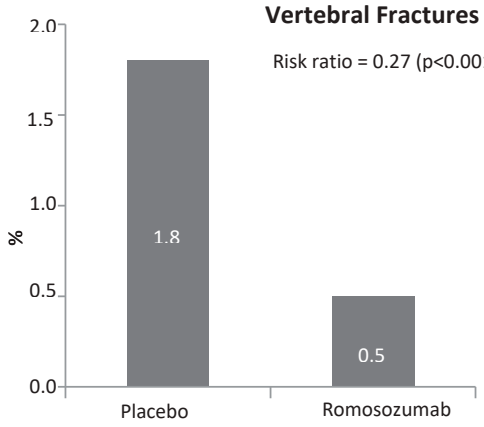

Figure 1. New vertebral fractures after 1 year. Romosozumab with a 73% reduction in new vertebral fractures compared to placebo.

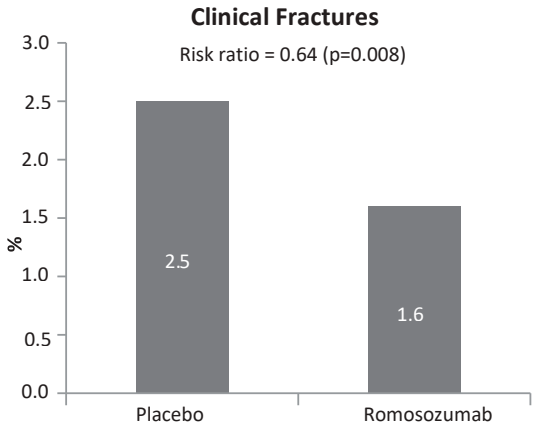

Figure 2. New clinical fractures after 1 year. Romosozumab with a 35% reduction in new clinical fractures compared to placebo.

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.

Bandeira et al. report that after two years, there was a decrease of 75% new vertebral fractures in the romosozumab/denosumab group compared to the placebo ($p = 0.002$). Bandeira et al. found no statistical difference in clinical fractures when comparing both groups at the end of two years ($p = 0.1$). However, Bandeira et al. found that when Latin American participants were excluded, there was a statistical difference in clinical fractures when comparing the romosozumab/denosumab group compared to the placebo ($p < 0.04$). A limitation of this study is that 46% of the participant group was Latin American ethnicity, which baseline 10-year risk of osteoporotic fractures is 8.7% in Latin Americans compared to 17% everywhere else in the world. This limitation skewed the data toward a nonsignificant reduction in non-vertebral fractures due to an increased Latin American participant being a part of the placebo group.

A metanalysis by Bhattacharyya, Pal, and Chattopadhyay (2018) investigates the efficacy of romosozumab. It was found by Bhattacharyya et al. that romosozumab increased BMD in postmenopausal women in the lumbar spine by 13.3%, total hip by 6.8%, and femoral neck by 5.2% from baseline, but was not effective in increasing the BMD in the wrist or radius. Overall,

treatment with romosozumab 210 mg monthly subcutaneous injections for 12 months reduced the new vertebral fracture risk ratio to 0.27 and nonvertebral fracture risk to 0.75 (Bhattacharyya et al., 2018). Bone resorption markers (βCTX) decreased by 50% below the baseline during the first week and remained below baseline throughout the 12-month treatment course (Bhattacharyya et al., 2018). A limitation of this study is that it only compared treatment with romosozumab to blosozumab, another sclerostin inhibitor, and did not have a placebo treatment group.

Horne, Mihov, and Reid (2018) performed a meta-analysis of the effects of romosozumab treatment followed by denosumab treatment in postmenopausal women with a T-score of -2.5 to -3.5 at the total hip and femoral neck. This study by Horne et al. found that spine BMD was 17.3% above baseline at the end of a 12-month trial that involved 210 mg monthly injections with romosozumab (CI 61%). When this treatment was followed by denosumab for 12 months, BMD continued to be 12.3% above baseline (CI 85%), which is a 73% retention of treatment benefit (Horne et al., 2018). Total hip BMD was increased by 10.7% at the end of the 12-month trial with romosozumab (CI 77%) and continued to be 9.2% above baseline after another 12 months of denosumab treatment (CI 98%), which is an 87% retention of treatment effect (Horne et al., 2018). Horne et al. found that participants who did not receive denosumab treatment after the completion of romosozumab treatment lost 80-90% of BMD, suggesting a rapid off-set of action. A limitation of this study is that the participants started bisphosphonate therapy at varying times after ending romosozumab treatment; some started the month after, and some did not begin until four months after stopping romosozumab.

This phase II study by Ishibashi et al. compared osteoporosis treatment with romosozumab 70 mg, 140 mg, and 210 mg once-monthly injections, along with a placebo group.

Romosozumab is a monoclonal antibody that inhibits sclerostin and rapidly increases BMD by increasing bone formation along with decreasing bone resorption. The study included postmenopausal Japanese women with osteoporosis. Requirements for participants included having a lumbar spine, total hip, or femoral neck DEXA T-score ≤ -2.5. Participants were excluded if they had any previous osteoporosis treatment or underlying metabolic disease. The study was double-blind, placebo-controlled, and dose-ranging. Women were randomly chosen to receive placebo or romosozumab 70 mg, 140 mg, or 210 mg subcutaneous once-monthly injections for 12 months. Patients in each treatment group also received ≥ 500 mg calcium and ≥ 600 IU vitamin D. DEXA scans were completed at six and 12 months to determine percent change from baseline BMD. Serum bone turnover markers procollagen type 1 N-terminal propeptide (P1NP) and C-terminal telopeptide of type 1 collagen (βCTX) were tested at multiple visits. Ishibashi et al. found that all participants receiving romosozumab significantly increased BMD at the 12-month DEXA scan compared to the placebo ($p = 0.01$, CI 95%). BMD increased from baseline to 12 months, with romosozumab 210 mg monthly injections by 16.9% at the lumbar spine, 4.7% at the total hip, and 3.8% at the femoral neck (Ishibashi et al., 2017). Romosozumab 210 mg monthly injections showed significantly higher efficacy in increasing BMD compared to placebo and the lower (70 mg and 140 mg) monthly romosozumab injections (Ishibashi et al., 2017). According to Ishibashi et al., all doses of romosozumab also significantly increased the levels of bone formation marker P1NP and reduced levels of bone resorption marker βCTX by week one compared to placebo (p 0.001, CI 95%). However, Ishibashi et al. found in the romosozumab 210 mg monthly injection group, the P1NP levels peaked at one month and fell below placebo levels by 12 months, but βCTX levels were the lowest at week one and remained below placebo through the 12-month mark. The strengths of the study include

eliminating pre-disposing health issues that would skew results. The limitations of this study were that it only included Japanese women and that the dose of calcium and vitamin was not consistent between participants.

This systematic review and meta-analysis by Liu et al. of randomized control trials evaluate the safety and efficacy of romosozumab in the treatment of postmenopausal women with osteoporosis. Amongst analyzing six trials it was found that romosozumab had a significantly lower risk of new vertebral fractures (95% CI, $p= 0.005$), non-vertebral fractures (95% CI, $p < 0.0001$), and hip fracture (95% CI, $p= 0.0004$) compared to placebo, alendronate, and teriparatide (Liu et al., 2018). BMD was significantly increased with romosozumab treatment versus placebo (Liu et al. 2018). According to Liu et al. lumbar spine had a weighted mean difference (WMD) increase of 12.33 (95% CI, $p < 0.00001$), total hip WMD increase of 5.09 (95% CI, $p < 0.00001$), and femoral neck WMD increase of 4.70 (95% CI, $P < 0.00001$). The largest gains in BMD were dose-dependent, the highest increase of BMD seen in the participants receiving romosozumab 210 mg monthly injections (Liu et al., 2018). A more recent study found that romosozumab treatment after previous bisphosphonate treatment continued to show significantly increased BMD at the lumbar spine, total hip, and femoral neck 12 months after the switch from a bisphosphonate to romosozumab therapy (Liu et al., 2018). A limitation of this study is that the follow-up time was short, only 12 months.

In this 12-month, phase I clinical study by Makras, Delaroudis, and Anastasilakis (2015) of postmenopausal females with low BMD, it was found that bone formation markers increased, and bone resorption markers decreased dose-dependently following a single subcutaneous injection of romosozumab. Makras et al. found the maximum increase of bone formation markers and decrease in bone resorption occurred around day 15 following the injection and

returned to baseline after two months. Phase II studies showed that romosozumab increased BMD after 12 months of monthly injections at the lumbar spine by 11.3%, total hip by 4.1%, and femoral neck by 3.7%, but no increase in BMD at the distal radius (Makras et al., 2015). The increase in BMD was found to be dose-dependent, with the highest increase in the participants receiving romosozumab 210 mg subcutaneous injections (Makras et al., 2015). According to Makras et al., these results are reported to be considerably higher than observed in phase II clinical studies for alendronate ($p < 0.001$). A limitation of this study is that the participant's baseline BMD varied between low BMD to osteoporotic levels.

Efficacy of Alendronate, Prototypical Bisphosphonate, in Postmenopausal Women

This prospective open-label randomized study by Cesareo et al. (2014) compared BMD of a treatment group of alendronate/cholecalciferol (70 mg- 2800 IU) weekly oral dosing versus a control group of vitamin D (2800 IU) weekly oral dosing alone over 12 months. The participants were all postmenopausal women with osteoporosis (T-score -2.5) and with primary normo-calcemic hyperparathyroidism (NPHPT). BMD was measured using DEXA scans at L1-L4, total hip, and femoral neck. Cesareo et al. found that after 12 months, BMD increased significantly from baseline at the lumbar spine, femoral neck, and total hip in the treatment group ($p= 0.001$). The most considerable increase of BMD was at the lumbar spine, with a rise of 4.7% in the treatment group (Cesareo et al., 2014). According to Cesareo et al., the control group resulted in a significant decrease in BMD compared to baseline after 12 months of treatment at all sites ($p = 0.001$). Cesareo et al. found that bone turnover markers (BTM) significantly decreased in the treatment group compared to the control group at three months and six months ($p < 0.001$). Both the treatment and control groups did not affect serum or urinary calcium (Cesareo et al., 2014). Limitations of this study include that it was not a double-blind trial, and

the sample size was small, with only 30 participants. It also only included participants with norm-calcemic primary hyperparathyroidism, which is a small subset of patients with osteoporosis.

A study by Hassler et al. compared the micro-spectroscopic analysis of iliac crests biopsies from postmenopausal osteoporosis patients that were treated with alendronate for ten years compared to five years. It was found by Hassler et al. that 10-year therapy with alendronate restores material bone indices to premenopausal non-osteoporotic values. Both alendronate treated groups had higher values in both cancellous and cortical bone (Hassler et al., 2014). A limitation of this study includes not having a placebo group for either of the five years or ten-year alendronate groups.

A randomized, open-label, active comparator-controlled study by Zhang et al. of Chinese postmenopausal women with osteoporosis. The study compared the efficacy of alendronate/vitamin D5600 weekly infusions and calcitriol oral daily intake. BMD was assessed via DEXA. Zhang et al. found that alendronate/vitamin D5600 had a more significant increase in lumbar spine BMD 5.2% versus a 2.3% increase in the calcitriol group at 12 months ($p > 0.001$). Zhang et al. also found that alendronate/vitamin D5600 had a more significant decrease in bone turnover markers compared to the calcitriol group at both six and 12 months ($p < 0.001$). A limitation of this study was that it was an open-label design that allowed participants to know what medication they were taking.

Direct Comparison of Romosozumab and Alendronate

A systematic review by Ferrari (2018) compares romosozumab and alendronate in the treatment of osteoporosis. Bone formation occurs through two main mechanisms, bone resorption, and bone remodeling. Romosozumab works by activating the Wnt-β-catenin

signaling pathway, and alendronate works by inhibiting bone remodeling. Ferrari reports that in the FRAME trial, postmenopausal women with osteoporosis that were treated with romosozumab increased spine BMD by 13.3% and hip BMD by 6.8%. Ferrari also found that romosozumab decreased the risk of vertebral fractures by 73% and clinical fractures by 36% after 12 months of treatment compared to placebo, which was statistically significant. Ferrari also discovered a decreased risk of non-vertebral fractures by 25% with romosozumab, but this was not statistically significant. According to Ferrari, the ARCH trial found that romosozumab increased BMD 2.5-fold at the spine and 2-fold at the hip after 12 months of treatment compared to alendronate. Ferrari also found that vertebral fracture was 37% lower with romosozumab treatment than alendronate at 12 months of treatment and 48% lower after 24 months of treatment. At the end of 33 months, the participants treated with romosozumab had 27% less clinical fractures, 19% less non-vertebral fractures, and 38% fewer hip fractures compared to the participants who received treatment with alendronate (Ferrari, 2018). The ARCH trial also noted that participants who were treated with romosozumab had an increased incidence of severe cardiovascular events compared to the alendronate treatment group. Still, it remains unclear if this adverse event is related to sclerostin inhibition or if it is due to the older population having an increased cardiovascular risk (Ferrari, 2018). A limitation of this article is that the duration of the two studies reviewed only lasted 12 months each. Data is still needed for long-term comparison of these two medications.

This meta-analysis by Khosla (2017) compares the newer medication romosozumab to a more traditionally used medication alendronate in the treatment of osteoporosis in postmenopausal women. Romosozumab is a sclerostin inhibitor that stimulates bone formation and inhibits bone resorption and increases bone mass, which reduces fracture risk. According to

Khosla, the ARCH trial randomly assigned postmenopausal women with osteoporosis and fragility fracture with 12 months of either once monthly romosozumab injections or once-weekly oral alendronate followed by open-label alendronate in both groups for another 12 months. The results at the end of the study showed that romosozumab was superior to alendronate in decreasing new fractures, romosozumab decreased new vertebral fractures by 48%, clinical fractures by 27% and hip fractures by 38% (Khosla, 2017). In a phase II study, 210 mg once-monthly injection of romosozumab increased spine BMD by 11.3% in 12 months, compared to a decrease of 0.1% with placebo and an increase of 4.1% with alendronate (Khosla, 2017). According to Khosla, adverse events were more severe in participants receiving romosozumab compared to those receiving alendronate. Khosla reports that cardiovascular events occurred in 2.5% of participants receiving romosozumab, and 1.9% of participants receiving alendronate (CI 95%). Khosla also found that 0.8% of participants receiving romosozumab experienced cardiac ischemic events compared to 0.3% of the participants being treated with alendronate (CI 95%). Khosla reports that the FRAME trial did not identify a difference between cardiovascular adverse events in participants receiving romosozumab compared to placebo groups. With this information, it is unsure if romosozumab increases cardiovascular adverse events or if alendronate is cardioprotective. It was also found by Khosla that the women included in the ARCH trial were less healthy than the women who were involved in the FRAME trial. There were twice as many cardiovascular adverse events with the control group, alendronate (1.9%), of the ARCH trial versus the control group, placebo (1.1%), in the FRAME trial (Khosla, 2017). Even with this information, it is still believed that romosozumab slightly increases the risk of cardiovascular events in women with multiple co-morbidities. The biologic probability for this is because of the effect romosozumab has on Wnt signaling, and its role in cardiovascular

remodeling and sclerostin levels are increased at sites of vascular calcification. A limitation of this article is that there is still insufficient research on whether romosozumab increases cardiovascular adverse events or if alendronate is cardioprotective, and that's why there is a difference in the adverse event profile.

A phase II multicenter, randomized, and placebo-controlled study by Larsson (2016) involved postmenopausal women who received romosozumab 70 mg, 140 mg, or 210 mg subcutaneous injections monthly or every three months for a 12-month duration. These study groups were compared to 70 mg oral alendronate given once a week, 20 g of teriparatide subcutaneous injections once daily, and a placebo group for a 12-month duration. Established treatment for osteoporosis is currently almost exclusively bisphosphonate therapy. Bisphosphonate therapy has been around longer than any other osteoporosis treatment and is inexpensive, which also contributes to its dominance in 1st line osteoporosis therapy options. Bisphosphonates work by blocking osteoclasts from breaking down the bone (Larsson, 2016). However, Larsson found that all dose levels of romosozumab had a significant increase in BMD. The most considerable increase being in the participants who received 210 mg romosozumab, in which the lumbar spine BMD increased 11.3% from baseline (Larsson, 2016). The placebo group lumbar spine BMD decreased by 0.1% (Larsson, 2016). The alendronate group lumbar spine BMD increased by 4.1%, and the teriparatide lumbar spine BMD increased by 7.1% (Larsson, 2016). According to Larsson, biochemical markers for the alendronate group showed a non-significant increase in the bone formation marker P1NP and no change in the bone resorption marker βCTX. A similar rise in BMD was also noted in DEXA scans of the hip, and femoral neck was found by Larsson, with the most significant increase in patients treated with 210 mg romosozumab. There was no difference in increased BMD of the hip or femoral head in

the alendronate or teriparatide groups (Larsson, 2016). The conclusion of this study revealed that romosozumab was associated with increased BMD and bone formation, along with decreased bone resorption. Side effects were equal in rate and type between all treatment groups compared with the placebo group. A limitation of this study is that the underlying health and age of the patient population was not considered; the only requirement was being a postmenopausal woman. This article also only provides evidence that romosozumab increases BMD but does not have evidence that an increase in BMD will translate into decreased fractures in postmenopausal osteoporosis patients.

A systematic review and meta-analysis by Liu et al. of randomized control trials in the evaluation of the safety and efficacy of romosozumab in the treatment of postmenopausal women with osteoporosis. According to Liu et al. 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. found 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, $p = 0.02$). A limitation of this study is that the follow-up time was short; being only 12 months long, the safety of romosozumab needs a longer duration of follow up to confirm the results of adverse events.

A meta-analysis by Romosozumab (Evenity) for Postmenopausal Osteoporosis of studies compares romosozumab to other therapies, including placebo and bisphosphonates such as alendronate. The ARCH trial compared outcomes of postmenopausal women with osteoporosis who received romosozumab 210 mg subcutaneous monthly injections for 12 months to alendronate 70 mg once weekly injections for 12 months (Romosozumab (Evenity) for

Postmenopausal Osteoporosis, 2019). New vertebral fractures occurred in 6.2% of participants who received romosozumab and 11.9% who received alendronate, a statistically significant difference (Romosozumab (Evenity) for Postmenopausal Osteoporosis, 2019). Clinical fractures, which included nonvertebral and symptomatic vertebral fractures, occurred in 8.7% of participants receiving romosozumab and 13% who received alendronate, a statistically significant difference (Romosozumab (Evenity) for Postmenopausal Osteoporosis, 2019). Rates of nonvertebral and hip fractures were lower with romosozumab compared to alendronate but were not statistically different (Romosozumab (Evenity) for Postmenopausal Osteoporosis, 2019). Serious cardiovascular events occurred in 2.5% of participants receiving romosozumab and 1.9% participants receiving alendronate, and therefore was decided that romosozumab should not be used in patients who have had a myocardial infarction or stroke within the previous year (Romosozumab (Evenity) for Postmenopausal Osteoporosis, 2019). A limitation of this article that should be addressed with future research is if anti-romosozumab antibodies change the efficacy of romosozumab or not.

This systematic review by Song and Lee (2018) compares romosozumab versus alendronate in the treatment of osteoporosis in postmenopausal women. Sclerostin is expressed in aortic vascular smooth muscle and up regulated at sites of vascular calcification. Blocking sclerostin may lead to vascular calcification and result in arterial stiffening and severe cardiovascular disease (Song & Lee, 2018). Therefore, advanced abdominal aortic calcification is more common in patients with vertebral fractures. In the ARCH trial, 96% of participants had vertebral fractures before starting the trial compared to only 18% of participants in the FRAME trial. (Song & Lee, 2018). According to Song and Lee, the participants in the ARCH trial likely had more advanced abdominal aortic calcification before the initiation of the study. Song and

Lee found that postmenopausal women with osteoporosis that were treated for 12 months with romosozumab followed by alendronate had a significantly lower risk of fracture than the participants who only received alendronate. Romosozumab has a time-limited bone-forming effect and has only been studied as a 12-month course of treatment and is not intended for continuous long-term use (Song & Lee, 2018). A limitation of this article is there is no data about the evidence that the ARCH trial contained participants who were more prone to cardiovascular events compared to the FLAME trial.

Discussion

Osteoporosis is a complex disease. There are many risk factors and genetic variations that make the treatment of osteoporosis challenging to optimize for each patient. The standard treatment has been bisphosphonates for many years, but with new research, there are now more options in the treatment of osteoporosis, such as sclerostin inhibitors. The following section is a discussion of the review of the literature, focusing on answering the question if there is a statistical difference in the safety and efficacy between romosozumab, the prototypical drug in the new drug class of sclerostin inhibitors, versus alendronate, the prototypical bisphosphonate, in the treatment of postmenopausal osteoporosis.

Safety of Romosozumab, Prototypical Sclerostin Inhibitor, in Postmenopausal Women

A useful systematic review and meta-analysis by Liu et al. compared the side effect profiles of the two most extensive studies of romosozumab, the ARCH, and FRAME trial. Liu et al. did not find a statistically significant difference in the adverse events between romosozumab, alendronate, and placebo treatment groups. Similarly, a phase II study conducted by Ishibashi et al. reported the placebo group having 6.3% serious adverse events and the romosozumab group having 5.3% serious adverse events, which did not appear to be dose related. The placebo group

experienced 68.3% mild adverse events compared to romosozumab experiencing 74.6% mild adverse events, which also did not appear to be dose-related (Ishibashi at el., 2017).

The meta-analysis performed by Bandeira et al. found that some patients who received romosozumab developed anti-romosozumab antibodies. However, there were no clinical side effects in the patients who developed the antibodies. Since romosozumab is a bone-forming agent, there was concern about increasing cancer formation, but Bandeira et al. found there to be no difference between the romosozumab and placebo groups. Romosozumab (Evenity) for postmenopausal osteoporosis, identifies that the increased risk of cardiovascular events due to romosozumab only occurs in patients with a significant cardiac history. The clinical trials showed an increase of cardiovascular adverse effects with romosozumab compared to alendronate but similar events when comparing romosozumab to placebo.

In conclusion, there does not appear to be a statistically significant difference in adverse effects of romosozumab compared to placebo groups. There is not sufficient 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, Prototypical Bisphosphonate, in Postmenopausal Women

Zhang et al. concluded that there is not a statistically significant difference in adverse effects with the treatment of alendronate plus vitamin D versus vitamin D alone. A narrative review by Milat and Ebeling found the most common adverse effects of oral bisphosphonate treatment to be gastrointestinal symptoms and, therefore, should be avoided in patients with active upper gastrointestinal disease, dysphagia, or achalasia. Milat and Ebeling found the most common adverse event of intravenous bisphosphonate therapy to be flu-like symptoms. A study

performed by Iwamoto et al. also found upper gastrointestinal side effects to be the most common, but not statistically significant, adverse events with bisphosphonate therapy in Japanese patients with osteoporosis. With more adverse events reported with weekly injections versus monthly injections.

An analysis of iliac crest biopsies performed by Hassler et al. revealed minimal alterations in bone material properties when comparing 5-year and 10-year alendronate therapy, which is associated with no difference in side effect profiles of short term versus long term alendronate therapy. Bisphosphonates can lower serum calcium, but this is uncommon without an underlying vitamin D deficiency (Milat & Ebeling, 2016). Milat and Ebeling found that over suppression of bone remodeling could lead to microdamage accumulation, which could lead to increased fragility. Atypical femoral fractures are more common in patients who have been exposed to long-term bisphosphonate therapy for seven or more years (Milat & Ebeling, 2016).

In conclusion, 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 should be the focus of future research.

Efficacy of Romosozumab, Prototypical Sclerostin Inhibitor, in Postmenopausal Women

Bhattacharyya et al. explain that romosozumab works by both anti-resorptive and anabolic properties, which were found to increase BMD in postmenopausal women in the lumbar spine, total hip, and femoral neck. Bone resorption markers in romosozumab treated patients decreased by 50% below baseline during the first week and remained below the baseline throughout the 12-month treatment course (Bhattacharyya et al., 2018). Studies performed by

Bandeira et al., Makras et al., and Ishibashi et al. found similar results that romosozumab significantly increase bone formation markers along with a statistically significant decrease in bone resorption markers, all being dose dependent. According to Makras et al., these results are reported to be considerably higher than those observed in phase II clinical studies for alendronate. Bandeira et al. concluded that bone formation markers returned to baseline after nine months of treatment, and bone resorption markers remained below baseline after 12 months of treatment. Phase III studies showed that after one-year romosozumab showed a 73% reduction in new vertebral fractures along with a 36% decrease in clinical fractures compared to the placebo group (Bandeira et al., 2017). After two years of treatment, there was a decrease of 75% of new vertebral fractures in the romosozumab group compared to placebo but no statistical difference in clinical fractures between the romosozumab and placebo group (Bandeira et al., 2017).

Similar results were found by Liu et al. and Ishibashi et al. that romosozumab had a significantly lower risk of new vertebral fractures, non-vertebral fractures, and hip fractures compared to placebo and alendronate. BMD was also increased dramatically with romosozumab versus placebo (Liu et al., 2018) (Horne et al., 2018). The most substantial gains in BMD were dose-dependent, the highest increase of BMD seen in participants receiving 210 mg monthly romosozumab injections. Liu et al. also found that treatment with romosozumab after previous bisphosphonate treatment also showed a significant increase in BMD at the lumbar spine, total hip, and femoral neck 12 months after switching from bisphosphonate therapy to romosozumab therapy. Horne et al. reported that BMD after 12 months of romosozumab treatment with an additional 12 months of denosumab accounted for a 73% retention of treatment benefit, with similar results were found with total hip BMD treatment retention of 87%. Participants who did

not receive denosumab after the completion of romosozumab treatment lost 80-90% of BMD (Horne et al., 2018).

In conclusion, romosozumab significantly increase 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, Prototypical Bisphosphonate, in Postmenopausal Women

According to Cesareo et al. and Zhang et al., participants receiving alendronate plus vitamin D treatment significantly increased BMD from baseline at the lumbar spine, femoral neck, and total hip compared to the control group, vitamin D alone, which had a significant decrease in BMD after 12 months. Bone turnover markers significantly decreased in the alendronate treatment group compared to the control group (Cesareo et al., 2014) (Zhang et al. 2015). Hassler et al. found that iliac crest biopsies from postmenopausal osteoporosis patients showed that treatment with alendronate for ten years restores bone material indices to premenopausal non-osteoporotic values. Both alendronate 5-year and 10-year treatment groups had higher values in both cancellous and cortical bone compared to placebo groups.

This research provides statistically significant data that alendronate plus vitamin D is superior in increasing BMD than the conservative treatment of vitamin D alone. It also provides evidence that alendronate therapy continues to increase cancellous and cortical bone even during an extended length of therapy. This study was conducted longer than 12-24-month therapy time frames, which most other studies did not.

Direct Comparison of Romosozumab and Alendronate

According to Ferrari, Khosla, and Liu et al. in both the FRAME and ARCH trial, romosozumab is superior to alendronate in decreasing new fractures and increasing BMD. These trials also showed a reduced risk of vertebral fractures and clinical fractures after treatment with romosozumab which, was significantly more than compared to placebo (Ferrari, 2018) (Liu et al., 2018). A phase II study by Larsson found that romosozumab is statistically superior to alendronate in increasing BMD and that biochemical markers for the alendronate group did not show a significant increase in bone formation marker P1NP and there was no change in the bone resorption marker βCTX. Song and Lee found that postmenopausal women with osteoporosis that were treated with romosozumab followed by alendronate had a significantly lower risk of fracture than participants who only received alendronate.

Liu et al. and Larsson found no significant difference in the incidence of adverse events in patients treated with romosozumab compared to placebo and alendronate. The ARCH trial noted that participants who were treated with romosozumab had an increased incidence of severe cardiovascular events compared to the alendronate treatment group (Ferrari, 2018) (Khosla, 2017). However, Khosla reports that the FRAME trial did not identify any difference between the cardiovascular adverse events between the romosozumab and the placebo groups. Ferrari suggests that it remains unclear if this adverse event is related to sclerostin inhibition or if it is due to the romosozumab treatment group containing an older population, which may have increased the cardiovascular risk. A systematic review by Song and Lee explains that romosozumab's mechanism of action of blocking sclerostin may lead to vascular calcification and result in arterial stiffening and severe cardiovascular disease. Therefore, advanced abdominal aortic calcification is more common in patients with vertebral fractures (Song & Lee,

2018). According to Song and Lee, participants in the ARCH trial likely had more advanced abdominal aortic calcification before the initiation of the study.

Taking this information into consideration, it is unsure if romosozumab increases cardiovascular adverse events or if alendronate is cardioprotective. Khosla points out that 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. Further research needs to be conducted on the effect romosozumab has on Wnt signaling, and its role in cardiovascular remodeling and sclerostin levels are increased at sites of vascular calcification. However, 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.

Applicability to Clinical Practice

With the information in this literature review, the medical provider will be able to make the most effective and safest decision based solely on evidence-based medicine in the treatment of osteoporosis in postmenopausal patients. 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. With the USPSTF recommendation of bone density scans in females 65 and older, many patients will have the diagnosis of osteopenia or osteoporosis. As 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 begin 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). Fractures, as a result of

osteoporosis, can be debilitating to the patient and the patient's family/caretakers. 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 will 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. The research presented shows there is no "perfect" solution in treating postmenopausal osteoporosis. In general, 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. However, we, as providers, must weigh the risks and benefits of this treatment regimen, being extra cautious 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.

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