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Comparison of Pharmacologic Treatments for Postmenopausal Osteoporosis

Kaitlyn Wirtz
University of North Dakota

Comparison of Pharmacologic Treatments for Postmenopausal Osteoporosis

by

Kaitlyn Rae Wirtz, PA-S

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Contributing author: Jeanie McHugo, PA-C, Chair of Physician Assistant Studies Department

Contributors and Reviewers:

Dawn Hackman, MS, AHIP

Marilyn G. Klug, PhD

Daryl Sieg, Associate Professor and PA-C

Stephanie Gagelin, PA-S

Ashley Pommer, PA-S

Amy Quinn, PA-S

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Abstract

Osteoporosis is defined as a "generalized skeletal disorder characterized by compromised bone strength and deterioration of bone quality, often leading to fragility fracture" (DynaMed Plus, 2018). The prevalence of osteoporosis in the United States in adults aged greater than or equal to 50 years of age is "more than 10 million people overall and 33 million have low bone mineral density at the hip" (DynaMed Plus, 2018). Of these affected, one in two women will experience an osteoporotic fracture in their lifetime (International Osteoporosis Foundation, 2017). To combat postmenopausal osteoporosis, two treatment options include bisphosphonates and the anti-receptor activator of nuclear factor kappa β ligand (RANKL) agent. The purpose of this scholarly project is to determine if there is a statistical significance regarding safety, efficacy, and preference between bisphosphonates and the anti-RANKL agent due to different mechanisms of action. Three databases were searched: PubMed, CINAHL, and Cochrane Database of Systematic Reviews. Topics researched included: postmenopausal osteoporosis, bisphosphonates, anti-RANKL agent, treatment outcome, adverse effects, and efficacy. Research was conducted from September 12, 2018 to January 29, 2019. All works were published within the last 10 years. Limitations and strengths were considered within each modality. The most effective treatment for postmenopausal osteoporosis is the anti-RANKL agent. It is just as safe, more efficacious, better adhered to, and more preferred than bisphosphonates. This scholarly project compares the treatment options available to providers and allows them to choose the best treatment option based on the patient's needs, safety, efficacy, preference, and cost.

Comparison of Pharmacologic Treatments for Postmenopausal Osteoporosis

Introduction

Osteoporosis is defined as a "generalized skeletal disorder and is characterized by compromised bone strength and deterioration of bone quality, often leading to fragility fracture" (DynaMed Plus, 2018). This most often affects women greater than or equal to 65 years of age, Asian and Caucasian descents, and those with a small body frame. The prevalence of osteoporosis in the United States in adults aged greater than or equal to 50 years of age is "more than 10 million people overall and 33 million have low bone mineral density (BMD) at the hip" (DynaMed Plus, 2018). Of these affected, one in two women will experience an osteoporotic fracture in their lifetime (International Osteoporosis Foundation, 2017). For women, this incidence is greater than breast cancer, heart attack, and stroke combined; therefore, it is one of the leading public health problems (International Osteoporosis Foundation, 2017).

To comprehend osteoporosis and low BMD, the bone remodeling process in healthy bones must be understood. In healthy bones, bone formation by osteoblast cells is in balance with bone resorption by osteoclast cells. This process is maintained in normal bones throughout life. However, when bone resorption by the osteoclast cells outpaces bone formation by the osteoblast cells, the result is bone loss. The decrease in bone mass leads to an increase in fracture risk. Fractures occur when the weak bones are overloaded.

Two forms of osteoporosis exist: primary and secondary. Primary osteoporosis is the result of aging and sex steroid deficiency. The sex steroid particularly deficient is 17beta-estradiol in menopause women (DynaMed Plus, 2018). This sex steroid inhibits bone resorption without increasing bone formation. Secondary osteoporosis is the result of multiple causes and risk factors. These include, but are not limited to, low calcium intake, low vitamin D intake,

glucocorticoid use, long-term anticoagulation use, long-term proton pump inhibitor use, hormonal therapies, inadequate physical activity, alcohol use, tobacco use, and genetic factors (DynaMed Plus, 2018). Due to the postmenopausal interest of this scholarly project, primary osteoporosis will be the focus.

To combat postmenopausal osteoporosis, two common treatments include bisphosphonates and the anti-receptor activator of nuclear factor kappa β ligand (RANKL) agent. The mechanism of action (MOA) varies between these two classes. Bisphosphonates inhibit bone resorption by osteoclasts which decreases bone turnover. The anti-RANKL agent binds to receptor activator of nuclear kappa-β ligand, which inhibits osteoclast formation and reduces bone resorption and turnover.

Therefore, the purpose of this scholarly project is to determine if there is a statistical significance regarding safety, efficacy, and preference between bisphosphonates and the anti-RANKL agent due to differing MOAs.

Statement of the Problem

The United States Food and Drug Administration (U.S. FDA) approved the first bisphosphonate for the treatment of postmenopausal osteoporosis in 1995 (Food and Drug Administration, n.d.). The U.S. FDA approved the first anti-RANKL agent for the treatment of postmenopausal osteoporosis in 2010 (Food and Drug Administration, n.d.). Fifteen years separated the approval of each treatment option for postmenopausal osteoporosis. In those years, countless amounts of research was completed on bisphosphonates for their safety and efficacy and now similar research is being completed on the anti-RANKL agent. The American Association of Clinical Endocrinologists approved both bisphosphonates and the anti-RANKL agent as first-line treatment (Camacho, 2016). This scholarly project analyzes both

bisphosphonates and the anti-RANKL agent that have been heavily researched to determine the safest and most efficacious treatment. However, with differing MOAs, one treatment option may be statistically superior. This scholarly project will uncover if there is a statistical significance between treatments regarding safety, efficacy, and preference. Providers need to be informed on the latest research to provide their patients with optimal first-line treatment for postmenopausal osteoporosis.

Research Question

In the treatment of postmenopausal osteoporosis, is there a statistical difference in the safety, efficacy, and preference when using bisphosphonates versus the anti-RANKL agent?

Methods

For this scholarly project, three databases were searched, which included PubMed, CINAHL, and Cochrane Database of Systematic Reviews, from September 12, 2018 to January 29, 2019. PubMed database was the primary resource for researching postmenopausal osteoporosis treatment. Subject headings included “Osteoporosis, Postmenopausal" [Major], “Diphosphonates” [Mesh], “Denosumab” [Mesh], “RANK Ligand” [Mesh], "Diphosphonates/adverse effects" [Mesh], "Denosumab/adverse effects" [Mesh], “Treatment Outcome” [Mesh], "Bone Density Conservation Agents" [Pharmacological Action]. The CINAHL database subject headings included “Postmenopausal Osteoporosis” [MH], “Treatment” [MH], and “Efficacy” [MH]. The Cochrane Systematic Review database was searched with “Postmenopausal osteoporosis treatment.” To further refine the search, “AND” and “OR” were used between subject heading. Inclusion criteria for this scholarly project included meta-analysis, systematic reviews, and randomized control trials (RCTs). All works were published within the last 10 years and written in the English language.

Literature Review

Theme 1: Safety of Bisphosphonates

In theme one, safety of bisphosphonates, three studies were reviewed. Safety profiles were investigated for the historic first line treatment, bisphosphonates. This theme studies different safety measures of the most common bisphosphonates available for treatment of postmenopausal osteoporosis.

Wang (2017) conducted a meta-analysis on the safety of zoledronic acid for the treatment of postmenopausal osteoporosis utilizing a placebo-used approach. The meta-analysis included eight RCTs (n= 13,355), a target population of women with postmenopausal osteoporosis, treatment with zoledronic acid (five milligrams (mg) intravenous (IV)), and a secondary end-point of safety. The results of the incidence of any adverse events (AEs) in the zoledronic acid group and placebo group were 91.9% and 90.3%, respectively (Wang, 2017). Using a fixed-effect model, this resulted in participants receiving zoledronic acid having a significantly higher incidence of any AEs than those receiving placebo (risk ratio (RR) 1.02 (1.01-1.03), 95% confidence interval (CI), $p = 0.000$) (Wang, 2017). The incidences of any serious adverse events (SAEs) in the zoledronic acid group and placebo group were 30.0% and 31.2%, respectively (Wang, 2017). Using a fixed-effect model, this resulted in no significant difference between the two groups (RR 0.96 (0.92-1.01), 95% CI, $p = 0.087$) (Wang, 2017). The most frequent AEs included first-dose acute-phase reaction such as pyrexia, myalgia, arthralgia, headache, chills, and influenza-like symptoms (Wang, 2017).

Wang (2017) declared no conflict of interest. This is significant because it demonstrates there is no bias towards treatment versus placebo. However, he highlighted several limitations which included substantial heterogeneity, small sample size, and variable duration of follow-up

(Wang, 2017). Overall, Wang (2017) is significant because it establishes the foundation for the safety of bisphosphonates, specifically zoledronic acid, to treat women with postmenopausal osteoporosis.

Researchers Eriksen, Diez-Perez, and Boonen (2014) explored the latest long-term safety data of bisphosphonate treatment for the management of postmenopausal osteoporosis. Nine primary articles were included in this systematic review. Bisphosphonates were compared to placebo, and the bisphosphonates under investigation included alendronate, risedronate, ibandronate (oral), and zoledronic acid. For alendronate (alendronate for 10 years (n= 553) and alendronate for five years followed by placebo for five years (n= 361)), no significant differences between the groups in the incidence of AEs, upper gastrointestinal AEs, SAEs, or discontinuation due to AEs were reported (Eriksen et al., 2014). For risedronate (risedronate for five years (n= 130) and placebo for five years (n= 135)), five years of treatment was associated with similar rates of AEs, SAEs, and discontinuation due to AEs as placebo (9.6 versus 8.6%) (Eriksen et al., 2014). For ibandronate (n= 309), gastrointestinal AEs were reported in 1.7 to 7.4% of participants and were the most common AEs reported (Eriksen et al., 2014). For zoledronic acid (zoledronic acid for six years (n= 450) and zoledronic acid for three years followed by placebo for three years (n= 467)), there was comparable incidence of AEs, SAEs, and deaths between participants who had received treatment for six years and those who discontinued treatment after three years (Eriksen et al., 2014). The results concluded no unexpected AEs developing from long-term use of any of the bisphosphonates for the treatment of postmenopausal osteoporosis (Eriksen et al, 2014).

Overall, Eriksen et al. (2014) is significant because of the long-term trials. Safety analyses are of paramount importance because not all possible safety concerns can be identified

during initial short-term trials (Eriksen et al., 2014). However, the main limitation was the lack of statistical analyses for the overall AEs and SAEs regarding the long-term safety of bisphosphonates. Confidence intervals, risk ratios, and p-values were not recorded for this area of research. Also, the heterogeneity between groups was pronounced between populations, interventions, lengths of follow-up and drugs tested which lead to no formal meta-analysis (Eriksen et al., 2014).

Lin et al. (2012) conducted a meta-analysis to compare the safety profiles between the anti-RANKL agent (denosumab) and the bisphosphonate (alendronate) in postmenopausal osteoporosis. The meta-analysis included four RCTs each with a double-blinded and placebo-based approach. Each trial had a target population of women with postmenopausal osteoporosis and results included safety profiles of each treatment. The treatments were 60 mg of denosumab subcutaneous (SC) injections every six months or 70 mg orally (PO) of alendronate weekly. Results showed similar safety profiles at the one-year follow-up (Lin et al., 2012). Total AEs were 14 fewer per 1000 with denosumab treatment (odds ratio (OR) 0.91 (0.72-1.15), 95% CI, $p = 0.66$) (Lin et al., 2012). SAEs were 61 fewer per 1000 with denosumab treatment (OR 0.91 (0.63-1.33), 95% CI, $p = 0.65$) (Lin et al., 2012). Neoplasms were three more per 1000 with denosumab treatment (OR 1.10 (0.62-1.86), 95% CI, $p = 0.62$) (Lin et al., 2012). Infections were 12 fewer per 1000 with denosumab treatment (OR 0.95 (0.76-1.15), 95% CI, $p = 0.62$) (Lin et al., 2012). Therefore, the meta-analysis provided low to very low evidence that denosumab SC every six months could neither reduce the risk of AEs and SAEs nor increase the risk of neoplasms and infections compared with alendronate PO weekly (Lin et al., 2012).

The researchers assured their funding sources were independent and had no influence when publishing their findings (Lin et al., 2012). This is significant because it demonstrates there

was no bias towards either treatment. Limitations included failure to follow-up leading to incomplete outcome data in some trials, substantial heterogeneity, observational duration of only one-year, only four trials were included, and all included studies were sponsored by the pharmaceutical company related to denosumab (Lin et al., 2012). Overall, having a direct comparison of the safety of current first line treatment, bisphosphonates, to the upcoming treatment option, denosumab, makes this a foundational study.

Theme 2: Safety of the anti-RANKL agent

In theme two, safety of the anti-RANKL agent (denosumab), four studies were reviewed. This theme investigates the safety profile of denosumab, an upcoming treatment option for treatment of postmenopausal osteoporosis.

Researches Bone et al. (2008) evaluated the safety of denosumab versus placebo over 24 months with a randomized, double-blind, phase III study. The target population included women with a lumbar spine BMD T-score between -1.0 and -2.5 (Bone et al., 2008). The participants were assigned to receive either 60 mg denosumab SC every six months or placebo for two years (denosumab (n= 116) and placebo (n= 116)) (Bone et al., 2008). In the denosumab group, one participant discontinued due to AEs and in the placebo group, two participants discontinued due to AEs (Bone et al., 2008). The results of the overall incidence of AEs over 24 months was similar between the denosumab (60%) and placebo (61%) groups (Bone et al., 2008). SAEs were reported for 18 participants in the denosumab group (11%) and nine participants in the placebo group (5.55%) ($p = 0.074$) (Bone et al., 2008). Neoplasms were reported in four participants in the denosumab group and one participant in the placebo group ($p = 0.215$) (Bone et al., 2008). No deaths occurred during the study (Bone et al., 2008).

The main limitation was the briefness of the safety analysis because the primary focus of the study was to report the efficacy which will be discussed in theme four. Overall, Bone et al. (2008) is a significant addition to the foundation of the safety of denosumab.

Researchers Keyserlingk et al. (2011) assessed the safety of offering denosumab in postmenopausal women with low BMD. Keyserlingk et al. (2011) included four RCTs and the results included the safety and incidence of SAEs (infection, neoplasms, and percentage of discontinuation due to AEs). The SAEs of denosumab compared to placebo were statistically insignificant (RR 1.33 (0.8-2.14), 95% CI) (Keyserlingk, 2011). The SAEs related to infection of denosumab compared to placebo were statistically insignificant (RR 2.10 (0.64 to 6.90), 95% CI) (Keyserlingk, 2011). The SAEs related to neoplasm of denosumab compared to placebo were statistically insignificant (RR 1.11 (0.91 to 1.36), 95% CI) (Keyserlingk, 2011). The discontinuation due to AEs of denosumab compared to placebo were statistically insignificant (RR 1.10 (0.83 to 1.47), 95% CI) (Keyserlingk, 2011). The incidence of death of denosumab compared to placebo was statistically insignificant (RR 0.78 (0.57 to 1.06), 95% CI) (Keyserlingk, 2011). Overall, there was no significant increase in relative SAEs in participants on denosumab compared to placebo.

The limitations include heterogeneity between sample sizes and variable participant characteristics. However, a major strength is the inclusion of only RCTs that treated thousands of participants with denosumab. This illustrates very strong evidence for the safety of denosumab.

Researcher Deeks (2018) summarized the relevant data of denosumab for the treatment of postmenopausal osteoporosis. Deeks (2018) highlighted the long-term safety of denosumab by selecting phase III and IV trials. The most comprehensive information came from the three-year phase III trial FREEDOM (n= 7,808) and its seven-year extension (n= 4,550). The FREEDOM

trial is the focus of the results section due to its number of participants. The other trials used by Deeks (2018) to support his research included DECIDE (n= 1,179), STAND (n= 504), Recknor et al. (n= 833), Roux et al. (n= 870), and Miller et al. (n= 643). The results declared 60 mg denosumab SC every six months was well tolerated for up to 10 years in postmenopausal women with low BMD and most AEs were mild to moderate (Deeks, 2018). Over the initial three-year study, denosumab did not significantly differ from placebo in percentage of treatment-emergent adverse events (TEAEs) (93 versus 93%), serious TEAEs (26 versus 25%), death (1.8 versus 2.3%), or discontinuation of treatment because of TEAEs (4.9 versus 5.2%) (Deeks, 2018). The TEAEs that were statistically significant in denosumab versus placebo include eczema (3.0 versus 1.7%) and flatulence (2.2 versus 1.4%) ($p < 0.01$) (Deeks, 2018). Whereas, the TEAEs that were statistically significant in placebo versus denosumab include non-fracture related falls (4.5 versus 5.7%) ($p = 0.02$) (Deeks, 2018). The serious TEAEs that were statistically significant included cellulitis (0.3 versus <0.1%) and concussion (<0.1 versus 0.3%) ($p < 0.005$) (Deeks, 2018). There was no statistical difference between the incidence of infection, cancer, or delayed fracture healing between denosumab and placebo (Deeks, 2018). In terms of the overall incidence of AEs of denosumab compared to bisphosphonates, TEAEs (60-81 versus 56-82%), TEAEs leading to discontinuation (1-2 versus 1-4%), death ($\leq$ 0.4 versus $\leq$ 0.3%), or serious TEAEs (6-8 versus 6-9%) were reported (Deeks, 2018). Looking at select AEs, denosumab did not significantly differ from alendronate or ibandronate in the incidence of infections, neoplasms, or fractures (Deeks, 2018). However, statistically significant value occurred in denosumab versus ibandronate with serious TEAEs (10 versus 5%) ($p < 0.05$) (Deeks, 2018). Other statistically significant values of denosumab versus ibandronate include gastrointestinal (1.2 versus 0.2%) and respiratory disorders (1.2 versus 0%) (Deeks, 2018). The last statistically significant value

occurred in denosumab compared to zoledronic acid AEs of musculoskeletal pain (13 versus 20%) ($p < 0.05$) (Deeks, 2018).

The limitations include heterogeneity between studies, specifically regarding sample size. Additionally, during the peer review process, the manufacturer of denosumab was offered the opportunity to review this article; however, any changes made were claimed to be made based on scientific and editorial merit (Deeks, 2018). Overall, Deeks (2018) compares the safety of denosumab against not only placebo but also bisphosphonates which specifically addresses the research question at hand.

Zhou et al. (2014) assessed the safety of denosumab in postmenopausal women with osteoporosis or low BMD. Zhou et al. (2014) included 11 RCTs to compare the safety of denosumab to bisphosphonates and placebo which included any adverse events (AAEs) and SAEs related to infection, neoplasm, non-vertebral fracture, and death. No significant difference between denosumab compared to placebo was demonstrated in AAEs (RR of 0.99 (0.98-1.01), 95% CI, and $p = 0.29$), SAEs (RR of 1.05 (0.98-1.13), 95% CI, and $p = 0.18$), neoplasms (RR of 1.14 (0.95-1.37), 95% CI, and $p = 0.16$), and deaths (RR of 0.77 (0.57-1.04), 95% CI, and $p = 0.09$) (Zhou et al., 2014). However, participants assigned to denosumab compared to placebo did show a statistically significant risk for SAE related to infection (RR of 1.23 (1.00-1.52), 95% CI, and $p = 0.05$) (Zhou et al., 2014). Furthermore, denosumab compared to bisphosphonates indicated no statistically significant evidence to prove the difference in AAEs (RR of 0.98 (0.95-1.02), 95% CI), SAEs (RR of 1.06 (0.84-1.34), 95% CI), SAEs related to infection (RR of 1.13 (0.63-2.03), 95% CI), neoplasms (RR of 1.17 (0.73-1.87), 95% CI), non-vertebral fracture (RR of 1.31 (0.87-1.98), 95% CI), and death (RR of 0.72 (0.20-2.59), 95% CI) (Zhou et al., 2014). Overall, based on the results of the statistical analysis, there were no significant differences in

AAEs, SAEs, neoplasms, or death. However, statistical significance did arise in the risk of infection for denosumab compared to placebo, but this finding was not consistent with denosumab compared to bisphosphonates.

The main limitation was small sample size in all studies, except one. Zhou et al. (2014) continues to advocate the safety of denosumab compared to placebo and the current first line treatment, bisphosphonates.

Theme 3: Efficacy of Bisphosphonates

In theme three, efficacy of bisphosphonates, three studies were reviewed. This theme investigates the changes in BMD and the fracture risk of bisphosphonates.

Wang (2017) conducted a meta-analysis on the efficacy of zoledronic acid for the treatment of postmenopausal osteoporosis with a placebo-used approach. The meta-analysis included eight RCTs (n= 13,355), a target population of women with postmenopausal osteoporosis, and treatment with zoledronic acid (five mg IV). Primary end-points included vertebral fracture, non-vertebral fracture, and hip fracture. Non-vertebral fracture incidence with zoledronic acid was 5.4% versus placebo which was 7.5%, and when using a fixed-effect model, zoledronic acid significantly reduced the incidence of non-vertebral fracture compared to placebo (RR 0.75 (0.67-0.83), 95% CI, $p = 0.000$) (Wang, 2017). Vertebral fracture incidence with zoledronic acid was 3.4% versus placebo which was 7.9%, and when using a fixed-effect model, zoledronic acid significantly reduced the incidence of non-vertebral fracture compared to placebo (RR 0.43 (0.34-0.53), 95% CI, $p = 0.000$) (Wang, 2017). Hip fracture incidence with zoledronic acid was 2.3% versus placebo which was 2.9%, and when using a fixed-effect model, zoledronic acid significantly reduced the incidence of non-vertebral fracture compared to placebo (RR 0.76 (0.61-0.96), 95% CI, $p = 0.020$) (Wang, 2017). The effect of BMD at the

lumbar spine with zoledronic acid was associated with a significant increase compared to placebo (weighted mean difference (WMD) 3.76 (0.95-6.56), 95% CI, $p = 0.009$) (Wang, 2017). The effect of BMD using zoledronic acid was associated with a significant increase compared to placebo at the total hip (WMD 3.89 (2.52-5.26), 95% CI, $p = 0.000$), femoral neck (WMD 3.51 (2.37-4.65), 95% CI, $p = 0.000$), and trochanter (WMD 4.12 (1.56-6.68), 95% CI, $p = 0.002$) (Wang, 2017). Overall, treatment with zoledronic acid significantly reduced the risk of fractures and increased BMD for postmenopausal women with osteoporosis (Wang, 2017).

Wang (2017) addressed several limitations which included substantial heterogeneity, small sample size, and duration of follow-up varied from 12 months to 36 months (Wang, 2017). However, Wang (2017) is beneficial because it identifies the efficacy of zoledronic acid to treat women suffering from postmenopausal osteoporosis.

Researchers Eriksen, Diez-Perez, and Boonen (2014) explored the latest long-term efficacy data of bisphosphonate treatment for the management of postmenopausal osteoporosis. Nine primary articles were included in this systematic review. Bisphosphonates were compared to placebo, and the bisphosphonates under investigation included alendronate, risedronate, ibandronate (oral), and zoledronic acid. The results concluded long-term use of bisphosphonates in postmenopausal women had persistent beneficial effects on fracture risk and BMD beyond three years of treatment (Eriksen et al., 2014). For alendronate, the study compared the effect of 10 years of continuous treatment (n= 662) versus five years of treatment followed by five years of placebo (n= 437). Continuous treatment showed significantly lower risk of vertebral fracture versus those who discontinued treatment (2.4 versus 5.3%, 95% CI, RR 0.45 (0.24-0.85)) (Eriksen et al., 2014). However, discontinuation of treatment did not seem to increase the risk of non-vertebral or morphometric vertebral fractures (Eriksen et al., 2014). Results found that five

additional years of treatment sustained BMD at the total hip, femoral neck, trochanter, lumbar spine, total body and forearm compared with five years of placebo ($p < 0.001$) (Eriksen, et al., 2014). For risedronate, the study compared five years of continuous treatment (n= 135) versus three years of treatment followed by two years of placebo (n= 130). Continuous treatment showed a vertebral fracture risk reduction of 59% versus those who discontinued treatment (95% CI, $p = 0.01$) (Eriksen et al., 2014). Results regarding BMD indicated two additional years of treatment continued to increase lumbar spine BMD (Eriksen et al., 2014). For ibandronate, five years of treatment (n= 309) was associated with a continual increase in BMD at the lumbar spine (2.2 to 2.4%) (Eriksen et al., 2014). For zoledronic acid, the study compared six years of continuous treatment (n= 616) versus three years of treatment followed by three years of placebo (n= 617). Continuous treatment showed a significantly lower morphometric vertebral fracture risk versus those who discontinued treatment (RR 0.51 (0.26-0.95), 95% CI, $p = 0.035$) (Eriksen et al., 2014). Results regarding BMD indicated an increase in femoral neck and lumbar spine BMD (0.24 and 3.20%, respectively) ($p \leq 0.0002$). Interesting to note, the incidence of morphometric vertebral, non-vertebral, and hip fractures remained below the placebo group which may suggest residual benefit after discontinuation of treatment (Eriksen et al., 2014). Overall, long-term use of bisphosphonates has persistent beneficial effects on fracture risk (Eriksen et al., 2014).

A limitation was the heterogeneity between groups which was pronounced between populations, interventions, lengths of follow up and drugs tested which lead to no formal meta-analysis. However, this article is beneficial because it discusses the long-term efficacy of bisphosphonates for the treatment of postmenopausal women with osteoporosis.

Lin et al. (2012) compared the efficacy between the bisphosphonate (alendronate) and the anti-RANKL agent (denosumab). The meta-analysis included four RCTs with a double-blinded and placebo-used approach. Each trial had a target population of women with postmenopausal osteoporosis; treatments were either 60 mg of denosumab SC injections every six months or 70 mg PO of alendronate weekly. The results for efficacy were two-fold including fracture risk reduction and BMD variation. The results of the fracture risk reduction were 11 more per 1000 with denosumab treatment compared to alendronate treatment (OR 1.42 (1.84-2.40), 95% CI, $p = 0.19$) (Lin et al., 2012). Therefore, the meta-analysis provided low evidence that 60 mg denosumab every six months versus 70 mg alendronate PO weekly could result in 11 more women per 1000 facing a clinical fracture (Lin et al., 2012). The results of BMD variation for both denosumab and alendronate increased BMD significantly at the distal radius, total hip, lumbar spine, and femoral neck after six and 12 months compared to baseline (Lin et al., 2012). Furthermore, BMD variation with denosumab obtained greater bone mass at the distal radius, total hip, lumbar spine, and femoral neck after six and 12 months than alendronate ($p < 0.01$) (Lin et al., 2012). The evidence quality for BMD analysis was moderate to high; therefore, the results concluded denosumab as more effective for increasing BMD for postmenopausal women as compared to alendronate (Lin et al., 2012).

The researchers assured their funding sources were independent and had no influence when publishing their findings (Lin et al., 2012). Limitations included failure to follow-up leading to incomplete outcome data in some trials, substantial heterogeneity, an observational duration of one-year, only four trials included, and the four RCTs in the meta-analysis were sponsored by the pharmaceutical company related to denosumab (Lin et al., 2012). Overall, Lin

et al. (2012) is significant because it compares the effects of historical first line treatment, alendronate, to the upcoming treatment option, denosumab, for postmenopausal osteoporosis.

Theme 4: Efficacy of anti-RANKL agents

In theme four, efficacy of the anti-RANKL agent (denosumab), six studies were reviewed. This theme investigates the changes in BMD and the fracture risk of denosumab in postmenopausal women with low BMD.

Researchers Bone et al. (2008) evaluated the ability of denosumab to increase BMD in postmenopausal women with low BMD. The study specifically measured denosumab versus placebo for 24 months with a randomized, double-blind, phase III study. The target population of included women with a lumbar spine BMD T-score between -1.0 and -2.5 (Bone et al., 2008). The participants were assigned to receive either 60 mg denosumab SC every six months (n= 116) or placebo (n= 116) for two years (Bone et al., 2008). Significant increases were observed with denosumab compared to placebo as early as month one and continued through month 24 (Bone et al., 2008). The results listed are at month 24, denosumab compared to placebo significantly increased BMD at the lumbar spine (6.5 versus -0.6%), at the total hip (3.4 versus -1.1%), femoral neck, trochanter, radius (1.4 versus -2.1%), and total body (2.4 versus -1.4%) ($p < 0.0001$) (Bone et al., 2008). At month 24, the proportion of women who gained BMD overall with denosumab compared to placebo at the lumbar spine was 96% versus 39% ($p < 0.0001$) (Bone et al., 2008). Similarly, at the total hip denosumab compared to placebo was 96% versus 31%, and at the radius denosumab compared to placebo was 71% versus 22% (Bone et al., 2008). Clinical fractures occurred in two participants (1%) in the denosumab group and seven participants (4%) in the placebo group (Bone et al., 2008).

The main limitation was the small sample size for both the denosumab and placebo group. Overall, Bone et al. (2008) is a significant demonstration of the efficacy of denosumab in the treatment of postmenopausal osteoporosis.

Researchers Keyserlingk et al. (2011) assessed the clinical efficacy of offering denosumab to postmenopausal women with low BMD. The meta-analysis included four RCTs with results of efficacy focusing on fracture incidence. Fracture incidence with denosumab compared to placebo was statistically significant (RR 0.58 (0.52-0.66), 95% CI) (Keyserlingk et al., 2011).

The limitations included heterogeneity between the studies in sample sizes and variability in participant characteristics. However, this meta-analysis includes RCTs in thousands of people which illustrates comprehensive evidence of the efficacy of denosumab as a treatment for postmenopausal osteoporosis. Furthermore, Keyserlingk et al. (2011) affirms a clinical correlation between an increase in BMD and fracture risk reduction.

McClung et al. (2013) reported the effects on eight years of continuous denosumab treatment on BMD. The study design was open-label 60 mg denosumab SC every six months with a target population of postmenopausal women who had a BMD T-score between -1.8 to -4.0 for the lumbar spine or between -1.8 and -3.5 for either the total hip or femoral neck (n= 138) (McClung et al., 2013). The results on efficacy, specifically BMD, compared their findings between the participants who received eight years of continuous denosumab treatment and participants who received four years of placebo followed by four years of denosumab treatment (McClung et al., 2013). For the participants who received eight years of denosumab from the parent study baseline, BMD at the lumbar spine (16.5%), total hip (6.8%), and femoral neck (6.8%) significantly increased, while the BMD at the radius (1.3%) remained stable. For the

participants who received eight years of denosumab from the extension study baseline, BMD at the lumbar spine (5.7%), total hip (1.8%), femoral neck (2.3%), and radius (0.8%) all increased, but to a lesser degree (McClung et al., 2013).

The limitations included the lack of a placebo group after the four-year parent study and the small number of participants completing the full eight-year parent and extension study (n= 138) which markedly decreased the ability to assess the safety of denosumab (McClung et al., 2013). They do mention this was a limitation to their study; however, they look to the FREEDOM extension trial to characterize the safety of denosumab long-term (McClung, 2013). McClung (2013) demonstrates the efficacy of denosumab for treatment of postmenopausal osteoporosis.

The goal of researchers Beck et al. (2008) was to report BMD data from hip structural analysis (HSA) by dual-energy x-ray absorptiometry (DXA) scans in participants who were treated with denosumab, alendronate, or placebo for up to 24 months. The purpose was to monitor the effect of treatment on BMD of the proximal femur (Beck et al., 2008). Beck et al. (2008) outlined the study in the methods which, "Consisted of 116 participants who received either denosumab 60 mg every six months (n= 39), alendronate 70 mg once weekly (n= 38), or placebo (n= 39) with baseline, 12-month, and 24-month scans conducted in a blinded manner" (p. 352). The results included DXA-BMD at the femoral neck and HSA-BMD at the narrow neck, intertrochanter, and shaft at 24 months (Beck et al., 2008). At the femoral neck, DXA-BMD was increased with denosumab by 4.52% ($p < 0.001$ compared to placebo), increased with alendronate by 2.99% ($p < 0.001$ compared to placebo), but decreased with placebo by -1.40% (Beck et al., 2008). At the narrow neck, HSA-BMD was increased with denosumab by 3.85% ($p < 0.001$ compared to placebo), increased with alendronate by 2.53%

($p < 0.001$ compared to placebo) but decreased with placebo by -2.11% (Beck et al., 2008). At the intertrochanter, HSA-BMD was increased with denosumab by 6.99% ($p <0.001$ compared to placebo, $p < 0.05$ compared to alendronate), increased with alendronate by 4.43% ($p < 0.001$ compared to placebo), but decreased with placebo by -1.16% (Beck et al., 2008). At the shaft, HSA-BMD was increased with denosumab by 5.73% ($p < 0.001$ compared to placebo, $p < 0.001$ compared to alendronate), increased with alendronate by 1.59% ($p < 0.05$ compared to placebo), but decreased with placebo by -0.27% (Beck et al., 2008). Overall, improvement of DXA-BMD and HSA-BMD at the proximal femur, in all regions, was most pronounced with denosumab as opposed to alendronate or placebo.

One limitation is the body size of the participants. Beck et al. (2008) focused on measuring the geometry and strength of the bones, and body size can affect these parameters. Beck et al. (2008) did note, "Small difference in mean body weight at baseline with higher weights in the treated groups" (p. 358). However, they further went on to say, "This did not translate to a significant difference in baseline BMD or any geometric parameter" (Beck et al., 2008, p. 358). Another limitation included small sample size. Lastly, denosumab-related effects did not demonstrate improved fracture outcomes. However, Beck et al. (2008) is very beneficial to the research question because it reported on the geometrical parameters using HSA which gives robust evidence to the efficacy of denosumab.

Researcher Deeks (2018) summarized data relevant to the efficacy of denosumab in the treatment of postmenopausal osteoporosis by specifically highlighting BMD and fracture incidence. Deeks (2018) started by selecting phase III and IV trials and the most comprehensive information came from the three-year phase III trial FREEDOM (n= 7,808) and its seven-year extension (n= 4,550). The FREEDOM trial and the extension are the focus of the results section.

The other trials include DECIDE (n= 1,179), STAND (n= 504), Recknor et al. (n= 833), Roux et al. (n= 870), and Miller et al. (n= 643). In the three-year FREEDOM study, BMD variation was significantly improved with denosumab compared to placebo at the total hip (4.9 versus -1.2%), lumbar spine (9.4 versus 0.6%), femoral neck (4.2 versus -0.9%) and trochanter (7.1 versus -1.2%) ($p \leq 0.0001$ for all above measurements) (Deeks, 2018). The results for 10 years of continuous denosumab compared to placebo for three years followed by denosumab for seven years include total hip (9.2 versus 7.4%), lumbar spine (21.7 versus 16.5%), femoral neck (9.0 versus 7.1%) and radius (2.7 versus 2.3%) ($p \leq 0.05$ for all above measurements) (Deeks, 2018). Furthermore, denosumab continued to be associated with BMD improvements up to 10 years of treatment with no evidence of plateau (Deeks, 2018). In the FREEDOM study, denosumab significantly reduced the risk of new vertebral fracture by 68%, non-vertebral fracture by 20%, and hip fracture by 40% compared to placebo (Deeks, 2018). Furthermore, the incidence of new clinical vertebral fracture was more favorable with denosumab than with placebo (0.8 versus 2.6%; hazard ratio (HR) 0.31 (0.20-0.47), 95% CI) and multiple new vertebral fractures (0.6 versus 1.6%; RR 0.39 (0.24-0.63), 95% CI) ($p < 0.001$) (Deeks, 2018). However, the risk of wrist fracture did not significantly differ between treatment groups (2.5 versus 2.9%) (Deeks, 2018). Looking at the extension of the FREEDOM study, longer term antifracture benefit with denosumab was sustained up to 10 years of treatment (Deeks, 2018). The other studies compare denosumab with bisphosphonates in a one-year phase III and IV study. The results indicated denosumab was more effective than bisphosphonates (once-weekly alendronate, once-monthly ibandronate and risedronate) in increasing BMD at the total hip, lumbar spine, femoral neck, trochanter, and/or radius in postmenopausal women with low BMD (Deeks, 2018). Similarly, denosumab significantly increased BMD at the lumbar spine, total hip, femoral neck, and radius

compared to once-yearly zoledronic acid (Deeks, 2018). The results of denosumab compared to various bisphosphonates are listed below in Table 1 as reported by Deeks (2018).

Table 1

Effect of denosumab on BMD in postmenopausal women with low BMD or osteoporosis in phase III or IV trials.

				Mean change from baseline in BMD (%)				
Study	Regimen	N	Tx Duration	Lumbar Spine	Total Hip	Femoral Neck	Trochanter	Radius
FREEDOM	DEN	3902	3	9.4 *** [a]	4.9*** [a]	4.2*** [a]	7.1*** [a]	
	PL	3906		0.6 [a]	-1.2 [a]	-0.9 [a]	-1.2 [a]	
FREEDOM ext	DEN	2343	10	21.7† [b]	9.2† [b]	9.0†		2.7††
	PL→DEN	2207	7	16.5† [b]	7.4† [b]	7.1†		2.3†††
DECIDE [c]	DEN	593	1	5.3***	3.5*** [d]	2.4***	4.5***	1.1***
	ALN	586		4.2	2.6 [d]	1.8	3.4	0.6
STAND [c]	DEN	253	1	3.0***	1.9*** [d]	1.4 [a]		0.9* [a]
	ALN	251		1.9	1.1 [d]	0.4 [a]		0.2 [a]
Recknor et al.	DEN	417	1	4.1**	2.3** [d]	1.7**		
	IBA	416		2.0	1.1 [d]	0.7		
Roux et al.	DEN	435	1	3.4***	2.0*** [d]	1.4***		
	RIS	435		1.1	0.5 [d]	0		
Miller et al. [c]	DEN	321	1	3.2*** [d]	1.9***	1.2***		0.6*
	ZOL	322		1.1 [d]	0.6	-0.1		0

Tx treatment, *DEN* subcutaneous denosumab 60 mg once every 6 months, *PL* placebo, *ALN* oral alendronate 70 mg once weekly, *IBA* oral ibandronate 150 mg once monthly, *RIS* oral risedronate 150 mg once monthly, *ZOL* intravenous zoledronic acid 5 mg once yearly

*$p < 0.05$, **$p \leq 0.001$, ***$p \leq 0.0001$ vs. comparator
†$p<0.05$ vs. FREEDOM baseline and ext baseline, ††$p<0.05$ vs. FREEDOM baseline, †††$p<0.05$ vs. FREEDOM ext baseline

[a] Value estimated from a graph
[b] FREEDOM ext baseline
[c] Noninferiority trial; assessed noninferiority and, subsequently, superiority of DEN vs. comparator, using a sequential testing procedure
[d] Primary endpoint

Note. Adapted from "Denosumab: A Review in Postmenopausal Osteoporosis," by E. D. Deeks, 2018, *Drugs & Aging*, *35* (2), p. 167. Copyright 2018 by Springer International Publishing AG, part of Springer Nature 2018.

The limitations include heterogeneity between studies, specifically regarding sample size. Another limitation includes the peer review process where the manufacturer of denosumab was

offered the opportunity to review this article (any changes made were claimed to be made based on scientific and editorial merit). However, this article addresses the efficacy of denosumab against not only placebo but also bisphosphonates which are the current first line of treatment.

Theme 5: Preference, adherence, and satisfaction between bisphosphonates and anti-RANKL agents

In theme five, preference, adherence, and satisfaction between bisphosphonates and the anti-RANKL agent, three studies were reviewed. The purpose of theme five is motivated by clinical relevancy. For treatment to be effective, the medication must be taken as directed. If the medication is not taken as directed, the efficacy declines. Therefore, theme five expands the research question by asking, which medication and dosing schedule will participants adhere to for treatment of their chronic disease?

Researchers Freemantle et al. (2012) performed the Denosumab Adherence Preference Satisfaction (DAPS) study which evaluated the adherence (compliance and persistence) to either 60 mg denosumab SC every six months or 70 mg alendronate PO weekly using a randomized, cross-over design. The design randomized eligible participants to one of two treatment sequences, denosumab followed by alendronate or alendronate followed by denosumab (Freemantle et al., 2012). Each participant received two years of treatment (one year for each medication) (Freemantle et al., 2012). Adherence was reported along with participant beliefs, preference, satisfaction, and bother after participants received both treatments (Freemantle et al., 2012). At each follow-up visit, participants completed an adaptation of the Beliefs about Medicines Questionnaire (BMQ) that includes 22 questions regarding the necessity of the prescribed medication to manage osteoporosis now and in the future, concerns about the potential AEs taking the prescribed medication to manage osteoporosis, and preference for one

medication to manage osteoporosis (Freemantle et al., 2012). They also completed the Preference Satisfaction Questionnaire (PSQ) that included questions regarding preference, pill satisfaction, injection satisfaction, pill bother, and injection bother (Freemantle et al., 2012). Of the 250 participants who originally enrolled, 221 entered the second-year of the study (106 denosumab, 115 alendronate) (Freemantle et al., 2012). By the end of the first 12 months, 11.9% of participants were non-adherent to denosumab and 23.4% were non-adherent to alendronate, representing a 46% reduction in the risk of non-adherence for denosumab compared to alendronate (Freemantle et al., 2012). The non-adherence rate after crossover was 7.5% for denosumab and 36.5% for alendronate (95% CI), representing an 80% lower risk of non-adherence with denosumab (Freemantle et al., 2012). Non-compliance after crossover was 6.6% for denosumab and 32.2% for alendronate, representing an 80% relative risk reduction of non-compliance with denosumab (Freemantle et al., 2012). Non-persistence in the first year was 9.5% for denosumab and 20.2% for alendronate, representing a 50% relative risk reduction of non-persistence with denosumab (Freemantle et al., 2012). Non-persistence after crossover was 2.8% for denosumab and 28.7% for alendronate, representing a 91% relative risk reduction of non-persistence with denosumab (Freemantle et al., 2012). Participant beliefs about the need for treatment was greater for denosumab than alendronate at the six-month visit before crossover ($p = 0.022$) (Freemantle et al., 2012). Participant concerns about potential AEs was lower for denosumab than alendronate at the six ($p = 0.010$) and 12 ($p = 0.028$) month visits after crossover (Freemantle et al., 2012). Participant preference for a certain medication was greater for denosumab than alendronate at every visit ($p < 0.001$) (Freemantle et al., 2012). Freemantle et al. (2012) reported, “At the end of the study, of the 198 participants who expressed a preference between treatment, 183 (92.4%) preferred denosumab. Of the 204 participants who

expressed a preference between treatments for the long-term, 186 (91.2%) preferred denosumab" (p. 322). Freemantle et al. (2012) went on to say, "Regardless of the treatment sequence, a greater proportion of participants stated they were quite or very satisfied with frequency of administration, mode of administration, and convenience of denosumab compared with alendronate" (p. 322). To conclude the study Freemantle et al. (2012) stated, "Postmenopausal women with low BMD preferred treatment with denosumab. Increased preference may influence persistence and adherence with treatment, which are important characteristic in treatment of a chronic condition that requires long-term treatment" (p. 325).

A major limitation was the treatment was provided to the participants by the sponsor. This removed the cost of adherence which, in reality, can majorly affect the capability to adhere to medications. Taking this factor out was wise to identify the true preference of participants, however, the clinical relevancy is jeopardized because cost is a significant factor to medication adherence.

Kendler et al. (2011) evaluated treatment adherence (compliance and persistence) with 60 mg denosumab SC every six months or 70 mg alendronate PO once weekly. In this randomized, open-label, two-year crossover study, 250 postmenopausal women with low BMD were allocated to receive denosumab or alendronate for 12 months, then the other treatment for 12 months (Kendler et al., 2011). Follow-up visits were scheduled for six, 12, 18, and 24 months, and at each visit participants completed an adaptation of the BMQ that included 22 questions, as previously outlined by Freemantle et al. (2012). At the six and 12-month visits, participants also completed the bother and satisfaction subscale which were taken from the PSQ (Kendler et al., 2011). The bother subscale ranged from one (not at all bothered) to five (severely bothered) and the satisfaction subscale ranged from one (not at all satisfied) to five (very satisfied) (Kendler et

al., 2011). The rate of non-adherence was 23.4% in the alendronate group and 12.7% in the denosumab group, representing a 42% lower risk of non-adherence in the denosumab group (Kendler et al., 2011). The rate of non-compliance was 21.8% in the alendronate group and 9.5% in the denosumab group, representing a 52% relative risk reduction of non-compliance in the denosumab group (Kendler et al., 2011). The rate of non-persistence was 20.2% in the alendronate group and 10.3% in the denosumab group, representing a 46% relative risk reduction of non-persistence in the denosumab group (Kendler et al., 2011). Scores for subject beliefs about the necessity for treatment were not significantly different between the alendronate and denosumab group at baseline (3.32 versus 3.26, $p = 0.491$); however, by the six-month visit, they were significantly lower for alendronate than for denosumab (3.14 versus 3.31, $p = 0.024$) (Kendler et al., 2011). Scores for participant concerns about potential AEs from treatment were not significantly different between the alendronate and denosumab groups at baseline (2.33 versus 2.43, $p = 0.066$) or at the six-month visit (2.22 versus 2.12, $p = 0.135$) (Kendler et al, 2011). However, concerns tended to decrease after exposure to treatment in the denosumab group than in the alendronate group (Kendler et al., 2011). Participants reported significantly lower preference score for alendronate than for denosumab at baseline (2.97 versus 3.47, $p < 0.001$) and at the six-month visit (3.01 versus 3.73, $p < 0.001$) (Kendler et al., 2011). The PSQ results regarding satisfaction at 12 months was 4.29 for alendronate and 4.59 for denosumab ($p = 0.001$) and PSQ results regrading bother was 1.32 for alendronate and 1.11 for denosumab ($p = 0.006$) (Kendler et al., 2011). At 12 months, participants in the denosumab group were more likely than participants in the alendronate group to report being either very satisfied or quite satisfied with the dosing frequency, route of administration, convenience, and overall satisfaction with treatment (Kendler et al., 2011).

Several limitations are highlighted by the authors. The open-label study design did not blind the participants to their treatment assignment, which may introduce bias (Kendler et al., 2011). Participants knew the purpose of the study which may have resulted in increased adherence in both treatment groups compared with actual clinical practice (Kendler et al., 2011). Furthermore, participants knew their adherence to alendronate was monitored by a medication event monitoring system (MEMS) which could have increased the treatment adherence in the alendronate group (Kendler et al., 2011). This study addresses the clinical applicability of the research question. Evidence-based medicine needs to be implemented to provide the best care to patients, but patients need to be adherent, compliant, and persistent to treatment for the full benefits to be reached.

Palacios et al. (2015) evaluated the change in treatment satisfaction in postmenopausal women who were suboptimally adherent to daily or weekly oral bisphosphonates who transitioned to denosumab. The target population was postmenopausal women who were previously treated with a daily or weekly oral bisphosphonate (alendronate for the Transition to Risedronate (TTR) study and any oral bisphosphonate for the Transition to Ibandronate (TTI) study) for at least one month prior to screening (Palacios et al., 2015). Participants had to have either discontinued bisphosphonate treatment before the screening visit or were still taking a bisphosphonate but with low adherence (Palacios et al., 2015). Eligible participants were randomly assigned to receive open-label 60 mg denosumab SC every six months or open-label 150 mg ibandronate or risedronate PO once monthly for 12 months (Palacios et al., 2015). A total of 1,703 participants were included in the analysis (851 oral bisphosphonates (416 from TTI and 435 from TTR) and 852 denosumab (417 from TTI and 435 from TTR) (Palacios et al., 2015). The study monitored the change in participant-reported treatment satisfaction using the

Treatment Satisfaction Questionnaire for Medication (TSQM) (Palacios et al., 2015). The TSQM consists of 14 items to assess an individual's perception on four domains of treatment satisfaction including effectiveness, side effects, convenience, and global satisfaction with higher scores indicating greater treatment satisfaction (Palacios et al., 2015). Changes in TSQM domain scores from baseline to months six and 12 were monitored (Palacios et al., 2015). Compared with baseline, participants in both treatment groups reported greater satisfaction in all TQSM domains at six and 12 months, and changes from baseline persisted from month six to month 12 (Palacios et al., 2015). However, changes in TQSM scores for all four domains were significantly greater in participants who transitioned to denosumab at all post-baseline time points (all $p < 0.001$) (Palacios et al., 2015). Least square mean differences between the groups (denosumab versus oral bisphosphonates) were notable for the convenience domain at month six (12.9 (11.3-14.5), 95% CI) and month 12 (12.4 (10.7-14.4), 95% CI) ($p < 0.001$) and global satisfaction domain at month six (9.2 (7.3-11.0), 95% CI) and month 12 (10.2 (8.1-12.2), 95% CI) (both $p < 0.001$) (Palacios et al., 2015). The corresponding differences between the groups (denosumab versus oral bisphosphonates) were notable for effectiveness domain at month six (5.1 (2.9-7.2) 95% CI) and month 12 (5.2 (2.9-7.5) 95% CI) and for the side effect domain at month six (3.8 (2.3-5.2) 95% CI) and month 12 (3.5 (2.1-5.0) 95% CI) (all $p < 0.001$) (Palacios et al., 2015). In conclusion, in participants who were suboptimally adherent to oral bisphosphonate treatment, switching to denosumab led to greater treatment satisfaction than switching to another oral bisphosphonate (Palacios et al., 2015). Greater treatment satisfaction may lead to better treatment adherence in women with postmenopausal osteoporosis and, ultimately, improvements in treatment effectiveness.

The main limitations of this randomized study include the open-label design and the one-year study duration to evaluate treatment satisfaction for a condition that generally requires longer treatment. However, Palacios et al. (2015) is foundational because it is one of the only studies that emphasizes the transition from bisphosphonates to denosumab due to low adherence. This adds a new dimension to clinical applicability where clinicians often face low adherence to medication for chronic diseases.

Discussion

This project revealed the important factors to evaluate when selecting the best treatment for postmenopausal osteoporosis. Each medication has its own safety, efficacy, and adherence profile that should be considered for the individual patient. Within each theme of the literature review the statistics were reported, and the conclusion of this project will determine the best treatment option based on the above research.

In the treatment of postmenopausal osteoporosis, is there a statistical difference in the safety, efficacy, and preference when using bisphosphonates versus the anti-RANKL agent?

When analyzing the research in theme one, safety of bisphosphonates, Wang (2017) reported zoledronic acid compared to placebo had a higher incidence of any AEs but similar incidence of SAEs. Eriksen et al. (2014) concluded by stating long-term use of bisphosphonates in postmenopausal women had no unexpected AEs emerging from long-term treatment and tolerability profiles remained favorable. Lin et al. (2012) determined the overall rates of AEs and SAEs were balanced between alendronate and denosumab.

Based on the above research several conclusions were made by the researchers. First, Wang (2017) noted the safety of bisphosphonates compared to placebo which was vital in first

starting patients on the historic first line treatment for postmenopausal osteoporosis. Next, Eriksen et al. (2014) focused on the long-term use of bisphosphonates in postmenopausal osteoporotic women which is crucial since this is a chronic disease. The long-term trials are paramount when studying safety profiles since many AEs may not show in shorter trials. Lastly, Lin et al. (2012) stated the overall rates of AEs and SAEs were balanced between both alendronate and denosumab. Therefore, not only are bisphosphonates just as safe as placebo but they appear to be just as safe as denosumab.

When evaluating the research in theme two, safety of the anti-RANKL agent (denosumab), Bone et al. (2008) concluded denosumab had an overall incidence of AEs similar to placebo. Keyserlingk et al. (2011) concluded there were no significant increase in relative SAEs in participants taking denosumab versus placebo. Deeks (2018) concluded no significant differences between denosumab and bisphosphonates in terms of the overall incidence of TEAEs or TEAEs leading to discontinuation. Zhou et al. (2014) noted no difference between the safety of denosumab versus bisphosphonates but did show an increased risk SAE related to infection with denosumab versus placebo.

Continuing with theme two, Bone et al. (2008) and Keyserlingk et al. (2011) proved denosumab had a similar safety profile as placebo. Furthermore, Deeks (2018) and Zhou et al. (2014) concluded there were no significant differences between denosumab and bisphosphonates. However, Zhou et al. (2014) did note an increased risk of SAE related to infection with denosumab versus placebo. Therefore, denosumab may increase risk of infection when compared to placebo. However, denosumab is as safe as bisphosphonates.

When assessing the research in theme three, efficacy of bisphosphonates, Wang (2017) concluded zoledronic acid significantly reduced the risk of fractures and increased BMD among

postmenopausal women with osteoporosis. Eriksen et al. (2014) concluded long-term use of bisphosphonates in postmenopausal women had persistent beneficial effects on fracture risk and BMD beyond three years of treatment. Lin et al. (2012) concluded denosumab might be more effective for increasing BMD of postmenopausal women than alendronate treatment. However, Lin et al. (2012) went on to say the analysis of relevant clinical outcome demonstrated inconclusive benefits of denosumab over alendronate regarding fracture risk reduction.

To further develop theme three, Wang (2017) identified the reduced risk of fractures and increased BMD with a bisphosphonate in postmenopausal women with osteoporosis. Expanding on this was Eriksen et al. (2014) who reported long-term use of bisphosphonates in postmenopausal women had persistent beneficial effects on fracture risk and BMD beyond three years of treatment. Lastly, Lin et al. (2012) found that denosumab might be more effective in increasing BMD over alendronate but this may or may not be clinically relevant in reducing fracture risk. Therefore, bisphosphonates can increase BMD and decrease fracture incidence.

When examining the research in theme four, efficacy of the anti-RANKL agent (denosumab), Bone et al. (2008) concluded denosumab increased BMD in postmenopausal women with low BMD. Keyserlingk et al. (2011) concluded significant reduction in relative fracture risk in the denosumab compared with placebo. McClung et al. (2013) concluded sustained effects of denosumab treatment on bone remodeling and progressive, substantial increases in BMD over eight years in postmenopausal women with low BMD. Furthermore, McClung et al. (2013) stated long-term treatment with denosumab is an effective treatment option for the management of postmenopausal osteoporosis. Beck et al. (2008) concluded denosumab treatment improved DXA-BMD and HSA-BMD better than alendronate or placebo. Deeks (2018) stated in one-year trials, denosumab was more effective in improving BMD than

bisphosphonates in postmenopausal women with low BMD. He hypothesized this could be due to the MOA of denosumab being distinct from, and earlier in the bone remodeling process than, that of bisphosphonates (Deeks, 2018). However, Deeks (2018) reported no significant difference between denosumab and bisphosphonates in terms of anti-fracture efficacy.

To further expand on theme four, Bone et al. (2008) found that denosumab increased BMD; additionally, Keyserlingk et al. (2011) reported a significant reduction in relative fracture risk in the denosumab compared with placebo. Next, McClung et al. (2013) realized the sustained effects of denosumab treatment on bone remodeling and substantial increases in BMD over eight years in postmenopausal women with low BMD. Beck et al. (2008) identified the superiority of denosumab versus alendronate or placebo in improving BMD. Deeks (2018) confirmed the superiority of denosumab in improving BMD and believed it was possibly due to the differing MOAs. Therefore, when choosing a treatment option to increase BMD in postmenopausal women, it is clear to see the superiority of denosumab versus placebo and bisphosphonates. However, Deeks (2018) and Lin et al. (2012) both agreed although denosumab in superior in increasing BMD, this may not translate to reduced fracture risk.

When reviewing the research in theme five, Freemantle et al. (2012) concluded postmenopausal women with low BMD who received alendronate followed by denosumab or denosumab followed by alendronate, preferred treatment with denosumab. Furthermore, increased preference may influence persistence and adherence, which are important characteristics in treatment of a chronic condition that requires long-term management (Freemantle et al., 2012). Kendler et al. (2011) concluded treatment adherence during the first 12 months of this randomized, crossover study was significantly greater for participants who received denosumab compared with participants who received alendronate. Therefore,

participants in the denosumab group were more likely to report being satisfied with the dosing schedule and route of administration with denosumab, and they reported less bother and greater preference for denosumab compared with alendronate (Kendler et al., 2011). Palacios et al. (2015) concluded participants who were suboptimally adherent to oral bisphosphonates and switched to denosumab led to greater treatment satisfaction than switching to another oral bisphosphonate. Greater treatment satisfaction may lead to better treatment adherence in women with postmenopausal osteoporosis and, ultimately, improvements in treatment effectiveness (Palacios et al., 2015). Therefore, providers should consider denosumab as an alternate effective option for the treatment of postmenopausal osteoporosis in women who are suboptimally adherent to oral bisphosphonates (Palacios et al., 2015).

Based on the research a single conclusion can be made. The decision among Freemantle et al. (2012), Kendler et al. (2011), and Palacios et al. (2015) was unanimous when they recognized the increased adherence and preference of denosumab versus alendronate. Keyserlingk et al. (2011) agreed with these authors when he stated denosumab could present as an effective new treatment for osteoporosis with fewer adherence barriers than present options. Therefore, from a clinical standpoint of adherence and preference, denosumab is clearly superior.

After analyzing the research, similar safety profiles exist between bisphosphonates and denosumab. Denosumab is more efficacious in increasing BMD as opposed to bisphosphonates; however, denosumab and bisphosphonates have similar fracture risk incidence. Most importantly, denosumab has a much stronger adherence and preference profile than bisphosphonates. Therefore, the treatment of choice when managing the chronic condition of postmenopausal osteoporosis is denosumab.

With denosumab as the superior treatment choice, the natural next question is cost. For six months of treatment (without considering insurance), denosumab would cost about $1,400.00 and alendronate would cost about $120.00. The pricing difference may seem quite startling initially; however, do not forget to consider the secondary cost due to non-adherence with alendronate. As we discussed in theme five, the non-adherence rate as reported by Freemantle et al. (2012) after one year was 11.9% of participants using denosumab and 23.4% of participants using alendronate. The number one risk factor of non-adherence with a medication used to treat postmenopausal osteoporosis is fracture. If an osteoporotic postmenopausal woman were to fall and break her hip, the cost of this surgery is roughly $40,000.00 (without considering insurance). This is the cost for surgery alone and does not include the cost of the hospitalization, long-term care facility stay, and therapies needed to regain the lifestyle the patient once lived. As a nation, if we are wanting to begin shifting from reactive to proactive medical care and keeping the cost of healthcare at a lower level, the decision to treat with the anti-RANKL agent is clear. Denosumab is just as safe, more efficacious, better adhered to, and more preferred than bisphosphonates. Therefore, the anti-RANKL agent, denosumab, is clearly superior to bisphosphonates in the treatment of postmenopausal osteoporosis.

Applicability to Clinical Practice

Due to the increase in patients presenting with postmenopausal osteoporosis, the need for safe, effective, and preferred treatments has never been so prevalent. This project demonstrates the different legs of importance when analyzing medication options for postmenopausal osteoporosis. Providers are faced with the choice to select either the historic first line treatment, bisphosphonates, or use the newer, safer, more effective and preferred treatment, the anti-RANKL agent. The patient's needs must be taken into consideration and each decision must be

on an individual basis. For example, if the patient has insurance that will cover denosumab, this is the obvious first line treatment. However, if denosumab is not covered, then using a bisphosphonate first may be necessary. Nevertheless, if bisphosphonates are not tolerated, denosumab is the next best medication.

Clinicians should be well-versed on the treatment options for postmenopausal osteoporosis available and be able to educate patients on the different factors of each medication. With continuing research, scientists will be able to discover new treatments and providers can continue to provide the best options for patients with postmenopausal osteoporosis. With early detection and prompt initiation of treatment, we will slowly begin to see the disease progression fade.

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