JMM Journal of Menopausal Medicine
pISSN: 2288-6478, eISSN: 2288-6761
https://doi.org/10.6118/jmm.22007
J Menopausal Med 2022;28:85-91
REVIEW ARTICLE

Up-to-Date Knowledge on Osteoporosis Treatment Selection in Postmenopausal Women

Hye Gyeong Jeong[1,2], Min Kyung Kim[3], Hee Jeung Lim[4], Seul Ki Kim[2,3]

[1]Department of Obstetrics and Gynecology, Korea University Anam Hospital, Seoul, Korea, [2]Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, Korea, [3]Department of Obstetrics and Gynecology, Seoul National University Bundang Hospital, Seongnam, Korea, [4]Department of Obstetrics and Gynecology, Seoul National University Hospital, Seoul, Korea

The concept of a super-aged society has led to a steady increase in the average lifespan and hence, interest in a healthy life has increased. Aging is a major risk factor for many diseases, including osteoporosis. Osteoporotic fractures have a significant impact on the quality of life of the elderly and hence, it is pivotal to provide effective treatment of osteoporosis after menopause. Osteoporosis requires proper management and the treatment must be centered on long-term goals. New drugs with diverse mechanisms have been developed for treating osteoporosis. Current management of osteoporosis generally focuses on the importance of risk-based strategies to maximize the effectiveness of existing treatments and mitigate potential negative side-effects. Additionally, there is a need for sequential treatment of osteoporosis in the future. This review discusses the dynamic strategies for osteoporosis treatment and the importance of long-term management in postmenopausal women.

Key Words: Bone density, Menopause, Osteoporosis, Osteoporotic fractures, Quality of Life

INTRODUCTION

According to the 2019 data published by Statistics Korea [1], the mean life expectancy in South Korea was 83.3 years (80.3 years in males and 86.3 years in females), which has increased by approximately 8 years compared to that reported 20 years ago. The average menopausal age in women is approximately 51 years, which implies that women should live approximately 30 years or more, i.e., one-third of their entire life or more, in postmenopause. The lack of estrogen observed in menopausal women results in various physical and psychological changes, such as osteoporosis, a problem of bone metabolism. According to a survey conducted by the Korea Disease Control and Prevention Agency between 2008 and 2011, the prevalence of osteoporosis in South Korea was as high as one in five adults (22.4%) while approximately one in two adults (47.9%) had osteopenia, a step preceding osteoporosis [2]. In addition, data from the Korea National Health and Nutrition Examination Survey [3] showed a steady increase in the annual number of patients with osteoporosis in South Korea, exceeding 821,754 cases in 2015 and one million cases in 2020. Notably, the prevalence of osteoporosis in men and women aged 50 years or above was 2.8% and 29.2%, respectively, and a steep increase with age was observed in women with a prevalence of 68.5% among those in their 70s. Interest in healthy life expectancy and emphasis on osteoporosis treatment and management has continuously increased with increasing lifespan, especially considering the life expectancy and prevalence of osteoporosis in women.

Received: February 28, 2021 **Revised:** August 20, 2021 **Accepted:** September 12, 2021
Address for Correspondence: Seul Ki Kim, Department of Obstetrics and Gynecology, Seoul National University Bundang Hospital, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea
Tel: 82-31-787-7264, **E-mail:** skkim@snubh.org, **ORCID:** https://orcid.org/0000-0002-1647-6711

THE RATIONALE FOR THE SEQUENTIAL TREATMENT APPROACH IN OSTEOPOROSIS THERAPY

The increase in life expectancy has changed the awareness of osteoporosis from a disease that can be treated within a short period with single therapy to a chronic illness that necessitates long-term management throughout the middle-aged and elderly life.

Therapeutic agents currently used for osteoporosis can be broadly divided into antiresorptive and anabolic agents. Antiresorptive agents include menopausal hormone therapy, selective estrogen receptor modulators (SERMs), bisphosphonates (BPs), and denosumab (DMAb), while anabolic agents include teriparatide and romosozumab.

Most of these drugs have been reported to be effective in reducing the risk of fracture in placebo-controlled studies despite slight differences. The use of anti-osteoporotic drugs has been reported to reduce the relative fracture risk of osteoporosis to 40%–73% in vertebral fractures and 40%–53% in hip fractures [4,5]. The mechanisms and characteristics of each drug vary; hence, the sequential application of osteoporosis drugs may lead to varying effects. The side effects and additional positive effects of each drug should be considered in addition to the health insurance criteria in South Korea.

The Endocrine Society Clinical Practice Guideline of 2020 [6] recommends that treatment choice should vary according to the risk of fracture based on the treatment algorithm for women with osteoporosis. Figure 1 shows the algorithm of the Endocrine Society Clinical

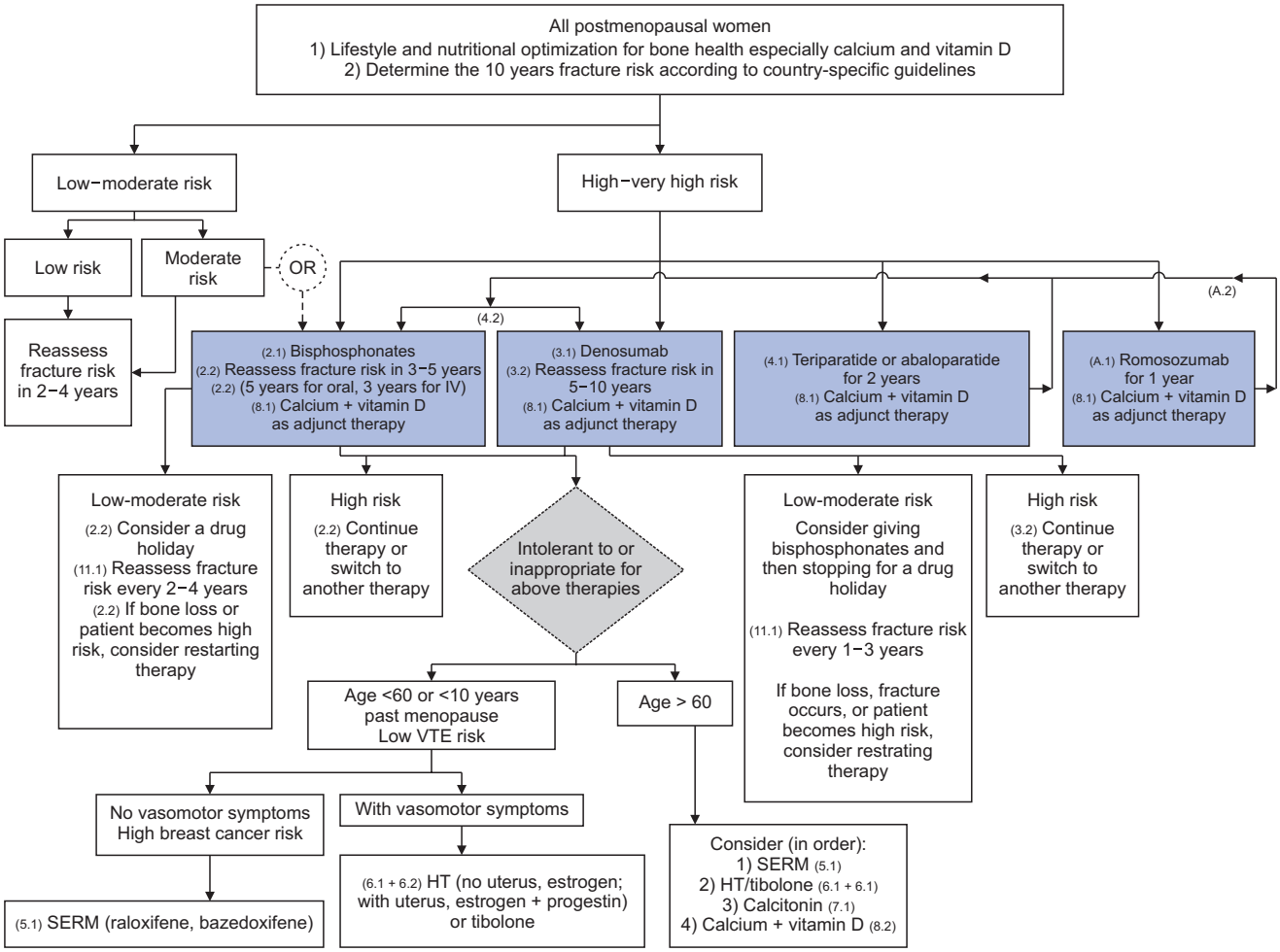

Fig. 1. Updated algorithm for management of postmenopausal osteoporosis. SERM: selective estrogen receptor modulator, IV: intravenous, VTE: venous thromboembolism, HT: hormone therapy. Adapted from the article of Shoback et al. (J Clin Endocrinol Metab 2020;105:dgaa048) [6] with original copyright holder's permission.

Practice Guideline of 2020 [6].

Osteoporosis treatment in the low to moderate fracture risk group

The low-risk group is defined as menopausal women with a bone mass density (BMD) T-score exceeding –1.0 without hip joint or vertebral fracture, < 3% 10-year risk of hip joint fracture, and < 20% risk of major osteoporotic fractures. Non-drug treatment was recommended for this group [6].

Non-drug treatment such as lifestyle modification, nutrition and exercise, or the use of BPs is recommended for menopausal women with BMD T-score ranging from –1.0 to –2.5 i.e., those diagnosed with osteopenia but with no hip joint or vertebral fracture, those with < 3% 10-year risk of hip joint fracture, and those with less than 20% risk of major osteoporotic fractures, as the moderate-risk group. In the moderate-risk group, it is generally recommended to re-evaluated within 2–4 years of non-drug treatment. However, it is also recommended that reassessment of fracture risk after using bisphosphonates for 3–5 years, or calcium or vitamin D is recommended as adjunct therapy [6].

Osteoporosis treatment for high to very-high fracture risk groups

The use of BPs and DMAb is primarily recommended for osteoporosis treatment in menopausal women defined as a high fracture risk group with a history of hip joint or vertebral fracture and who show ≥ 3% 10-year risk of hip joint fracture or ≥ 20% risk of major osteoporotic fractures.

Women with osteoporosis and multiple spine fractures are defined as the very-high fracture risk group. Parathyroid hormones, including teriparatide and romosozumab, could be the primary choice in osteoporosis treatment in this group [7].

The treatment of the high and very-high fracture risk groups should always include adequate calcium and vitamin D supplementation.

OSTEOPOROSIS AND THE CLINICAL EFFICACY OF HORMONAL TREATMENTS

One of the first treatment methods to consider in postmenopausal women with osteoporosis is menopausal hormone therapy [8,9]. For osteoporotic postmenopausal women in high or very-high fracture risk groups showing incompatibility or poor drug tolerance to the primarily recommended treatment, a different method could be applied depending on the presence of vasomotor symptoms (VMS) in menopausal women aged below 60 years or less than 10 years postmenopause. The menopausal hormone therapy including tibolone treatment may be considered in the presence of VMS while the SERMs, such as raloxifene and bazedoxifene, may be considered in the absence of VMS and patients with a high risk of breast cancer. The ral-

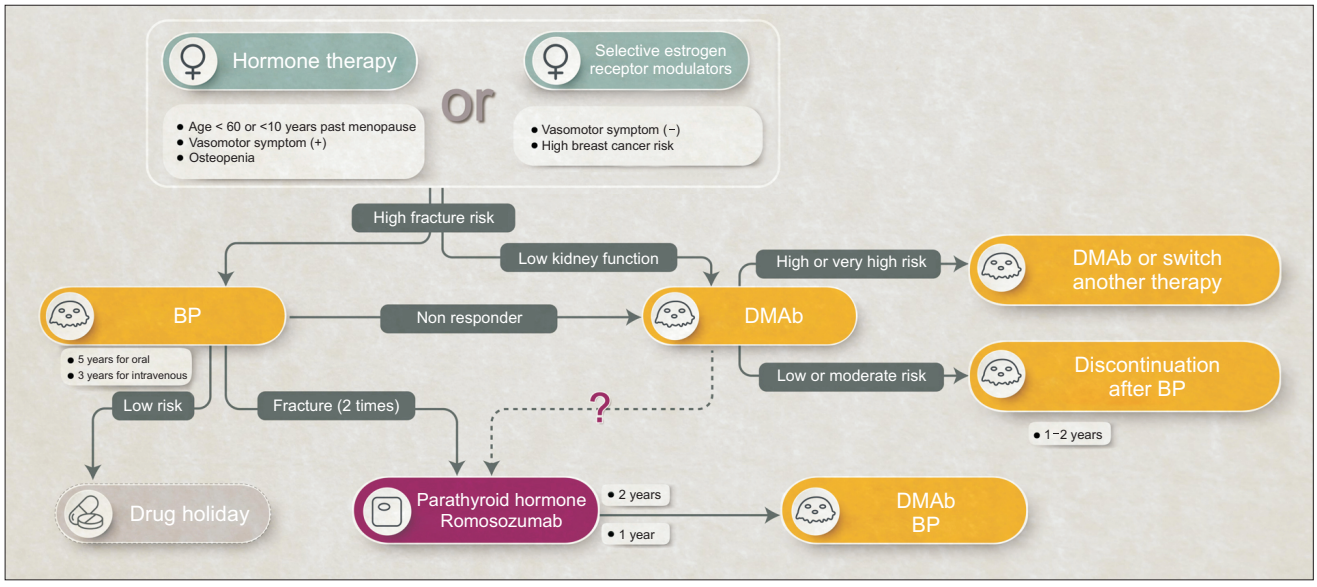

Fig. 2. Algorithm for the decision of sequential osteoporosis treatment. DMAb: denosumab, BP: bisphosphonate.

oxifene evaluation (MORE; Multiple outcomes of raloxifene evaluation) trial that compared the raloxifene-treatment group and a placebo group showed that the daily dose of 60 mg raloxifene led to decreased 4-year cumulative relative risks (RR) one or more new vertebral fracture by 36% [RR, 0.64; 95% confidence interval (CI) 0.53, 0.76] and reduced the new vertebral fracture risk by 39% [RR, 0.61; 95% CI 0.43, 0.88] significantly, compared to that of the placebo group [10]. Similarly, in a study comparing a bazedoxifene 3-year treatment group and a placebo group, the risk of vertebral fracture in the treatment group compared to that in the placebo group was hazard ratio (HR) 0.58 with 42% relative risk reduction [11]. In menopausal hormone therapy, women without uterus may receive the estrogen-only treatment while women with uterus may receive the estrogen-progesterone combined treatment.

The effects of menopausal hormone therapy in postmenopausal women with osteoporosis are as follows:

1) Fracture prevention with BMD elevation equivalent to levels seen in the BP-treated group [12].

2) Applicable to osteopenia to prevent its progression to osteoporosis.

3) Additional benefits related to the VMS, such as hot flush.

Thus, menopausal hormone therapy is the recommended treatment choice for menopausal women aged below 60 years or less than 10 years post menopause, showing menopausal symptoms, including VMS accompanying osteoporosis.

THE SEQUENTIAL TREATMENT OUTCOMES IN OSTEOPOROSIS TREATMENT

Except for BPs, the effects of anti-osteoporotic drugs disappear on discontinuation; hence, maintenance medication is required (Fig. 2).

Switching from bisphosphonate to denosumab

For the high fracture risk group, the recommended duration of BPs is 5 years for oral administration and 3 years for intravenous injection while the risk of fracture should be reassessed within three to five years of treatment [5]. If the reassessment indicates a high fracture risk, the BP treatment may be continued or substituted with another treatment option. However, if the reassessment indicates a low to moderate risk of fracture, discontinuation is considered with reassessment repeated every 2–4 years to decide treatment resumption in cases of bone mass reduction or high fracture risk.

The transition to DMAb in patients with BP treatment failure increases the BMD. In a study conducted by Kamimura et al. [13] on 90 patients undergoing BP treatment for 2 or more years, the use of DMAb resulted in a more significant increase in BMD for patients with higher levels of bone density reduction. The mean age of the patients was 71.2 ± 6.9 years, and the mean treatment duration was 59.9 ± 34.3 months. In a recent study [14], the increase in BMD was more significant in the group that transitioned to DMAb with less than 3 years of BP treatment compared to that in the group with 3 or more years of BP treatment before transitioning. Both groups showed a more significant increase in BMD than the group with continued BP treatment. The results of these studies suggest that for patients showing little or no therapeutic effect with BP, a rapid transition to DMAb could be advantageous.

Switching from denosumab to bisphosphonate

For the administration of DMAb in patients with a high risk of fracture, fracture risk reassessment within 5 to 10 years is recommended to decide whether the treatment should be continued or substituted with another therapy [5]. If the reassessment after DMAb treatment indicates a low to moderate fracture risk, maintenance medication with BP is initiated before discontinuation is considered. It is recommended that the fracture risk be reassessed every 1 to 3 years to decide on retreatment in cases of bone mass reduction, the incidence of fracture, or when the patient shows a high fracture risk.

On DMAb discontinuation, the resulting increase in bone remodeling may reduce bone density and rapidly increase the risk of vertebral fracture. Such a "rebound effect" is known to arise from the sudden increase in osteoclast formation after DMAb discontinuation [15].

In the Denosumab Adherence Preference Satisfaction (DAPS) study [16], an increase in BMD and a decrease in bone turnover markers were maintained with the administration of alendronate after DMAb discontinuation. In a study of 250 postmenopausal women with osteoporosis in the U.S. and Canada, 124 women were injected with alendronate for 12 months before DMAb treatment, and 126 women were injected with DMAb before alendronate, and the results were compared. In the group administered with DMAb for 12 months before alendronate, the BMD during the first 12 months

increased by 5.6% in the lumbar, 3.2% in the hip joint, and 3.1% in the hip joint femoral neck while the increased level was maintained at 2.9% in the lumbar, 1.5% in the hip joint, and 1.7% in the hip joint femoral neck after 24 months. The Type I Collagen Crosslinked C-Telopeptide also indicated that the effect of bone turnover marker reduction was maintained in the group administered DMAb before alendronate, 0.465 ng/mL (n = 75) before treatment, 0.139 ng/mL (n = 108) after 12 months, and 0.223 ng/mL (n = 92) after 24 months. In a study by Kendler et al. [17], the patients were treated with DMAb for 12 months, the mean percentage change in BMD was 5.4% in the lumbar spine, 3.1% in the hip joint, and 2.7% in the hip joint femoral neck. The subsequent transition to alendronate after 2 years showed that the mean percent change in BMD after 12–24 months was 0.5% in the lumbar spine, 0.5% in the hip joint, and –0.2% in the hip joint femoral neck. Throughout the study period, the mean percent change in BMD was 5.9% in the lumbar spine, 3.6% in the hip joint, and 2.5% in the hip joint femoral neck.

In a study by Everts-Graber et al. [18], treatment of 219 postmenopausal women with DMAb for 2 to 5 years (average 3 years) followed by zoledronate administration after 6 months of DMAb discontinuation led to the maintenance of more than half the bone density increase resulting from DMAb administration while the risk of vertebral fracture was significantly reduced to HR 0.16 (95% CI, 0.03, 0.94; $P = 0.042$).

Thus, treatment with DMAb should be followed by administration of BP (alendronate or zoledronate) for 1–2 years before considering DMAb discontinuation. However, as the effects of BP administration might not be significant in patients who received long-term DMAb treatment, close follow-up monitoring should be performed to ensure thorough monitoring of bone density and bone markers.

Switching from anabolic agent to denosumab or bisphosphonate

Representative drugs of anabolic agents include teriparatide and romosozumab. Teriparatide is a recombinant human parathyroid hormone (PTH) analogue and stimulates bone formation via the PTH receptor [5]. Romosozumab is stimulating bone formation and inhibition of bone resorption at the same time [5]. The current health insurance in South Korea restricts the use of parathyroid hormones and romosozumab for up to 24 months and 12 months, respectively.

In a study comparing patients who transitioned from teriparatide to BP or DMAb [19], the group treated with BP showed that the increase in BMD from the baseline after 12 months was 2.6% ($P < 0.01$) in the lumbar and 1.1% ($P < 0.01$) in the hip joint, whereas no increase was observed for the hip joint femoral neck. In comparison, the DMAb group showed that the increase in BMD after 6 and 12 months was 4.6% ($P < 0.001$) and 6.2% ($P < 0.001$), respectively, in the lumbar; 2.6% ($P < 0.01$) and 4.2% ($P < 0.001$) in the hip joint; and 2.2% ($P < 0.01$) and 3.5% ($P < 0.01$) in the hip joint femoral neck. The increase in BMD was significantly higher in the DMAb group than in the BP group. Thus, DMAb is likely a better choice of antiresorptive agents after the administration of teriparatide.

Several studies have demonstrated that romosozumab is effective in the treatment of osteoporosis in postmenopausal women [20-22]. In particular, it was reported that when romosozumab was used for 12 months and then replaced with BP or DMAb, a higher increase in BMD was observed than in the reverse case [21].

In the ARCH study [22], the transition to alendronate after the administration of romosozumab for 12 months was shown to lead to a relative risk of vertebral fracture of 0.52 ($P < 0.001$) with significant fracture risk reduction compared to that in the group that received alendronate continuously for 24 months. For the first incidence of non-vertebral fracture, the transition to alendronate after the administration of romosozumab compared to that after the administration of alendronate alone also led to a lower cumulative prevalence of fracture ($P = 0.04$) in the 48-month follow-up.

In the FRAME study [23], menopausal women with osteoporosis were administered 210 mg of romosozumab or a placebo once a month for 12 months, followed by a switch to 60 mg DMAb every 6 months for 12 months, and the bone density continued to increase. The administration of romosozumab for 1 year led to a 13% and 7% increase in the spine and hip joint bone density, respectively. The transition to DMAb over 24 months, compared to the transition from placebo, showed that the use of DMAb after romosozumab had a greater effect on the risk of fracture reduction as the vertebral and clinical fractures decreased by 76% ($P < 0.001$) and 33% ($P = 0.096$), respectively.

Thus, the administration of DMAb or BP is necessary to maintain the treatment effects of an anabolic agent.

Switching from denosumab to anabolic agent

In the DATA-SWITCH study [24], the use of teriparatide after DMAb discontinuation was shown to reduce the bone density in the lumbar spine, total hip, and femoral neck, and it is recommended that the teriparatide after DMAb should be avoided if possible. The subjects were randomized between placebo and various romosozumab dosages from the baseline up to month 24. From months 24–36, the subjects were administered DMAb or placebo, and from month 36 to month 48, all subjects were administered romosozumab. The subjects in the placebo group were randomized once more after the 12-month administration of DMAb (n = 16) or placebo (n = 12) so that they could receive romosozumab for 12 months. The female subjects randomized into the DMAb group after the placebo administration maintained an increase in the hip joint BMD (the mean change after DMAb discontinuation was 0.9%) and an additional increase in BMD in the lumbar region (the mean change after DMAb discontinuation was 5.3%) after 12 months of romosozumab administration [25].

In recent studies analyzing the treatment effects of drugs used before romosozumab therapy, the increase in BMD was relatively lower for the group treated with romosozumab after DMAb administration than for the placebo group or for those treated with romosozumab after the administration of BP or teriparatide [26,27].

Thus, for patients receiving DMAb before treatment with an anabolic agent, close follow-up monitoring of bone density and markers should be performed.

The importance of early treatment for reducing the risk of imminent fractures

The frequency of imminent fracture within 1 year of the first fracture was 7.1%, and patients with at least one fracture incidence were defined as the high-risk group. The imminent fracture risk is the highest within 6 months of the first fracture [6]. Thus, for patients with at least one fracture incident, treatment should focus on the rapid reduction of fracture risk. The drugs with excellent imminent fracture risk-reducing effects were shown to be romosozumab, teriparatide, DMAb, and alendronate, in the order [28]. And for very-high–risk patients, the use of an anabolic agent could ensure a reliable initial treatment.

CONCLUSION

Similar to other chronic diseases, osteoporosis requires management and treatment with long-term goals. With the development of new classes of drugs, new clinical data and research outcomes are continuously being reported, requiring an approach of consistent interest and studies. Due to the interest in long-term treatment effects, management focused on the importance of risk-based strategies and sequential treatment is likely to increase further.

REFERENCES

1. Organisation for Economic Co-operation and Development. OECD health statistics 2021. Paris: OECD, 2021 [cited 2021 Dec 17]. Available from: https://www.oecd.org/health/health-data.htm.
2. Kim Y, Kim JH, Cho DS. Gender difference in osteoporosis prevalence, awareness and treatment: based on the Korea National Health and Nutrition Examination Survey 2008-2011. J Korean Acad Nurs 2015; 45: 293-305.
3. Healthcare Bigdata Hub; Health Insurance Review & Assessment Service. Healthcare statistics data. Healthcare statistics per disease/behavior. High-interest diseases. Osteoporosis. Wonju: Health Insurance Review & Assessment Service, [cited 2021 Nov 30]. Available from: http://opendata.hira.or.kr/op/opc/olapMfrnIntrsIlnsInfo.do.
4. Hassan N, Gregson CL, Tobias JH. Anabolic treatments for osteoporosis in postmenopausal women. Fac Rev 2021; 10: 44.
5. Langdahl BL. Overview of treatment approaches to osteoporosis. Br J Pharmacol 2021; 178: 1891-906.
6. Shoback D, Rosen CJ, Black DM, Cheung AM, Murad MH, Eastell R. Pharmacological management of osteoporosis in postmenopausal women: An Endocrine Society Guideline update. J Clin Endocrinol Metab 2020; 105: dgaa048.
7. Banefelt J, Åkesson KE, Spångéus A, Ljunggren O, Karlsson L, Ström O, et al. Risk of imminent fracture following a previous fracture in a Swedish database study. Osteoporos Int 2019; 30: 601-9.
8. Camacho PM, Petak SM, Binkley N, Diab DL, Eldeiry LS, Farooki A, et al. American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the diagnosis and treatment of postmenopausal osteoporosis-2020 update. Endocr Pract 2020; 26(Suppl 1): 1-46.
9. Barrionuevo P, Kapoor E, Asi N, Alahdab F, Mohammed K, Benkhadra K, et al. Efficacy of pharmacological therapies for the prevention of fractures in postmenopausal women: a network meta-analysis. J Clin Endocrinol Metab 2019; 104: 1623-30. Erratum in: J Clin Endocrinol Metab 2021; 106: e1494.
10. Delmas PD, Ensrud KE, Adachi JD, Harper KD, Sarkar S, Gennari C, et al. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results

from a randomized clinical trial. J Clin Endocrinol Metab 2002; 87: 3609-17.
11. Silverman SL, Christiansen C, Genant HK, Vukicevic S, Zanchetta JR, de Villiers TJ, et al. Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial. J Bone Miner Res 2008; 23: 1923-34.
12. Eastell R, Rosen CJ, Black DM, Cheung AM, Murad MH, Shoback D. Pharmacological management of osteoporosis in postmenopausal women: An Endocrine Society* Clinical Practice guideline. J Clin Endocrinol Metab 2019; 104: 1595-622.
13. Kamimura M, Nakamura Y, Ikegami S, Uchiyama S, Kato H, Taguchi A. Significant improvement of bone mineral density and bone turnover markers by denosumab therapy in bisphosphonate-unresponsive patients. Osteoporos Int 2017; 28: 559-66.
14. Miller PD, Pannacciulli N, Malouf-Sierra J, Singer A, Czerwiński E, Bone HG, et al. Efficacy and safety of denosumab vs. bisphosphonates in postmenopausal women previously treated with oral bisphosphonates. Osteoporos Int 2020; 31: 181-91.
15. Anastasilakis AD, Makras P, Yavropoulou MP, Tabacco G, Naciu AM, Palermo A. Denosumab discontinuation and the rebound phenomenon: a narrative review. J Clin Med 2021; 10: 152.
16. Freemantle N, Satram-Hoang S, Tang ET, Kaur P, Macarios D, Siddhanti S, et al. Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. Osteoporos Int 2012; 23: 317-26.
17. Kendler D, Chines A, Clark P, Ebeling PR, McClung M, Rhee Y, et al. Bone mineral density after transitioning from denosumab to alendronate. J Clin Endocrinol Metab 2020; 105: e255-64.
18. Everts-Graber J, Reichenbach S, Ziswiler HR, Studer U, Lehmann T. A single infusion of zoledronate in postmenopausal women following denosumab discontinuation results in partial conservation of bone mass gains. J Bone Miner Res 2020; 35: 1207-15.
19. Ebina K, Hashimoto J, Kashii M, Hirao M, Kaneshiro S, Noguchi T, et al. The effects of switching daily teriparatide to oral bisphosphonates or denosumab in patients with primary osteoporosis. J Bone Miner Metab 2017; 35: 91-8.
20. Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, et al. Romosozumab treatment in postmenopausal women with osteoporosis. N Engl J Med 2016; 375: 1532-43.
21. Cosman F, Kendler DL, Langdahl BL, Leder BZ, Lewiecki EM, Miyauchi A, et al. Romosozumab and antiresorptive treatment: the importance of treatment sequence. Osteoporos Int 2022; 33: 1243-56.
22. Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. N Engl J Med 2017; 377: 1417-27.
23. Cosman F, Crittenden DB, Ferrari S, Khan A, Lane NE, Lippuner K, et al. FRAME Study: the foundation effect of building bone with 1 Year of romosozumab leads to continued lower fracture risk after transition to denosumab. J Bone Miner Res 2018; 33: 1219-26.
24. Leder BZ, Tsai JN, Uihlein AV, Wallace PM, Lee H, Neer RM, et al. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. Lancet 2015; 386: 1147-55.
25. McClung MR, Bolognese MA, Brown JP, Reginster JY, Langdahl BL, Shi Y, et al. Skeletal responses to romosozumab after 12 months of denosumab. JBMR Plus 2021; 5: e10512.
26. Ebina K, Hirao M, Tsuboi H, Nagayama Y, Kashii M, Kaneshiro S, et al. Effects of prior osteoporosis treatment on early treatment response of romosozumab in patients with postmenopausal osteoporosis. Bone 2020; 140: 115574.
27. Kobayakawa T, Suzuki T, Nakano M, Saito M, Miyazaki A, Takahashi J, et al. Real-world effects and adverse events of romosozumab in Japanese osteoporotic patients: a prospective cohort study. Bone Rep 2021; 14: 101068.
28. Laura I, Felicia B, Alexia C, Aude M, Florence B, Murielle S, et al. Which treatment to prevent an imminent fracture? Bone Rep 2021; 15: 101105.