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Osteoporosis
A Review of Novel Agents

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Osteoporosis is a bone disease characterized by decreased new bone formation, increased bone resorption, or both processes occurring simultaneously. This disease affects more than 10 million individuals older than 50 years in the United States. If this disease is left untreated, it can result in fragility fractures, which are currently seen in more than 1 million people in the United States. New agents have been developed to add to the list of treatment options that can be used to treat this disease. This article summarizes two specific agents that were approved by the Food and Drug Administration within the last few years: abaloparatide (Tymlos) and romosozumab (Evenity). This article also highlights the crucial role that nursing staff may play in the management of osteoporosis.

Introduction

According to data from the National Health and Nutrition Examination Survey of 2017-2018, the prevalence of osteoporosis among adults aged 50 years and older increased by over 3% when compared to data from 2007-2008 and affected over 10 million people in the United States (Sarafrazi et al., 2021). An additional 34 million individuals are considered at risk of having osteoporosis, also known as osteopenia (U.S. Office of the Surgeon General, 2010). Osteoporosis is a bone disease characterized by decreased new bone formation, increased bone resorption, or both processes occurring simultaneously. The peak bone mass is achieved by 18–25 years of age, but depending on genetic factors, endocrine status, nutrition, physical activity, and overall health, the bone mass is lost with age (Cosman et al., 2014; U.S. Preventive Services Task Force et al., 2018; Watts et al., 2010). If left unchecked, this disease process can lead to fragility fractures. In the United States, an estimated 1.5 million people have fractures related to osteoporosis or osteopenia (U.S. Office of the Surgeon General, 2010). Although there are multiple different risk factors for osteoporosis, as listed in Table 1, age and female sex are the two most prominent factors. Nurses can play a key role in equipping patients with the proper knowledge to mitigate their risk of developing osteoporosis and provide education regarding proper intake of calcium and vitamin D. Nurses can often identify patients who may have nutrient deficiencies or increased fall risk who may benefit from additional intervention. In addition, nurses may be involved in administering some of the in-clinic medications for osteoporosis treatment and therefore a sound understanding of available treatment options is imperative.

Pathophysiology of Osteoporosis

Bone remodeling involves osteocytes, osteoblasts, and osteoclasts. With the help of numerous hormones such as estrogens, androgens, vitamin D, and parathyroid hormone (PTH) and growth factors such as insulin like growth factor-1 (IGF-1), PTH-related peptides, interleukins, prostaglandins, and tumor necrosis factor, osteoclasts lead the bone resorption process, which is followed by a bone formation process by osteoblasts (Lindsay & Cosman, 2018). The main functions of PTH are to increase calcium reabsorption from renal tubules, increase vitamin D production to enhance intestinal calcium absorption, and regulate bone remodeling (Canalis et al., 2007). The latter effect of PTH is due to its impact on various growth factors such as IGF-1 and growth factor antagonists such as sclerostin; the resulting effect is increased osteoblasts and therefore increased bone formation and decreased osteoclasts via cell apoptosis and therefore decreased bone resorption. Receptor activator of nuclear factor-kappa B ligand (RANKL) is a cytokine responsible for communication between these cells (Lindsay & Cosman, 2018). In addition, the Wnt signaling pathway can increase bone formation by osteoblasts and decrease RANKL production to decrease resorptive activity of osteoclasts. Sclerostin is an osteocyte protein that opposes Wnt signaling and bone formation. Therefore, inhibiting sclerostin can help increase bone formation.

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These authors have no conflicts of interest to disclose.

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DOI: 10.1097/NOR.0000000000000899

Table 1. Common Risk Factors for Osteoporosis and Related Fractures

Lifestyle factors	Alcohol abuse, smoking, low calcium intake, vitamin D insufficiency, inadequate physical activity, immobility, high salt intake, history of frequent falls, etc.
Genetic diseases	Cystic fibrosis, glycogen storage diseases, hypophosphatasia, Gaucher's disease, etc.
Endocrine disorders	Central obesity, hyperparathyroidism, diabetes, Cushing's syndrome, thyrotoxicosis, premature menopause, hyperprolactinemia, androgen insensitivity, panhypopituitarism, etc.
Gastrointestinal disorders	Celiac disease, gastric bypass, malabsorption, inflammatory bowel disease, primary biliary cirrhosis, gastrointestinal surgery, etc.
Hematological disorders	Hemophilia, leukemia and lymphomas, multiple myeloma, sickle cell disease, thalassemia, etc.
Rheumatological and autoimmune disorders	Rheumatoid arthritis, systemic lupus, ankylosing spondylitis, etc.
Neurological and musculoskeletal disorders	Epilepsy, Parkinson's disease, multiple sclerosis, muscular dystrophy, stroke, etc.
Miscellaneous disorders	Anorexia nervosa, HIV/AIDS, COPD, end-stage renal disease, congestive heart failure, chronic metabolic acidosis, depression, idiopathic scoliosis, etc.
Medications	Anticonvulsants, barbiturates, corticosteroids, proton-pump inhibitors, depomedroxyprogesterone, methotrexate, selective serotonin reuptake inhibitors, aromatase inhibitors, tamoxifen, thyroid hormones in excess, thiazolidinediones, cancer chemotherapy agents, etc.

Note. AIDS = acquired immunodeficiency syndrome; COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus.

Screening and Diagnosis

Assessment of bone mineral density (BMD) is recommended for all female patients older than 65 years, but it can occur as early as 50 years of age if fractures or additional risk factors are present (Cosman et al., 2014; U.S. Preventive Services Task Force et al., 2018; Watts et al., 2010). The consensus for screening male patients is not strong, but the National Osteoporosis Foundation recommends screening men 70 years or older without any clinical risk factors (Cosman et al., 2014). BMD is measured via dual-energy x-ray absorptiometry (DEXA) scan. The interpretation of BMD results per the World Health Organization (WHO) criteria is summarized in Table 2. This screening usually is accompanied by a 10-year fracture risk assessment (FRAX), which utilizes patient-specific risk factors to estimate their risk of osteoporotic fractures in the next 10 years. Vertebral imaging, other radiographic tests, biochemical markers for bone turnover, and assessment of secondary causes of osteoporosis may also accompany BMD screening in selected patients.

Treatment Approach

Universal recommendations for preserving bone strength include appropriate calcium and vitamin D intake, regular weight-bearing and muscle strengthening exercises, tobacco cessation, limitation of alcohol use, fall prevention and fall risk reduction (Cosman et al., 2014; U.S. Preventive Services Task Force et al., 2018; Watts et al., 2010). In addition to these universal recommendations, pharmacological treatment is recommended for those 50 years and older with:

- Hip or vertebral fracture evidence from vertebral imaging;

Table 2. The World Health Organization Criteria for BMD Interpretation

Classification	BMD	T-Score
Normal	Within 1 *SD* of the mean level for a young-adult reference population	Equal or above −1.0
Low bone mass (osteopenia)	Between 1.0 and 2.5 *SD* below that of the mean level for a young-adult reference population	Between −1.0 and −2.5
Osteoporosis	2.5 *SD* or more below that of the mean level for a young-adult reference population	Equal or below −2.5
Severe osteoporosis	2.5 *SD* or more below that of the mean level for a young-adult reference population with fractures	Equal or below −2.5 PLUS one or more fracture

Note. From "The Diagnosis of Osteoporosis," by J. A. Kanis, L. J. Melton, 3rd, C. Christiansen, C. C. Johnston, and N. Khaltaev, 1994, Journal of Bone and Mineral Research, *9*(8), pp. 1137–1141 (https://doi.org/10.1002/jbmr.5650090802). BMD = bone mineral density.

- T-score of less than −2.5 at femoral neck, total hip, or lumbar spine; and
- Low bone density (T-score of −1.0 to −2.5 at femoral neck or lumbar spine) and 10-year probability of hip fracture of more than 3% or major osteoporosis-related fracture of more than 20%.

Duration of therapy with pharmacological agents can vary depending on the agent selected, but it should be noted that evaluation of benefits and risk should occur within 3–5 years of being on the treatment. BMD testing should occur every 2 years, but in addition, evaluation of the patient's overall interval medical history, fall risk, height, and vertebral imaging should be done when necessary. Currently, there are eight different pharmacological classes of drugs that are Food and Drug Administration (FDA) approved for the treatment of osteoporosis. They are bisphosphonates, calcitonin, estrogen or testosterone, selective estrogen receptor modulator, tissue-selective estrogen modulator, RANKL inhibitor, recombinant PTH, and sclerostin inhibitor. The latter two are the newest category of agents available in the market. Up until the introduction of recombinant PTH and sclerostin inhibitor, osteoporosis therapy mainly consisted of antiresorptive agents, which inhibited osteoclasts-led bone resorption but had no impact on osteoblast-led bone formation activity. Both recombinant PTH (teriparatide and abaloparatide) and sclerostin inhibitor (romosozumab) have direct effects on osteoblasts and thus both augment active bone formation. Teriparatide is an older recombinant PTH agent available since 2002 and to keep the focus on new agents, the rest of the article discusses abaloparatide and romosozumab only.

Abaloparatide (Tymlos)

Abaloparatide was approved by the FDA in 2017 for the treatment of osteoporosis in postmenopausal women who are at a high risk of fracture for a lifetime treatment duration of 2 years in addition to adequate calcium and vitamin D supplementation (U.S. National Library of Medicine, 2021). After teriparatide (Forteo), it is the second PTH agent approved for the treatment of osteoporosis in this population. The primary effect of abaloparatide is on calcium homeostasis where it promotes calcium reabsorption from kidneys, converts vitamin D to its active metabolite in the kidneys, and augments intestinal absorption of calcium. In addition, abaloparatide acts as an agonist at the PTH1 receptor that triggers cyclic AMP signaling pathways to have direct anabolic effects on bones and increase BMD in vertebral and nonvertebral bones.

Abaloparatide is available as a parenteral agent in a single-patient-use pen. It is injected subcutaneously in the abdomen as an 80 μg daily dose. Patients will also require a prescription for pen needles to be used daily along with the injection. The unused pen is stored in the refrigerator, but once in use, it can be stored at room temperature for up to 30 days. The drug was not studied in patients needing dialysis, but it does not require dose adjustments in those with renal impairment. No recommendations are available from the manufacturer regarding its use in patients with hepatic impairment.

In an 18-month study against placebo, abaloparatide increased BMD at total hip, lumbar spine, and femoral neck regions ($p < .001$), decreased vertebral fractures (absolute risk reduction [ARR] = 3.6%; 95% CI [2.1, 5.4]), and decreased nonvertebral fractures (ARR = 2%; $p = .049$) (Miller et al., 2016). In a 25-month follow-up open-label study, abaloparatide and placebo were discontinued after 18 months, but alendronate 70 mg plus appropriate calcium and vitamin D supplements were continued (Cosman et al., 2017). The patients who took abaloparatide showed an increase in BMD at total hip, lumbar spine, and femoral neck, decreased vertebral fractures (ARR = 3.9%; 95% CI [2.1, 5.9]), and decreased nonvertebral fractures (ARR = 2.9%; $p = .017$).

The most common safety concerns with this drug are hypercalcemia, hypercalciuria, hyperuricemia, dizziness from orthostatic hypotension, palpitations, nausea, headache, and injection site reactions (U.S. National Library of Medicine, 2021). Because of the risk of hypercalcemia, baseline and periodic serum calcium assessments should be completed. Patients should be educated to report signs and symptoms of hypercalcemia such as lethargy, muscle weakness, nausea, vomiting, and constipation to the prescribing provider or pharmacist. Abaloparatide should not be used in patients with hypercalcemia or hyperparathyroidism. The drug can also result in higher excretion of calcium in the urine than placebo, but it is unknown if it increases risk of kidney stones in patients with a history of kidney stones. Periodic monitoring of urine calcium may be necessary in such patients or when kidney stones are suspected. Abaloparatide can also result in more uric acid levels than placebo, but it is not associated with increased gout precipitation or joint pain than placebo. Orthostatic hypotension is reported more frequently within 4 hours of the injection when the patient is new to the treatment, but the rate is similar between abaloparatide and placebo later in use. Associated symptoms such as dizziness, palpitations, tachycardia, and nausea may occur. The symptoms resolve after the patient lies down or sits down after taking the dose. Some clinicians therefore recommend dosing this medication at bedtime and storing the drug at bedside to avoid possible falls due to the resulting hypotension and dizziness. Injection site reactions include erythema, pain, swelling, pruritus, and rash near the site of injection. Antibodies can develop as high as 49% in the clinical trials; however, it bears little to no clinical significance during the treatment.

When compared with teriparatide, the only other agent available in the recombinant PTH category, abaloparatide 80 μg led to larger BMD increase in total hip than the marketed dose of 20 μg of teriparatide ($p = .006$) (Leder et al., 2015). Abaloparatide resulted in more dizziness and headache than teriparatide, however. Other adverse effects such as hypercalcemia were no different between the two agents in this trial; however, the 18-month study conducted by Miller et al. (2016) found significantly lower rates of hypercalcemia with abaloparatide than with teriparatide ($p = .006$).

Both recombinant PTH agents (teriparatide and abaloparatide) have FDA boxed warning for the risk of

osteosarcoma (U.S. National Library of Medicine, 2021). No human cases of osteosarcoma have been reported; however, the rates of osteosarcoma in rat models were noted to be dose dependent. Patients at higher risks of osteosarcoma, such as those with Paget's disease, skeletal malignancies or bone metastasis, unexplained alkaline phosphatase elevations, and radiation therapy to bones, should avoid recombinant PTH therapy. In all other eligible patients, the recommended lifetime duration of treatment with recombinant PTH agents is 2 years or less. Antiresorptive therapy after 2 years of anabolic therapy with recombinant PTH agents can take place to maintain the BMD.

Abaloparatide is only available as a brand agent in the United States and can cost nearly $20,000 per year (U.S. National Library of Medicine, 2021). A cost-effective analysis compared placebo, teriparatide, and abaloparatide treatment with alendronate follow-up for a total of 10 years (Le et al., 2019). The analysis found that abaloparatide plus alendronate therapy accrued more quality-adjusted life years and produced an incremental cost-effective ratio relative to teriparatide and placebo.

Overall, abaloparatide is recommended for postmenopausal osteoporosis treatment along with proper calcium and vitamin D supplementation in women who are at high risk of fracture and who have failed other pharmacological agents or cannot use them due to safety concerns.

Romosozumab (Evenity)

Romosozumab is a monoclonal antibody that was approved by the FDA in 2019 for the treatment of osteoporosis in postmenopausal women who are at a high risk for fracture and those who have failed or are unable to take other therapies. Romosozumab is the first and only sclerostin inhibitor currently in the market. Sclerostin interferes with signaling pathways that can ultimately lead to a decrease in bone formation and can also indirectly increase osteoclast activity and bone resorption (Delgado-Calle et al., 2017). Romosozumab increases bone formation and may also decrease bone resorption by inhibiting sclerostin (U.S. National Library of Medicine, 2021).

Romosozumab is packaged in prefilled syringes and is injected subcutaneously once a month for a total of 12 months (U.S. National Library of Medicine, 2021). The medication is to be administered by a healthcare provider who will inject two 105 mg per 1.17-ml syringes one after another for a total dose of 210 mg. Abdomen, thigh, or upper arm are acceptable administration sites. The syringes should be stored in the refrigerator and can be taken out 30 minutes prior to use in order for them to warm to room temperature.

Romosozumab was approved on the basis of the findings of two Phase 3 clinical trials. Cosman et al. (2016) completed a randomized controlled trial that compared 12 months of romosozumab with placebo in postmenopausal women with confirmed osteoporosis. After 12 months, both groups received open-label denosumab for an additional 12 months. The primary endpoint, cumulative incidence of vertebral fractures, was assessed at 12 months (after study drug was completed) and at 24 months (following denosumab administration). Patients were also evaluated for any clinical fracture during this time as a secondary endpoint. At 12 months, romosozumab was associated with a 73% lower risk of vertebral fracture (0.5% and 1.8% in the romosozumab and placebo groups, respectively; $p < 0.001$) and a 36% lower risk of any clinical fracture than placebo (1.6% and 2.5% in the romosozumab and placebo groups, respectively; $p = .008$). At 24 months, romosozumab maintained a 75% lower risk of vertebral fracture (0.6% and 2.5% in the romosozumab and placebo groups, respectively; $p < .001$). However, there was no significant difference in any clinical fracture or nonvertebral fractures at this time point.

The ARCH trial (Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk), completed by Saag et al. (2017), compared romosozumab with alendronate therapy. This study enrolled postmenopausal women with osteoporosis and required that they have a fragility fracture. Patients were included if they had a BMD T-score of −2.5 or less with at least one moderate to severe vertebral fracture or at least two mild vertebral fractures. Patients with a BMD T-score of −2.0 or less were required to also have either two or more moderate or severe vertebral fractures or a femoral fracture 3–24 months prior to enrollment in the study. Once enrolled, patients were randomized to receive either romosozumab 210 mg injected subcutaneously each month or alendronate 70 mg orally every week for a total of 12 months. After this, both groups received open-label alendronate weekly for an additional 12 months. Overall incidence of vertebral fractures and the incidence of any clinical fracture at the time of the primary analysis (once fractures were seen in 330 patients) were the two primary endpoints of this study. Romosozumab was found to have a significantly lower incidence and risk of vertebral and clinical fractures. At 24 months, 6.2% of patients in the romosozumab group (127 of 2,046 patient) and 11.9% of patients in the alendronate group (243 of 2,047) had developed a vertebral fracture ($p < .001$). Clinical fractures were seen in 9.7% of patients receiving romosozumab (198 of 2,046 patients) and 13% of patients receiving alendronate (266 of 2,047 patients) ($p < .001$).

BMD has also been shown to increase in patients who received romosozumab. Cosman et al. (2017) identified a 13.3% increase in BMD at the lumbar spine, 6.9% in the total hip, and 5.9% in the femoral head after 12 months of romosozumab treatment. In an extension study by Lewiecki et al. (2019), these patients and those who received placebo were continued on denosumab therapy for another 24 months and reevaluated. While both the romosozumab–denosumab and placebo–denosumab groups had increases in BMD during the 24 months of denosumab therapy, the romosozumab–denosumab group maintained significantly higher improvements of BMD than the control group.

The most common adverse effects of romosozumab include arthralgia, headache, and injection site reactions. In clinical trials, some serious cardiovascular adverse effects, osteonecrosis, and hypocalcemia were also seen. The ARCH study demonstrated an increased

risk of cardiovascular death, myocardial infarction, or stroke with romosozumab as compared with alendronate within the first year (2.5% vs. 1.9%; OR = 1.31; 95% CI [1.85, 2.00]) (Saag et al., 2017). Similar findings were not seen or not assessed in other clinical trials (Cosman et al., 2016; Langdahl et al., 2017). Romosozumab should be avoided in patients who have had a myocardial infarction or stroke in the last 12 months (U.S. National Library of Medicine, 2021). Osteonecrosis of the jaw, which is also associated with bisphosphonate therapy, occurred in less than 0.1% of patients in one of the clinical trials (Cosman et al., 2016). Patients should be encouraged to maintain good oral hygiene throughout therapy and an oral examination should be done prior to initiation (U.S. National Library of Medicine, 2021). Patients should also be evaluated for hypocalcemia and therapy should be avoided or delayed until hypocalcemia has been corrected. Patients taking romosozumab should be adequately supplemented with calcium and vitamin D to keep levels within normal limits.

Although romosozumab has some significant benefits in patients with osteoporosis, it does come with a price that is higher than other treatments. A 1-month supply (two prefilled syringes) of romosozumab costs approximately $2,300 (based on the average wholesale price in October 2021) (Red Book, 2021). Although this is much higher than oral bisphosphonates such as alendronate ($80 per month), it is similar in price to the injectable agent abaloparatide ($2,546 per month) and cheaper than injectable teriparatide ($4,533 per month) (Red Book, 2021). In addition, both abaloparatide and teriparatide are daily injections, whereas romosozumab is injected only once per month, which may make it preferable to a patient.

Like abaloparatide, romosozumab offers another treatment option for severe osteoporosis in patients who are unable to tolerate or who have failed other options. The risk of cardiac complications should be considered in those with existing cardiovascular disease, but it may be a good option for patients without a history of cardiovascular events.

Conclusion

Abaloparatide (Tymlos) and romosozumab (Evenity) are two new injectable options for treatment of postmenopausal women with osteoporosis who are at a high risk of fracture. Despite some safety concerns, both agents demonstrate a significant increase in BMD and a decrease in vertebral and clinical fractures. Concomitant daily supplementation with calcium and vitamin D is recommended to maintain and support bone health. These two agents provide additional options in patients who develop fractures while taking other osteoporosis treatments or cannot tolerate other agents. Long-term efficacy and safety data will help us better understand the true role of these agents in practice. The role of nursing staff will continue to be foundational in providing patients with proper education, administering some of these in-clinic medications, monitoring for medication side effects, and managing fall risk.

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