Long-Term Care Updates

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Cracking the Code: Approaches to Osteoporosis Diagnosis and Treatment

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Introduction

It is generally understood in the healthcare world that if a patient has high blood pressure, high cholesterol, or diabetes, it is recommended to start guideline-directed medical therapy (GDMT). The same could be said for virtually every disease state that has medical treatment options. However, less than one-third of patients with osteoporosis receive treatment.[1]

The CDC estimated that in 2010, more than 10 million Americans over the age of 50 had osteoporosis, and more than 40 million had osteopenia, or low bone mass, the precursor to osteoporosis.[2] The CDC estimates more than 300,000 older adults across the U.S. require hospitalization due to a hip fracture each year. Hip fractures affect a person's quality of life and ultimately, 20-30% of patients die within one year of having a hip fracture.[3] So, why are patients not receiving treatment for osteoporosis?

Osteoporosis Diagnosis

First, osteoporosis is largely underdiagnosed.[1,3] To diagnose osteoporosis, patients need a dual x-ray absorptiometry (DEXA) scan. This is a painless and easy scan to evaluate bone density and track bone loss as patients age. Table 1 and Box 1 illustrate who should get a DEXA scan and what factors put patients at risk of osteoporotic fracture. Osteoporosis is a symptom-free disease that is mostly recognized only after a fracture. It is pertinent that patients get tested for osteoporosis, so treatment can be initiated to prevent fractures from occurring.

Table 1. Patients eligible to receive a DEXA scan[4,5]

Population	Ages
Females	65 years and older 50-64 years with risk factors
Males	70 years and older 50-69 years with risk factors
Any older adult after a fragility fracture	

Box 1. Osteoporosis fracture risk factors[6]	
Increasing age	Female sex
Postmenopausal patients (especially if menopause occurred before age 40)	Long-term use of certain medications (e.g., glucocorticoids)
History of parental hip fracture	Caucasian or Asian ethnicity
Previous fracture	Rheumatoid arthritis
Current smoker	Consuming more than 2 alcoholic drinks daily
Vitamin D deficiency / low calcium intake	High fall risk / physical inactivity
Low body weight	Estrogen deficiency

Osteoporosis Treatment

Osteoporosis may also be undertreated because of patient concern for medication side effects.[3] Osteoporosis treatment options have two rare but serious warnings: osteonecrosis of the jaw (ONJ) and atypical femur fracture. ONJ is a painful but reversible disease resulting in jawbone cell death. Patients are instructed to complete any necessary invasive dental work prior to starting osteoporotic therapy, which is the main risk factor for developing ONJ. Treatment may also be paused if invasive dental work is required after starting therapy. Atypical femur fractures can occur at any time, even when lying in bed. However, atypical femur fractures also occur in patients with osteoporosis that elect to not receive treatment, making it unclear if the risk is related to medications or the disease state itself.[7]

Oral bisphosphonates, such as alendronate and risedronate, are widely accepted as first-line therapy for osteoporosis.[6,8] The main concern for patients with this drug class is the risk of gastrointestinal (GI) and esophageal irritation. Depending on which medication is chosen, it may be taken orally once weekly, once monthly, or every three months. All oral bisphosphonates must be taken with a full glass of water and separated from any other medications or food. Patients must be able to remain in an upright position for at least 30 minutes after administration to prevent erosive esophagitis. In addition to oral bisphosphonates, there are other highly effective non-oral medications for osteoporosis treatment that are lesser known. Table 2 on the next page provides information on other osteoporotic therapies as recommended by the 2020 American Association of Clinical Endocrinology (AACE) osteoporosis guidelines.[8] In addition to prescription therapy, all patients with osteoporosis should receive 1,200 mg of calcium daily in two divided doses (from medication and diet), plus 800 to 1,000 international units (IU) of vitamin D3 daily.

Clinical Evidence

Abaloparatide: The ACTIVE clinical trial compared abaloparatide to placebo in 2,463 postmenopausal women with an average age of 68 years. This was an 18-month trial evaluating the primary endpoint of incidence of new vertebral fracture and secondary endpoint of incidence of nonvertebral fractures. At 18 months, abaloparatide showed an 86% relative risk reduction (RRR) ($p<0.0001$) in new vertebral fracture compared to placebo. It also showed a 43% RRR ($p=0.049$) in nonvertebral fractures compared to placebo. The overall incidence of side effects was 10% in the abaloparatide group versus 11% in the placebo group.[10]

Table 2. Non-oral osteoporosis treatment options[6,8,9]

Medication	Route / Frequency	Additional Information
Abaloparatide (Tymlos®) Teriparatide (Forteo®)	Subcutaneous injection given once daily at home (self-administered) for a maximum of 24 months followed by an alternative agent	Main adverse effects: redness and swelling at injection site, nausea, leg cramps, dizziness
Romosozumab (Evenity®)	Two subcutaneous injections given once monthly in clinic for maximum of 12 months followed by an alternative agent	Only approved for females The only drug currently available with dual mechanism to increase the build-up of bones and decreases bone breakdown Main adverse effects: joint stiffness, headache Boxed warning for rare but serious risk of myocardial infarction, stroke, and cardiovascular death
Denosumab (Prolia®)	Subcutaneous injection given every 6 months in clinic	Main adverse effects: skin irritation at injection site, joint stiffness/pain This medication must be continued indefinitely, or patients must switch to an alternative therapy if stopped. Stopping this medication can result in rapid bone deterioration and increased fracture risk
Zoledronate (Reclast®)	15-minute intravenous (IV) infusion given every 12 months at an infusion center	IV bisphosphonate (same mechanism as oral bisphosphonates but no risk of GI side effects) Main adverse effects: flu-like symptoms, nausea, fatigue, headache, joint stiffness/pain

The ACTIVExtend trial evaluated 1,139 postmenopausal women with an average age of 70 years after 18 months of abaloparatide or placebo who were switched to alendronate. This study showed a sustained vertebral fracture protection for an additional two years after completing abaloparatide therapy. For nonvertebral fractures, at 25 months and 43 months, abaloparatide showed an 87% RRR ($p<0.0001$) and 84% RRR ($p<0.001$) respectively, compared to placebo followed by alendronate.[11]

Teriparatide: A clinical trial evaluated teriparatide versus placebo for 19 months to primarily look at the effect on vertebral fractures in 1,637 postmenopausal women with an average age of 69 years. A new fracture occurred in 5% of the teriparatide group versus 14.3% of the placebo group (RRR 65%, $p<0.001$). Secondarily, they evaluated new nonvertebral fractures, which occurred in 2.6% of the teriparatide group versus 5.5% of the placebo group (RRR 53%, $p<0.05$). There were no significant differences in adverse effects between the treatment and placebo groups.[12]

Romosozumab: The FRAME clinical trial compared 12 months of romosozumab versus placebo in 7,180 postmenopausal women (average age: 70 years), followed by denosumab. The primary endpoint was incidence of new vertebral fracture at month 12 and 24. The secondary endpoint was the incidence of nonvertebral fractures. At 12 months, romosozumab showed a 73% RRR ($p<0.001$) of vertebral fracture compared to placebo, and a 75% RRR ($p<0.001$) at 24 months. However, the incidence of nonvertebral fractures was not statistically significantly different between romosozumab and placebo at both 12 and 24 months. There were no statistically significant differences in adverse effects between the groups.[13]

The ARCH clinical trial took place a year later and compared 12 months of romosozumab versus alendronate, followed by alendronate in both groups in 4,093 postmenopausal women with an average age of 74 years. The patient population in this trial was different from the FRAME clinical trial, as all subjects had a history of fracture, making them very high risk for future fractures. Despite all subjects having a fracture history, less than 10% had been on any previous osteoporosis treatment. This study looked at the primary endpoint of incidence of vertebral fracture at 24 months, and secondarily at time to first clinical fracture (nonvertebral and symptomatic vertebral fracture). Romosozumab demonstrated a 50% RRR ($p<0.001$) in vertebral fractures at month 24 compared to placebo. At 33 months, the secondary endpoint of nonvertebral fractures showed a 19% RRR ($p=0.04$) with romosozumab versus placebo, and a 38% RRR for hip fractures favoring romosozumab over placebo. However, this study showed a statistically significant increase in major adverse cardiac events (MACE) for romosozumab (2% vs 1.1%, hazard ratio 1.87), resulting in a boxed warning that romosozumab may increase the risk of myocardial infarction, stroke, and cardiovascular death.[14]

Denosumab: The PIVOTAL clinical trial studied denosumab versus placebo for 36 months in 7,868 women (average age: 72 years), looking at the primary endpoint of incidence of new vertebral fractures at 3 years. The secondary endpoints evaluated the first nonvertebral and hip fracture. For new vertebral fractures, denosumab showed a RRR of 61% ($p<0.0001$) at year 1, 71% ($p<0.0001$) at year 2, and 68% ($p<0.0001$) at year 3 compared to placebo. Denosumab had a 40% RRR ($p=0.04$) in hip fracture and a 20% RRR ($p=0.01$) in nonvertebral fractures at year 3 compared to placebo. Side effects were similar between the treatment and placebo group in the 3-year PIVOTAL study plus an open-label extension trial that reflected denosumab safety data through 10 years.[15]

Zoledronate: A 3-year clinical trial was conducted to compare zoledronate versus placebo to evaluate the incidence of vertebral fractures (in subjects not taking concomitant osteoporosis medications) and hip fracture in all subjects (included patients taking calcitonin, raloxifene, tamoxifen, and hormone replacement therapy). The study enrolled 3,889 postmenopausal women with an average age of 73 years. Zoledronate had a RRR of 70% during a 3-year period compared to placebo for vertebral fracture and a RRR of 41% compared to placebo for hip fracture. The study reported that adverse effects (including change in kidney function) were similar between the two groups, except serious atrial fibrillation occurred more frequently in the zoledronate group (50 patients versus 20 patients, $p<0.001$).[16]

Conclusion

Osteoporosis is underdiagnosed, and even diagnosed osteoporosis may be undertreated. Concern for adverse effects plays a large part in patients not willingness to pursue treatment for osteoporosis. There are multiple medications available for osteoporosis treatment that are not oral, may have less frequent administration than oral formulations, and have minimal and tolerable side effects. The risk of adverse effects is outweighed by the benefits of treatment to prevent a fracture from occurring. It is important to identify patients that qualify for a DEXA scan and encourage them to get one. Patients need to be educated on the various treatment options, non-pharmacological therapies in addition to medication, and the risks that untreated osteoporosis can bring.

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