Combined Pharmacologic Therapy in Postmenopausal Osteoporosis

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KEYWORDS

• Postmenopausal osteoporosis • Antiresorptive agent • Anabolic agent
• Teriparatide • Combination therapy

KEY POINTS

- Clinical guidelines recommend initiating pharmacologic treatment of patients with a history of hip or vertebral fracture, with a T score in osteoporotic range, or patients with significantly elevated fracture risks.
- Current pharmacologic treatments can be classified into antiresorptive and anabolic agents based on their mechanism of action; antiresorptive agents include raloxifene (selective estrogen receptor modulator [SERM]), bisphosphonates, and denosumab (receptor activator of nuclear factor κβ ligand inhibitor).
- Teriparatide is the only Food and Drug Administration–approved anabolic agent for osteoporosis treatment; synergistic effects of combining teriparatide with an antiresorptive agent have been proposed and studied in multiple clinical studies.
- Small increases of bone density were observed in the combination therapy for teriparatide and estrogen/SERM and that of teriparatide and denosumab; however, those studies were limited by small sample sizes and lack of fracture outcomes.
- Results of the combination therapy for teriparatide and bisphosphonates were mixed; heterogeneity of the pharmacologic characteristics of antiresorptive agents as well as trial designs may be significant contributors of inconsistent results.

INTRODUCTION

Osteoporosis is a common skeletal disease characterized by low bone density and increased bone fragility and, therefore, is associated with significant fracture risks. A clinical guideline from the National Osteoporosis Foundation recommends initiating

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pharmacologic treatment of patients with a hip or vertebral fracture or who have a bone mineral density (BMD) T score of − 2.5 or less or who have a BMD T score between 1.0 and 2.5 and a 10-year probability of a hip fracture 3% or greater or a 10-year probability of a major osteoporosis-related fracture of 20% or greater based on the Fracture Risk Assessment Tool algorithm.[1] Depending on their mechanism of action, pharmacologic treatments for osteoporosis can be classified into either antiresorptive agents or anabolic agents.[2] This classification is based on the phase of the bone remodeling process: if the main action of a drug is to inhibit the resorption process and/or shorten the life span of osteoclasts, then the agent is thought to be antiresorptive. On the other hand, if the main action of a drug is to stimulate osteoblast function and promote bone formation, then the agent is anabolic. **Table 1** lists the major pharmacologic agents that have been approved by the Food and Drug Administration (FDA) for the treatment of postmenopausal osteoporosis.

MECHANISMS OF ACTION FOR TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS

Many research efforts on the pathogenesis of osteoporosis were focused on postmenopausal women because estrogen plays a central role in bone remodeling.[3] Estrogen, mediated by estrogen receptor α, directly and indirectly attenuates resorption of trabecular bone.[4] In the postmenopausal state, estrogen deficiency results in an increase of bone resorption and remodeling. Binding of receptor activator of nuclear factor $\kappa\beta$ ligand (RANKL) to RANK also plays an essential role in this process: estrogen deficiency increased the expression of RANKL in B lymphocytes, which leads to more binding of RANKL to RANK that eventually gives rise to the initiation and differentiation of osteoclasts.[4,5] Postmenopausal bone change is a continuum. The aging process plays a significant role in bone loss.[6] Osteoporosis may develop in women in their 50s, 60s, 70s, or 80s, suggesting individual heterogeneity in pathogenesis.

Estrogen replacement therapy in postmenopausal women is known to prevent bone loss and vertebral and hip fractures.[7] Estrogen replacement is no longer routinely used because of increased risks of breast cancer and cardiovascular adverse effects. Raloxifene, a selective estrogen receptor modulator (SERM) that mimics estrogen's effects on bone remodeling, has been approved for treatment of postmenopausal osteoporosis. Clinical trial data of raloxifene showed that it inhibits bone turnover and increases BMD. It reduced the fracture risk in vertebrae but not in hip or nonvertebral sites.[8,9] Use of raloxifene is also associated with a reduced risk for breast cancer but has increased thromboembolic events.

Bones are woven structures of type I collagen strengthened with crystals of calcium hydroxyapatite. Bisphosphonates are nitrogen-containing analogues to pyrophosphates that actively bind to hydroxyapatite crystals in bone and, thus, interfere with isoprenylation of small guanosine triphosphatases in osteoclasts in a process that eventually causes reduced bone resorption and apoptosis of osteoclasts.[5] There are several bisphosphonates approved for osteoporosis treatment; differences in their side chain structure determine their binding strength to the bone as well as their distribution within the bone and dosing frequencies. Major clinical trials for alendronate, risedronate, and zoledronic acid demonstrated significant fracture risk reduction in vertebral, nonvertebral, and hip areas.[10–12] Increases in bone density were observed after 6 months of initiating use of bisphosphonates.[10–14] Common adverse events for oral bisphosphonates are gastrointestinal irritation and symptoms of esophagitis. Atypical femur fractures and osteonecrosis of the jaw are rare adverse events associated with this drug class. An acute phase reaction with flulike symptoms can occur in