



## Current and Emerging Trends in Pharmacological Management of Osteoporosis

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### ABSTRACT

Osteoporosis is a multifactorial progressive skeletal disorder characterized by reduced bone mass and deterioration of bone microarchitecture. Fragility fractures, the consequence of osteoporosis, are responsible for excess mortality, morbidity, chronic pain, admission to hospitals and economic costs. Approximately 1.6 million hip fractures occur each year worldwide, the incidence is set to increase to 6.3 million by 2050. No treatment can completely reverse established osteoporosis. Currently available therapies include bisphosphonates, SERMs, HRT, denosumab, teriparatide, calcitonin and strontium ranelate. Cathepsin K inhibitors (balicatib and odanacatib) are among recent drugs under development. Saracatinib is a novel orally available competitive inhibitor of Src kinase shown to inhibit bone resorption *in vitro*. Lasofoxifene, bazedoxifene, and arzoxifene are new SERMs in late-stage clinical trials.

**Keywords:** Osteoporosis, fracture, BMD, Bisphosphonates, SERMs.

### INTRODUCTION

Osteoporosis is a multifactorial progressive skeletal disorder characterized by reduced bone mass and deterioration of bone microarchitecture, predisposing it to increased fracture risk. Osteoporosis is called a "silent disease" because it progresses without symptoms and remains unnoticed for a long time as bone resorption process in early stages is almost asymptomatic and at later stages usually presents with a fracture due to trivial trauma.<sup>1</sup> Fragility fractures, the consequence of osteoporosis, are responsible for excess mortality, morbidity, chronic pain, admission to institutions and economic costs. They represent 80% of all fractures in menopausal women over age 50. Patients with hip or vertebral fractures have substantially increased risk of death after the fracture. Approximately 1.6 million hip fractures occur each year worldwide, the incidence is set to increase to 6.3 million by 2050.<sup>2</sup> According to a study, 20% of women and about 10-15% of men are osteoporotic in India.<sup>3</sup> Another estimate by a group of experts suggests that 26 million Indians suffer from osteoporosis, and this number is expected to reach 36 million by 2013.<sup>4</sup>

#### Current Pharmacological options for Osteoporosis

Currently, no treatment can completely reverse established osteoporosis. Early intervention can prevent osteoporosis in most people. For patients with established osteoporosis, medical intervention can halt its progression. Therapy should be individualized based on each patient's clinical scenario, with the risks and benefits of treatment discussed between the clinician and patient.

Guidelines from the American Association of Clinical Endocrinologists (AACE)<sup>5</sup>, published in 2010, include the following recommendations for choosing drugs to treat osteoporosis:

- First-line agents: alendronate, risedronate, zoledronic acid, denosumab
- Second-line agent: ibandronate
- Second- or third-line agent: raloxifene (SERMs)
- Last-line agent: calcitonin
- Treatment for patients with very high fracture risk or in whom bisphosphonate therapy has failed: teriparatide.

#### BISPHOSPHONATES

These are the most commonly used drugs used to treat osteoporosis. Alendronate was the first bisphosphonate to be approved for treatment of osteoporosis in the US in 1995. Since that time, newer bisphosphonates with less frequent dosing intervals have been introduced, partially in an attempt to improve compliance. Risedronate is an oral medication that can be administered daily, weekly, or monthly at varying doses. Zoledronic acid is the newer medication which is administered once yearly by intravenous transfusion. Bisphosphonates bind to hydroxyapatite crystals and thus have a very high affinity for bone. Bisphosphonates are released from the bone matrix upon exposure to acid and enzymes secreted by an active osteoclast. Out of all bisphosphonates, zoledronic acid has the highest affinity for binding to the bone mineral matrix. Suppression of bone resorption occurs within approximately three months of initiation of oral



bisphosphonate therapy regardless of dosing frequency, but it is more rapid after intravenous administration. After three years of treatment, bisphosphonates have shown to increase bone mineral density (BMD) of the hip by 3%-6% and at the spine by 5%-8%. In women with osteoporosis zoledronic acid, alendronate and risedronate also reduced nonvertebral fractures by 25%-40%, including hip fractures by 40%-60%. Zoledronic acid: 5 mg single i/v infusion annually, alendronate: 10mg/day orally, ibandronate: 2.5 mg oral daily or 150 mg once monthly, risedronate: 5 mg/day oral are commonly used bisphosphonates.<sup>6,7</sup>

Orally administered bisphosphonates may cause esophagitis. It is recommended to swallow oral bisphosphonates with full glass of plain water on arising in the morning, remaining upright for at least 30 minutes after swallowing the tablet and discontinuing the drug promptly if esophageal symptoms develop. Rapid intravenous administration of parenteral bisphosphonates may cause renal toxicity. For patients with creatinine clearance less than 30-35 mL/min, use of parenteral bisphosphonates is not recommended. Other concerns are risk of kidney damage and osteonecrosis of Jaw (Zoledronic acid), atypical fractures, atrial fibrillation.<sup>8-12</sup>

### Selective estrogen receptor modulators

Selective estrogen receptor modulators (SERMs) are nonsteroidal molecules that bind with high affinity to the estrogen receptor (ER), and act as agonists or antagonists depending on the target tissue. The ER agonistic effects of SERMs in bone have proven to be important for the treatment of osteoporosis in postmenopausal women. Currently, raloxifene is the only SERM approved by the U.S. Food and Drug Administration for prevention and treatment of postmenopausal osteoporosis. Clinical studies have clearly demonstrated the efficacy of raloxifene in significantly reducing the risk of vertebral fracture. Raloxifene is indicated for the treatment and prevention of osteoporosis in postmenopausal women in a dose of 60 mg given orally daily. It has been shown to prevent bone loss, and data in females with osteoporosis have demonstrated that raloxifene causes a 35% reduction in the risk of vertebral fractures. An additional benefit and indication is prevention of ER-positive breast cancer.<sup>13-15</sup>

### RANK-Ligand Inhibition: Denosumab

Denosumab is a fully human monoclonal antibody that binds with high affinity and specificity to the receptor activator of nuclear factor- $\kappa$ B ligand (RANKL), a key mediator of osteoclast formation, activity, and survival. The inhibition of RANKL by denosumab reduces osteoclast-mediated bone resorption. It is indicated for the treatment of postmenopausal women with osteoporosis who are at high risk of fracture, have multiple risk factors for fracture, are intolerant to other available osteoporosis therapies, or in whom osteoporosis therapies have failed. In postmenopausal

women with osteoporosis, denosumab reduces the incidence of vertebral, nonvertebral, and hip fractures. Denosumab was approved by the US Food and Drug Administration in June 2010. Approved dosage is 60 mg given subcutaneously every 6 months. Several recent studies have demonstrated the efficacy of this new antiresorptive therapeutic class in terms of increasing BMD, decreasing bone turnover markers (BTMs), and most important, reducing fractures at vertebral, hip, and other nonvertebral sites.<sup>16,17</sup>

### CALCITONIN

Calcitonin acts on the calcitonin receptor on osteoclasts to decrease their activity. Out of all recombinant or synthetic calcitonins that have been used for medical purposes, the salmon calcitonin preparation (SCT) is the most widely used. SCT as a nasal spray is the most commonly used calcitonin formulation due to its convenience of administration. It is recommended in conjunction with adequate calcium and vitamin D intake to prevent the progressive loss of bone mass. The intranasal spray is delivered as a single daily spray that provides 200 IU of the drug. It has reduced the incidence of vertebral fractures in women with pre-existing vertebral fractures. As a desirable additional effect, calcitonin has been noted to reduce the pain of clinical vertebral fractures. Calcitonin is an option for patients who are not candidates for other available osteoporosis treatments. Common side effects of nasally administered calcitonin include nasal discomfort, rhinitis, irritation of nasal mucosa, and occasional epistaxis. Nausea, local inflammatory reactions at the injection site, sweating, and flushing are side effects noted with parenteral use.<sup>18-20</sup>

### HORMONE REPLACEMENT THERAPY (HRT)

Hormone replacement therapy (HRT) was once considered a first-line therapy for the prevention and treatment of osteoporosis in women. Although HRT is not currently recommended for the treatment of osteoporosis, it is important to mention because many osteoporosis patients in a typical practice still use it for controlling postmenopausal symptoms. Data from the Women's Health Initiative confirmed that HRT can reduce fractures. However, the results of the Women's Health Initiative were distressing with respect to the adverse outcomes associated with combined estrogen and progesterone therapy (eg, risks for breast cancer, myocardial infarction, stroke, and venous thromboembolic events) and estrogen alone (eg, risks for stroke and venous thromboembolic events).<sup>21</sup>

### RECENT AND EMERGING DRUGS FOR OSTEOPOROSIS

#### Strontium ranelate

Strontium ranelate, a novel orally active agent, has been developed for the treatment of osteoporosis. It consists of two atoms of strontium and an organic moiety ranelic acid. Strontium ranelate acts by both stimulating bone formation and decreasing bone resorption. In vitro,



strontium ranelate has been shown to increase osteoblastic activity, including increasing collagen synthesis and modulating the OPG/RANKL system in favor of OPG, as well as decrease bone resorption by decreasing osteoclast differentiation and resorbing activity, and increasing osteoclast apoptosis. Strontium ranelate is approved for the treatment of osteoporosis in some countries in Europe. It reduces the risk of both spine and nonvertebral fractures. Strontium is not approved for the treatment of osteoporosis in the United States. Dose is 2 g sachet nightly Taken at bedtime, mixed with >30 mL of water at least 2 hours after food. Strontium ranelate has rarely been associated with VTE and severe hypersensitivity reactions, including Stevens-Johnson syndrome and drug rash with eosinophilia and systemic symptoms. Patients should be advised to seek immediate medical advice if they develop a rash.<sup>22, 23, 24</sup>

### Teriparatide

Teriparatide is a synthetic form of human parathyroid hormone which acts by inhibiting bone resorption and increasing bone formation. Normally in response to low serum calcium, PTH is secreted from parathyroid glands, and acts to increase the concentration of calcium in serum by mobilizing calcium from bone. Pharmacologically, when PTH is administered intermittently at low doses, it has been shown to have predominantly anabolic effects on osteoblasts. PTH initiates bone formation first and only later promotes bone formation, which is indicated by bone turnover markers. Teriparatide is also indicated for use in men with a high risk of fractures and where other treatments are unsuitable. Following a course of teriparatide it is recommended that patients use an antiresorptive medicine (eg. a bisphosphonate) to further increase BMD and maintain the antifracture effect. Dose is 20 µg subcutaneous injection daily in the thigh or abdomen. Use is Restricted to 18 month lifetime exposure (caused osteosarcoma in animal studies) informed consent is required. Now days, transdermal teriparatide is also under development.<sup>25, 26, 27</sup>

### Drugs under clinical development

- **Cathepsin K inhibitors**

Cathepsin K is critical for normal osteoclastic bone resorption. The two agents which are under development are balicatib (AAE581) and odanacatib (MK-0822). Clinical trials with these agents have demonstrated increase in hip and lumbar spine BMD, with a significant reduction in bone resorption markers. A newer highly potent cathepsin K inhibitor named relacatib is presently being studied in experimental animals.<sup>28, 29</sup>

- **Src Kinase Inhibitors**

Src kinase is a non-receptor tyrosine kinase and a member of the Src family of protein kinases which plays an important role in activity and survival of osteoclast cells. Osteopetrosis was caused in mouse due to Src

inactivation; therefore it clearly indicated that Src is an important requirement for osteoclastic bone resorption. Saracatinib is a novel orally available competitive inhibitor of Src kinase shown to inhibit bone resorption *in vitro*. In a randomized, double-blind, placebo-controlled, multiple-ascending- dose phase I trial treatment with saracatinib inhibited osteoclast mediated bone resorption in healthy men without any significant adverse effects. The results of this study show that saracatinib has the potential to become an agent for the treatment of osteoporosis.<sup>30-32</sup>

### NEW SERMs

#### Lasofloxifene

Lasofloxifene is a non-steroidal SERM which is under development for the prevention and treatment of osteoporosis and for the treatment of vaginal atrophy. In a dose of 0.5 mg/day, the dose that is intended for clinical use, it was associated with a reduction in the risk of ER-positive breast cancer, major coronary heart disease events, and stroke, although the numbers of these events were small in all groups. Lasofloxifene was significantly associated with the risk of venous thromboembolic events and pulmonary embolism.<sup>33</sup>

#### Bazedoxifene

Bazedoxifene is a third generation SERM) under development the prevention and treatment of postmenopausal osteoporosis. It is approved in the European Union (marketed in Italy and Spain), and is currently in the late phases of review by the US FDA. Bazedoxifene's combination with conjugated estrogens, Aprela, is currently undergoing Phase III studies for the treatment of postmenopausal symptoms (including the prevention of postmenopausal osteoporosis/treatment of osteopenia).<sup>34</sup>

### Inhibitors of Wnt signaling

The Wnt/β-catenin pathway regulates gene transcription of proteins important for osteoblast function. Study of the pathway has led to further discovery of inhibitors of Wnt signaling secreted by osteocytes. These include sclerostin and dickkopf1 protein (DKK1), both of which block binding of Wnt to LRP5 (lipoprotein receptor-like protein 5), thereby inhibiting osteoblast stimulation. Monoclonal antibodies designed to block the inhibiting action of both sclerostin and DKK1 are being considered for clinical trials based on promising results in animal models. Because both of these molecules appear to be secreted only by bone, it is hoped that they will have fewer systemic adverse effects. Therapies targeted at other molecules in the pathway, for example a small molecule inhibitor of GSK3β, the enzyme which causes degradation of β-catenin in the absence of Wnt signaling, are considered less desirable targets due to their action in many tissues in addition to bone.<sup>35</sup>



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