Drug Therapy for Postmenopausal Osteoporosis: A Review

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LEADING ARTICLE

New research has resulted in improved treatment options for postmenopausal osteoporosis. Therapeutic advances include the anticipated availability of anabolic agents, potent intravenous bisphosphonates such as zoledronic acid, and novel antiresorptive agents targeting receptor activator of nuclear factor-kappa B ligand (RANKL) inhibition. RANKL is a cytokine essential for the activation of osteoclasts, and its inhibition by denosumab, a fully human monoclonal antibody to RANKL, has been shown to reduce bone loss in Phase I and II clinical trials. Antiresorptives have also been further evaluated in landmark trials. Raloxifene has been found to be as effective as tamoxifen in preventing breast cancer in women with increased risk of this disease. Raloxifene use has also been shown to have no impact on the incidence of coronary events or stroke in women suffering from or at an increased risk of coronary artery disease, although a slight but significant increase in stroke mortality rates was noted; these data are currently being evaluated. The recent availability of anabolic agents complements existing antiresorptive therapy, and these treatments effectively improve both bone mineral density and the microarchitectural deterioration seen in advanced osteoporosis. This paper reviews the new research and current therapies in the field of postmenopausal osteoporosis. *Adv Osteoporotic Fract Manag* 2006;**4**(4):119–25.

Osteoporosis is characterized by a decrease in bone mineral density (BMD) and an associated deterioration of bone microarchitecture, which leads to increased bone fragility and higher risk of fracture [1]. In addition to lifestyle changes, therapy options for the prevention and treatment of osteoporosis include both antiresorptive therapies and recently approved anabolic agents. Antiresorptive (anticatabolic) agents inhibit osteoclast activity and decrease bone turnover [2], and the various agents have different mechanisms of action. Bisphosphonates decrease rates of bone turnover, allowing longer time periods for bone to mineralize. Bisphosphonate therapy is associated with modest increases in BMD. Estrogen acts on the estrogen receptors on both osteoblasts and osteoclasts, and results in suppression of RANKL-induced osteoclast differentiation, thereby decreasing bone remodeling [3]. Raloxifene, a selective estrogen receptor modulator (SERM), can bind to estrogen receptors and has tissue-specific agonist or antagonist effects. Raloxifene decreases bone remodeling, in addition to its other extraskeletal effects. Osteoclastic bone resorption is also inhibited by calcitonin acting on calcitonin receptors. The antiresorptive agents mentioned above are effective in decreasing fracture risk by approximately 30–50%; however, fractures still occur, and more effective options are desirable, particularly for severe disease states. Anabolic therapy is a welcome addition to the range of antiresorptive options available to date. It allows for increased production of bone matrix by enhancing osteoblastic function, resulting in a subsequent reduction in risk of fracture by approximately 65% over 18 months. The two currently approved anabolic agents are teriparatide (TPD) and strontium ranelate (SR).

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Calcium and vitamin D

Treatment regimens for osteoporosis prevention begin with lifestyle changes, such as more exercise, cessation of smoking, alcohol reduction, and adequate intake of calcium and vitamin D [2]. The Scientific Advisory Council of Osteoporosis Canada recommends [2]:

- 1500 mg/day of elemental calcium for women aged >50 years.
- 400 IU/day of vitamin D for all individuals <50 years of age.
- 800 IU/day for all people aged >50 years.

The WHI (Women's Health Initiative) trial involved 36 282 postmenopausal women who were given 1000 mg of calcium and 400 IU of vitamin D daily, and who were followed for an average of 7 years [4]. Patients were allowed

to take additional daily supplements of up to 1000 mg of calcium, and 600 IU of vitamin D. Personal use of bisphosphonates, calcitonin, selective estrogen receptor modulators (SERMs), and estrogen therapy was also permitted, and approximately 38% of subjects took >1200 mg of elemental calcium daily. In the WHI, the calcium and vitamin D study arm overlapped with the hormone replacement therapy (HRT) arm, thus approximately 51% of patients were receiving estrogen.

Treatment compliance was poor; by the end of the study, only 59% of patients were taking >80% of their medication. Notwithstanding, the study results demonstrated a 1.06% increase in hip BMD in patients taking 1000 mg of calcium and 400 IU of vitamin D daily versus placebo ($p<0.01$). The risk of hip fracture was not statistically different from the placebo group, with the hazard ratio (HR) standing at 0.88 (confidence interval [CI] 0.72–1.08). However, in the treatment-compliant group, the HR for hip fracture was 0.71 (CI 0.52–0.97), representing a statistically significant 29% decrease in hip fracture risk in those individuals taking >80% of their calcium and vitamin D supplements. Estrogen use was associated with a 42% decrease in hip fracture risk. There was a small but significant 17% increase in risk of renal stones in the treatment group compared with placebo, with a HR of 1.17 (CI 1.02–1.34) [4]. Clinicians must therefore ensure that patients are not inadvertently taking excessive calcium supplements and that their urinary calcium excretion is normal, particularly in those with a history of renal stone formation.

Vitamin D inadequacy was also noted in the WHI study and may have contributed to the findings. The mean 25-hydroxy vitamin D levels in the nested case-control study were 46 nmol/L in patients who sustained hip fractures, compared with 48.4 nmol/L in the controls [4]. Vitamin D supplementation of >600 IU/day may have reduced fracture risk, as has been demonstrated in other clinical trials. Ensuring adequate vitamin D supplementation is a key component of therapy in the prevention and treatment of osteoporosis.

Antiresorptive therapy

SERMs

SERMs demonstrate tissue-specific estrogen-agonistic or estrogen-antagonistic effects [5]. In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, patients treated with either 60 mg/day or 120 mg/day raloxifene over 4 years demonstrated 36% and 43% reductions in vertebral fracture risk, respectively [6]. However, no significant effect on the risk of non-vertebral fractures was noted [6]. This may have been due to multiple factors, including the very low incidence of non-vertebral fractures seen in the placebo arm of this trial, in comparison with the randomized clinical trials (RCTs) for other antiresorptives.

Recently, in the Study of Tamoxifen and Raloxifene (STAR), involving 19 747 postmenopausal women with increased risk of breast cancer, 60 mg/day raloxifene demonstrated equivalent effects with respect to breast cancer risk reduction in comparison to 20 mg/day tamoxifen over 5 years [7]. Both drugs reduce the risk of breast cancer by approximately 50%. Raloxifene use was associated with a better overall safety profile than tamoxifen, with 36% fewer uterine cancers and 29% fewer deep vein thromboses [7].

Recently released data for the Raloxifene Use for The Heart (RUTH) trial indicated that raloxifene did not increase or decrease the combined endpoint of non-fatal myocardial infarction, fatal myocardial infarction, and hospitalized acute coronary syndrome, in comparison to placebo, in women suffering from, or at increased risk of developing, coronary artery disease (CAD). However, stroke mortality rates increased slightly. Data analysis is required to further clarify these findings. Raloxifene is a valuable agent in the prevention and treatment of osteoporosis, particularly in those at increased risk of breast cancer. However, as with estrogen therapy, raloxifene increases the incidence of thromboembolic events and is contraindicated in those with a history of deep vein thrombosis or pulmonary emboli.

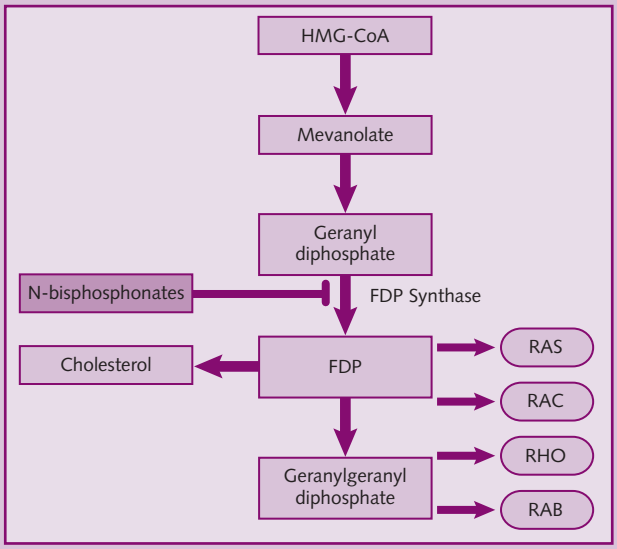
Bisphosphonates

Nitrogen-containing bisphosphonates (alendronate, risedronate, and zoledronic acid) demonstrate antiresorptive effects by binding to the calcium hydroxyapatite crystal at sites of bone resorption where the bone matrix is exposed [8]. The bisphosphonate is buried under the newly formed bone, where it lies inert and has no skeletal effects. During bone resorption, the drug is released from the bone matrix and is ingested by osteoclasts; it inhibits farnesyl diphosphate synthase (FPP), a key enzyme in the cholesterol synthesis pathway involved in post-translational modification of important signaling molecules (Ras, Rac, Rho, and Rab). FPP inhibition disrupts several pathways involved in cytoskeletal organization, cell survival, and cell proliferation, leading to osteoclast deactivation and apoptosis (Fig. 1) [9]. This results in decreased bone turnover and enhanced bone mineralization due to the extended time available for mineral accumulation. With the normalization of bone remodeling to premenopausal levels, overall bone strength is improved [9,10].

Alendronate

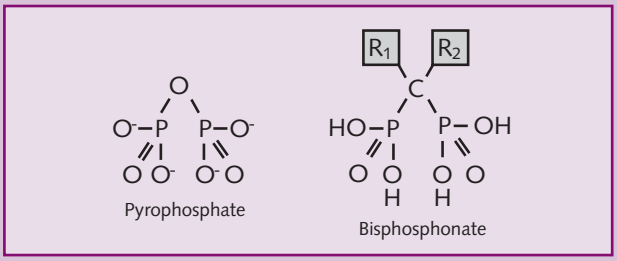
Alendronate effectively reduces the risk of vertebral fractures in postmenopausal women with and without baseline vertebral fractures, as has been demonstrated in the FIT (Fracture Intervention Trial) [11–13]. Several trials

Figure 1. Mechanism of action of N-bisphosphonates.



HMG-CoA: 3–hydroxy-3–methylglutaryl-Coenzyme A; FDP Farnesyl diphosphate.

Figure 2. Structure of pyrophosphate and bisphosphonates. The R_1 side chain affects the affinity for binding to the hydoxyapatite crystal, and the R_2 side chain affects the potency of the agent.



have shown that alendronate usage decreases bone resorption and improves BMD [13,14]. In early postmenopausal women aged 40–59 years, daily treatment with alendronate for 5 years inhibited bone loss at the spine, hip, and total body [12]. In a separate study involving women aged <60 years, daily 5 mg doses of alendronate resulted in a 3.5% increase in BMD at the lumbar spine, together with a 1.9% increase at the hip ($p<0.001$ vs. baseline at both sites) [14]. It is worth noting that the FIT Long-term Extension (FLEX) study reported that increases in BMD continued at the lumbar spine and hip through 10 years of treatment, with an associated fracture risk reduction [13]. Bone biopsies performed in patients following 10 years of alendronate treatment revealed double fluorescent tetracycline label in all biopsy samples, indicating ongoing bone remodeling and the absence of "frozen" bone [13]. This data provides reassurance that long-term alendronate therapy is capable of safely reducing vertebral and nonvertebral fractures .

Risedronate

Risedronate maintains bone mass and preserves bone microarchitecture [15]. A number of studies in postmenopausal women have shown risedronate to significantly reduce the risk of both vertebral and non-vertebral fractures [16–18]. Analysis of data from the VERT (Vertebral Efficacy With Risedronate Therapy) trials indicated that 5 mg/day doses of risedronate reduced the incidence of new fractures within 6 months of starting therapy, and significantly lowered the risk of new vertebral fractures within 1 year [16–18], with this reduction in fracture risk maintained for up to 7 years of treatment [16–19].

Risedronate has been shown to effectively reduce the risk of non-vertebral fractures after 3 years of treatment [20]. Another study, involving early postmenopausal women, demonstrated that daily 5 mg doses of risedronate increased BMD at the lumbar spine by >5% versus placebo during 2 years of treatment ($p<0.05$ vs. baseline and placebo) [21]. Other studies have confirmed these findings, showing that risedronate prevents bone loss and preserves trabecular architecture in early postmenopausal women [22]. In addition, key clinical trials have shown that reductions in vertebral fracture risk with risedronate were independent of increases in BMD [15].

Zoledronic acid

Zoledronic acid is the most potent bisphosphonate currently available [23,24]. It contains two nitrogen atoms in the R^2 sidechain, and the intravenous administration of 4 mg doses has been approved for the prevention and treatment of metastatic bone disease and hypercalcemia of malignancy. Zoledronic acid 5 mg has been approved as a treatment for Paget's Disease of bone in Canada.

In a double-blind, placebo-controlled, dose-ranging trial involving 351 postmenopausal women with low BMD, significant reductions in markers of bone resorption were noted, along with improvements in BMD in all treatment groups when compared to placebo [25]. In addition, the study noted that an annual 4 mg dose of zoledronic acid achieved reductions in bone turnover comparable to those seen with daily oral bisphosphonate therapy [25].

A large Phase III RCT currently in progress is the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) pivotal fracture trial (PFT), evaluating the effects of 5 mg of zoledronic acid annually on fracture incidence in men and women aged ≥50 years having sustained a recent low trauma hip fracture [26]. A separate 3-year trial, the HORIZON recurrent fracture trial (RFT), is assessing the

incidence of hip and vertebral fractures in postmenopausal osteoporotic women, with 5 mg of zoledronic acid annually versus placebo [27]. Results of these trials are expected to be available soon.

A major advantage of oral bisphosphonate therapy is the ease of administration and the excellent tolerability profile. The most common side effects associated with such therapy are abdominal pain and dysphagia. However, both alendronate and risedronate have demonstrated comparable upper gastrointestinal side effects to placebo in the RCTs conducted to date [28]. Intravenous (IV) administration of bisphosphonates provides a number of advantages including less frequent dosing and lower potential for gastrointestinal side effects compared to oral bisphosphonates.

Recently, reports of mandibular or maxillary osteonecrosis as a potential rare complication of bisphosphonate use have been published [29]. Osteonecrosis of the jaw (ONJ) is an avascular bone necrosis that may occur in patients at risk for this condition The majority of these reports are associated with frequent high-dose administration of intravenous pamidronate or zoledronic acid in oncology patients with a history of breast cancer or myeloma. A large number of these patients have been on concomitant chemotherapy and/or radiotherapy, both of which are risk factors for avascular bone necrosis. The condition has been reported in high-risk individuals most commonly following dental surgery such as dental extraction [30]. ONJ has rarely been reported with alendronate and risedronate use [29]. It is important to note that ONJ has not been seen in any of the clinical trials conducted to date, which represent prospective data obtained in >100 000 patients treated with aminobisphosphonates for an average of 3 years. All published cases reported have consisted of anecdotal reports. In a retrospective chart review by MD Anderson Cancer Center of 4000 cancer patients treated with zoledronic acid, pamidronate or both, ONJ was identified in 0.825% of the patient population [31].

Administration of potent bisphosphonates has been shown to provide a number of advantages in patients with metastatic disease, such as the ability to effectively control hypercalcemia and stabilize bone lesions while bypassing the gastrointestinal tract. Thus, IV bisphosphonates are of tremendous value in the management of skeletal complications in patients with malignancy, and are an important component of therapy in this patient population. The benefits of IV bisphosphonates far outweigh the risks of developing ONJ. Further prospective data is needed to understand the true incidence and pathophysiology of ONJ. The exact relationship between ONJ and the use of bisphosphonates also needs to be clarified. It should also be noted that the annual dose of IV bisphosphonates used in osteoporosis is significantly lower than that used in oncology patients. Generally, bisphosphonates are very well-tolerated and are a safe treatment option for osteoporosis.

HRT

Estrogen therapy has significant antiresorptive effects. Specifically, it enhances the osteoblastic production of osteoprotegerin (OPG), which has antiosteoclastic properties due to its ability to bind to RANKL and subsequently block the RANKL/RANK interaction required for osteoclast recruitment and activation [3,32].

In the WHI, a primary prevention trial, the combined estrogen plus progesterone arm demonstrated an increase in total hip BMD, along with a 34% reduction in hip and vertebral fractures, and 24% reduction in total osteoporotic fractures [33]. The estrogen-alone arm presented similar results, with a 30–39% reduction in fracture rates [34]. Therefore, this trial confirmed the antifracture effects of HRT suggested by previous clinical trials [35–36]. In early postmenopausal women, combined estrogen–progesterone therapy resulted in increases in BMD of 2–3% at the hip and spine over 2 years of therapy [35]. A decrease in the markers of bone turnover in response to HRT was also seen in early postmenopausal women [36].

Despite the beneficial effects of HRT on BMD and fracture risk, recent data on adverse effects associated with HRT from the WHI has led to a re-evaluation of its safety and efficacy. The combined estrogen and progesterone arm experienced a 26% increased risk of breast cancer and a 29% increased risk of cardiac events, prompting the early termination of this treatment group after 5.2 years of follow-up [37]. The estrogen-alone arm was also terminated prematurely due to a 41% increased risk of stroke and a two-fold rise in the risk of thromboembolic disease [34].

As the risks of HRT are significant and appear to outweigh its benefits, it is considered a treatment option for select patients unsuited to standard first-line antiresorptive therapies [38]. For such individuals, estrogen therapy can be used for limited time periods.

RANKL inhibitors

Examples of RANKL inhibitors include:

- OPG – a naturally occurring inhibitor.
- Genetically engineered OPG fusion protein, which has a longer circulating half-life than OPG.
- Denosumab.

Denosumab is a fully human monoclonal antibody to RANKL; it binds to human RANKL, thus preventing osteoclast activation and subsequently decreasing bone resorption. The Phase II study reported by McClung et al.

demonstrated that denosumab was well-tolerated and had a similar impact on bone turnover to alendronate [39]. Furthermore, BMD increased significantly in patients treated with denosumab compared with those who received placebo. Subcutaneous administration of the drug in doses of either 30 mg every 3 months, or 60 mg every 6 months, resulted in sustained decreases in urinary N-telopeptide excretion [39].

In addition, denosumab has been shown to effectively decrease bone turnover in patients with metastatic bone disease, with effects comparable to intravenous pamidronate [40]. It is currently being evaluated further in oncology patients with metastatic skeletal disease, as well as in those with postmenopausal osteoporosis, and it is expected to become a valuable additional option in the management of these conditions.

Anabolic agents

Until recently, postmenopausal osteoporosis treatment was limited to antiresorptive therapies. However, there has been a major advance with the availability of anabolic agents, namely parathyroid hormone (PTH) and strontium ranelate.

PTH: Teriparatide and full-length PTH

TPD is a 34-amino acid recombinant fragment of the 84-amino acid human PTH. In osteoporotic patients, it is administered subcutaneously in doses of 20 μg/day for 18 months. Although exposure to continuously elevated PTH levels is associated with bone loss, intermittent pulse therapy with PTH preferentially stimulates osteoblast activity and is associated with increases in BMD [41]. TPD promotes the differentiation of preosteoblasts into the bone-forming osteoblasts [42], resulting in a net increase in both the number and activity of bone-forming cells [41]. Several clinical trials have noted impressive effects of TPD on BMD and fracture risk [43–48].

In an RCT involving postmenopausal women with fragility fractures, those treated with 20 μg/day of TPD (median duration of observation = 21 months) showed a 9% increase in lumbar spine BMD, as well as improved BMD at the femoral neck and whole body [43]. Moreover, risks for vertebral and non-vertebral fractures were reduced by 65% and 53%, respectively [43].

Evidence for the anabolic effects of TPD on bone microarchitecture has been found in bone biopsies of patients treated with TPD. These show dramatic increases in the thickness, density, and number of trabeculae, as well as increases in cortical thickness and bone size [44]. A reduction in back pain has also been noted with TPD use.

The impact of the full-length PTH molecule (1–84) on fracture risk has been assessed in the Treatment of Osteoporosis (TOP) trial [45]. This 2-year study involved 2532 postmenopausal osteoporotic women who were randomized to receive 100 μg PTH (1–84) or placebo. PTH (1–84) was found to reduce the incidence of new vertebral fractures by 66%. The effect on non-vertebral fracture incidence has not yet been published. The full-length PTH is currently under review for approval for use in postmenopausal osteoporosis.

TPD is well-tolerated; however, several minor adverse events such as nausea and headaches, as well as transient mild hypercalcemia, have been noted [42]. Preliminary studies in rats, in which animals received near-lifelong exposure to high doses of TPD (≥5 μg/kg/daily), found a dose- and duration-dependent relationship between TPD and the development of osteosarcoma [49]. However, such doses are much higher than the 20 μg/day dose (approximately 0.28 μg/kg/daily) used in humans, and osteocarcoma has not been seen in humans or in the monkey studies. Furthermore, it is important to note that osteosarcoma does not occur with increased frequency in individuals with primary hyperparathyroidism.

Combination therapies have included TPD in combination with HRT or with bisphosphonates [46,47]. These studies are limited to BMD and biomarker data, and fracture data are not available. It has been found that TPD combined with estrogen therapy resulted in larger increases in lumbar spine BMD than HRT alone [46,47]. A separate study involving 238 postmenopausal osteoporotic women who were treated with either PTH (1–84) alone, or in combination with alendronate, revealed that the concurrent regimen had no advantage to PTH alone [48]. After 1 year of PTH (1–84) therapy, BMD gains were maintained or increased in patients who received follow-up therapy with alendronate for an additional year. However, BMD gains were lost if PTH therapy was followed by placebo over the following year [48]. Data suggest that pretreatment with alendronate may blunt the anabolic effects of PTH therapy [50]. Long-term fracture risk studies are required to determine if combination therapy is of value.

Strontium ranelate

SR becomes incorporated into bone and accumulates in the skeleton due to its physical and chemical similarities to calcium. It is absorbed in the bowel in a vitamin D-dependent manner [51]. SR provides skeletal benefits as it stimulates replication of preosteoblasts and synthesis of bone matrix, and prevents bone resorption by inhibiting osteoclasts [52,53].

In a study involving ovariectomized rats, SR prevented bone loss by decreasing bone resorption and enhancing bone formation [54]. RCTs assessing SR therapy in postmenopausal women have shown promising results. In a

Phase II study, 160 early postmenopausal women were randomized to one of several different doses of SR, or placebo [55,56]. Treatment with SR for 2 years resulted in increased lumbar spine BMD, compared with placebo. A separate Phase II RCT of 353 postmenopausal women who were given a 2 g/day dose of SR resulted in increased BMD versus placebo, together with a significant reduction in the incidence of vertebral fractures in the second year of treatment [57]. Recently published findings of a Phase III trial involving 1649 postmenopausal women demonstrated a 49% reduction in new vertebral fractures at 1 year in subjects administered 2 g/day SR compared with placebo [58]. A 16% reduction in non-vertebral fractures in the SR-treated group was also noted [59]. Furthermore, subjects at high risk of fracture (≥74 years of age with a femoral neck BMD T-score of ≤–3) demonstrated an even greater reduction in risk of hip fracture (36%, p=0.046) [59]. Side effects associated with SR have been limited to nausea and diarrhea during the first few months of therapy [53].

Conclusion

Osteoporotic fractures result in significant morbidity and increased mortality rates. The importance of both quantity and quality of bone in determining fracture risk has been recognized. A range of therapeutic options are now available for the prevention and treatment of osteoporosis. These include antiresorptive agents (SERMs, bisphosphonates, calcitonin, HRT, and RANKL inhibitors) and anabolic therapy (PTH and SR). Appropriate use of these valuable therapeutic options are likely to have a significant impact on fracture rates. Additional extraskeletal benefits of these agents have also been documented. With the availability of anabolic agents to complement anti-catabolic therapy, we are entering a new era in the management of osteoporosis. A focus on early diagnosis and treatment of osteoporosis with selection of the most suitable agent for each individual will contribute to the improved health and well-being of postmenopausal women.

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