GENERAL GYNECOLOGY

Combination therapy for treatment of osteoporosis: A review

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Combination therapy for osteoporosis has been tested in small trials of short duration with various combinations. Pertinent human and animal randomized clinical trial data were identified through Medline and reviewed with a focus on the risks and benefits of different types of combination therapies. Improvements in bone density were found in some, but not all, combinations. There are no large trials of adequate length or numbers to determine fracture efficacy. Consider combination therapy if monotherapy is unsuccessful, if there is an added nonskeletal benefit to the proposed combination or as sequential treatment with an anabolic agent followed by an antiresorptive agent. Although combination therapy, in general, has limitations based on cost, concern about potential oversuppression of bone, and lack of long-term safety and fracture efficacy, selected patients may benefit.

Key words: bisphosphonate, combination therapy, estrogen, hormone therapy, osteoporosis therapy, osteoporosis, selective estrogen receptor modulator

Osteoporosis is characterized by low bone mass and microarchitectural deterioration of bone tissue that results in increased bone fragility and fracture risk. Despite the variety of available therapeutic approaches, osteoporosis continues to be under diagnosed and under treated and is associated with significant costs to society in direct and indirect medical expenses and lost productivity. Food and Drug Administration–approved options for osteoporosis prevention or treatment include agents that primarily target bone (such as bisphosphonates; alendronate, risedronate, ibandronate), teriparatide (parathyroid hormone [PTH] 1-34), selective estrogen receptor modulators (SERMs; raloxifene), hormone therapy (HT; estrogen alone, estrogen and progesterone), and nasal calcitonin. The ability of bisphosphonates to prevent bone loss and/or increase bone mineral density (BMD) and to reduce the risk of fracture has been demonstrated thoroughly in numerous trials. SERMs have modest effects on bone density with the added benefit of reduction of breast cancer risk.

Estrogen increases BMD and protects against bone loss and fractures[1-4] and relieves up to 90% of vasomotor symptoms.[5,6] The findings of the Women's Health Initiative[4,7-9] confirmed that HT significantly reduced the rate of osteoporotic fractures and colorectal cancer but increased the odds of the development of breast cancer, deep venous thrombosis, stroke, or cardiovascular disease. The need to administer progestin in combination with estrogen for those with a uterus has been associated with an increased incidence of adverse events.[10-12] The current recommendation to administer the lowest effective doses of HT for the shortest period of time[3,13,14] may provide relief of menopausal symptoms but may not provide adequate protection against bone loss in all women.

Recent reviews of combination therapy confirm potential benefits of increased bone density or bone architecture and suggest potential risks of increased number of side-effects and concern about over suppression of bone turnover, increased cost, and a lack of long-term safety and efficacy data.[15-17] In addition, fracture protection data are unavailable to help guide clinicians to determine risks and benefits for individual women. For this article, pertinent human and animal randomized clinical trials (RCTs) of combination therapies were identified through Medline (1990-May 2007) and were reviewed with a focus on risks and benefits of different types of combination therapy, differentiating between anabolic and antiresorptive combinations.

In general, single agents or monotherapy is recommended for the treatment and prevention of osteoporosis, particularly because there are no fracture data or long-term studies to prove that combination therapy is superior to monotherapy. However, in our clinical opinion, combination therapy may be appropriate for certain women, such as those who have had negative evaluation for secondary causes of bone loss and for whom noncompliance has been addressed, yet they continue to lose significant bone density while receiving single agent therapy. Additionally, those women who continue to fracture, have higher fracture risks, or who need additional nonskeletal benefits may be candidates for combination therapy.

Combination of Anabolic Agent With Antiresorptive Agents

Current osteoporosis therapies are based mostly on antiresorptive agents the efficacy of which is limited, in part, because their effects mainly target bone resorption.[18,19] Anabolic agents may help overcome these limitations and further stimulate bone formation and increase BMD that, in turn, may lead to a greater reduction of fracture risk. Anabolic agents such as PTH increase bone mass and bone remodeling (turnover), which results in an enhanced resorption of corti-

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cal bone. Indeed, in patients with primary hyperparathyroidism, a preferential loss of cortical bone over trabecular bone is well-recognized.[20] Similarly, BMD changes at sites that contain predominantly cortical bone may exhibit little, if any, change in response to recombinant human PTH (rhPTH) treatment.[21] The addition of an antiresorptive agent to PTH potentially could reduce cortical bone turnover and facilitate the prevalence of the anabolic effects.[22]

PTH and bisphosphonates: concurrent vs sequential use

Initially, it was hoped that bisphosphonates and PTH that were given concomitantly would lead to added bone benefits. However, several trials have shown negative effects with these 2 agents when they are given together, although sequential therapy has proved more promising.

In a 2-year double-blind, placebo-controlled RCT, 238 women with osteoporosis received (1) PTH (PTH1-84 100 μg/d) for year 1 followed by alendronate (10 mg/d) for year 2 (sequential therapy), (2) PTH plus alendronate for year 1 followed by alendronate for year 2 (combination therapy), (3) alendronate for 2 years, or (4) PTH for year 1 followed by placebo for year 2. After 1 year, BMD at the spine increased in all women. Although the volumetric density of the trabecular bone at the spine as assessed by quantitative computerized tomography scanning increased significantly in all women, the increases in the PTH-alone group were twice as large as those observed in the other 2 groups. Thus, no synergy was found in this trial between PTH and alendronate. Indeed, observed changes in the volumetric density of trabecular bone, cortical volume at the hip, and levels of markers of bone turnover suggested that the combination of these agents may reduce the anabolic effects of PTH.[23] Gains in BMD in trabecular bone at the spine (11%) in the alendronate group were similar to placebo (14%) and substantially smaller than those gains that were achieved with combination therapy (31%). Compared with placebo (placebo year 2, PTH year 1), sequential therapy led to significant increases in BMD over 1 year, mainly in trabecular bone at the spine. Although these observations discourage the concomitant administration of PTH and alendronate, they suggest sequential administration of PTH followed by alendronate offers a viable approach to treatment.[24] Similar results of attenuated anabolic activity of PTH, when given concurrently with alendronate, were found in a 30-month trial of 83 men with low BMD who were given PTH (1-34).[25]

The effectiveness of sequential treatment of PTH and bisphosphonate therapy was also studied by Rittmaster et al[22] in a 1-year RCT using the full-length PTH molecule, (50 and 100 μg daily) followed by alendronate 10 mg daily in 66 postmenopausal women for an additional 12 months. During the initial year, PTH therapy significantly increased BMD at the spine but not the femoral neck. After discontinuation of PTH, alendronate treatment resulted in further significant increases in BMD at both the spine and hip, which suggests again that sequential treatment with PTH followed by a bisphosphonate appears to be an effective strategy to increase BMD.

PTH and SERMs

Early animal[26] and human[27] studies supported the potential combined use of raloxifene and PTH. Combination therapy with rhPTH 1-34 (20 μg/d) and raloxifene (60 mg/d) was compared with rhPTH 1-34 monotherapy (20 μg/d) in 137 postmenopausal osteoporotic women. At 6 months, bone formation increased similarly in both treatment groups. The rise in bone resorption was significantly less and the increase in total hip BMD significantly greater in the women who received combination therapy, compared with those women who received rhPTH 1-34 alone, which suggests that the anabolic effects of rhPTH 1-34 could be enhanced through combination with raloxifene. Larger trials of longer duration are needed to understand the clinical significance of the potential of additive effects of combining PTH and raloxifene or other SERMS.

PTH and HT

PTH was studied as an add-on treatment (400 U/25 μg daily) to osteoporotic women who received low-dose HT by Lindsay et al[28] in a 3-year RCT. After an observation period of 1 year receiving estrogen, 34 patients were assigned randomly to receive PTH and HT or HT alone. Those women who received combination therapy experienced continuous increases in vertebral BMD, with a concomitant reduction in vertebral fractures and an overall increase in total body skeletal mass, with no detrimental effects on cortical bone. Bone turnover significantly increased, which suggested that, despite the concomitant use of an antiresorptive agent, PTH induced osteoblast recruitment, thus showing a significant anabolic effect on the central skeleton of patients undergoing HT.

During a 3-year RCT of 52 postmenopausal women who received HT for 2 years, Cosman et al[29] reported that the addition of 400 IU/d of PTH induced dramatic increases of spine, total hip, and trabecular bone mass, compared with the HT-alone group who maintained their bone density with stable bone turnover markers. PTH + HT reduced the incidence of vertebral fractures. In the combination group, bone turnover markers peaked at 6 months and remained elevated, which suggested that some osteoporotic patients who received HT could further benefit from PTH. As in other studies, the antiresorptive actions of estrogen did not prevent PTH from stimulating bone formation.[28,30]

Combination of 2 Antiresorptives

Bisphosphonates and SERMs

In contrast with bisphosphonates, which inhibit bone resorption by binding hydroxyapatite and reducing osteoclast numbers and activity,[31,32] SERMs act as estrogen agonists in bone.[33-35] Given their different modes of action, the combination of bisphosphonates and SERMs

has the potential to enhance their individual effect on BMD and fracture risk.

In a double-blind RCT of 331 postmenopausal women with osteoporosis, raloxifene (60 mg/d) and alendronate (10 mg/d) both alone and in combination increased lumbar spine and femoral neck BMD and decreased bone turnover, with significantly greater increases in femoral neck in the combination therapy group compared with either agent alone.[36] The similar improvements in lumbar spine and bone turnover in both the alendronate and combination therapy groups were significantly greater than those in the raloxifene group with both independent and additive effects.

The effects of sequential alendronate and raloxifene were examined in 99 postmenopausal women who previously underwent alendronate therapy who received either placebo, raloxifene, or continued on alendronate for 12 months followed by a 12-month open-label extension.[37] At the lumbar spine, the placebo group had a significant decline in BMD, although either alendronate or raloxifene maintained BMD. At the femoral neck, BMD did not change in placebo group but continued to increase in those women who received raloxifene (12 months) or alendronate (12 and 24 months). Bone turnover markers rose significantly in the placebo group but remained at baseline in the alendronate group. Subjects changed to raloxifene had intermediate rates of bone turnover, which suggested that the effects of alendronate begin to diminish within 6 months of stopping therapy and that raloxifene is less potent than alendronate in its actions on bone formation and resorption.

Bisphosphonates and HT

Many menopausal women are concerned with both vasomotor symptoms (VMS) and bone loss. Estrogen treatment, unlike SERMs, alleviates menopausal symptoms, including VMS and vaginal dryness. The Women's Health Initiative confirmed fracture efficacy with both estrogen treatment and estrogen and progesterone therapy.[7,9] However, in women who need VMS relief but have ongoing bone loss on HT, it may be appropriate to consider the combination of HT and bisphosphonates.

A RCT of 428 postmenopausal osteoporotic women who received low-dose HT for at least 1 year assessed the effects of the addition of alendronate (10 mg/d).[38] Compared with HT alone, the HT-alendronate group showed significantly greater increases in BMD at the lumbar spine and hip trochanter ($P < .001$). The magnitude of these increases was less than previously reported in trials of estrogen and alendronate monotherapy, possibly because of the population studied which had, on average, received HT for 10 years.[39-42]

Greenspan et al[43] performed a double-blind RCT of combined HT and alendronate in 373 community-dwelling elderly women. After 3 years, women in the combination therapy group had significantly greater BMD increases at femoral and vertebral sites, compared with those who received monotherapy. Subsequently, Greenspan et al[44] reported that, in this study, both estrogen and alendronate significantly reduced both markers of bone formation and resorption with similar suppression of turnover for alendronate-HT combination, compared with alendronate alone and greater than for estrogen alone. These studies and a small study of cyclic etidronate HT[45] suggest that a bisphosphonate combined with estrogen may be more potent at increasing BMD than either agent alone without the risk of further suppression of bone remodeling.

Bone et al[46] evaluated the effects of conjugated equine estrogen (CEE) and alendronate in a double-blind RCT of 425 postmenopausal osteopenic women who had undergone hysterectomy (HT naïve) who received either placebo, alendronate (10 mg/d), CEE (0.625 mg/d), or alendronate (10 mg/d) plus CEE (0.625 mg/d). After 2 years, the use of alendronate-CEE produced significantly greater increases in BMD at the total hip ($P = .001$) and trochanter hip subregion ($P < .001$) but not significantly different from alendronate alone. All treatments induced significant increases relative to baseline in total body BMD without significant differences among the active groups. Both markers of bone formation and resorption declined with estrogen, alendronate, or the combination. Although of a small (<10%) magnitude, the reduction in bone turnover markers was greater for those individuals on combination therapy than when either agent was given alone. Bone biopsy specimens showed low remodeling in the patients on alendronate and HT, although clinical implications of this are unknown as there is no fracture data.

The combination of alendronate (10 mg daily) and HT (0.625 CEE/2.5 mg MPA) was evaluated in 151 postmenopausal osteoporotic Chinese women by Tseng et al[47] with findings of significant increases in BMD of 10.1% in lumbar spine and 4.6% at femoral neck, compared with baseline and placebo ($P < .01$) after 36 months. A significant decrease in bone markers was also found in the combination group, with no differences in side-effects.

In contrast, Evio et al[48] evaluated 90 elderly osteoporotic women (mean age, 71 years) who received either alendronate alone or a combination of daily alendronate 10 mg plus estrogen and progesterone therapy (2 mg estradiol, 1 mg norethisterone) and found that monotherapy with alendronate was not statistically different from the combination of alendronate plus estrogen on BMD gains.

Positive results were found when HT and the bisphosphonate risedronate combination was investigated in an 1-year double-blind RCT of 524 postmenopausal women (risedronate [5 mg] plus CEE [0.625 mg/d] or CEE monotherapy).[49] Combination therapy showed a favorable effect on BMD that was similar to that of HT alone at the lumbar spine and slightly, but significantly ($P < .05$), greater than that of HT alone at the femoral neck and mid shaft radius. Bone biopsy specimens showed less pronounced inhibition of remodeling with risedronate and HT.

Taken together, these studies suggest the combination of bisphosphonates and HT could represent an option further to improve bone density among women who do not achieve an adequate response on monotherapy. For those

women who choose lower doses of HT with ongoing significant bone loss or new fracture, the increases in BMD found when low-dose HT is combined with a bisphosphonate may contribute to a reduction in the risk of fracture. The combination appears safe and well-tolerated, although it is important to remember that increased BMD does not fully equate with fracture reduction.

SERMs and estrogen: an option for the future?

Although SERMs act as estrogen agonists in bone and lipid metabolism, they exert an antiestrogenic effect on breast and endometrial tissue.[33-35,50-55] Raloxifene (the Food and Drug Administration–approved SERM for the prevention and treatment of osteoporosis) exerts a modest effect in the prevention and treatment of osteoporosis, with a lesser effect on BMD and reduction of fracture risk than HT and bisphosphonates.[56-58] It has been associated with a small increased incidence of VMS[59-62] and venous thromboembolic events.[56,63] Stovall et al[64] published a small RCT of 149 women with raloxifene (60 mg) added to estrogen (CEE 0.625/MPA 2.5 mg). VMS were not changed from baseline with raloxifene but were decreased significantly in those who received raloxifene + estrogen. BMD data were not obtained. The raloxifene + estrogen group was found to have increased endometrial thickness over placebo (0.74 ± 0.28 mm) at 52 weeks ($P < .05$) with 2 cases of hyperplasia (1 atypical), thus limiting this combination of raloxifene and estrogen.

Third-generation SERMs with potentially improved therapeutic profiles are currently under development. Two new agents, bazedoxifene and lasofoxifene, which are currently in phase III evaluation for the treatment of osteoporosis, have been shown to protect the skeleton similar to raloxifene (albeit with different potency) in animal models. To date, combination studies in the ovariectomized rat have been promising and suggest that SERM treatment may prevent HT-induced endometrial growth and have little effect on HT reduction of VMS, while effectively preventing bone loss.[50,51] The efficacy and safety of these therapies are being tested currently in preclinical and clinical trials.[34,35] If ongoing multicenter trials confirm preclinical findings, then the combination of a SERM and estrogen holds the potential of protecting bones against fractures (estrogen + SERM), alleviating menopausal symptoms (estrogen), and improving the lipid profile (estrogen + SERM), while protecting breast and endometrial tissue (SERM).

Summary of RCT

At the current time, the recommendation is not to combine the anabolic agent PTH with an antiresorptive bisphosphonate because the anabolic response is blunted. Sequential use of a bisphosphonate after PTH is recommended to maintain the BMD gains that would otherwise be lost after discontinuing PTH. Weaker antiresorptive agents, such as raloxifene and HT, that are given concurrently with PTH do not appear to inhibit the anabolic activity of PTH and may be additive on BMD. Many combinations of antiresorptive agents (bisphosphonate + raloxifene or HT) have shown a benefit in bone density over monotherapy in short-term studies. However, the addition of raloxifene to HT revealed endometrial thickening and 2 cases of hyperplasia. New SERMS in testing with preclinical and early clinical studies suggesting stronger antiestrogen effects on the uterus have the potential to combine with estrogen to provide symptomatic relief for hot flashes and yet offer potential bone protection, obviating the need for progesterone therapy with its increased side effects. Calcitonin is a weak antiresorptive agent, and no additive benefit has been found.

Comment

Combination therapy has the potential to improve the therapeutic effect of individual osteoporotic agents. Although moderate gains in BMD have been reported for some combinations of osteoporotic agents (ie, bisphosphonates and HT, bisphosphonate and SERMs) compared with monotherapy, to date, none of the studies have had sufficient power to establish whether antifracture efficacy of combinations is higher than with monotherapy. Indeed, the correlation between the effects that were observed in BMD and fracture risk is not known. More studies with appropriate statistical power are needed but unlikely to occur because of the large numbers of women who are required to show fracture efficacy.

Estrogen is currently the only osteoporotic agent shown to alleviate menopausal symptoms. The ability of future SERMs to exert estrogenic agonistic/antagonistic activity in a tissue-specific manner may allow these agents to improve bone health while protecting uterine and breast tissue. The combination of a SERM and low-dose estrogen could protect bone, alleviate menopausal symptoms, and improve lipid profile without stimulating proliferation of uterine and breast tissue, which could represent a viable alternative for the treatment of younger menopausal women. Controlled clinical trial data will be needed to confirm these effects.

The use of combination therapy for the prevention and treatment of osteoporosis is not often recommended because of cost,[65] the possibility of increased side-effects, and the lack of proven fracture prevention efficacy. However, in our opinion, there may be select women, such as those who have more severe bone loss or who have not achieved an adequate response to monotherapy, those who continue losing significant BMD on therapy or have a new fracture on therapy, who may be considered for combination therapy. In addition, women who receive weaker antiresorptive agents (such as HT for VMS relief or raloxifene for potential breast cancer reduction) may have improved BMD gains (and thus potentially less fracture risk) with combination therapy. If multicenter clinical trials of bazedoxifene and estrogen treatment confirm BMD gains and relief of VMS without the need for progestin therapy for uterine protection, this may be another combination for those women with VMS and bone loss.

Although the definition of "responder" vs "nonresponder/failure" to

osteoporosis treatment may vary, in our opinion, ongoing significant declines in bone density at a threshold of 4%-5% compared with baseline (depending on type of DXA machine and user accuracy) indicates a lack of response. In most clinical trials, some patients sustain an osteoporotic fracture, despite an increase in BMD. In that light, a single new fracture while receiving treatment does not categorize an individual automatically as a nonresponder.

One concern regarding combination therapy is that of "frozen bone," the state of oversuppression of bone remodeling that could result in a paradoxic increase in bone fragility or impair bone healing after a fracture. In general, the reduction in markers of osteoclast and osteoblast function decline by 20%-40% with hormone replacement therapy or SERMs and, to a greater extent (40%-75%), with bisphosphonates. Most studies have documented that both osteoblast and osteoclast markers decline to a similar degree in monotherapy with a bisphosphonate, when compared with combination therapy. Although published combination studies are of inadequate size to assess the full array of osteoporotic fractures, there are no reports in otherwise healthy women with osteoporosis of an excess fracture rate in combination therapy protocols. Data on postcessation BMDs suggest a residual effect of bisphosphonate on maintaining bone turnover suppression, unlike estrogen therapy that appears to lose its beneficial effect on BMD rapidly after cessation. Bone biopsies have not shown adverse effects on histomorphometric features with long-term use of alendronate or risedronate.[66-68] With canine animal models, some evidence of accumulation in microfractures at trabecular sites has been reported.[69,70] In humans, there exists a single publication that reported 9 cases of spontaneous nonspine fractures with delayed healing in patients who received alendronate.[71] Three of the 9 patients were also receiving glucocorticoid therapy, which can itself inhibit osteoblast function while another 3 patients were on a combination of estrogen and alendronate. In the individuals receiving combination therapy, the fracture sites were not typical of osteoporotic fractures, and fracture healing occurred after discontinuation of the bisphosphonate. Combination therapy with PTH and hormone replacement therapy is associated with an increase in bone turnover, compared with hormone replacement therapy alone; hence, adynamic bone should not be a concern in those individuals. With current study results, we believe that adynamic bone remains a potential concern with insufficient data to establish it as either a frequent or a predictable outcome of treatment. However, lacking long-term fracture data and with the concern that oversuppression could be deleterious in a minority of patients, clinicians should be cautious about using combination therapy.

In our practice, in general, we initiate osteoporosis treatment with a single agent, most commonly a bisphosphonate. Thereafter, we follow DXA measurements of bone density. In those patients with ongoing bone loss despite proper dosing, we assess compliance with the medications, adequate calcium intake, vitamin D levels, and participation in strength training or weight-bearing exercise. Work-up for secondary causes includes serum calcium, alkaline phosphatase, total protein, thyroid, vitamin D 25 hydroxy levels, 24-hour urine for calcium, markers of bone turnover, and selected other testing. If the work-up is negative and bone marker indices within the lower one-half of the premenopausal range, we interpret those results as reflecting suppression of bone turnover and continue with monotherapy. For those individuals with high bone turnover, we consider adding a second agent, such as estrogen or a SERM, depending on patient risk. Within 3-6 months, we again measure bone turnover to assess response to treatment. For those patients in whom PTH is considered appropriate, we do not discontinue hormone replacement therapy routinely before PTH. However, we discontinue bisphosphonate before treatment with PTH and restart the bisphosphonate at the completion of the 2-year treatment with PTH. We recognize that there are no long-term fracture data to confirm or disprove our clinical practice and include the patient in discussions about concerns of side effects and oversuppression.

There appear to be ample data to suggest that the combinations of agents that are used in the treatment of the osteoporotic patient may outperform monotherapy, at least for improvements in BMD. Sequential treatment of the anabolic agent PTH by a bisphosphonate appears to maintain the BMD gains from the anabolic therapy. Combining antiresorptive agents such as bisphosphonates, SERMs, and HT may allow added skeletal and nonskeletal benefits if significant side-effects or negative outcomes (such as adynamic bone) are not found. In select cases, consider combination therapy when standard therapy does not appear sufficient. Strategies to optimize treatment with newer agents may well offer an even greater opportunity to tailor therapy specifically for an individual patient. ■

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