



Controversies in Osteoporosis Management: Antiresorptive Therapy for Preventing Bone Loss: When to Use One or Two Antiresorptive Agents?

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Abstract: Women who have significant bone loss or a new fracture on monotherapy are considered for combination therapy. Combination therapies increase bone density more than monotherapy by targeting different parts of the osteoclast pathway. In early postmenopausal women who are symptomatic, the use of combination antiresorptives should include hormone therapy with a bisphosphonate or with bazodoxifene. In women who initially receive a weaker antiresorptive such as the SERM raloxifene, a

combination with bisphosphonates and calcium supplementation is necessary to prevent bone loss. In older women over 65 years of age who often have impaired calcium absorption, the combination of calcitriol with bisphosphonates has been shown to increase bone density more than monotherapy.

Key words: osteoporosis, bisphosphonates, teriparatide, denosumab, SERMs, calcitriol

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Introduction

Osteoporosis is characterized by decreased bone mass, decreased bone strength, and increased risk of fracture.

In most patients the cause is because of bone loss from increased bone resorption that occurs over many years. It is often associated with a decrease in the ability of bone formation to compensate for the volume of bone lost. Usually, the remodeling process of bone formation and resorption are tightly coupled. This means that for each quantum of bone lost from resorption, there is a corresponding replacement of an equal amount of bone. This “uncoupling” of formation and resorption is first clearly evident at the time of the menopause and is due to estrogen deficiency. The menopausal uncoupling in bone leads to an acute calcium loss of about 200 mg/d from bone that declines exponentially over the next 4 to 5 years to 50 mg/d.¹

Monotherapy

For many years, estrogen therapy (ET), or hormone therapy (HT), was the primary treatment for postmenopausal women whether they were symptomatic or not. When prescribed in the right dose, ET/HT completely prevented bone loss and alleviated symptoms.² After the negative publicity concerning the adverse events of HT/ET that followed publication of the WHI study,³ the use of ET/HT was discontinued or doses were reduced. In place of ET or HT, other antiresorptives such as bisphosphonates and SERMs began to be used or usually no treatment was given.

In 2013, we believe that in the early postmenopause, that is, within 5 to 10 years of menopause, ET and HT should still be considered as first-line therapy for preventing bone loss, especially in women who have vasomotor symptoms or vaginal atrophy, whereas SERMs and bisphosphonates do not treat these symptoms. However, in older patients over the age 60 years with osteoporosis or significant osteopenia, bisphosphonates should be the first choice. SERMs are usually a second or third option when neither

estrogen nor bisphosphonates treatments are tolerated.

All postmenopausal women should be advised on lifestyle modifications that reduce the risk of bone loss and fracture such as exercise, adequate protein intake (1 g/kg of body weight), and avoiding risk factors such as smoking and excessive caffeine intake. Women should have a total calcium intake of 1200 mg daily and probably it is better if calcium comes from dietary sources rather than supplements. Vitamin D 800 IU daily is recommended by the Institute of Medicine, certainly in the winter months, but may not be needed in the summer for those who get 5 to 10 minutes of sun exposure 5 days a week.⁴

In women who continue to lose significant bone mass while receiving monotherapy, the use of combination therapy is appropriate and often necessary. This is especially true in those who are on lower doses of estrogen (0.3 mg, 0.45 mg) or those who use weaker antiresorptive agents such as SERMs to prevent breast cancer but which have less potency in preventing bone loss at the hip. In those women who continue to lose bone, secondary causes of bone loss such as thyrotoxicosis or gluten sensitivity as discussed in another chapter need to be investigated. Older women with increased fracture risk or who have fractures on monotherapy may be candidates for combination therapy.

When Should We Consider Using Combination Therapies in the Management of Osteoporosis?

CASE

A 48-year-old woman came into the clinic after being on hormone therapy for 2 years. At her first visit, she complained of moderate vasomotor symptoms. Her weight was 135 pounds and she had a

slender build. She had no risk factors for osteoporosis but as part of her menopausal care, she was offered a bone mineral density (BMD) test by using dual-energy x-ray absorptiometry (DEXA). The result showed a spine *T*-score of -1.8 , which represents moderate osteopenia. Hip BMD was normal. Estrogen treatment was a good option for her management in view of her symptoms and moderate osteopenia. She was started on continuous combined conjugated estrogens (CEE; 0.625 mg) plus medroxyprogesterone acetate (MPA; 2.5 mg daily) and was counseled on a dietary calcium intake of 1200 mg/d. Six months later during follow-up, her symptoms had disappeared and the HT dose was reduced to CEE 0.3 mg plus MPA 1.5 mg daily. At her 2-year visit, the DEXA was repeated and showed a *T*-score of -2.0 . She said that she had been compliant with her hormone therapy and a quick call to her pharmacist confirmed that she consistently picked up her therapy on time. The decrease in spine BMD was 3%, which was a significant decrease. Her insurance will not pay for another DEXA for 2 years, so our options are as follows:

- To continue HT for another 2 years and then repeat the DEXA, cross our fingers, and hope that BMD has stabilized by then.
- Because the antiresorptive effect of estrogen is dose-related, it is possible that she metabolizes estrogen rapidly and actually has a lower plasma estrogen level than expected. Unfortunately, the measurement of plasma estrogens is difficult to interpret in patients on conjugated estrogens. We can increase hormone therapy because higher doses are more antiresorptive; however, her menopausal symptoms have stopped and increasing the estrogen dose to 0.625 mg conjugated estrogens in the current state of opinion may be problematic.
- Stop estrogen and replace it with another antiresorptive agent.

- Continue with estrogen and add a second antiresorptive agent.

Because she is a younger menopausal woman, we opted for the last choice so that she continues to receive the benefits of estrogen. A brief review of studies using monotherapy highlights some of the issues.

Hormone Regimens (HT|ET)

A 2-year randomized controlled study in 822 early postmenopausal women (HOPE trial) evaluated bone loss with low 0.3 mg, medium 0.45 mg, and normal doses 0.625 mg of CEE with or without MPA 1.5 mg for lower and 2.5 mg for higher doses (HT). After 2 years on lower dose ET (0.3 mg), 10% lost bone density at the hip and spine, whereas on higher dose HT (0.625 mg) the number of losers was $<5\%$, indicating that progestin has a synergistic effect with estrogen on bone. Women on higher doses of HT and ET had larger increases in BMD.⁵ Because physicians now try to use lower doses of CEE (0.3 mg) to treat vasomotor symptoms, there will be a higher number of “bone losers.” If it is not possible to measure changes in BMD, then women on low-dose ET should be given a second antiresorptive agent.

Similar findings of estrogen/progestin synergy were evident in the 2-year randomized clinical trial (CHART study) that compared the effect of 4 low doses of a combination of norethindrone (NETA) plus ethinyl estradiol compared with monotherapy-ethinyl estradiol or placebo in 1265 early postmenopausal women with an intact uterus. After 2 years, the combination of norethindrone acetate plus ethinyl estradiol produced a dose-related increase in BMD that was significantly higher when compared with ethinyl estradiol alone.⁶

In early postmenopausal women, besides HT/ET, other monotherapies are available for osteoporosis prevention such as bisphosphonates and SERMS.

In a comparison study of alendronate 5 mg daily against either estradiol 2 mg and norethindrone or conjugated estrogens 0.625 mg plus MPA 2.5 mg, spine BMD increased 3.5% on alendronate and 4% to 5% on estrogen-progestin therapy. However, changes in hip BMD were similar.⁷ Thus, low-dose alendronate is comparable in efficacy to HT and can be combined with lower HT/ET doses to increase more BMD.

SERMs may be prescribed as a first-line therapy in women who are concerned about breast cancer. Their efficacy on bone, particularly at the hip, however, is weak. In a 3-year randomized study of 619 postmenopausal women, mean age 53 years, raloxifene 60 mg/d or 150 mg/d was compared with 0.625 mg/d of conjugated equine estrogen or placebo. At the end of 3 years, there was no increase in spine BMD on raloxifene compared with an increase of 4.6% on CEE 0.625 mg ($P < 0.001$). Hip BMD increased 3.0% on ET and was unchanged on raloxifene, indicating that probably 50% lost bone.⁸ Raloxifene is a weak bone active agent in these early postmenopausal women and always should be given with another antiresorptive agent such as a bisphosphonate.

The following section reviews in detail what we know about studies that tested a combination of different therapies for preventing bone loss.

Combination of Bisphosphonates With Estrogen

Bisphosphonates inhibit bone resorption by binding to hydroxyapatite and reducing osteoclast number and activity. When alendronate is added to HT in postmenopausal women with osteoporosis, there is a significant increase in bone density at both the spine and hip trochanter and the combination is well tolerated. There are 5 major studies that examined this combination on BMD. A total of 428 postmenopausal women with a mean age of 61

years and 15 years from menopause, who were already on HT for at least 1 year, were randomized to receive either alendronate 10 mg/d or placebo for 12 months. The combination of alendronate plus HT compared with HT alone produced significantly greater increases in BMD of the spine (3.6% vs. 1.0%, $P < 0.001$) and the trochanter (2.7% vs. 0.5%, $P < 0.001$). Bone markers decreased more significantly at 12 months on the combination of alendronate plus HT than HT alone.⁹ A 4-arm trial of postmenopausal women with a mean age of 61 years compared the effects of 10 mg alendronate and 0.625 mg ET per day alone or in combination for 24 months, in 425 hysterectomized postmenopausal women.¹⁰ At 24 months, the increase in spine BMD was 6.0% on alendronate monotherapy, 6.0% on ET, and 8.3% on the combination of alendronate and ET ($P < 0.001$); the placebo group showed no change in BMD. Total hip BMD increased 4.0% on alendronate, 3% on ET, and 4.7% on the combination ($P < 0.001$). Femoral neck BMD increased by 2.9%, 2.6%, and 4.2% on alendronate, ET, and the combination, respectively ($P < 0.001$). Similar changes were observed in bone turnover markers, urine Ntx decreased 61%, 52%, and 70% on alendronate, ET, and the combination, respectively ($P < 0.001$).

In a similar 3-year study of 373 postmenopausal women, aged 72 years, spine BMD increased 3.9% on HT, 5% on alendronate, and 7.5% on the combination versus -1.6% on placebo ($P < 0.001$). Total hip BMD increased to 1.5% on HT, 3% on alendronate, 4.3% on the combination versus -2.4% on placebo ($P < 0.001$). For both bone sites the combination was significantly better than monotherapy ($P < 0.001$).¹¹

In a study from China, a combination of alendronate 10 mg daily and an HT dose of 0.625 mg CEE/2.5 mg MPA was compared with placebo for 3 years in 151 postmenopausal women aged 61 years. Spine BMD

increased 10% and femoral neck BMD increased 4.6% on the combination compared with placebo ($P < 0.01$).¹²

In another 1-year, double-blind, placebo-controlled study, 524 postmenopausal women, with a mean age 59 years, were randomized to ET-conjugated equine estrogens 0.625 mg alone or in combination with risedronate 5 mg and calcium 1000 mg. Both therapies led to significant increase in femoral neck BMD at 12 months (1.8% and 2.7%, respectively) and at the trochanter (3.2% and 3.7, respectively), but there was no difference at the spine.¹³

Wimalawansa¹⁴ assessed the effect of HT, etidronate, the combination of HT plus etidronate, or placebo on BMD in 72 postmenopausal women with established osteoporosis. After 4 years, women who received the combined therapy had increased spine BMD of 10.4% ($P < 0.001$) and hip BMD of 7.0% ($P < 0.001$). Patients who received combined therapy had significantly higher BMD in both the spine and femoral neck ($P < 0.05$) in comparison with patients who were treated with HRT or etidronate alone after 4 years.

Taken together, these studies suggest that a combination of bisphosphonates with HT/ET is a valuable option for increasing BMD in women who have an inadequate response to monotherapy, in those who use lower doses of HT/ET, or in those with a higher fracture risk.

Combination of Alendronate With Raloxifene

The combination of bisphosphonates and SERMs has the potential to enhance their individual effect on BMD and fracture risk, given their different modes of action. Alendronate inhibits bone resorption by binding to hydroxyapatite crystals and reducing osteoclast number and activity and

raloxifene acts as an estrogen agonist and decreases osteoclastic resorption activity.

A study compared the effects of combining 60 mg daily raloxifene with 10 mg alendronate with monotherapy in 331 postmenopausal women (from age < 75 to 2 y since menopause) with osteoporosis (femoral neck BMD T -score, < -2). The increase in spine BMD in the combination group was 5.3%, 4.3% on alendronate, and 2% on raloxifene ($P < 0.001$). The combination was not better than alendronate alone. The increase in femoral neck BMD in the combination group was 3.7%, 2.7% on alendronate, and 1.7% on raloxifene ($P < 0.001$); for the hip, the combination was significantly better than either monotherapy.¹⁵

Combination Therapy in Older Women With HRT and Calcitriol

Because there is an age-related decrease in calcium absorption that contributes to negative calcium balance, secondary hyperparathyroidism, and increased bone resorption, calcitriol can be used to increase calcium absorption. In a trial of ET/HT, calcitriol, ET/HT plus calcitriol, or placebo in 489 elderly women aged 71 years for 3 years, all treated groups had significantly higher BMD compared with placebo. The combination group had significantly higher spine BMD of 4.9% compared with 4.4% on HT/ET and 1.65% on calcitriol ($P < 0.0001$). Total hip BMD was -1.8% on placebo, -0.3% on calcitriol, 3.14% on HT/ET, and 5.35% on the combination. The combination was significantly more effective on the hip ($P < 0.001$).¹⁶

Combination of Bisphosphonates and Calcitriol

A study compared the effects of intermittent cyclical etidronate therapy alone with

a combination of cyclical etidronate and calcitriol on spine and femoral neck BMD at 1-year in postmenopausal women with at least 1 nontraumatic vertebral fracture or Z-score < -1.5. The increase in lumbar spine BMD was 5.2% in the combination group and was significantly greater than 2.7% in etidronate group alone ($P < 0.036$). Femoral neck BMD in the combination group increased 2.0% compared with -0.4% on etidronate alone ($P = 0.046$).¹⁷ In another Italian study, it was shown that continuous treatment for 9 months with calcitriol or calcium in combination with alendronate significantly increased both spine and femoral neck BMD from 3.8% to 4.5% and from 0.61% to 2.36%, respectively, in osteopenic postmenopausal women.¹⁸

Combination of HT|ET With Calcium

In a meta-analysis, Nieves et al¹⁹ showed that women treated with estrogen and supplemental calcium (total calcium 1183 mg/d) had a spine BMD that was 2% higher than estrogen-treated women who were unsupplemented (calcium 563 mg/d). Similarly, femoral neck BMD was 1.5% higher in the calcium supplemented group.

Combination of SERMS and Estrogen [Tissue-Selective Estrogen Complex (TSEC)]

A new concept is the TSEC, a combination of estrogen with SERM. An ideal TSEC will provide the same clinical benefits as ET and EPT but with an improved safety and tolerability profile. The therapeutic profile of a TSEC would optimally include relief of hot flashes, treatment of vulvo-vaginal atrophy and its symptoms, and prevention of bone loss, while providing safety for the endometrium and breast. Recent data

indicate that the TSEC containing the SERM bazedoxifene (BZA) and conjugated estrogens relieves hot flashes, improves vulvo-vaginal atrophy and its symptoms, and prevents loss of bone mass without stimulating the endometrium with a good safety and tolerability profile.

The effect of different doses of BZA and conjugated estrogens on spine BMD were compared to placebo and Raloxifene in women within 1-5 years of menopause in a 2 year trial,²⁰ All Bazedoxifene/CEE doses significantly increased spine and hip BMD more than raloxifene or placebo ($P < 0.001$). The optimum combination for uterine protection and effect on BMD appears to be conjugated equine estrogens 0.625 mg and 0.45 mg combined with bazedoxifene 20 mg.

Discussion

In our practice, in general, we initiate osteoporosis treatment with a single agent. However, much depends on follow-up of BMD or the availability of DEXA. In an ideal world, bone density should be reevaluated at least after 2 years and if the BMD is stable or increased, then recheck after 5 eling years. If BMD declines at the 2-year timepoint, then a combination agent should be added and BMD should be rechecked after 1 year to assess the response. If stable, then BMD is rechecked at 5 years. In those patients with ongoing bone loss and good medication compliance, it is important to review the intake of calcium (1200 mg), vitamin D (600 to 800 IU, especially in winter), and exercise. For women who are losing bone, the practitioner should always consider secondary causes of bone loss, for example, thyroid hormone, smoking, excessive caffeine intake, and high alcohol intake. Once the secondary bone loss is ruled out or is confirmed, one should consider adding a second antiresorptive agent.

In the prevention and treatment of osteoporosis, the use of combination therapy is not often recommended because of cost, 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, and those who may be considered for combination therapy. A concern with regard to combination therapy is the possible development of “frozen bone” because of over suppression of bone remodeling that might result in a paradoxical increase in bone fragility or impaired bone healing after fracture. This is a theoretical concern; however, there are no reports of impaired fracture healing. Bone biopsies from women on denosumab, which is the most potent of the antiresorptive drugs, show marked suppression of bone remodeling as demonstrated by lack of tetracycline labeling, yet fracture reduction after 8 years persists.²¹

In women who want to use low-dose estrogen of 0.3 mg or 0.45 mg, which have less efficacy on bone than the higher dose of 0.625 mg, it is recommended to add other antiresorptive agent such as a bisphosphonate to preserve the BMD and increase the bone strength. Women who are treated with a less potent antiresorptive agent such as raloxifene that has a high failure rate on preventing bone loss at the hip should always add another bone active agent such as bisphosphonates that has been evaluated. The TSEC is another option that looks promising from an overall clinical perspective and is presently under review by the FDA.

Combination therapies have shown significant increases in BMD when compared with monotherapies. None of the combinations have performed studies on fracture prevention. However, these

combinations prevent bone loss by 50% to 60% and increase BMD that is very likely to decrease fracture risk.

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