Published in final edited form as:

Clin Obstet Gynecol. 2013 December ; 56(4): 749–756. doi:10.1097/GRF.0b013e3182a982c2.

Anti-resorptive therapy for preventing bone loss: When to use one or two anti-resorptive agents?

J Christopher Gallagher, MD* and Sri Harsha Tella, MD#

* Department of Endocrinology, Creighton University School of Medicine 601 N 30th St, Suite 6718 Omaha, NE-68131

Department of Internal Medicine, Creighton University School of Medicine 601 N 30th St, Suite 6718 Omaha, NE-68131

Abstract

Women who have significant bone loss or a new fracture on monotherapy are considered for combination therapy. Combination therapies increases bone density more than mono-therapy by targeting different parts of the osteoclast pathway.

In early post-menopausal women who are symptomatic the use of combination anti resorptives should include hormone therapy with a bisphosphonate or with bazodoxifene. In women who initially receive a weaker anti-resorptive such as the SERM raloxifene, then a combination with bisphosphonates and calcium supplementation is necessary to prevent bone loss. In older women over 65 years who often have impaired calcium absorption, the combination of calcitriol with bisphosphonates has been shown to be increase bone density more than monotherapy.

Introduction

Osteoporosis is characterized by decreased bone mass, decreased bone strength and increased risk of fracture. In most patients the cause is due to 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 200mg /day from bone that declines exponentially over the next 4-5 years to 50mg/day (1).

* Corresponding author Phone: 402-280-4518 Fax: 402-280-4517 jcg@creighton.edu.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Mono-therapy

For many years estrogen therapy (ET), or hormone therapy (HT), was the primary treatment for post-menopausal 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 anti-resorptives such as bisphosphonates and SERMs began to be used, or usually no treatment was given.

In 2013 we believe that in the early post-menopause, i.e. within 5-10 years of menopause, estrogen therapy (ET) and hormone therapy (HT) should still be considered 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 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 (1gm/ kg of body weight), and avoiding risk factors such as smoking and excessive caffeine intake. Women should have a total calcium intake of 1200mg/daily and probably it is better if calcium comes from dietary sources rather than supplements. Vitamin D, 800 IU daily as recommended by the Institute of Medicine, certainly in the winter months, but may not be needed in the summer for those who get 5-10 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 anti-resorptive 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 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 women comes into the clinic after 2 years on hormone therapy. 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 density (BMD) test by DEXA (dual energy X ray absorptiometry). 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) 0.625mg plus medroxyprogesterone

acetate (MPA) 2.5mg daily and counseled on a dietary calcium intake of 1200mg/day. Six months later in follow up her symptoms had disappeared and the HT dose was reduced to CEE 0.3mg plus MPA 1.5mg 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 percent, a significant decrease. Her insurance will not pay for another DEXA for 2 years, so our options are

- to continue hormone therapy for another 2 years and then repeat the DEXA, cross our fingers and hope that BMD has stabilized by then
- Because the anti resorptive 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 anti resorptive, however her menopausal symptoms have stopped and increasing the estrogen dose to 0.625mg conjugated estrogens in the current state of opinion may be problematic.
- Stop estrogen and replace with another anti-resorptive agent
- Continue with estrogen and add a second anti-resorptive 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 two year randomized controlled study in 822 early post-menopausal women (HOPE trial) evaluated bone loss with low 0.3mg, medium 0.45mg, and normal doses 0.625mg of CEE with or without MPA 1.5mg for lower and 2.5 mg for higher doses (HT). After 2 years on lower dose ET 0.3mg, 10 % lost bone density at the hip and spine whereas on higher dose HT 0.625 mg the number of losers was less than 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 0.3mg 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 anti-resorptive 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 post-menopausal 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 than with ethinyl estradiol alone (6).

In early post-menopausal women besides HT/ET, other mono-therapies are available for osteoporosis prevention such as bisphosphonates and SERMS. In a comparison study of

Alendronate 5 mg daily against either estradiol 2mg and norethindrone or conjugated estrogens 0.625mg plus MPA 2.5mg, spine BMD increased 3.5 % on alendronate and 4-5 % 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 post-menopausal women, mean age 53 years, raloxifene 60 mg/d or 150 mg/d was compared to 0.625 mg/d of conjugated equine estrogen or placebo. At end of 3 years, there was no increase in spine BMD on Raloxifene compared to an increase of 4.6% on CEE 0.625mg ($P < .001$). Hip BMD increased 3.0% on ET and was unchanged on raloxifene indicating that probably 50 percent lost bone (8). Raloxifene is a weak bone active agent in these early post-menopausal women and always should be given with another anti-resorptive 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 post-menopausal 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 post-menopausal women with mean age of 61 years and 15 years from menopause, who were already on HT for at least one year, were randomized to receive either alendronate 10 mg/day 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 four arm trial of post-menopausal women of mean age 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 post-menopausal 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 noted 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 post-menopausal women, age 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 1.5% on HT, 3% on alendronate, 4.3% on the

combination versus -2.4% on placebo ($P < .001$). 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 HT 0.625 CEE/2.5 mg MPA was compared to 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 ($P < .01$) (12).

In another 1-year, double blind, placebo-controlled study, 524 postmenopausal women, 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 increases 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)

Wimalawansa SJ et al (14) assessed HT, etidronate, the combination of HT plus etidronate or placebo on BMD in 72 post-menopausal women with established osteoporosis. After 4 years, women who received the combined therapy increased spine BMD 10.4% ($P < 0.001$) and hip BMD 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 of the effects of combining 60 mg daily Raloxifene with 10 mg Alendronate compared to monotherapy in 331 postmenopausal women (from age <75 to 2 years since menopause) with osteoporosis (femoral neck BMD T-score, less than -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 age 71 years for 3 years, all treated groups had significantly higher BMD than placebo. The combination group had significantly higher spine BMD 4.9% compared to 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 bone mineral density (BMD) at one year in post-menopausal women with at least one non-traumatic 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 to -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 al, showed that women treated with estrogen and supplemental calcium (total calcium 1183mg/d) had a spine BMD that was 2 percent higher than estrogen treated women that were unsupplemented (calcium 563mg/d). Similarly femoral neck BMD was 1.5% higher in the calcium supplemented group (19).

Combination of SERMS and Estrogen (TSEC-Tissue selective estrogen complex)

A new concept is the TSEC, a combination of estrogen with a SERM. An ideal TSEC will provide the same clinical benefits of 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 0.625mg and 0.45mg combined with bazedoxifene 20mg.

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 BMD is stable or increased then recheck after 5 elingyears. If BMD declines at the 2 year time point then a combination agent should be added and BMD re checked after one year to assess the response. If stable, then recheck BMD at 5 years. In those patients with ongoing bone loss and good medication compliance, it is important to review the intake of calcium (1200mg), vitamin D (600-800IU, especially in winter) and exercise. For women who are losing bone, the practitioner should always consider secondary causes of bone loss e.g 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 anti resorptive 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, who may be considered for combination therapy. A concern regarding combination therapy is 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 that is the most potent of the anti resorptive 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 doses of 0.3 mg or 0.45 mg, that have less efficacy on bone than the higher dose of 0.625 mg, it is recommended to add other anti-resorptive agent such as a bisphosphonate to preserve the BMD and increase bone strength. Women who are treated with a less potent anti-resorptive 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 tissue-selective estrogen complex (TSEC), is another option that looks promising from an overall clinical perspective is presently under review by the FDA.

Combination therapies have shown significant increases in BMD when compared to 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.

References

1. Gallagher JC, Goldgar D, Moy A. Total Bone Calcium in Normal women: Effect of Age and Menopause Status. *J Bone Min Res.* 496; 2(6):491–496.

2. Lindsay R, Gallagher JC, Kleerekoper M, Pickar JH. Effect of lower doses of conjugated equine estrogens with and without medroxyprogesterone acetate on bone in early postmenopausal women. *JAMA*. 2002; 287:2668–2776. [PubMed: 12020302]
3. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002; 288:321–333. [PubMed: 12117397]
4. Institute of Medicine. Dietary reference intakes for calcium and vitamin D. The National Academies Press; Washington, DC: 2011.
5. Lindsay R, Gallagher JC, Kleerekoper M. Bone response to treatment with lower doses of conjugated estrogens with and without medroxyprogesterone acetate in early postmenopausal women. *Osteoporos Int*. Apr; 2005 16(4):372–9. [PubMed: 15654581]
6. Speroff L, Rowan J, Symons J, Genant H, Wilborn W. The comparative effect on bone density, endometrium, and lipids of continuous hormones as replacement therapy (CHART study). A randomized controlled trial. *JAMA*. Nov 6; 1996 276(17):1397–403. [PubMed: 8892714]
7. Hosking D, Chilvers CE, Christiansen C, Ravn P, Ross P, McClung M, Balske A, Daley M, Yates AJ. Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. Early Postmenopausal Intervention Cohort Study Group. *N Engl J Med*. Feb 19; 1998 338(8):485–92. [PubMed: 9443925]
8. Reid IR, Eastell R, Fogelman I, Adachi JD, Rosen A, Netelenbos C, Watts NB, Seeman E, Ciaccia AV, Draper MW. A comparison of the effects of raloxifene and conjugated equine estrogen on bone and lipids in healthy postmenopausal women. *Arch Intern Med*. Apr 26; 2004 164(8):871–9. [PubMed: 15111373]
9. Lindsay R, Cosman F, Lobo RA, Walsh BW, Harris ST, Reagan JE, Liss CL, Melton ME, Byrnes CA. Addition of alendronate to ongoing hormone replacement therapy in the treatment of osteoporosis: A randomized, controlled clinical trial. *J Clin Endocr Metab*. 1999; 84:3076–3081. [PubMed: 10487668]
10. Bone HG, Greenspan SL, McKeever C, Bell N, Davidson M, Downs RW, Emkey R, Meunier PJ, Miller SS, Mulloy AL, Recker RR, Weiss SR, Heyden N, Musliner T, Suryawanshi S, Yates AJ, Lombardi A. Alendronate and Estrogen Effects in Postmenopausal Women with Low Bone Mineral Density. *J Clin Endocrinol Metab*. Feb; 2000 85(2):720–6. [PubMed: 10690882]
11. Greenspan SL, Resnick NM, Parker RA. Combination therapy with hormone replacement and alendronate for prevention of bone loss in elderly women: A randomized, controlled trial. *JAMA*. 2003; 289:2525–2533. [PubMed: 12759324]
12. Tseng LN, Sheu WH, Ho ES, Lan HH, Hu CC, Kao CH. Effects of alendronate combined with hormone replacement therapy on osteoporotic postmenopausal Chinese women. *Metabolism*. 2006; 55:741–747. [PubMed: 16713432]
13. Harris ST, Eriksen EF, Davidson M, Ettinger MP, Moffett AH Jr, Baylink DJ, Crusan CE, Chines AA. Effect of combined risedronate and hormone replacement therapies on bone mineral density in postmenopausal women. *J Clin Endocrinol Metab*. May; 2001 86(5):1890–7. [PubMed: 11344179]
14. Wimalawansa SJ. A four-year randomized controlled trial of hormone replacement and bisphosphonate, alone or in combination, in women with postmenopausal osteoporosis. *Am J Med*. Mar; 1998 104(3):219–26. [PubMed: 9552083]
15. Johnell O, Scheele WH, Lu Y, Reginster JY, Need AG, Seeman E. Additive effects of raloxifene and alendronate on bone density and biochemical markers of bone remodeling in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab*. 2002; 87:985–992. [PubMed: 11889149]
16. Gallagher JC, Fowler S, Sherman SS. Combination treatment with Estrogen and Calcitriol in the prevention of Age-Related Bone Loss. *J.Clin.Endocrinol.Metab*. 2001; 86:3618–3628. [PubMed: 11502787]
17. Masud T, Mulcahy B, Thompson AV, Donnelly S, Keen RW, Doyle DV, Spector TD. Effects of cyclical etidronate combined with calcitriol versus cyclical etidronate alone on spine and femoral neck bone mineral density in postmenopausal osteoporotic women. *Ann Rheum Dis*. Jun; 1998 57(6):346–9. [PubMed: 9771208]

18. Malavolta N, Zanardi M, Veronesi M, Donnelly S, Keen RW, Doyle DV, Spector TD. Calcitriol and alendronate combination treatment in menopausal women with low bone mass. *Int J Tissue React.* 1999; 21(2):51–9. [PubMed: 10568224]
19. Nieves JW, Komar L, Cosman F, Lindsay R. Calcium potentiates the effect of estrogen and calcitonin on bone mass: review and analysis. *Am J Clin Nutr.* Jan; 1998 67(1):18–24. [PubMed: 9440370]
20. Lindsay R, Gallagher JC, Kagan R, Pickar JH, Constantine G. Efficacy of tissue-selective estrogen complex of bazedoxifene/conjugated estrogens (BZA/CE) for osteoporosis prevention in at-risk postmenopausal women. *Fertil Steril.* 2009; 92:1045–1052. R. [PubMed: 19635616]
21. Reid IR, Miller PD, Brown JP, Kendler DL, Fahrleitner-Pammer A, Valter I, Maasalu K, Bolognese MA, Woodson G, Bone H, Ding B, Wagman RB, San Martin J, Ominsky MS, Dempster DW. Effects of denosumab on bone histomorphometry: the FREEDOM and STAND studies. *J Bone Miner Res.* Oct; 2010 25(10):2256–65. [PubMed: 20533525]