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Osteoporosis: Combination therapy for better or worse

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Abstract

Osteoporosis is a condition that is associated with an increased susceptibility for fractures. In the past few years, several drugs have become available that can reduce the incidence of fractures in patients with osteoporosis. Since these drugs work through different cellular mechanisms, combining agents of different classes may have an additive or multiplicative effect on fracture risk reduction. Combination treatments that have been evaluated in clinical trials include bisphosphonates with estrogen, raloxifene or PTH/ bisphosphonates and PTH/ estrogen. In general, these trials have shown increases in bone mineral density over that observed with each agent alone. However, whether anti-fracture efficacy is improved, or worsened remains to be established. This article reviews the combination treatments that have been evaluated in clinical trials, with a discussion of the potential benefits and risks that those treatments entail. Integrating safety and cost issues will eventually determine whether those combinations will become the standard of care.

Introduction

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture[1]. Bone is remodeled throughout life, and the rate of remodeling is increased in older adults. At the cellular level, bone remodeling occurs at discrete foci in the skeleton called bone-remodeling units. Bone remodeling proceeds in an orderly fashion, with bone resorption (by osteoclasts) always being followed by bone formation (by osteoblasts), a phenomenon referred to as coupling. At the cellular level, bone loss results from an imbalance in the bone remodeling unit (this could be due to a change in the lifespan, production and/or activity of osteoblasts and osteoclasts)[2].

Estrogen was recommended for years for bone density maintenance in postmenopausal osteoporosis. In recent years, other pharmacological agents that maintain or improve bone density have been developed for the prevention and treatment of osteoporosis. These drugs can be grouped into those that decrease bone resorption, and those

that increase bone formation[3]. Antiresorptive drugs include estrogens, selective estrogen receptor modulators (SERMs), bisphosphonates and calcitonin. In contrast to drugs that slow bone turnover, anabolic agents directly stimulate bone formation. These drugs include parathyroid hormone (PTH), growth hormone (GH), and sodium fluoride.

Combination treatments

Combination treatments were first used in microbiology. When two antimicrobial agents are combined, they may have one of three types of activity against a given organism *in vitro*: (1) an additive effect, (2) synergism, or (3) antagonism. Two drugs are said to be additive when the activity of the drugs in combination is equal to the sum (or a partial sum) of their independent activities when studied separately. The combined effect of a synergistic pair of agents is greater than the sum of their independent activities when measured separately. If two drugs are antagonistic, the activity of the combination is less than the sum of their independent effects when measured alone[4]. The concepts of synergism and antagonism are nowadays applied to other types of combination treatments. Sequential therapy involves the use of two agents in sequence (one after the other). Combination drug therapy is currently used in several disease states, from hypertension to cancer, congestive heart failure, asthma and many more. Osteoporosis is another condition where sever-

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al combinations of treatments have been tried. These will be discussed in the following section.

Estrogen/bisphosphonates

Estrogens and bisphosphonates seem to be the two most widely used medications for the prevention and treatment of osteoporosis in the US. A number of studies using a combination of those two classes of agents have been published.

The first of those trials, published in 1995, studied the combination of cyclical etidronate with percutaneously administered hormonal replacement therapy (17β-estradiol)[5]. The study followed 58 early postmenopausal women who were not osteoporotic for 4 years. All women received 1 g of elemental calcium daily. The effect of the combined treatment was additive in increasing the bone mineral density significantly as compared to the use of a single agent alone in the vertebrae (p <0.05), and in the hip (p <0.01) over 4 years. Three of nine patients treated on cyclical etidronate and calcium developed osteomalacia.

The second trial, published by the same author in 1998[6], followed 72 postmenopausal women with established osteoporosis for 4 years. All women received elemental calcium (1 g/d) and vitamin D (400 U/d) and then were randomly allocated into one of four treatment groups: The HRT group (n=18) received oral cyclical estrogen and progesterone; the etidronate group (n=17) received 400 mg oral etidronate daily for 14 days every 12 weeks; the combined therapy group (n=19) received HRT and etidronate; and the control group (n=18) received only calcium and vitamin D. Fifty-eight of 72 subjects (80%) completed the study. In patients who received the combined therapy, BMD increased in the lumbar spine by 10.4% (p <0.001) and in the hip by 7.0% (p <0.001) at 4 years. Patients who received combined therapy had significantly higher BMD in both the vertebrae and in the femoral neck (p <0.05) in comparison with patients who were treated with HRT or etidronate alone after 4 years. Height loss was significantly less in the combined therapy group, in comparison with the HRT (p <0.02) and the etidronate (p <0.001) groups.

Those two trials had small sample sizes, and used etidronate, a bisphosphonate that is no longer routinely used in the management of osteoporosis. Nevertheless, both studies showed an additive effect of etidronate and HRT on hip and bone BMD in postmenopausal women.

The effects of alendronate at a dose of 10 mg/d and conjugated equine estrogens (CEE) at a dose of 0.625 mg/d alone and in combination were studied in a 2-year trial of 425 hysterectomized postmenopausal women[7]. All women received a supplement of 500 mg elemental calcium daily. 75.3% of the subjects completed the study, and the combination was well tolerated. The alendronate plus CEE produced slightly greater decreases in markers of bone turnover (urinary N-telopeptide of type I collagen (NTX) and serum bone-specific alkaline phosphatase) than with either treatment alone, but the mean values remained within the normal premenopausal range. At two years, lumbar spine BMD was increased by 6.0% in the estrogen alone and alendronate alone groups and by 8.3% in the combined therapy group. Femoral neck BMD was increased by 2.6% in the estrogen group, 2.9% in the alendronate group, and 4.2% in the combination therapy group. The BMD increases relative to baseline seen in the combination group at both the lumbar spine and femoral neck were significantly greater than those in either the alendronate (p < 0.001 and p = 0.022, respectively) or CEE (p < 0.001 and p = 0.003, respectively) group. The trial was not powered to study the effect on fracture risk. The incidence of clinical fractures was 8% in the placebo group compared with 5%, 7%, and 6% in the alendronate, estrogen, and combination groups, respectively (differences were not statistically significant). In the subset of patients who underwent bone biopsy, histomorphometry showed no change in the mineral apposition rate. A decrease in osteoid thickness and volume (indicating a decrease in bone turnover) was seen in the treatment groups compared to placebo and was significantly more pronounced in the combination group. The authors did note the absence of tetracycline label in cancellous bone in 3 of the 92 biopsies, all belonging to patients in the combination group.

A second study from Turkey[8] randomized 95 young postmenopausal women with osteoporosis to either alendronate 10 mg/d, 17ß-estradiol, or both. At the end of 12 months, increases in spinal BMD were significantly higher in the alendronate and combination groups compared to the HRT alone group. There was no significant difference at the femoral neck BMD changes between all three groups after one year of treatment.

The effects of adding alendronate (10 mg/d) or placebo to estrogen were also examined in a 1-year study of 428 postmenopausal women who were already receiving ongoing HRT for at least 1 year[9]. All participants were required to have a T-score of <-2 for the lumbar spine BMD. Vitamin D supplements (400 IU) were given to all subjects, and calcium was added only in those women whose baseline intake was less than 1000 mg per day. Ninety-two percent of the patients completed the trial. Biochemical markers of bone turnover were significantly decreased in the HRT/alendronate group, but remained within premenopausal levels. Lumbar spine BMD was increased by 1% in the HRT/placebo group and by 3.6% in the HRT/alendronate group (p <0.001). Femoral neck BMD was increased by 0.8% in the HRT/placebo group and by 1.7% in the HRT/alendronate group (Figure 6). The difference in change in femoral neck BMD at 12 months was not significant (p = 0.072). In the HRT/alendronate group, 15 women (7%) had fractures compared with 9 women (4.2%) in the HRT/placebo group, but this was not statistically different. There was also no statistically significant increase in upper gastrointestinal side effects.

Only one published study has examined the effect of combining risedronate with HRT[10]. This was a one-year, double-blind, placebo-controlled study, in which 524 postmenopausal women received daily treatment with conjugated equine estrogens (0.625 mg) alone or in combination with risedronate (5 mg). All women received 1 g of elemental calcium daily, and vitamin D was supplemented in those with low 25-hydroxyvitamin D lev-

els. Most (76%) women had undergone menopause over 5 years before study entry. Seventy-three percent of patients completed the study. At 12 months, both groups had significant decreases in the biochemical markers of bone turnover, with somewhat greater decreases on combination. The difference between the HRT-only and the combined risedronate-HRT groups was statistically significant (p <0.05) only at the femoral neck (1.8% and 2.7%, respectively), but not in lumbar spine BMD (HRT-only: 4.6%, combined risedronate-HRT: 5.2%), femoral trochanter (3.2% and 3.7%), and distal radius (1.7% and 1.6%). At 12 months, new vertebral fractures were found in 4 of 155 (2.6%) patients with invaluable radiographs in the HRT-only group, and in 3 of 168 (1.8%) patients in the combined risedronate-HRT group. The difference between the two groups was not statistically significant (p = 0.625). One non-traumatic nonvertebral fracture occurred by 12 months, in a woman from the HRT-alone group. Bone biopsies done in 47 women (24 from the HRT-only group and 23 from the risedronate-HRT group) were analyzed after 12 months of treatment. No mineralization abnormalities were found as demonstrated by the unchanged mineral apposition rate from baseline. Activation frequency and osteoid surface, both markers of bone turnover at the tissue level, decreased from baseline biopsies in both groups, but did so to a significantly larger extent in the combination group. Cancellous tetracycline label was found in all biopsy specimens in the risedronate-HRT group, and in all but one specimen in the HRT-alone group.

Raloxifene/bisphosphonate

The effects of 60 mg/d raloxifene and 10 mg/d alendronate, alone or in combination, were studied in a 1-year trial of 330 postmenopausal women[11]. Lumbar spine BMD was increased in the raloxifene group by 2%, in the alendronate group by 4.3%, and in the raloxifene/alendronate group by 5.2% (no statistically significant difference between the combination therapy and individual agents). Femoral neck BMD was significantly increased in the raloxifene group by 1.4%, in the alendronate group by 2.4%, and in the raloxifene/alendronate group by 3.4%. The increase in femoral neck BMD was statistically greater in the raloxifene + alendronate group compared with the alendronate alone group (p <0.05).

Despite their great value, antiresorptive drugs are generally not associated with dramatic increases in bone mass, while anabolic therapy, in which bone formation is directly stimulated, lead to larger bone mass increases. Thus, newer approaches to combination therapy with antiresorptive and anabolic agents have been evaluated. These will be discussed in the following section.

PTH/estrogen

A study has examined the combination of simultaneous hormone replacement therapy and PTH[12]. The participants were postmenopausal osteoporotic women who had been taking hormone replacement therapy for at least 2 years and who were randomized so that 27 received hPTH-(1-34) (recombinant human PTH peptide 1-34) plus estrogen and 25 received estrogen alone for 3 years. During the first 6 months of PTH treatment, serum osteocalcin increased by more than 50%, while urinary N-telopeptide increased by 20%. After 6 months, both markers had similar increases and gradually returned to baseline. The patients in the PTH group had a continuous, significant increase in vertebral bone mineral density over the 3 years of the study, reaching 13.4%, while the control group had no significant change in vertebral bone mineral density. There was only a modest gain of 4.4% in the total hip BMD for the PTH-treated patients, with no significant decline in the estrogen-treated patients. Using the 15% height reduction cut point, PTH reduced the percent of women who had incident vertebral fractures from 37.5% to 8.3% (p <0.02). As the patients were already taking estrogen for over two years prior to the addition of PTH, the largest gain in BMD with hormone replacement therapy is likely to have taken place prior to randomization. Thus, this trial was not a concurrently conducted comparison of the combination therapy with either agent alone, but it only showed that adding PTH to ongoing estrogen is likely to produce greater gains than with continuing estrogen alone. It is also not possible to conclude whether PTH alone would improve BMD more than the combination of PTH with estrogen.

PTH/bisphosphonates

The effect of the combination of PTH and alendronate was not directly compared to each agent alone in any published trial, and simultaneous treatment with PTH and alendronate has not been reported. Only one trial has examined using these agents sequentially[13]: At the conclusion of a 1-year, placebo-controlled study in postmenopausal women with daily sc injections of PTH-(1-84) at three doses (50, 70, and 100 mcg) versus placebo, a small subset of patients (n = 66) were treated with 10 mg open-label alendronate daily for the following year. Patients were supplemented with 500 mg of elementary calcium and 400 IU of vitamin D. All markers of bone turnover increased during treatment with PTH and decreased to below baseline after one year of alendronate. After the first year of PTH therapy, there were no significant changes in femoral neck BMD, but increases of 6.9% and 9.2% were noted at the spine BMD in the patients who received the two highest doses of PTH. The investigators observed further increases of up to 14% in spinal bone mass during the subsequent year of treatment with alendronate in the group that had previously received the highest dose of PTH. Although they observed a trend in improved hip bone mass compared with baseline, this was not statistically significant at two of the doses of PTH after 2 years of this sequential therapy. Whole body BMD decreased after the first year of therapy with PTH, but did improve after the year of alendronate therapy.

In an accompanying editorial[14], the authors wonder whether this sequential therapy is a potential trade-off where loss of cortical bone at some sites leads to the improvement in vertebral bone mass– "Robbing Peter to pay Paul". This sequential therapy of PTH followed by alendronate, has not been compared to a single antiresorptive agent, such as alendronate alone, that could significantly improve hip bone mass after 2 years. The question of whether anti-resorptive therapy should be given before, during or after PTH remains to be answered, but this trial seems to suggest a potential benefit of using a bisphosphonate after treatment with PTH, to maintain the gain in bone density.

GH/bisphosphonates

A randomized controlled trial in 18 osteoporotic adult GH-deficient (GHD) patients assessed whether additional treatment with a bisphosphonate would further favorably influence parameters of bone turnover and bone mineral density measurements (BMD)[15]. All patients were receiving stable recombinant human (rhGH) replacement therapy for 4 years at the start of the study. Eighteen GHD patients with osteoporosis were randomized to continue their rhGH maintenance dose or to receive combination therapy with rhGH and alendronate for 12 months. All patients were calcium and vitamin replete, and there were no changes in hormone replacement therapy for the duration of the study. In the alendronate group, all measured parameters of bone turnover significantly decreased after 6 months, with no further decrease thereafter. No changes were observed in the control group. In the alendronate group, lumbar spine BMD increased significantly from baseline by 3.4% at 6 months (p = 0.001) and by 4.4% at 12 months (p <0.001) of treatment, with no further significant increase between 6 and 12 months (p = 0.217). No changes in lumbar spine BMD were observed in the control group. There were no significant changes in femoral neck BMD in either group for the duration of the study. No incident vertebral or peripheral fractures were documented in either group at the end of the study.

Prior studies on combination GH with bisphosphonate treatment suggested that the GH treatment negated[16] or did not enhance[17] any BMD response to the bisphosphonate. Despite the small number of patients in this study, the data indicate a beneficial effect of bisphosphonates in GH-deficient patients with osteoporosis maintained on hGH replacement.

GH/calcitonin

Another study has looked at the possible effect of growth hormone and calcitonin on 84 osteopenic but otherwise healthy postmenopausal women[18]. At two years, groups receiving GH plus calcitonin (CT), and GH plus placebo increased lumbar spine BMD from baseline by 2.70±0.81% (p <0.01) and 1.72±0.74% respectively (p <0.05; intention

to treat analysis). No significant change in femoral neck BMD was observed in any group. These gains were less marked than those achieved with estrogen or bisphosphonates and were associated with a relatively high incidence of adverse experiences, making it even less likely that cyclic GH with or without antiresorptive agents will prove clinically useful in the treatment of postmenopausal women with osteoporosis.

Summary of trials on combination therapy in osteoporosis

A summary of the major trials using combination treatment for osteoporosis is presented in Figure 1. Although it is known that estrogen, bisphosphonates and calcitonin increase bone mass by decreasing bone resorption, these agents seem to act by different mechanisms: Estrogen may increase calcium absorption. In addition, current evidence suggests that estrogen blocks cytokines in the bone microenvironment that increase formation of osteoclasts and extend their lifespan[19,20]. On the other hand, bisphosphonates exert their effect on resorption primarily through alterations in the structure and function of the osteoclast, and possibly by promotion of osteoclast apoptosis[21,22]. Calcitonin inhibits the development of osteoclast precursors and decreases committed pre-osteoclasts fusion to form multinucleated cells[23]. Thus, the use of two antiresorptive agents may produce greater inhibition of osteoclastic activity, leading to a larger suppression of bone turnover. Bone turnover rates, which are elevated in postmenopausal women, are reduced to rates within the range seen in healthy premenopausal women when estrogen, bisphosphonates, or raloxifene are given individually.

Studies combining these agents have demonstrated decreases in markers of turnover larger than those seen with individual agents, suggesting a greater suppression of bone resorption. Bone biopsies support this finding. Microdamage in the form of microscopic cracks that average 30-80 μm in cross-sectional length occurs in bone secondary to physiological repetitive loading during daily activity. The accumulation of microcracks in bone leads to reduced strength, and microdamage may increase the risk of fatigue fractures, and is implicated in the increased susceptibility of older bone to fracture. Microdamage is normally repaired through physiologic remodeling processes by replacing damaged bone with new bone. Indirect evidence suggests that extremely low bone turnover rates may produce detrimental consequences in the bone, leading to an increased fracture incidence[24]. Trials on combination therapy have shown increases in BMD over what occurs with each agent. The magnitude of the increased difference is not significant at some sites in some studies, and is relatively small, less than 2% after 1 year of therapy. The effect of these anti-resorptive combinations on BMD, as seen in these studies, was not truly additive and certainly not synergistic. Finally, none of these studies has shown a significant difference in subsequent fracture incidence when a bisphosphonate is given in addition to estrogen, compared with each agent alone.
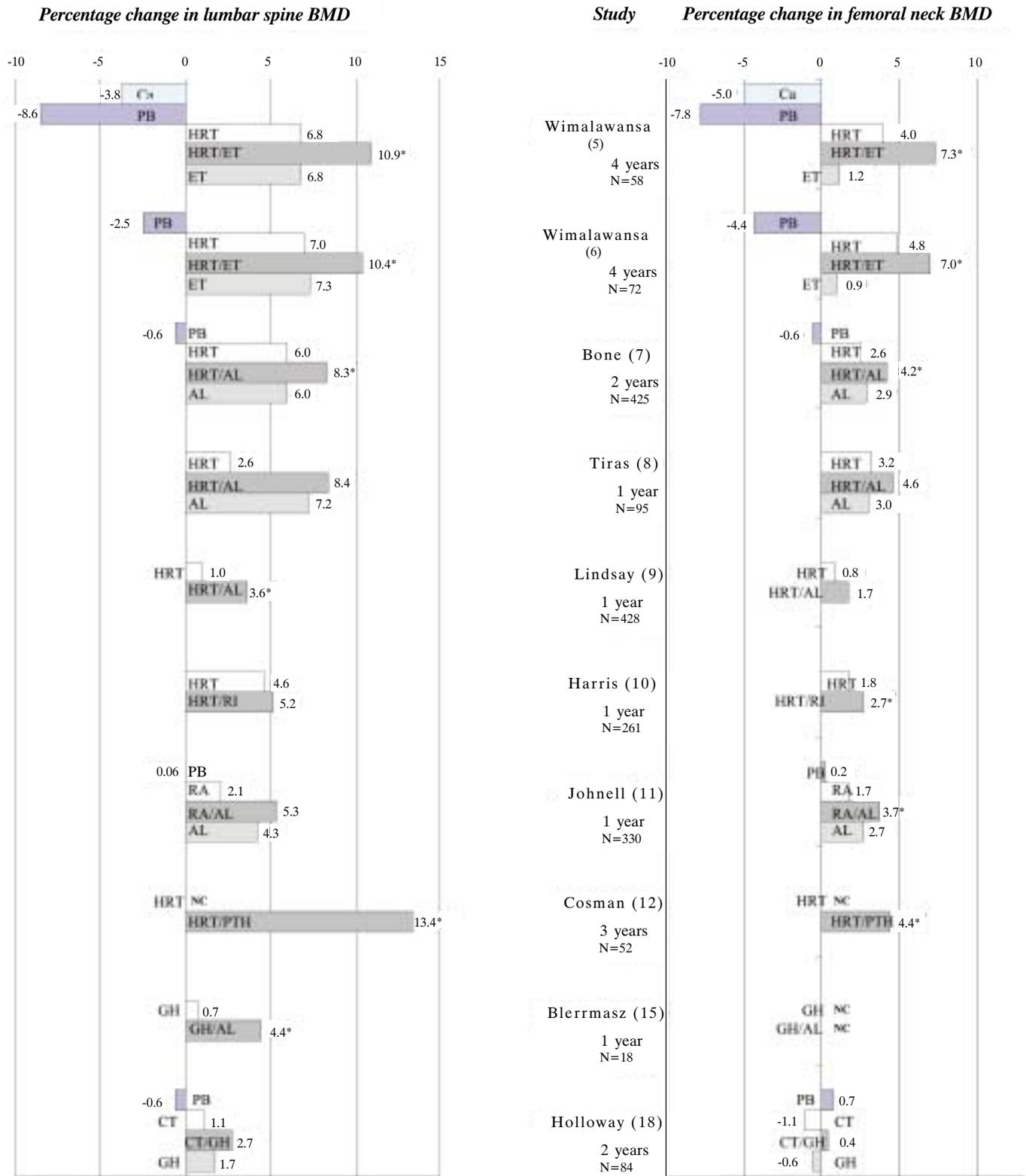
Figure 1. Effect of combination therapy on bone mineral density in the randomized trials reviewed in the article. For each study, the reference number is given in parentheses, and the study duration and the number of participants are provided.

Legend: Ca: Calcium, PB: Placebo, HRT: Hormone Replacement Therapy, ET: Etidronate, AL: Alendronate, RI: Risedronate, RA: Raloxifene, PTH: Parathyroid Hormone, GH: Growth Hormone, CT: Calcitonin.

* indicates significant difference ($p < 0.05$) in BMD between the group receiving combination therapy and the groups receiving the individual agents.

NC indicates "no significant change" although the exact figures are not given in the article.

Regarding combinations with anabolic agents, GH does not seem to have a role in the treatment of postmenopausal osteoporosis, but adding alendronate to GH therapy in GHD osteoporotic patients improves BMD. Adding PTH to ongoing HRT causes improvement in BMD at the spine and the femur, the two most vulnerable areas for subsequent fractures, but the effect on the distal radius has not been reported. Animal studies suggest that there is no advantage to giving antiresorptives before or during PTH administration and in some situations, there might be a disadvantage[25]. The place for antiresorptive therapy appears to be after PTH is stopped. In humans, simultaneous treatment with PTH and alendronate has not been reported, but an NIH-sponsored trial is underway[26]. The next set of studies will need to address how these combinations affect BMD and fracture risk in the long term.

Other considerations in combination therapy

Antifracture efficacy

Doubts remain about whether bone mineral density changes are a reliable surrogate for antifracture efficacy. The sodium fluoride example is cited frequently[27], where change in BMD was not enough. Although some additive effects on BMD were consistently observed in the double-blind, randomized, placebo-controlled prospective combination therapy trials, none of these studies had adequate statistical power to demonstrate a significant decrease in fractures. In fact, in one of the studies, the number of fractures in the group on combined alendronate/estrogen was greater than in the placebo/estrogen group. Nevertheless, there has never been a study demonstrating any antifracture efficacy in osteoporosis in the absence of an increase in bone mass.

Safety concerns

Optimal efficacy of a pharmaceutical agent in some instances may not be achieved without doses high enough to cause unacceptable side effects. Thus combination therapies may give desired efficacy at doses low enough to avoid the unacceptable side effects of single agent therapy. Most drugs used for the treatment of osteoporosis have unpleasant side effects. Use of low-dose estrogen or SERMs (to avoid adverse effects such as thrombotic events and the breast tenderness experienced by some women), or low-dose PTH (to avoid hypercalcemia for instance) in combination with other agents may prove to be effective.

The safety question regarding the risk of long-term reduction in the remodeling rates that might result in the inability to repair skeletal microdamage resulting in loss of antifracture efficacy despite maintaining bone mass was discussed in an earlier section. The risks of over-suppressing bone turnover are probably not a purely theoretical concern, and hence evaluation of markers of bone turnover is suggested prior to adding a second antiresorptive agent to the regimen of an osteoporotic patient.

Sequential therapy

The use of sequential therapy with an anabolic agent for a few months to cause an increase in bone mass by true bone formation followed by an anti-resorptive agent for a longer period of time to maintain that bone mass is also a promising potential therapy that will need further evaluation.

Long-term effects

The studies on combination treatments are relatively short as osteoporosis trials go. Most of them have observed subjects for 1-2 years only. Initial changes in BMD over the first few months may be partially explained by the introduction of supplemental calcium and vitamin D and may be due to the filling of the remodeling space. Besides, short-term studies provide no data on the steady-state effects of the combinations used. Thus, the questions about long-term utility and safety remain unanswered.

Cost considerations

The use of combination therapies brings added cost. The question of whether the added bone mass benefit of a combination is worth the sum of the side effects and the additional costs has not been addressed so far. The answer must include consideration of the non-skeletal risks and benefits of those agents. The real question, though, is whether the combination therapies are cost effective in ultimately reducing fractures, and any direct and indirect costs associated with them, including considerations of quality of life.

Conclusions

None of the studies on combination therapy for osteoporosis has shown fracture-reduction data. Combining two anti-resorptive agents may cause over-suppression of bone turnover, which may lead to decreased bone quality. Until future research demonstrates anti-fracture efficacy, combined therapy cannot be recommended and should not be used routinely. Integrating safety and cost issues will eventually determine whether those combinations should become the standard of care.

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