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REVIEW

The use of combination therapy in the treatment of postmenopausal osteoporosis

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Abstract In recent years, there has been growing interest in the potential use of combination therapy in the management of osteoporosis in postmenopausal women. Possible regimens include sequential or combined use of anti-resorptive drugs or combinations of anabolic and anti-resorptive agents, given concurrently or in sequence. Combined therapy with anti-resorptive drugs usually produces greater increases in bone mineral density (BMD) than monotherapy but there is no evidence that this results in greater anti-fracture efficacy. The use of bisphosphonates before strontium ranelate or PTH peptides blunts the BMD response. Combined PTH and anti-resorptive therapy results in more rapid gains in spine BMD and a greater increase in hip BMD than PTH monotherapy in the first year of treatment but greater gains in both spine and hip BMD are seen with PTH monotherapy than combined therapy after 2 years of treatment. Anti-resorptive therapy after PTH therapy maintains or increases the gains in BMD. Further research is required to establish the cost-effectiveness and safety of combined and sequential regimens.

Keywords Combination therapy · Osteoporosis · Anti-resorptives · Anabolics · Bone mineral density

Introduction

A range of pharmacological interventions is available for the prevention of fragility fractures in postmenopausal women. Anti-resorptive drugs are most commonly used; these include the bisphosphonates alendronate, risedronate, ibandronate and zoledronic acid, the selective oestrogen receptor modulator raloxifene and a humanised monoclonal antibody to receptor activator of NFκB ligand (RANKL), denosumab. Also available are the parathyroid hormone (PTH) peptide PTH [1–34] (teriparatide) and the full length molecule PTH [1–84], which have anabolic skeletal effects, and strontium ranelate, which probably acts mainly through effects on bone material properties.

Interest in the potential use of combination therapy has increased in recent years for several reasons. First, combination of interventions with different modes of action might produce synergistic effects on bone strength with greater efficacy against fracture than the use of a single agent. Second, use of anabolic agents is limited to 24 months; since, bone mineral density (BMD) declines following withdrawal of treatment, subsequent intervention with other drugs may be required to maintain the skeletal benefits. Third, particularly with potent anti-resorptive agents, it may be desirable to limit the duration of therapy to a finite period of time, for example 5 years, and some other form of treatment may be required in individuals who remain at high risk of fracture after this period. Finally, in patients who develop intolerance to a treatment and switch to an alternative option, the issue arises of whether their initial treatment, particularly if it was a bisphosphonate, will affect the response to the subsequent intervention.

Whilst monotherapy is the most widely used approach to management of postmenopausal osteoporosis, combination therapy may also be considered in some cases [1]. For the purposes of this review combination therapy includes the use of more than one treatment either concomitantly or in sequence. Calcium and vitamin D supplements are considered as an adjunct to therapy and will not be discussed further.

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Combination anti-resorptive therapy

A number of studies have addressed the use of combinations of anti-resorptive agents in postmenopausal osteoporosis. Concurrent use of hormone replacement therapy (HRT) and bisphosphonates has generally produced greater increases in BMD than either treatment alone, although how this translates to fracture risk is unknown. Wimalawansa compared the effects of cyclic etidronate and HRT, alone or in combination, in early and late postmenopausal women and demonstrated significantly greater increases in spine and hip BMD after 4 years with the combined therapy [2, 3]. In postmenopausal women already established on HRT for at least 1 year and then randomised to alendronate or placebo whilst continuing with HRT, Lindsay et al. [4] reported significantly greater increases in lumbar spine and trochanter, although not femoral neck, BMD at 1 year in women treated with combined HRT and alendronate Bone et al. [5] studied the effects of alendronate and HRT, alone or in combination, in a placebo-controlled study in postmenopausal women. After 2 years, BMD in the spine and hip was significantly greater in women receiving combination therapy than in those on HRT alone, although no significant difference was seen between women treated with combination therapy and those treated with alendronate alone. In a study of community dwelling women aged 65 years or older, BMD in the spine and hip was significantly greater at 3 years in women treated with alendronate and HRT compared to either drug alone [6]. Similarly, risedronate combined with HRT produced greater increases in BMD than risedronate alone in postmenopausal women treated for 1 year, although the difference was only significant for lumbar spine BMD at 6 months and femoral neck BMD at 1 year [7].

Other studies evaluating the effects of combination therapy with anti-resorptive drugs have included raloxifene and alendronate, HRT and calcitonin, and oestrogen and methyltestosterone [8–11]. With the exception of the latter study, in which effects on BMD were similar in women treated with oestrogen alone or combined therapy, greater benefits on BMD were seen in women treated with combination than monotherapy. Finally, in a recent study in postmenopausal women with osteoporosis, the addition of clodronate 800 mg daily to HRT did not result in any additional gain in BMD compared to the use of HRT alone [11].

Overall, therefore, these studies indicate that the use of anti-resorptive drugs in combination usually results in greater increases in BMD in the spine and hip. In most studies, the magnitude of difference has been relatively small and the clinical significance with respect to fracture reduction is uncertain. None of the studies has been adequately powered to show differences in fracture rate between groups. Although no significant excess of adverse effects with combination therapy was reported from any of the above studies, this remains a potential concern and in view of the greater cost and lack of evidence for greater fracture reduction, simultaneous use of two anti-resorptive drugs is not generally recommended.

Sequential treatment with anti-resorptive drugs

In clinical practice, switching treatment from one to another anti-resorptive commonly occurs, often from one bisphosphonate to another or less commonly from a bisphosphonate to raloxifene or denosumab. An interesting question that arises is whether, in a patient already established on a potent anti-resorptive drug, another potentially more potent anti-resorptive agent can produce greater benefits. This has recently been studied in the STAND trial, in which postmenopausal women with low BMD treated with alendronate 70 mg once weekly for at least 6 months were randomised to continue with alendronate or switch to denosumab 60 mg sc every 6 months [12]. Both at the lumbar spine and hip, BMD increases at 6 months and 1 year were significantly greater and bone turnover markers were significantly more suppressed in those women who had transitioned to denosumab compared with those who remained on alendronate. However, the study was not powered to show differences in fracture rate between the two groups, and the clinical significance of the greater increase in BMD is unknown. Nevertheless, the results of this study support the use of denosumab in patients who need to switch from bisphosphonate therapy.

Sequential therapy with bisphosphonates and strontium ranelate

The mechanism of action of strontium ranelate remains to be clearly established. In humans, there is evidence for weak effects on bone remodelling but it is difficult to explain the well-documented anti-fracture efficacy of the drug on the basis of these effects and changes in bone material properties may be more important [13–15]. In clinical practice, it is not uncommon for patients to switch from a bisphosphonate to strontium ranelate but until recently it was unknown whether prior bisphosphonate therapy would affect the response to strontium ranelate.

In a prospective study in postmenopausal women with osteoporosis or low BMD (T-score ≤ -2) and fracture, 56 bisphosphonate-naïve women and 52 women treated with an oral bisphosphonate for at least 1 year, who had stopped bisphosphonate therapy within the last month due either to an adverse effect or inadequate response, were given

strontium ranelate 2 g daily, together with calcium and vitamin D supplements [16]. After 1 year of treatment BMD in the lumbar spine had increased by 5.6% in bisphosphonate-naïve women and by 2.1% in women previously treated with bisphosphonates; at both 6 and 12 months the BMD increase in the former group was significantly less than in the latter. At the total hip there was no significant change in BMD at 1 year in the bisphosphonate pre-treated women compared to an increase of 3.4% in the treatment naive group. A similar pattern was seen for heel BMD measurements. In a recently reported extension of this study up to 2 years, it was shown that BMD in the spine in pre-treated women increased in parallel with treatment naïve women from 6 months onwards, whereas some blunting of the BMD response at the hip was still observed after 2 years of treatment and no increase in heel BMD was demonstrated [17].

These interesting data suggest that in women previously treated with bisphosphonates, the uptake of strontium into newly formed bone is inhibited because of suppression of bone turnover and the consequent reduction in newly formed bone. The alternative explanation, namely that suppression of bone turnover by bisphosphonates prevented anabolic effects of strontium ranelate on bone formation is less likely since its administration to bisphosphonate-naïve women was associated with a reduction in P1NP and only a small and non-significant increase in serum bone specific alkaline phosphatase. The clinical significance of the blunting in BMD response in women previously treated with bisphosphonates is unclear, particularly since a significant proportion of the BMD increase observed with strontium ranelate therapy is due to strontium uptake into bone rather than a true increase in BMD. Whilst the implications for protection against fracture are uncertain, the results of these studies indicate that in patients who are switched from bisphosphonate to strontium ranelate therapy, a longer time on treatment than in bisphosphonate-naïve women is required before BMD measurements can be used to detect a treatment response.

Anabolic and anti-resorptive therapy

Sequential therapy: anti-resorptive before anabolic therapy

In clinical practice PTH therapy is frequently used in patients previously treated with an anti-resorptive agent, usually a bisphosphonate. Since, the anabolic effects of intermittent PTH therapy depend at least in part on the stimulation of new remodelling units, persisting suppression of bone turnover after bisphosphonates are withdrawn could reduce the effects of PTH molecules. Evidence to support this theory was reported by Ettinger et al. [18] in a study of postmenopausal women switched from either raloxifene or alendronate to teriparatide. During the first 6 months of teriparatide therapy, greater increases in hip and spine BMD were observed in women who had previously received raloxifene than in those with prior alendronate therapy, and after 18 months the mean increases in spine BMD were 10.2 and 4.1%, respectively. In the total hip, BMD did not change significantly over 18 months in the women who had received alendronate, but showed a mean increase of 1.8% in women with prior raloxifene therapy. Similarly, in postmenopausal women with osteoporosis, addition of teriparatide to on-going alendronate therapy produced significant increases in bone formation markers [19], and significant increases in spine and total hip BMD (9.6 and 2.7%, respectively) were also reported after 1 year of treatment with PTH [1–34] in women previously treated with raloxifene [20]. Cosman et al. [21] reported that in postmenopausal women with osteoporosis who had been taking alendronate for at least 1 year, both daily and cyclic PTH [1–34] treatment for 15 months were associated with significant increases in spine and hip BMD, the increase in spine BMD being significantly greater than in women who continued on alendronate alone. In a non-randomised, prospective study in postmenopausal women with osteoporosis, Miller et al. [22] reported the effects of 12 months teriparatide therapy following previous treatment for at least 24 months with either risedronate or alendronate. A significant greater increase in the bone formation marker, P1NP, and in spine areal and volumetric BMD was seen in the prior risedronate group when compared to the prior alendronate group. The difference in response to teriparatide in women pre-treated with risedronate and alendronate could not be explained by differences in baseline bone turnover before teriparatide therapy, as measured by serum levels of biochemical markers.

In the European Study of Forsteo (EUROFORS), the effect on BMD of teriparatide therapy was compared in postmenopausal women with established osteoporosis who had or had not received prior anti-resorptive therapy. The majority of women in the latter group had been treated with a bisphosphonate, most commonly alendronate, for a median period of 11 months. Prior anti-resorptive treatment was associated with modest blunting of BMD response in the spine and hip; after 2 years teriparatide therapy the increase in spine BMD was 10.2% in the prior anti-resorptive group compared with 13.1% in the treatment naïve group. In the total hip, the corresponding figures were 2.3 and 3.8% [23]. In a secondary subgroup analysis in which women with prior anti-resorptive treatment were subdivided into four groups (alendronate, etidronate, risedronate and non-bisphosphonate) increases in spine and hip BMD were seen in all groups after

24 months of teriparatide, the largest of which occurred in etidronate pre-treated women. The BMD response in all four groups was unaffected by the duration of previous anti-resorptive therapy and the period of time between stopping anti-resorptive therapy and starting teriparatide [24].

The ability of PTH peptide therapy to produce anabolic effects despite prior anti-resorptive therapy has also been demonstrated in postmenopausal women established on HRT. After 3 years treatment with PTH [1–34], increases in BMD of 13 and 2.7% in the spine and hip respectively were seen, whilst those women remaining on HRT only showed no significant change in BMD at either site [25]. In a subsequent report from the same group, a significantly lower vertebral fracture rate was reported in the women taking HRT and PTH [1–34] than in those receiving HRT alone (zero versus seven fractures using a 20% criterion) [26].

Taken together, these results indicate that some attenuation of the anabolic effect of intermittent PTH therapy occurs in women previously treated with anti-resorptive therapy, the magnitude of which is likely to depend on the anti-resorptive potency of the drug. In general, blunting of the BMD response appears to be relatively small, but the consequences, if any, on fracture reduction have not been established.

Sequential therapy: anti-resorptive after anabolic therapy

PTH therapy is approved for a maximum duration of 24 months. Following its discontinuation, loss of BMD in the following year has been reported in the total hip and femoral neck [27] and spine [27–29]. Although, there is some evidence that vertebral and non-vertebral fracture protection may be maintained over a median follow-up period of 18 and 30 months, respectively [27, 30], the BMD losses provide a rationale for initiating anti-resorptive therapy after PTH therapy is withdrawn. In a study of postmenopausal women with osteoporosis treated with PTH [1–84] or placebo for one year and then with alendronate 10 mg/d for the following year, further gains in spine, femoral neck and total body BMD were seen in the women previously treated with PTH [31]. Similarly, Black et al. reported that following 1 year of PTH [1–84] treatment in postmenopausal women, subsequent alendronate treatment for 1 year maintained or increased the gains in BMD in the spine and hip [28]. Similarly, following 1 year of teriparatide therapy in postmenopausal women with osteoporosis, Eastell et al. reported that treatment with raloxifene in the following year maintained spine BMD and increased hip BMD [32]. In men treated for 2 years with teriparatide, bisphosphonate therapy for the subsequent 2 years was associated with further gains in lumbar spine BMD, whereas a decrease in BMD was seen in men who received no treatment after teriparatide withdrawal [33].

Combined anabolic and anti-resorptive therapy

The different mechanisms of action of anabolic and anti-resorptive drugs suggest that by both stimulating bone formation and inhibiting bone resorption, combined use might result in greater efficacy than the use of either alone. Conversely, suppression of remodelling by anti-resorptives might blunt the response to PTH by preventing the increase in remodelling rate required for its anabolic skeletal effects. Evidence in support of the latter was provided by Delmas et al. in a study in sheep, in which the effects of PTH alone were compared to those of combined PTH [1–34] and tiludronate therapy [34]. Over the 3 month treatment period, biochemical and histological indices of bone turnover were decreased in sheep receiving combination therapy, but increased in those receiving PTH [1–34] alone; indices of bone resorption and formation in the combination group did not differ from an untreated control group. Although only one dose of tiludronate was tested in this study, the results suggested that combining anti-resorptive therapy with PTH could abrogate the anabolic effect of PTH.

Studies of combined anabolic and anti-resorptive therapy in postmenopausal women have produced conflicting results. Deal et al. [35] compared the effects of combination teriparatide and raloxifene therapy to teriparatide alone in postmenopausal women with osteoporosis in a double-blind randomised study conducted over a 6 month period. Serum P1NP increased to a similar extent in both treatment groups, whilst the bone resorption marker CTx decreased less in the teriparatide alone group. Similar increases in lumbar spine BMD were observed in the two treatment groups (6.19% in the combination group, 5.19% in the teriparatide alone group) whilst combination therapy was associated with a significantly greater increase in total hip BMD.

In the parathyroid hormone and alendronate study (PATH), 238 postmenopausal women with low BMD were randomised to PTH [1–84] 100 μg/day, alendronate 10 mg/day or both [36]. After 1 year of treatment, spine BMD measured by DXA had increased in all treatment groups and to a similar extent in the combined treatment and PTH alone treatment groups; however, the increase in volumetric BMD, measured by quantitative computed tomography (QCT), was almost twofold greater in the PTH alone group than that observed in either of the other treatment groups. At the total hip and femoral neck, BMD did not change significantly in the PTH alone group but increased in the other

two groups, and the increase in the combination group was significantly greater than that in the PTH alone group. Volumetric BMD in the total hip decreased significantly in the PTH group, did not change significantly in the combination group and showed a small increase in the alendronate group. Conversely, cortical bone volume increased significantly at the total hip and femoral neck in the PTH group, but did not change significantly in the other two groups. The authors concluded that based on the changes in spine volumetric BMD and hip cortical volume, concurrent use of alendronate blunted the anabolic effects of PTH.

In a smaller but longer term study in 83 men with low BMD, the effects of PTH [1–34], alendronate 10 mg/day or both were investigated [37]. PTH was started at month 6 of the study and continued for 24 months whilst alendronate was given for the total study period of 30 months. After 2 years treatment, the increase in lumbar spine BMD was significantly greater in the PTH alone group than in the other two groups and femoral BMD had increased significantly more in the PTH than in the alendronate group, the increase in the combination group being intermediate. These results again suggested that alendronate therapy given in combination with PTH attenuated the anabolic effects of PTH. Similar results were subsequently reported in postmenopausal women by the same authors [38]. However, it should be noted that in these two studies the dose of PTH [1–34] was 40 μg/day, twice the approved dose for treatment of osteoporosis.

A recent study, however, suggests that combination therapy using intravenous zoledronic acid and teriparatide may be superior to teriparatide alone in terms of the rate of increase in lumbar spine BMD and in the magnitude of increase in hip BMD [39]. Postmenopausal women with osteoporosis were randomised to a single infusion of zoledronic acid 5 mg plus daily subcutaneous teriparatide 20 μg, zoledronic acid alone, or teriparatide alone and were studied over a 1 year period. In the spine, BMD changes were similar in the PTH alone and combination group at 1 year, but the rate of increase was more rapid in the combination group than in the other two groups at earlier time points. In the hip, the increase in BMD in the combination group was significantly greater than that in the PTH alone group at all time points; after 1 year total hip BMD values were similar in the combination and zoledronic acid groups, with a higher rate of increase in the combination versus zoledronic acid group at week 13. In the combination therapy group, the bone resorption marker β-CTX showed a rapid decrease that was sustained for 2 months but then increased to return to above baseline values at 1 year. Serum P1NP also showed an increase in the combination therapy group from around 6 months to 1 year. In contrast, in women receiving zoledronic acid only both markers remained suppressed throughout the duration of the study. These data indicate that any blunting of the response to PTH peptides in women on combination therapy was relatively short.

Whilst the results of this study might appear at first sight to conflict with those reported by Black et al., the data for areal BMD in the spine are in fact similar, in that both studies demonstrated a similar increase in lumbar spine BMD at 1 year in women treated with combination therapy or PTH alone, which was greater than that associated with anti-resorptive therapy alone. The greater frequency of measurements in the study of Cosman et al. enabled assessment of the rate of increase in BMD and demonstrated that, in the spine, this was greatest in women receiving combination therapy. Whether more rapid increases in BMD at early time points confers greater fracture protection during this period is unknown. Longer term studies indicate that by 2 years, the gain in spine BMD is greater with PTH monotherapy than with combination therapy [37, 38].

In the hip, it is clear that combination therapy or treatment with an anti-resorptive agent alone results in greater increases in BMD than PTH monotherapy in the early stages of treatment, although in longer term studies the increase with PTH exceeds that achieved with combination therapy or an anti-resorptive agent. Monotherapy with PTH is often associated with a transient decrease in hip BMD, probably as a result of increased cortical porosity [36, 40] and its prevention by concomitant anti-resorptive therapy presumably results from reduced cortical remodelling. Combination anti-resorptive and anabolic treatment may therefore be particularly beneficial in patients at high risk of hip fracture, in whom an increase in cortical porosity early in the course of treatment could expose them to increased risk. However, the effects of combination therapy on hip fracture risk have not been formally tested and whereas hip fracture reduction has been demonstrated for several anti-resorptive agents [41–43], this has not been shown with PTH peptides [40, 44].

Safety of combined anabolic and anti-resorptive treatment

In the PATH study, both hypercalcaemia and hypercalciuria occurred more frequently in the combination group and PTH group than in the alendronate group, although this was generally mild. Combination and PTH therapy were also associated with significant increases in the mean serum uric acid level, and three women developed gout (one in the PTH group and two in the combination group) [36]. In men, a higher incidence of hypercalcaemia and hypercalciuria was also reported with combination therapy or PTH alone compared to alendronate [37]. Finally, in the study of Cosman

et al. the reported percentages of women with serum calcium levels that were normal at baseline but above the normal range during the study were 13.4% for the combination group, 15% for the teriparatide group and 4% for the zoledronic acid group. Significant hypercalcaemia, defined as a serum calcium >2.89 mmol/l, occurred in one woman in the combination group and two in the teriparatide group [39].

Conclusions

Although the use of combination anti-resorptive therapy is associated with greater increases in BMD than the use of one anti-resorptive drug, the clinical significance of the relatively small benefits gained is unclear and there is no evidence for greater anti-fracture efficacy of combined regimens. Sequential treatment with different anti-resorptive drugs is commonly used in clinical practice and switching from a less to a more potent anti-resorptive results in greater gains in BMD, although it is not known whether this results in greater reduction in fracture risk. When treatment with strontium ranelate is initiated following bisphosphonate therapy, the BMD response to strontium ranelate is blunted for at least 6 months in the spine and up to 2 years in the hip.

Combined therapy with PTH and anti-resorptive agents produces similar benefits on lumbar spine areal BMD to PTH therapy alone in the first year of treatment although the rate of increase in BMD is more rapid with combination therapy, at least when zoledronic acid is used. In the hip, combination therapy is superior to PTH monotherapy in the first year of treatment; however, longer treatment periods are associated with greater increases in both spine and hip BMD with PTH alone than with combination therapy. Comparison of fracture reduction with PTH alone and combination therapy has not been studied; however, protection by combination therapy against the early bone loss in the hip associated with PTH monotherapy might be advantageous. Further studies are required to establish the cost-effectiveness and safety of combined anabolic and anti-resorptive treatment regimens.

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