Citation: BoneKEy Reports **3**, Article number: 518 (2014) | doi:10.1038/bonekey.2014.13

www.nature.com/bonekey

REVIEW

Combination therapy for osteoporosis: a reappraisal

Felicia Cosman[1,2]

[1]Department of Clinical Medicine, Columbia College of Physicians and Surgeons, Columbia University, New York, NY, USA.
[2]Clinical Research Center, Helen Hayes Hospital, West Haverstraw, NY, USA.

Combinations of anabolic and antiresorptive agents have potential to improve bone density and bone strength more than either agent alone. A large number of relatively small clinical trials have been performed evaluating combinations of PTH1-34 or PTH1-84 with a variety of antiresorptives, including hormone/estrogen therapy, raloxifene, alendronate (Aln), risedronate, ibandronate, zoledronic acid and denosumab (Dmab). Most of the studies evaluate dual-X-ray densitometry outcomes, with a few trials reporting volumetric bone mineral density (BMD) by quantitative computed tomography followed by finite element modeling of bone strength. None of the studies has been powered to assess differences in fracture incidence between combination therapy and monotherapy. BMD outcomes vary depending on the timing of introduction of the anabolic agent (before, during or after antiresorptive treatment), as well as according to the specific anabolic and antiresorptive used. Furthermore, effects of combination therapies are site dependent. The most consistent effect of combining antiresorptive agents with parathyroid hormone (PTH) is a superior hip BMD outcome compared with PTH alone. This is most evident when PTH is combined with a bisphosphonate or Dmab. In contrast to findings in the hip, in the majority of studies there is no benefit to spine BMD with combination therapy when compared with monotherapy. The two exceptions to this are when PTH is combined with Dmab and when PTH is given as monotherapy first for 9 months followed by the addition of Aln and continuation of PTH as combination treatment. On the basis of what we now know, in patients on bisphosphonates who suffer hip fractures or who have very low hip BMD, strong consideration should be given to starting teriparatide and continuing a bisphosphonate (possibly switching to zoledronic acid or even Dmab) to maximize hip BMD and strength. Furthermore, in treatment-naive individuals with very severe osteoporosis, such as those with spine and hip fractures, combination therapy with PTH and Dmab or PTH followed by combination treatment with a potent bisphosphonate or Dmab should be considered to maximize early increases in BMD.

BoneKEy Reports **3**, Article number: 518 (2014) | doi:10.1038/bonekey.2014.13

Introduction

Although there is rarely, if ever, a rationale for combining two antiresorptive medications, various anabolic and antiresorptive therapies have been combined in an attempt to attain superior bone mass and strength effects compared with monotherapy. Although teriparatide (aminoterminal PTH1-34; TPTD) or PTH1-84 combined with antiresorptive agents could theoretically produce additive or perhaps even synergistic effects, studies on combination therapy have produced different outcomes based on skeletal site (spine vs hip vs radius), type of assessment (dual-energy X-ray absorptiometry (DXA) vs quantitative computed tomography (QCT)), specific antiresorptive therapy utilized and whether patients are previously treatment naive or treatment experienced. This review will summarize the key combination trials and evolving concepts regarding combination treatment.

Treatment-Naive Women

Although there are some parallels between treatment naive and treatment-experienced populations, differences in the magnitude of active bone surface, effects of acute antiresorptive agents on parathyroid dynamics, effects of acute withdrawal of previous antiresorptive treatments on osteoclast activity and perhaps unique acute effects of antiresorptive agents on osteoblast function might all have a role in producing distinct responses to combination therapy in previously treated vs treatment-naive individuals.

Correspondence: Dr F Cosman, Clinical Research Center, Helen Hayes Hospital, Route 9W, West Haverstraw, NY 10993, USA.
E-mail: cosmanf@helenhayeshosp.org

Received 18 September 2013; accepted 4 December 2013; published online 2 April 2014

Therefore, in trying to interpret the many different combination therapy studies, it is important to take note of these distinctions.

TPTD and hormone therapy (HT) or raloxifene (Ral) in treatment-naive women

Ste-Marie *et al.*[1] identified two cohorts of women (total $n = 247$), half of whom were treatment naive ($n = 125$) and half of whom had been on previous HT (discussed below). Within each cohort, women were randomized to receive HT alone or HT with 40 mcg TPTD daily for 1 year. In the treatment-naive cohort, there were increases due to HT itself and much larger increases in the group receiving HT with TPTD (16% in the spine and 6% in the hip). The increases from TPTD appeared additive to those of HT. Although the findings suggest no obvious blunting of TPTD effect by HT (based on the findings of another study utilizing 40 mcg TPTD as monotherapy)[2] there was no TPTD monotherapy arm to confirm that conclusion.

Deal *et al.*[3] randomized 137 postmenopausal treatment-naive women to receive TPTD or TPTD plus Ral for 6 months. Mean serum PINP (aminoterminal propeptide of Type I Procollagen) level rose similarly in the two groups, whereas mean serum CTX (crosslinked C-terminal telopeptide) level increased less with combination TPTD/Ral vs TPTD monotherapy. Spine BMD increments were similar in the two groups, whereas hip BMD increased significantly more in the TPTD/Ral combination group.[3] The greater increment in hip BMD has been a consistent finding in almost all of the combination treatment studies across treatment-naive and treatment-experienced individuals.

TPTD or parathyroid hormone (PTH) and bisphosphonates in treatment-naive women

Finkelstein *et al.*[2] randomized 93 women to receive alendronate (Aln) for 6 months before the addition of TPTD vs either agent alone. About 40% of women ($n = 35$) discontinued the study early or never took the study drug. A substantial proportion of women in both the TPTD groups required dose adjustment (by 25–50%) because of hypercalcemia or side effects. BMD gains in both spine and hip by DXA were lower in those given TPTD after the 6-month course of Aln (and with ongoing Aln) compared with those given TPTD monotherapy; however, the difference in spine BMD gain was not significant if groups were restricted to those who did not discontinue study medication prematurely.[2] Radius BMD declined more in women who received TPTD monotherapy compared with combination treatment, and the increment in total body BMD did not differ between the groups. In contrast to the previous studies and the subsequent studies discussed, total hip and femoral neck BMD increased more with TPTD monotherapy than with combination therapy (in total hip 8.1% for TPTD monotherapy vs 2.9% for combination; in femoral neck 10.8% vs 3.1%, respectively). This is one of the only studies to evaluate the effects of TPTD over a full 24-month period, and hip BMD continued to increase during the latter 6 months. The treatment duration is unlikely to be the only explanation for the difference in hip effect in this study vs all other studies, however, as the increment in femoral neck BMD was already significantly higher at 18 months with TPTD monotherapy vs combination therapy. The TPTD dose used here was double the approved dose (40 mcg daily TPTD), and, as TPTD/PTH effects on BMD are clearly dose dependent, the applicability to other combination treatment studies is unclear. Bone turnover markers of both formation and resorption increased in the combination group above the suppressed baseline (after 6 months of Aln alone). Black *et al.*[4] randomized 238 treatment-naive women to PTH1-84 (referred to as PTH) with Aln vs each agent as monotherapy. Spine BMD by DXA increased similarly in the PTH monotherapy and PTH/Aln combination groups (6.3% and 6.1%, respectively). Total hip BMD increased significantly in the combination group (1.9%) but not with PTH monotherapy (0.3%). Radial BMD declined more with PTH alone (-3.4%) than with combination therapy (-1.1%). Although QCT-measured increases in the integral spine and total hip were similar between the PTH monotherapy and combination groups, trabecular spine BMD increased more with PTH monotherapy (25.5%) than with combination treatment (12.6%). In contrast, QCT-assessed cortical bone density declined in the hip (-1.7%) with PTH alone but was unchanged in the combination group. The DXA results demonstrated no evidence of additive effect in the spine with combination therapy compared with PTH monotherapy. However, hip BMD increments were superior with the combination (**Figure 1**). Evidence of a blunted effect with combination PTH/Aln treatment was apparent primarily by assessment of trabecular bone by QCT. As single-energy QCT-based BMD increments induced by PTH may be artifactually elevated by reductions in bone marrow fat,[5,6] it is unclear how to interpret the QCT findings vs DXA results. There were only a small number of fractures, with no group differences, and incident morphometric vertebral fractures were not reported.

Cosman *et al.*[7] randomized 412 treatment-naive postmenopausal women to receive TPTD monotherapy, intravenous zoledronic acid (Zol) monotherapy or a combination of TPTD and Zol. With combination therapy, serum CTX levels declined similarly to that seen with Zol monotherapy, whereas serum PINP levels declined only modestly compared with that seen with Zol monotherapy. With combination TPTD/Zol therapy, at 12 months, the spine BMD increase was similar to that seen with TPTD monotherapy (7.5% vs 7.0% TPTD monotherapy), whereas with combination therapy the hip BMD increase was larger (2.3% vs 1.1%), as was the femoral neck BMD increase (2.2% vs 0.1%). Therefore, there was clearly an additive effect of TPTD/Zol in the hip region compared with TPTD monotherapy. In the combination group, peak BMD increments were reached the fastest at both spine and hip sites, compared with either agent alone (**Figure 2**), with the most rapid increases seen in the first 3 months corresponding to the most prominent reduction in CTX levels. Between 6 and 12 months, as the antiresorptive effect of Zol was lost, hip BMD leveled off with combination treatment, and the BMD increase due to Zol alone reached the same level as that seen for the combination group. The study illustrated very clearly that the best and most efficient net anabolic effect of this combination therapy is when the antiresorptive agent is most potent, during the early treatment period (3–6 months). Clinical fractures occurred in 9.5% of patients in the Zol monotherapy group, in 5.8% of the TPTD monotherapy group and in 2.9% of the combination treatment group ($P < 0.05$ vs Zol alone).

TPTD and denosumab (Dmab) in largely treatment-naive women

Tsai *et al.*[8] randomized 94 women (largely treatment naive) to receive TPTD monotherapy, Dmab monotherapy or

combination TPTD/Dmab therapy. Previous oral bisphosphonate use was noted in about 35% of patients but all had completed their course at least 6 months before recruitment into the trial, and the mean time since discontinuation of the previous bisphosphonate was between 27 and 42 months for the three treatment groups. Therefore, this is largely a treatment-naive population. Spine, total hip and femoral neck and radius BMD (**Figure 3**) increased significantly more in the combination group (9.1, 4.9 and 4.2%, respectively) than in the TPTD monotherapy (6.2, 0.7 and 0.8%, respectively) or Dmab monotherapy (5.5, 2.5 and 2.1%, respectively) groups. In addition, radius BMD increased more with combination therapy (2.6%) compared with TPTD monotherapy (-1.8%). With TPTD/Dmab combination therapy, serum CTX levels paralleled the prominent decline seen with Dmab monotherapy throughout the 12-month study, whereas serum PINP declined more slowly and did not overlap Dmab monotherapy values until sometime between 6 and 12 months. Mean serum osteocalcin level in the TPTD/Dmab combination group was still above that seen with Dmab monotherapy throughout the study. In contrast to the study with TPTD/Zol combination treatment, none of the mean bone turnover marker levels exceeded baseline at any time point during the trial. Most importantly, in contrast to the serum CTX escape with waning of the Zol effect on bone resorption during the second half of the year when TPTD is coadministered with Zol, serum CTX level remained completely suppressed in the combination group in this trial, overlapping the pattern with Dmab monotherapy. The increments in BMD in this trial in the combination group were very similar to those seen in the PTH/Zol study during the first several months, but with the TPTD/Dmab combination BMD levels continued to increase during the second half of the year.

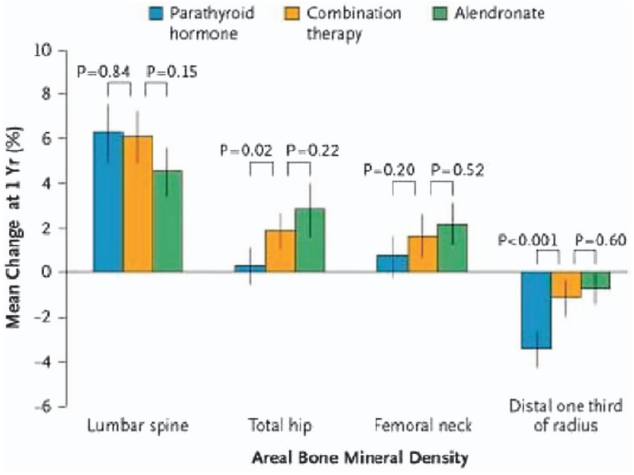

Figure 1 Mean percent changes in areal bone mineral density of the spine, hip and radius by DXA in patients on PTH plus Alendronate vs PTH monotherapy and Alendronate monotherapy. Adapted from Black *et al.*[4]

Women on Established Antiresorptive Therapy

TPTD combination treatment studies in women on previous and ongoing HT or Ral

In 52 women with osteoporosis who were treated with HT,[9,10] daily TPTD produced rapid increases in markers of bone formation and delayed increases in markers of bone resorption.[10] This period of time, when augmentation of bone formation exceeds stimulation of bone resorption, has been referred to as the anabolic window and may represent the most efficient bone-building opportunity with TPTD. Furthermore, bone turnover levels remained elevated for only 18–24 months, after which marker levels declined.[9] The mechanism of this apparent resistance to ongoing TPTD administration has still not been determined but is consistently seen with biochemical markers in both TPTD monotherapy and combination therapy trials. BMD increased by about 14% over 3 years in women receiving TPTD + HT, with evidence of the most rapid increase in BMD within the first 6 months. Total body and hip BMD increased by 4% in patients on TPTD/HT combination treatment. After 3 years of treatment, vertebral deformity occurrence was significantly reduced in patients receiving TPTD/HT combination therapy compared with HT monotherapy.[9] Another study of similar design performed in women who had previously been treated with HT showed BMD increments by DXA in the TPTD group of 30% in the lumbar spine and 12% in the femoral neck, compared with placebo.[11] No fracture data were presented from this trial, and the data have never been published in a peer-reviewed journal. A third study, utilizing TPTD at 40 mcg per day, enrolled one subgroup of women on previous HT ($n = 122$), as in the two previously discussed trials.[1] BMD increments were approximately 11% in the spine and 3% in the total hip in women randomized to TPTD at 40 mcg daily plus ongoing HT.

Cosman *et al.*[12] evaluated postmenopausal women on Ral for at least 1 year ($n = 42$) and randomized them to stay on Ral monotherapy or to receive TPTD/Ral combination treatment.

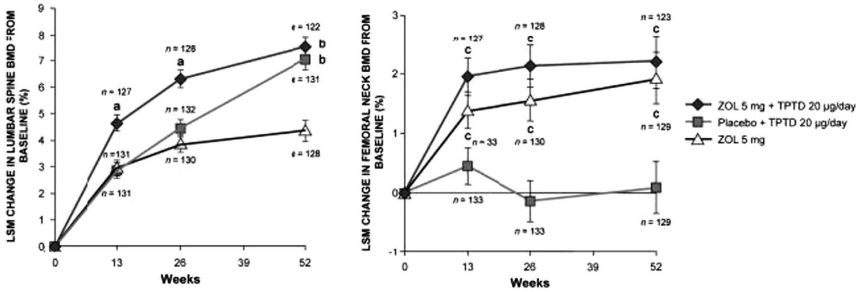

Figure 2 LSM percentage change in Hip BMD from baseline at total hip and femoral neck according to treatment with teriparatide (TPTD) alone; versus treatment with zoledronic acid (ZOL) alone; versus treatment with zoledronic acid (ZOL) and teriparitide (TPTD) combination therapy. Data are from intent-to-treat population excluding missing values. Bars show standard error. From Cosman *et al.*[9]

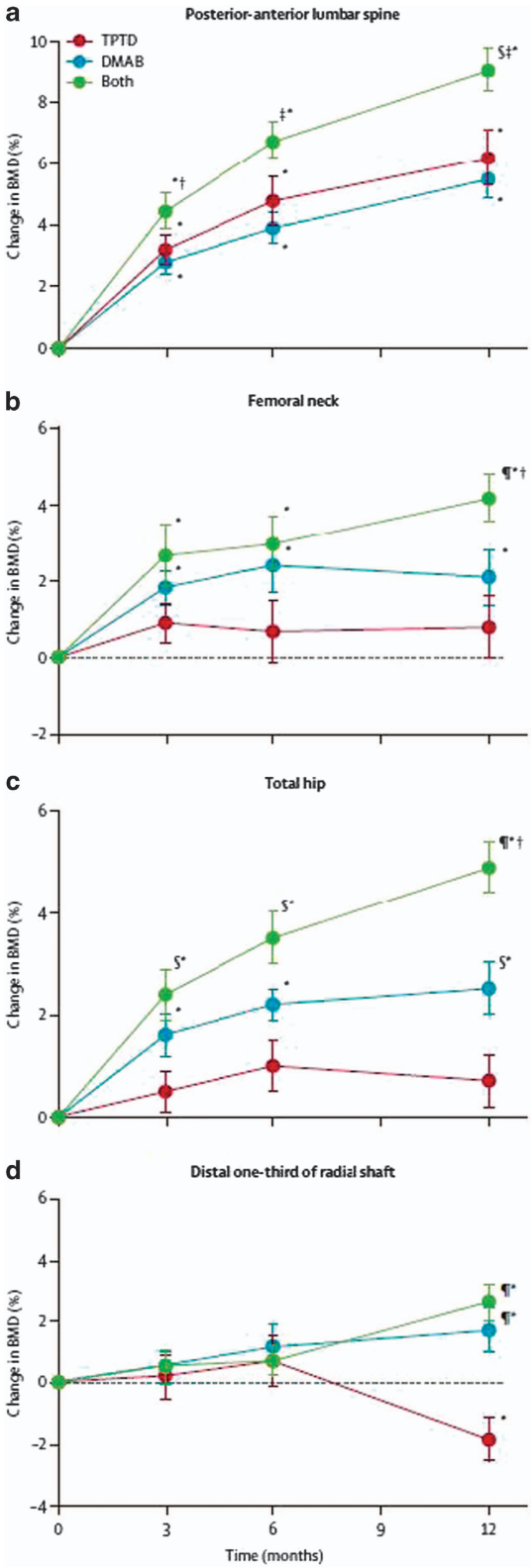

Figure 3 **Mean (SE) percentage changes in bone mineral density** (**a**) Posterior-anterior lumbar spine. (**b**) Femoral neck. (**c**) Total hip. (**d**) Distal one-third of the radial shaft. *$P<0.05$ *vs* baseline. †$P<0.05$ *vs* denosumab alone. ‡$P<0.001$ *vs* denosumab alone. §$P<0.05$ *vs* teriparatide alone. ¶$P<0.001$ *vs* teriparatide alone. TPTD = teriparatide. DMAB = denosumab. BMD = bone-mineral density.

The TPTD/Ral combination group had an increment of about 10% in the lumbar spine and 3% in the total hip, whereas those randomized to the ongoing Ral monotherapy had no BMD change. Increases in both biochemical turnover markers at 3 months correlated with increases in spine BMD at 1 year.

TPTD combination treatment studies in women on previous and ongoing bisphosphonate therapy

Patients maintained and stabilized on long-term bisphosphonate treatment constitute a distinct but clinically very important population, as many of these patients have fractures or do not achieve a BMD above osteoporotic range and thus might benefit from anabolic therapy. At least 50% of all TPTD/PTH treatment is initiated in patients who have received previous antiresorptive agents, most of which is bisphosphonate.

Studies evaluating TPTD treatment in treatment-experienced women have followed two basic designs: antiresorptive agents are stopped when TPTD is started,[13–15] or antiresorptive agents are continued when TPTD is started.[12,16] Outcomes differ with these distinct study designs. In studies in which bisphosphonates are discontinued, the spine BMD increment is of lesser magnitude and hip BMD declines consistently over the first year, an effect not seen in protocols in which TPTD is added to ongoing bisphosphonate.

Studies in which bisphosphonates were stopped when TPTD or PTH was started

In an observational study in which TPTD was given to women after cessation of long-term Aln or Ral,[15] bone turnover markers increased as did spine BMD, but these increases were somewhat delayed and of lower magnitude in patients pretreated with Aln compared with patients pretreated with Ral. In the cohort on previous Aln, but not in the cohort on previous Ral, a significant reduction in hip BMD was seen at 6 months, although hip BMD was back to baseline by 18 months.

Similarly, in a nonrandomized, prospective study of women previously treated with risedronate ($n=146$) or Aln ($n=146$), Miller *et al.*[13] found that biochemical markers of bone resorption were already increased within 1 month of treatment with PTH monotherapy in both cohorts, an outcome not seen within the first month in treatment-naive patients treated with TPTD or PTH monotherapy.[17,18] Furthermore, increases in markers of bone resorption at 1 month are not seen in patients on previous antiresorptive therapy with combination therapy—that is, continuing the antiresorptive agent during administration of TPTD.[9,10,16] Consistent with the study by Ettinger *et al.*,[15] Miller *et al.*[13] demonstrated that hip BMD declined significantly in both the cohort on previous risedronate and in the cohort on previous Aln for the duration of the 1 year PTH monotherapy observational trial (**Figure 4**). Finally, average spine BMD in a cohort of women who had been on previous bisphosphonates and then were switched to TPTD increased less than in a cohort of treatment-naive women (9.8–10.2% for the bisphosphonate-treated and 13.1% for treatment-naive women[14,19]). More importantly, women on previous bisphosphonates, who were switched to TPTD monotherapy, had a decline in hip BMD over the first year of treatment, an effect not seen in treatment-naive women[19] or in women given TPTD in combination with ongoing bisphosphonate combination treatment.[9,10,16,20]

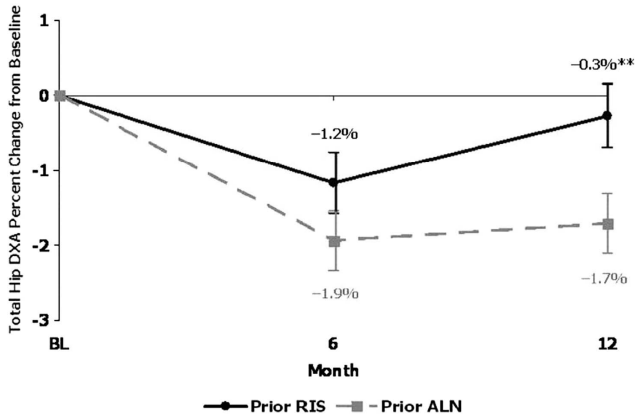

Figure 4 Total hip percent change in BMD from baseline in patients with prior Risedronate (RIS) treatment versus prior Alendronate (ALN) treatment. From Miller *et al.*[13]

Studies in which antiresorptive therapy was continued when TPTD was initiated (combination therapy)

In the study by Cosman *et al.*, 126 women previously treated with long-term Aln (average duration 3.2 years) were randomized to continue Aln and to receive daily TPTD, cyclic TPTD (given in a 3-month-on/3-month-off regimen) or Aln monotherapy.[16] Over just 15 months, spine BMD rose by 6.1% in the daily TPTD/Aln combination group, a higher increment than the average changes seen in the studies above when the underlying bisphosphonate was discontinued and TPTD or PTH was given as monotherapy. Moreover, mean hip BMD did not decline at any time point during this study of TPTD/Aln combination treatment.

Comparing TPTD alone vs combination therapy in a randomized controlled trial of women on previous Aln or Ral

In order to formally compare in a randomized trial the effect of continuing vs stopping the antiresorptive agent when TPTD is initiated, 198 women on previous Aln ($n = 102$) or Ral ($n = 96$) were randomized within each cohort to continue or stop their antiresorptive when TPTD was initiated.[20] This study was a direct randomized comparison of TPTD monotherapy vs TPTD combination therapy in treatment-experienced patients. Although an anabolic response was seen both biochemically and densitometrically in all the groups, all biochemical turnover markers increased more in those randomized to TPTD monotherapy. Of particular note was the early increase in CTX, which was already significantly elevated at 1 month in the patients assigned to TPTD monotherapy, suggesting a truncation of the anabolic window in patients following this approach, similar to the findings in the studies discussed above with TPTD or PTH monotherapy after previous bisphosphonate treatment.[13] It appears that withdrawal of bisphosphonate results in exaggerated bone resorption, particularly in cortical bone, in which there is less buried bisphosphonate. As a result, BMD declined in the first 6 months in the hip (consistent with all TPTD or PTH monotherapy studies in bisphosphonate-experienced patients). The increases at both 6 and 18 months at both the spine and the hip were greater in those patients randomized to TPTD/Aln combination therapy compared with TPTD monotherapy, and at no time point did hip BMD decline in the combination therapy group (**Figure 5**). Differences between TPTD combination and monotherapy were less marked with Ral pretreatment. Volumetric BMD of the hip did not change in women who were switched to TPTD monotherapy but increased significantly at both 6 and 18 months in those who received combination therapy.[21] Volumetric BMD of the cortical compartment of the hip actually declined significantly in the TPTD monotherapy group. Although the strength of the hip, as assessed by finite element analysis, did not decline in the TPTD monotherapy group, implying that the decline in cortical BMD was not in an area most important for strength, hip strength increased significantly only with combination therapy.[21] (**Figure 6**). Again, differences between TPTD monotherapy and TPTD/Ral combination therapy were much less apparent. These findings have very important implications for the clinical use of TPTD in patients who have received previous antiresorptive therapy and are at high risk for hip and other skeletal sites that are rich in cortical bone. It may be that the withdrawal of the bisphosphonate actually facilitates an exaggerated bone resorption response to TPTD and offsets the expected positive bone balance, particularly in the cortical skeleton where there is little incorporated bisphosphonate.

TPTD followed by addition of Ral or Aln

Muschitz *et al.*[22] randomized 125 postmenopausal women who had received TPTD treatment for 9 months to subsequently stay on TPTD monotherapy or initiate combination therapy by adding Aln or Ral, while continuing TPTD. A majority of the subjects had previous osteoporosis treatment, including about 75% exposure to Aln before the initial 9 months of TPTD treatment. However, there are few details about the extent and recency of this treatment. Between 9 and 18 months, the serum CTX level was stable in the TPTD monotherapy group but declined with the addition of Ral and declined more prominently with the addition of Aln. Spine BMD by DXA increased more in the combination therapy groups (9.2% in the TPTD/Aln group and 10% in the TPTD/Ral group) than in the TPTD monotherapy group (6%). In the total hip, BMD increased significantly more in the TPTD/Aln combination group (7%) compared with either the TPTD/Ral combination group (4.2%) or TPTD monotherapy group (4.4%). There were similar differences in the femoral neck. Volumetric BMD changes in the spine were greater in both combination therapy groups than in the monotherapy group. In the hip, volumetric BMD increments (by QCT) were largest in the TPTD/Aln combination group and significantly higher for integral, trabecular and cortical BMD in the total hip and for integral and cortical BMD at the femoral neck compared with either TPTD monotherapy or TPTD/Ral combination therapy (**Figure 7**).[22]

Novel cyclic regimens of TPTD/PTH and bisphosphonates

Two studies evaluated combination regimens in which TPTD was given in 3-month cycles superimposed on continuing bisphosphonate treatment. The first investigation mentioned above randomized 126 women established on oral Aln to daily TPTD with ongoing Aln vs 3-month cycles of TPTD with ongoing Aln vs Aln monotherapy.[16] BMD changes were similar between the two arms of the study over 15 months. In the second trial, 44 women were randomized to receive concurrent PTH plus oral ibandronate concomitantly for 6 months, followed by ibandronate alone for 18 months vs two 1-year sequences of 3 months of PTH followed by 9 months of ibandronate.[23] Details

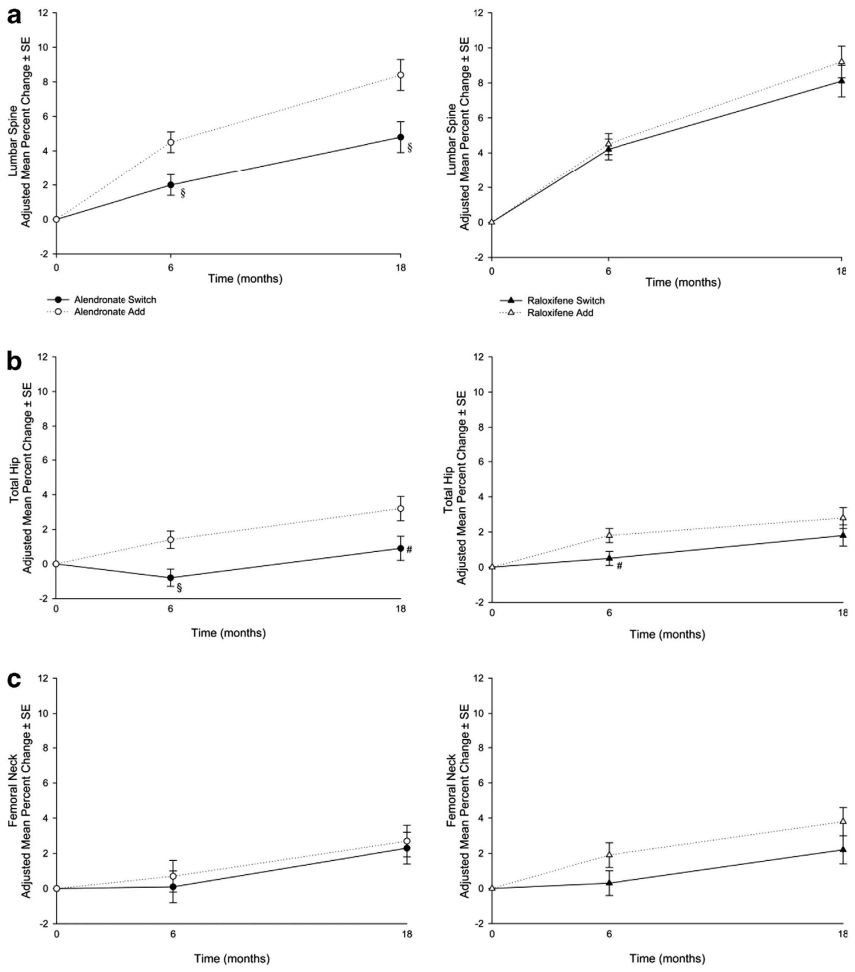

Figure 5 Percentage change in DXA BMD from baseline. A, Lumbar spine; B, total hip; C, femoral neck, by treatment group. Left panel shows prioralendronate groups, and right panel shows prior raloxifene groups. $^{\#}P<0.05$; and $^{\S}P<0.01$ for difference between groups within the alendronate or raloxifene stratum. Values are mean ± s.e. from Cosman *et al.*[20]

of previous osteoporosis medication were not reported in this second trial, although no patient was on osteoporosis medications for at least 1 month before enrollment. BMD changes at all sites were similar over the 2 years, consistent with the similar duration of PTH utilized in both arms of this study. In both studies, biochemical markers of bone formation increased during the second cycle of TPTD/PTH administration (although not necessarily to the same degree as seen during the first cycle).

Combination PTH Plus Antiresorptive Therapy in Men

TPTD plus Aln

Eighty-three men with osteoporosis were assigned to TPTD at 40 mcg per day, to Aln alone or to TPTD after 6 months of Aln pretreatment, with ongoing TPTD/Aln combination therapy.[24] A substantial proportion of men in both TPTD groups required dose adjustment (by 25–50%) due to hypercalcemia or side effects. After a total of 24 months of TPTD administration, spine BMD increased most in the TPTD monotherapy group (18.1%), compared with the combination group (14.8%) or Aln monotherapy group (7.9%). Similar trends were seen for the lateral spine and femoral neck; however, for the total hip and total body, increases were similar in the three treatment groups. In contrast, in the radius, BMD declined with TPTD monotherapy, with slight increases in the other groups. Spine trabecular bone density on QCT increased by 48% with TPTD alone, by 17% with the combination and by 3% with Aln alone.

TPTD plus risedronate

Walker *et al.*[25] randomized 29 men with low BMD to receive TPTD combined with risedronate vs TPTD or risedronate monotherapy. There was no significant difference between the spine BMD increment with the TPTD/risedronate combination treatment vs TPTD monotherapy (7% vs 5.7%) at 18 months. In the total hip and femoral neck, however, BMD increased significantly more with combination treatment (3.9% at total hip and 8.5% at the femoral neck) compared with TPTD monotherapy (0.3% and 3.9%, respectively). Biochemical marker levels for both PINP and CTX increased above baseline for the entire duration of the trial. With the PTH/Aln study,[4] the TPTD/Dmab study[8] and the PTH/Ibandronate study[23] in the combination groups, biochemical markers of bone resorption were below baseline for the entire trial. With the TPTD/Zol combination,[7] the mean CTX level was below baseline for the first 6 months of the study. Perhaps the difference in biochemical indices of bone resorption relates to risedronate's modest antiresorptive potency (at the dose utilized, compared

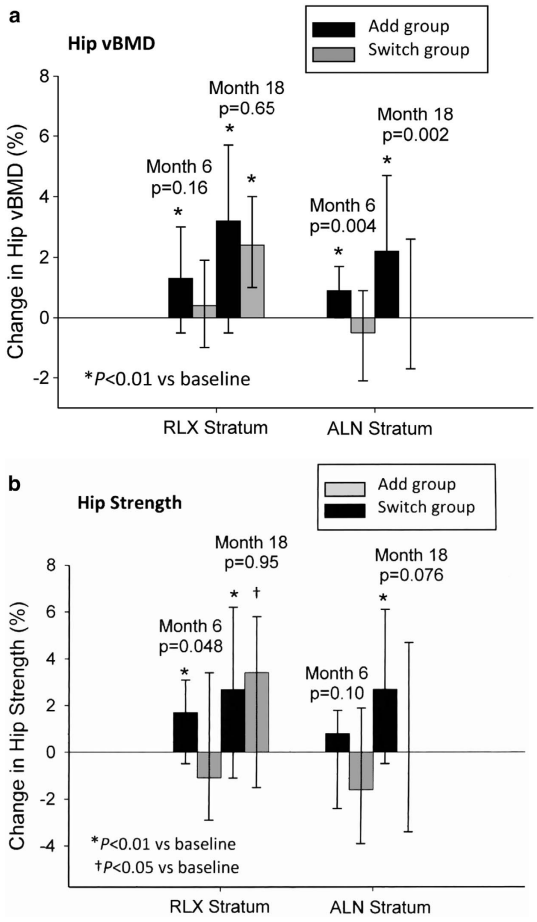

Figure 6 Effects of adding versus switching to teriparatide in postmenopausal women with osteoporosis pretreated with raloxifene or alendronate on (**a**) hip volumetric BMD at 6 and 18 months and (**b**) hip strength at 6 and 18 months. Note that statistically significant changes from baseline are indicated by footnote symbols, and *P* values from statistical comparisons between the Add and Switch groups in each stratum are shown above each pair of bars. Adapted from Cosman *et al.*[21]

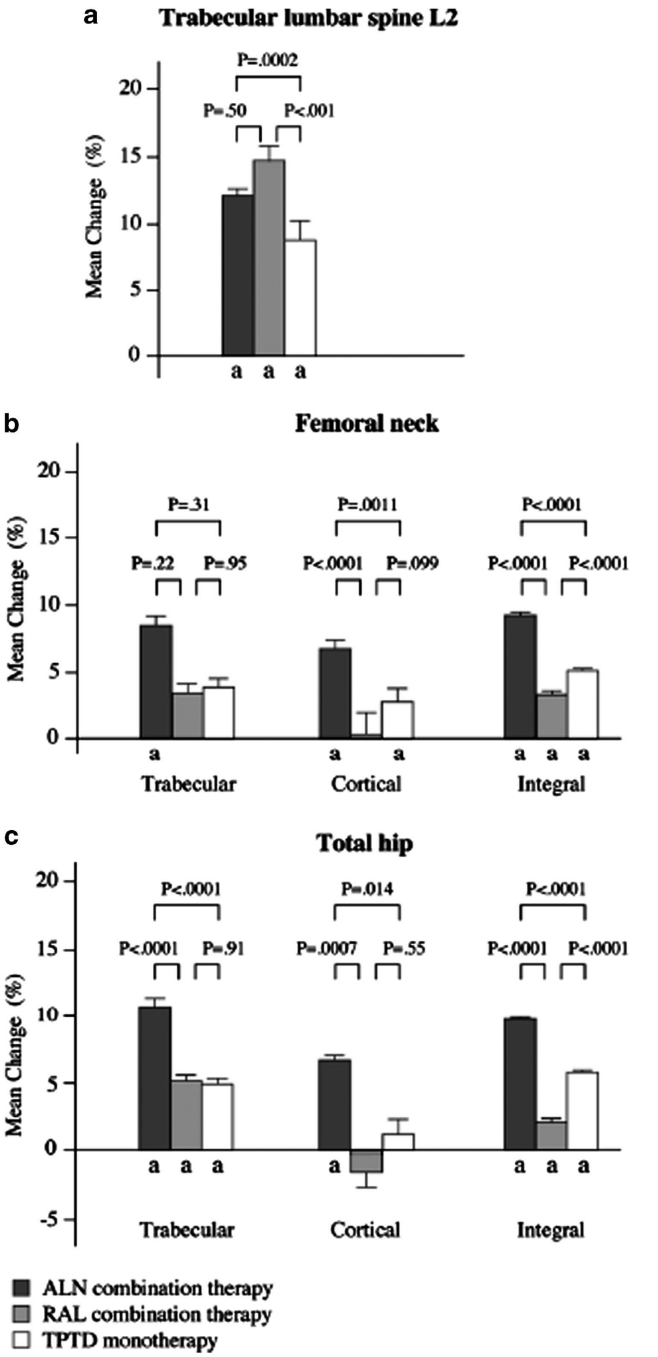

Figure 7 Mean percent changes (± s.e.m.) in volumetric BMD of (**a**) trabecular bone in 2nd lumbar vertebra; (**b**) cortical, trabecular, and integral bone in femoral neck and (**c**) total hip between randomization and at study endpoint. Values of *P* indicate differences between groups. a, $P<0.05$ within-group changes. TPTD = teriparatide; RAL = raloxifene; ALN = alendronate; L2 = 2nd lumbar vertebra. From Muschitz *et al.*[22]

with Aln, Zol or Ibandronate). In the study by Deal *et al.*,[3] in which TPTD was combined with Ral (another low-potency agent), the CTX level was above baseline at 3 and 6 months, although the increase was of lower magnitude with TPTD/Ral combination than with TPTD monotherapy.

Commentary and Conclusion

All TPTD/PTH combination studies with antiresorptive therapies produce unique effects, at least in terms of the magnitude of biochemical marker and BMD changes. However, there are some consistent findings, at least with regard to qualitative observations. First, it does appear that both HT and Ral are consistently permissive with the use of TPTD/PTH both in treatment-naive and treatment-experienced women, allowing additive effects of both agents in both spine and hip sites. With bisphosphonates, the impact of combination administration of an agent such as PTH with Aln or TPTD with Zol in treatment-naive women or TPTD with risedronate in men does not provide greater increments in spine BMD compared with TPTD/PTH monotherapy but does result in consistent improvements in hip BMD outcomes compared with PTH or TPTD monotherapy (in all studies utilizing the approved dose of TPTD). The improved hip BMD outcome from studies in treatment-naive individuals is also consistent with all combination treatment studies in bisphosphonate treatment-experienced women, in which PTH/TPTD monotherapy results in an early decline in hip BMD

compared with an increase in hip BMD with combination therapy. The only combination treatments that clearly show an additive benefit on spine BMD (in addition to hip BMD) are the TPTD/Dmab combination[8] or TPTD followed by combination TPTD/Aln at 9–18 months.[22] Of course there are many limitations to the currently available data. Most importantly, there are no adequately powered fracture outcome studies. Furthermore, when trying to distinguish the effects of treatment combinations in treatment-naive vs treatment-established individuals, it is not known how much time needs to elapse after treatment discontinuation to consider a patient 'treatment naive' again. This will be an increasingly difficult distinction as more and more medication holidays from bisphosphonates are being attempted. Full mineralization of newly formed bone may not be seen in short-term studies. DXA cannot measure all properties that might improve bone strength with TPTD therapy.

It is clearly time to reevaluate the potential benefits of combination therapy. Differences in BMD responses between combination treatment and monotherapy might be clinically meaningful in some patients. For example, in patients on previous bisphosphonates who sustain a hip fracture or who have a very low hip BMD or declining hip BMD while on their bisphosphonate, adding TPTD might provide a substantial benefit over continuing bisphosphonate monotherapy or switching to TPTD monotherapy. Furthermore, in treatment-naive (and previously treated) individuals with multiple previous fractures, particularly those involving spine and nonspine sites, certain combination treatments might be warranted above monotherapy to achieve optimal short-term benefits on bone mass and potentially bone strength.

Conflict of Interest

FC has received honoraria as a consultant, advisory board member or speaker from Eli Lilly, Amgen, Novartis and Merck.

References

1. Ste-Marie LG, Schwartz SL, Hossain A, Desaiah D, Gaich GA. Effect of teriparatide [rhPTH(1-34)] on BMD when given to postmenopausal women receiving hormone replacement therapy. *J Bone Miner Res* 2006;**21**:283–291.
2. Finkelstein JS, Wyland JJ, Lee H, Neer RM. Effects of teriparatide, alendronate, or both in women with postmenopausal osteoporosis. *J Clin Endocrinol Metab* 2010;**95**:1838–1845.
3. Deal C, Omizo M, Schwartz EN, Eriksen EF, Cantor P, Wang J *et al.* Combination teriparatide and raloxifene therapy for postmenopausal osteoporosis: results from a 6-month double-blind placebo-controlled trial. *J Bone Miner Res* 2005;**20**:1905–1911.
4. Black DM, Greenspan SL, Ensrud KE, Palermo L, McGowan JA, Lang TF *et al.* The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. *New Engl J Med* 2003;**349**:1207–1215.
5. Gluer CC, Genant HK. Impact of marrow fat on accuracy of quantitative CT. *J Comput Assist Tomogr* 1989;**13**:1023–1035.
6. Kuiper JW, van Kuijk C, Grashuis JL, Ederveen AG, Schutte HE. Accuracy and the influence of marrow fat on quantitative CT and dual-energy X-ray absorptiometry measurements of the femoral neck in vitro. *Osteoporos Int* 1996;**6**:25–30.
7. Cosman F, Eriksen EF, Recknor C, Miller PD, Guanabens N, Kasperk C *et al.* Effects of intravenous zoledronic acid plus subcutaneous teriparatide [rhPTH(1-34)] in postmenopausal osteoporosis. *J Bone Miner Res* 2011;**26**:503–511.
8. Tsai JN, Uihlein AV, Lee H, Kumbhani R, Siwila-Sackman E, McKay EA *et al.* Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial. *Lancet* 2013;**382**:50–56.
9. Cosman F, Nieves J, Woelfert L, Formica C, Gordon S, Shen V *et al.* Parathyroid hormone added to established hormone therapy: effects on vertebral fracture and maintenance of bone mass after parathyroid hormone withdrawal. *J Bone Miner Res* 2001;**16**:925–931.
10. Lindsay R, Nieves J, Formica C, Henneman E, Woelfert L, Shen V *et al.* Randomised controlled study of effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on oestrogen with osteoporosis. *Lancet* 1997;**350**:550–555.
11. Roe EB, Sanchez SD, del Puerto GA, Pierini E, Bacchetti P, Cann CE *et al.* Parathyroid hormone 1–34 (hPTH 1–34) and estrogen produce dramatic bone density increases in postmenopausal osteoporosis- results from a placebo-controlled randomized trial. *J Bone Miner Res* 1992;**12**(Suppl. 1):S137 (Abstr).
12. Cosman F, Nieves JW, Zion M, Barbuto N, Lindsay R. Effect of prior and ongoing raloxifene therapy on response to PTH and maintenance of BMD after PTH therapy. *Osteoporos Int* 2008;**19**:529–535.
13. Miller PD, Delmas PD, Lindsay R, Watts NB, Luckey M, Adachi J *et al.* Early responsiveness of women with osteoporosis to teriparatide after therapy with alendronate or risedronate. *J Clin Endocrinol Metab* 2008;**93**:3785–3793.
14. Boonen S, Marin F, Obermayer-Pietsch B, Simoes ME, Barker C, Glass EV *et al.* Effects of previous antiresorptive therapy on the bone mineral density response to two years of teriparatide treatment in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 2008;**93**:852–860.
15. Ettinger B, San Martin J, Crans G, Pavo I. Differential effects of teriparatide on BMD after treatment with raloxifene or alendronate. *J Bone Miner Res* 2004;**19**:745–751.
16. Cosman F, Nieves J, Zion M, Woelfert L, Luckey M, Lindsay R. Daily and cyclic parathyroid hormone in women receiving alendronate. *New Engl J Med* 2005;**353**:566–575.
17. McClung MR, San Martin J, Miller PD, Civitelli R, Bandeira F, Omizo M *et al.* Opposite bone remodeling effects of teriparatide and alendronate in increasing bone mass. *Arch Intern Med* 2005;**165**:1762–1768.
18. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY *et al.* Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *New Engl J Med* 2001;**344**:1434–1441.
19. Obermayer-Pietsch BM, Marin F, McCloskey EV, Hadji P, Farrerons J, Boonen S *et al.* Effects of two years of daily teriparatide treatment on BMD in postmenopausal women with severe osteoporosis with and without prior antiresorptive treatment. *J Bone Miner Res* 2008;**23**:1591–1600.
20. Cosman F, Wermers RA, Recknor C, Mauck KF, Xie L, Glass EV *et al.* Effects of teriparatide in postmenopausal women with osteoporosis on prior alendronate or raloxifene: differences between stopping and continuing the antiresorptive agent. *J Clin Endocrinol Metab* 2009;**94**:3772–3780.
21. Cosman F, Keaveny TM, Kopperdahl D, Wermers RA, Wan X, Krohn KD *et al.* Hip and spine strength effects of adding versus switching to teriparatide in postmenopausal women with osteoporosis treated with prior alendronate or raloxifene. *J Bone Miner Res* 2013;**28**:1328–1336.
22. Muschitz C, Kocijan R, Fahrleitner-Pammer A, Lung S, Resch H. Antiresorptives overlapping ongoing teriparatide treatment result in additional increases in bone mineral density. *J Bone Miner Res* 2013;**28**:196–205.
23. Schafer AL, Sellmeyer DE, Palermo L, Hietpas J, Eastell R, Shoback DM *et al.* Six months of parathyroid Hormone (1-84) administered concurrently versus sequentially with monthly ibandronate over two years: the PTH and ibandronate combination study (PICS) randomized trial. *J Clin Endocrinol Metab* 2012;**97**:3522–3529.
24. Finkelstein JS, Hayes A, Hunzelman JL, Wyland JJ, Lee H, Neer RM. The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. *New Engl J Med* 2003;**349**:1216–1226.
25. Walker MD, Cusano NE, Sliney Jr J , Romano M, Zhang C, McMahon DJ *et al.* Combination therapy with risedronate and teriparatide in male osteoporosis. *Endocrine* 2013;**44**:237–246.