INTRODUCTION

As a result of its unique mechanism of action, parathyroid hormone (PTH), the only approved anabolic therapy for bone, produces larger increments in bone mass (particularly in the spine), than those seen with antiresorptive therapies. PTH treatment first stimulates bone formation and subsequently stimulates both bone resorption and formation; the balance remains positive for formation, even in this latter phase of PTH activity [1–3]. The growth of new bone with PTH permits restoration of bone microarchitecture, including improved trabecular connectivity and enhanced cortical thickness [4, 5]. Bone formation may also be induced on the outer periosteal surface [6–8], possibly affecting bone size and geometry, with additional beneficial effects on bone strength [6–12], though this has not been conclusively proven.

This chapter reviews the clinical trial data using PTH as both monotherapy and in combination and sequential regimens with antiresorptive agents in women and men and briefly overviews trials in a few special populations [13]. PTH will be referred to as teriparatide when it is the recombinant or biochemically synthesized human PTH aminoterminal (1-34) fragment and PTH (1-84) as the intact human recombinant molecule. PTH without other designation denotes either of the compounds. Currently, PTH is routinely given as a daily subcutaneous injection.

CANDIDATES FOR ANABOLIC THERAPY

Good candidates for PTH are women and men who are at high risk of future osteoporosis-related fractures, including those with vertebral compression fractures (clinical or radiographic), other osteoporosis-related fractures with bone mineral density (BMD) in the osteoporosis range, or very low BMD even in the absence of fractures (T-score below −3). PTH should also be recommended for individuals who have been on prior antiresorptive agents, and who have had a suboptimal response to treatment, defined as incident fractures or active bone loss during therapy, or who have persistent osteoporosis despite therapy. Individuals who might be at elevated risk for osteosarcoma, such as those with a history of Paget’s disease, bone irradiation, unexplained elevations in alkaline phosphatase, adults with open epiphyses, and children should not receive PTH treatment. Furthermore, people with metastatic bone cancer, primary bone cancer, myeloma, hyperparathyroidism and hypercalcemia should not receive PTH. The PTH treatment course is 18–24 months, a function of the duration of the pivotal...
fracture trial [14] as well as the finding that the effect appears to wane after this time.

**POSTMENOPAUSAL OSTEOPOROSIS**

**Teriparatide (TPTD) as monotherapy**

The largest study of TPTD action by Neer and colleagues included 1,637 postmenopausal women with prevalent vertebral fractures and an average age of 70 [14] who were randomized to receive TPTD [20 or 40 mcg], or placebo by daily subcutaneous injection. After a median treatment period of 19 months, TPTD increased spine BMD by 9.7% [20 mcg dose] and 13.7% [40 mcg dose], and hip and total body bone densities to a lesser extent. A small decline in radius BMD was seen (significant at the higher dose). Vertebral fracture risk reductions were 65% and 69%, respectively, with an absolute risk of 4% in the high dose group [19/434], and 5% in the low dose group [22/444], versus 14% in the placebo group [64/448]. There was also a reduction in the incidence of new or worsening back pain in both TPTD groups. In patients with incident vertebral fractures, height loss was reduced [mean 0.21 cm lost in TPTD compared with 1.11 cm in placebo]. Incident nonvertebral fractures were reduced by 40% (6% incidence in TPTD versus 10% in placebo) and by 50% for those defined as fragility fractures, as determined by individual investigators [no differences between TPTD groups]. Despite the small decline in radius BMD, there was an apparent reduction in wrist fracture occurrence in TPTD-treated women [though too small a number to statistically evaluate]. There were also numerically fewer hip fractures in TPTD-treated patients, though again too few to evaluate statistically.

Although transient increases in serum calcium were common when measured within 6 hours of the TPTD injection, sustained increases [confirmed with at least one subsequent measurement] were seen in only 3% of patients assigned to the 20-mcg group and 11% of those assigned to the 40-mcg group. There were no significant differences between TPTD or placebo groups with respect to deaths, hospitalizations, cardiovascular disorders, renal stones, or gout, despite an average increase in 24-hour urine calcium of 40 mg per day and an increase in serum uric acid of up to 25%. Animal studies have shown that administration of high-dose TPTD to rodents is associated with osteogenic sarcoma, dependent on dose and duration of administration [15, 16]. In patients with endogenous hyperparathyroidism or parathyroid cancer there is no evidence of an increased risk of osteogenic sarcoma. Furthermore, in over 9 years of postmarketing experience and about 3 million TPTD prescriptions, there is no evidence of an increased risk of osteosarcoma [17, 18]. Overall new cancer diagnoses occurred in fewer patients assigned to TPTD compared with placebo (2% vs 4%, p = 0.03 for the 20-mcg and 0.07 for the 40-mcg group) [14]. Possible side effects of TPTD are dizziness and leg cramps, redness and irritation at injection sites, headache, nausea, arthralgias, myalgias, lethargy, and weakness. The higher dose produced more side effects and withdrawals. TPTD-induced BMD changes in the Neer trial were not dependent on patient age, baseline BMD, or prior fracture history [19], but were related to baseline biochemical bone turnover indices [20]. Furthermore, early PTH-induced changes in bone turnover markers [at 1 and 3 months] were predictive of the ultimate change in spine BMD and bone structure [20, 21]. Finally, when women over age 75 years were examined relative to women younger than 75 years, age did not affect the safety or efficacy [22]. A longer duration of TPTD 14 months or more was associated with greater reduction in nonvertebral fracture incidence and reduced back pain, compared with shorter duration of therapy [23].

Two smaller studies have evaluated surrogate endpoints comparing TPTD to alendronate [1, 12]. In the first [12], where 146 women were randomized to receive TPTD (40 mcg/day) versus alendronate (10 mg/day), spine BMD increased 15% in the TPTD group versus 6% in the alendronate group after 1 year. Although there were fewer fractures in the TPTD than the alendronate group at the end of 14 months (3/73 vs 10/73), several of the fractures were minor (toe fractures).

McClung et al. studied 203 postmenopausal women with osteoporosis randomized to receive TPTD [20 mcg/day] or alendronate for 18 months [1]. Biochemical turnover increased substantially in the TPTD group [formation earlier than resorption] and declined substantially in the alendronate group [resorption earlier than formation]. In TPTD-treated women, markers peaked within 6 months, suggesting developing resistance, as has been seen in other TPTD trials [14, 24, 25]. Spine BMD by dual energy X-ray absorptiometry [DXA] increased 10.3% in TPTD-treated women versus 5.5% in alendronate-treated women. Volumetric spine BMD by quantitative computed tomography [QCT] in a subset of women increased 19% in the TPTD versus 3.8% in the alendronate group. Femoral neck BMD by DXA increased similarly in both groups, though by QCT, cortical volumetric femoral neck BMD increased 7.7% in the alendronate group and declined 1.2% in the TPTD group. The spine BMD change correlated with the PINP increment in the TPTD group and with the PINP decrement in the alendronate group [r = 0.53 and −0.51, respectively]. Clinical fracture incidence was similar in the TPTD [nine fractures] and alendronate [eight fractures] groups, but no radiographs were done to evaluate vertebral fractures. Moderate or severe back pain was reported significantly less often in women assigned to TPTD versus alendronate [15% vs 33%, p = 0.003].

TPTD delivered by a transdermal microneedle patch as a 30-minute daily wear in doses of 20, 30, or 40 mcg/day, versus placebo or subcutaneous injection of TPTD 20 mcg, over 6 months demonstrated that the 40-mcg patch had a BMD spine increase similar to the subcutaneous TPTD and the BMD response at the total hip was greater [26, 27]. In an investigation to determine the
importance of TPTD with an escalating daily dose (20 to 30 to 40 mcg) versus constant daily dose (30 mcg) in patients with osteoporosis, no difference was found over 6 months [28].

**PTH(1-84) as monotherapy**

In a dose ranging study, 217 women were randomized to 50, 75, or 100 mcg of PTH(1-84) or placebo. There was a dose-dependent increase in spine BMD; however, no increase in hip or total body BMD. The Treatment of Osteoporosis (TOP) trial was an 18-month, randomized, double-blind, study of 2,532 postmenopausal women with osteoporosis randomized to 100 mcg of recombinant PTH(1-84) or placebo by daily subcutaneous injection [27]. The mean age was 64, and 19% of subjects had a prevalent vertebral fracture. The average change in spine BMD was 7% in PTH(1-84)-treated subjects compared to those on placebo. In the per protocol adherent population (n = 1870), new or worsened vertebral fracture incidence was 3.4% in placebo and 1.4% in PTH(1-84) (relative risk reduction 58%), with reductions in both those with and without prevalent vertebral fracture, but nonvertebral fracture incidence was not reduced. The incidence of hypercalcemia was significantly higher in PTH(1-84)-treated women (28.3% vs 4.5% in placebo) [27]. PTH(1-84) therapy is currently available in Europe. There have been no head to head trials comparing PTH(1-84) with TPTD.

**PTH and antiresorptive combination/ sequential therapy**

Although PTH and antiresorptive agents could theoretically produce additive or even synergistic effects on bone strength, studies on combination therapy have shown different outcomes based on skeletal site (spine vs hip), type of measurement (DXA vs QCT), specific antiresorptive therapy utilized, and whether patients are previously treatment naïve or treatment experienced. Furthermore, in treatment-experienced patients, there appear to be differences in outcome based on whether the prior antiresorptive agent is continued or stopped when TPTD is initiated.

**Treatment naïve women: PTH and bisphosphonates**

Black et al. randomized 238 previously treatment naïve women to PTH(1-84) with alendronate versus each agent alone in a blinded fashion [29]. The BMD of the antero-posterior (AP) spine by DXA increased similarly in the PTH(1-84) alone and combination groups (6.3% and 6.1%, respectively). Total hip BMD (by DXA) increased in the combination group (1.9%) but not with PTH(1-84) alone (0.3%). Radial BMD declined more with PTH(1-84) 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(1-84) alone and combination groups, trabecular spine BMD increased more with PTH(1-84) alone (25.5%) than with the combination (12.6%). In contrast, QCT-assessed cortical bone density declined in the hip (−1.7%) with PTH(1-84) alone but was unchanged in the combination group. The cortical volume of the femoral neck of the hip [but not the total hip] increased significantly in PTH(1-84)-treated versus combination-treated women, but this was not due to periosteal expansion. The DXA results demonstrated no clear evidence of the additive effect with combination therapy compared to PTH(1-84) alone in the spine. However, hip BMD increments were superior with the combination. Evidence of a blunted effect with combination treatment was apparent only by QCT. Since single-energy QCT-based BMD increments induced by PTH may be artifactualy elevated by reductions in bone marrow fat [30, 31], it is unclear how important these findings are compared to DXA-based results. There were only a small number of fractures, with no group differences; incident morphometric vertebral fractures were not reported.

An unblinded study where 93 women were randomized to receive alendronate for 6 months prior to giving TPTD (versus either agent alone) suggested that BMD gains in both spine and hip by DXA were lower in those given TPTD after the brief course of alendronate (and with continued alendronate), compared to those given TPTD alone [32]. The difference in the DXA BMD of the spine was not significant if the groups were restricted to those who did not discontinue study medication prematurely. A larger difference in BMD between the TPTD alone and combination groups was seen by QCT. This is one of few PTH trials where treatment duration was a full 24 months; hip and femoral neck BMD levels increased most markedly during the latter year of treatment. However, radius BMD declined more in women who received TPTD alone compared to combination treatment, and the change in total body BMD did not differ between groups. Furthermore, the PTH dose used here was double the approved dose (40 mcg daily TPTD), and since PTH effects on BMD are clearly dose dependent, the clinical significance of these data is unclear.

Cosman et al. randomized 412 treatment naïve postmenopausal women (mean age 65, mean spine BMD T-score −2.9), to receive daily TPTD, an intravenous zoledronic acid (ZOL) infusion, or a combination of daily TPTD and an intravenous zoledronic acid infusion in a partial double-blind fashion (TPTD open label) [33]. With combination therapy, the bone resorption marker CTX declined similarly to that with ZOL alone, whereas the bone formation marker PINP declined only modestly compared to that seen with ZOL alone. Also with combination therapy, the spine BMD increase was similar to that seen with TPTD alone (7.5% vs 7.0% TPTD alone), whereas the hip BMD increase was larger (2.3% vs 1.1%) as was the femoral neck BMD increase (2.2% vs 0.1%). In the combination groups, peak BMD increments were reached the fastest at both sites. Although fractures were reported only as adverse events, the fractures were adjudicated. Clinical fractures occurred in 9.5% of patients.
in the ZOL alone group, 5.8% of the TPTD alone group and 2.9% of the combination group (p < 0.05 vs ZOL alone).

**Treatment naïve women: Teriparatide and raloxifene**

In a 6-month, double-blind, placebo-controlled trial, Deal et al. randomized 137 postmenopausal treatment-naïve women to receive TPTD or TPTD plus raloxifene. The bone formation marker PINP rose similarly in the two groups, while the bone resorption marker (CTX) increased more in the TPTD alone group. Spine BMD increments were similar in the two groups, while hip BMD increased more in the TPTD plus raloxifene group [34].

**PTH therapy in women on established bisphosphonate or raloxifene treatment**

Patients maintained and stabilized on long-term antiresorptive treatment are a distinct, but clinically very important population, since many of these patients have fractures or do not achieve a BMD above the osteoporotic range, and thus might benefit from anabolic therapy. At least 50% of all PTH treatment is initiated in patients who have received prior antiresorptive agents. Possible explanations for differences between treatment-naïve and treatment-experienced women include: reduced active bone surface in the treatment experienced, the increase in endogenous PTH seen for up to 12 months when potent antiresorptive agents are administered to treatment naïve individuals [which might produce a different response to exogenously administered PTH] and perhaps unique effects on osteoclast and/or osteoblast activation in treatment experienced individuals.

Prior studies evaluating TPTD treatment in treatment experienced women have followed two basic designs: antiresorptive agents are stopped when TPTD is started [35, 36, 37], or antiresorptive agents are continued when TPTD is started [38, 39]. Outcomes differ with these distinct study designs, particularly when the antiresorptive agents are oral bisphosphonates. In studies where 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 where TPTD is added to ongoing bisphosphonate.

**Studies where antiresorptive therapy was stopped when TPTD was started**

In an observational study where TPTD was given to women after cessation of long-term alendronate or raloxifene [35], bone turnover markers increased, as did spine BMD, but these increases were somewhat delayed and of lower magnitude in patients pretreated with alendronate compared to those in patients pretreated with raloxifene. A transient reduction in hip BMD was seen at 6 months in the group previously on alendronate but this reversed by the 18-month measurement.

Similarly, in an observational study of women previously treated with risedronate (n = 146) or alendronate (n = 146) biochemical responses showed increments in bone resorption already within 1 month in both groups of patients [36], an outcome not seen within the first month in treatment-naïve patients treated with TPTD [1, 14]. Furthermore, increases in bone resorption at 1 month are not seen in patients on prior antiresorptive therapy when the antiresorptive agent is continued during administration of TPTD [24, 38, 40]. In this trial [36], Miller found that spine BMD increases were not as great in patients receiving TPTD when the bisphosphonate was stopped, and hip BMD was below baseline for both the patients on long-term risedronate as well as those on long-term alendronate for the duration of the 1-year trial.

Finally, the average spine BMD in a cohort of women who had been on prior bisphosphonates and then switched to TPTD increased less than in a cohort of treatment-naïve women [9.8–10.2% for the bisphosphonate treated and 13.1% for treatment-naïve women]. Furthermore, women on prior bisphosphonates who were switched to TPTD had a decline in hip BMD over the first year of treatment [41].

In contrast, in 126 women previously treated with long-term alendronate (mean age 68 years, mean alendronate duration 3.2 years), the subjects were randomized to continue alendronate and to receive daily TPTD, cyclic TPTD [given in a 3-month on/3-month off regimen], or raloxifene alone [38]. In just over 15 months, spine BMD rose 6.1% in the TPTD group and 5.4% in the raloxifene group (p < 0.001 for each TPTD group, no group difference), both higher increments than the average changes seen in the studies above when the underlying bisphosphonate was discontinued. Moreover, mean hip BMD did not decline at any time point during this study.

In a separate study, Cosman et al. evaluated postmenopausal women on raloxifene for at least 1 year (n = 42) with persistent osteoporosis and randomized them to stay on raloxifene alone or to receive raloxifene plus TPTD. The TPTD plus raloxifene group had an increment of about 10% in the lumbar spine and 3% in the total hip, whereas those randomized to the raloxifene alone group had no BMD change [39]. Increases in both biochemical turnover markers at 3 months correlated with increases in spine BMD at 1 year.

In order to formally compare the effect of continuing versus stopping the antiresorptive agent when TPTD is begun in a randomized trial, 198 women treated with prior antiresorptive agents for at least 1 year (102 women on alendronate and 96 on raloxifene) were studied [42]. Women within each antiresorptive category were randomized to continue or stop their antiresorptive when TPTD was initiated. Although an anabolic response was seen both biochemically and densitometrically in all groups of patients, biochemical turnover markers increased more in those randomized to the switch design. Of particular interest was the early increase in CTX, which was already significantly elevated at 1 month in the patients who were switched from alendronate to...
TPTD, suggesting a truncation of the anabolic window in patients following this approach. As a result, BMD declined in the first 6 months in the hip (as seen in all switch studies above) and did not increase as much in the spine. The increases at both 6 and 18 months at both spine and hip were greater in those patients in whom TPTD was added to the ongoing alendronate, compared to those who switched to TPTD, and at no point in time did hip BMD decline in the combination group. Differences between combination and switch protocols were less marked with raloxifene pretreatment though hip BMD increased more in the combination than switch group.

These results suggest that there may be a role for combination therapy, particularly after prior bisphosphonate treatment. This might be particularly important in patients who begin with very low hip BMD and/or those in whom hip fractures have already occurred, where any early decline in BMD might be detrimental and a greater increase in BMD over 18 months a favorable outcome.

**PTH and hormone therapy**

In 52 women with osteoporosis (average age 60 years) treated with hormone therapy (HT) [24, 40], daily TPTD produced rapid increases in markers of bone formation, and delayed increases in markers of bone resorption [40]. This period of time, where 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 [24]. The mechanism of this apparent resistance to TPTD has still not been determined. BMD increased by about 14% over 3 years in women receiving TPTD + HT, with evidence of the most rapid rise in BMD within the first 6 months. Total body and hip BMD increased by 4% in patients on TPTD + HT. Although the study was not powered to assess fracture occurrence, after 3 years of treatment, vertebral deformity occurrence was significantly reduced in patients receiving TPTD + HT compared to HT alone [24].

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 versus placebo [43]. No fracture data were presented from this trial, and the data have never been published in a peer-reviewed journal. A third study was performed in 247 women, where one subgroup had been on prior HT (as in the previously discussed two trials) and a second subgroup consisted of treatment-naïve women about to receive HT for the first time [44]. In the former group, there were BMD increments of approximately 11% in the spine and 3% in the total hip in women randomized to TPTD (40mcg per day). In the women receiving de novo HT, there were increases due to HT itself [4% in the spine and 2% in the total hip], and 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 not synergistic.

**PTH TREATMENT OF MEN**

In a small study, men with idiopathic osteoporosis were randomized to receive TPTD or placebo [25]. Biochemical markers of bone turnover increased rapidly with TPTD administration, and spine BMD rose about 12%, with a plateau between 12 and 18 months. In the femoral neck and total hip, BMD increased 5% and 4%, respectively, and radius BMD did not change significantly.

A subsequent multicenter trial of TPTD [18] was performed in 437 men (mean age 49 years) with primary idiopathic or hypogonadal osteoporosis. Subjects were randomized to TPTD 20 or 40mcg daily, or placebo. After approximately 1 year, spine BMD rose 5.4% and 8.5% in the 20mcg and 40mcg groups, respectively, with no change in the placebo group. There were also dose-dependent increases in BMD at hip sites and total body. Of the original enrollees, 355 men participated in an observational follow-up study. Lateral spine radiographs repeated after approximately 18 months of follow-up (including the use of antiresorptive therapy in a substantial proportion of the men) showed a 50% reduction in vertebral fracture risk in those men initially assigned to TPTD compared to those who had received placebo (p = 0.07) [45].

In a third study, 83 men with osteoporosis were assigned to TPTD at 40mcg/day, alendronate alone, or TPTD after 6 months of alendronate pretreatment (with ongoing alendronate [26, 46]). 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 alone group [18.1%], compared to that in the combination group [14.8%] or alendronate alone [7.9%]. Similar trends were seen for the lateral spine and femoral neck, but for the total hip and total body, increases were similar in the three treatment groups. In contrast, in the radius, BMD declined in the TPTD alone group with slight increases in the other groups. Spine trabecular bone density on QCT increased 48% with TPTD alone, 17% with the combination, and 3% with alendronate alone.

Leder and colleagues [47] examined the BMD changes after discontinuation of TPTD. While the initial improvements in spine and hip BMD were similar in men and women, after TPTD was discontinued following 24 months of TPTD in eugonadal men and postmenopausal women, spine BMD decreased 4.1% in men compared to 7.1% in women over the next 12 months. Bone mass was stable at the hip in men, but decreased in women suggesting an even greater need for antiresorptive follow-up treatment in women.
Parathyroid Hormone Treatment for Osteoporosis

**PTH IN SPECIAL POPULATIONS**

**Glucocorticoid-Treated patients**

PTH could conceivably be a preferred treatment for glucocorticoid osteoporosis, since some of the major pathophysiologic skeletal problems with glucocorticoid administration are reduced osteoblast function and lifespan, both of which might be counteracted by PTH. Women with a variety of rheumatologic conditions on glucocorticoids and treated with hormone therapy were randomized to TPTD + HT or continued HT alone [48]. TPTD resulted in a 12% increase in spine BMD by DXA and a smaller increase in femoral neck BMD. No fracture results were reported.

In an 18-month active comparator trial of TPTD versus alendronate for the treatment of glucocorticoid-induced osteoporosis, patients treated with TPTD had BMD increases of 7.2% at the spine and 3.8% at the total hip, both significantly greater than the changes of 3.4% at the spine and 2.4% at the hip seen with alendronate therapy [49]. Furthermore, fewer new vertebral fractures occurred in the TPTD group compared to the alendronate group (0.6% vs 6.1%, p = 0.004). At 36 months, TPTD compared to alendronate resulted in 11% vs 5.3% increases at the lumbar spine, 5.2% vs 2.7% at the total hip, 6.3% vs 3.4% at the femoral neck [all p = 0.001], in addition to fewer vertebral fractures [1.7% TPTD vs 7.72 alendronate] [50]. There were no differences in nonvertebral fractures between the groups.

**Fracture repair**

PTH could potentially accelerate fracture repair. In a study with postmenopausal women who sustained a radial fracture, TPTD 20 mcg shortened time to healing, though this effect was not seen with TPTD 40 mcg [51]. Further studies are needed.

**PERSISTENCE OF EFFECT**

A series of observational studies suggests that BMD is lost in individuals who do not take antiresorptive agents after cessation of TPTD or PTH[1-84], whereas antiresorptive therapy can maintain PTH-induced gains or even provide further increments in BMD after a course of PTH [24, 45, 48, 52–54]. Black et al. have now provided clinical trial confirmation of this observation [55]. Subjects originally randomized to 1 year of treatment with PTH[1-84] were subsequently randomized to receive alendronate or placebo for an additional year. Over 2 years, women who received alendronate following PTH[1-84] had significant increases in spine BMD of 12.1% compared to 4.1% in women in the PTH[1-84] followed by placebo. Trabecular bone at the spine assessed by QCT demonstrated a 31% increase in women on PTH[1-84] followed by alendronate, compared to 14% in those assigned to PTH[1-84] followed by placebo. BMD at the femoral neck and total hip was increased above baseline in all groups except those receiving PTH followed by placebo. These data suggest that after 1 year of PTH treatment, the gains in bone mass are preserved or further improved with alendronate but lost in patients not on antiresorptive therapy. In women enrolled in the Fracture Prevention Trial [14], a 30-month observational follow-up, after discontinuation of TPTD indicated that nonvertebral fracture reduction risk remained lower compared with the prior placebo group, but the difference was not significant for the 20-mcg dose. The ad lib use of antiresorptive treatments in both groups complicates the interpretation of these findings [56].

**RECHALLENGE WITH PTH**

Women originally randomized to daily or cyclic TPTD in addition to ongoing alendronate were followed for a year after TPTD was discontinued [57]. BMD remained stable in these women during this year. A second 15-month course of TPTD was given to those volunteers who still had osteoporosis. The rechallenge with TPTD produced similar biochemical and BMD changes to those seen during the first course of therapy [57]. In a study by Finkelstein and colleagues [58], men and women who completed a 30-month randomized trial that included TPTD, alendronate, or the combination were rechallenged with TPTD following a 12-month discontinuation phase of TPTD. After 12 months of TPTD rechallenge, BMD of the spine increased but the increment was attenuated compared to the initial TPTD treatment.

**Cost-Effectiveness of TPTD**

Liu and colleagues examined the cost-effectiveness of TPTD, alendronate, or usual care of calcium and vitamin D only [59]. The cost of 2 years of TPTD followed by alendronate was $156,500 per quality-adjusted life year (QALY) compared with alendronate. Alendronate alone was $11,600 per QALY compared to usual care, and TPTD alone was $172,300 per QALY compared to usual care. The cost-effectiveness of TPTD improved with increasing age and lower BMD, suggesting TPTD may be cost effective for high risk patients.

**CONCLUSION**

PTH is a unique approach to osteoporosis treatment. Because of the underlying effects it produces on the microarchitecture, macroarchitecture, and mass of bone, PTH may be able to ensure more long-term protection...
against fracture occurrence than antiresorptive agents alone; however, data proving this principle are lacking. Antiresorptive agents are clearly needed after PTH to maintain PTH-induced gains. There are still many unanswered questions concerning PTH therapy, including the optimal duration and regimen of therapy, and the mechanism underlying resistance to PTH effect after 18 months. Different PTH peptides and alternative forms of delivery (oral, nasal, inhaled, transdermal) are currently under study.

REFERENCES


47. Leder BZ, Neer RM, Wyland JJ, Lee HW, Burnett-Bowie SM, Finkelstein JS. 2009. Effects of teriparatide...
Osteoporosis

48. Lane NE, Sanchez S, Modin GW, Genant HK, Pierini E, Arnaud CD. 2000. Bone mass continues to increase at the hip after parathyroid hormone treatment is discontinued in glucocorticoid-induced osteoporosis: Results of a randomized controlled clinical trial. J Bone Miner Res 15(5): 944–51.