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Parathyroid Hormone as an Anabolic Skeletal Therapy

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Contents

Abstract

The quest for effective treatment for osteoporosis merits great attention because of the widespread prevalence of this disease, which is not only associated with fragility fractures, but also with significant morbidity and mortality. The efficacy of the antiresorptive drugs in this disease is achieved by reducing bone turnover, increasing bone density and improving other aspects of bone quality. This article concentrates on another approach to the treatment of osteoporosis, namely the use of anabolic therapy, which has even greater prospects for improving bone quality.

Parathyroid hormone (PTH) is currently available only as the recombinant amino-terminal fragment, PTH(1-34), known as teriparatide. The full-length molecule, human PTH(1-84), is currently being investigated, as are other PTH molecules. Teriparatide improves bone quality through actions on bone turnover, bone density, bone size and bone microarchitecture. In postmenopausal women with osteoporosis, teriparatide reduces the incidence of vertebral and nonvertebral

fractures. In individuals who have previously been treated with an antiresorptive agent, the subsequent actions of teriparatide on bone density are transiently delayed if bone turnover has been markedly suppressed. Combination therapy with teriparatide or PTH(1-84) and an antiresorptive agent does not appear, at this time, to offer advantages over the use of PTH or an antiresorptive agent alone. However, in order to maintain the densitometric gains in bone density obtained with PTH, it is important to follow its use with that of an antiresorptive agent.

Anabolic agents represent an important new advance in the treatment of osteoporosis. Until now, the mainstay of therapy for osteoporosis has been drugs with an antiresorptive mechanism. Drugs such as estrogen, raloxifene, alendronate (alendronic acid), risedronate (risedronic acid), ibandronate (ibandronic acid) and calcitonin all inhibit osteoclast-mediated bone loss and, thus, reduce bone turnover.[1-7] This reduction in bone turnover leads to a reduction in the frequency at which new bone remodelling units are activated.[8,9] This mechanism, combined with a greater inhibition of bone resorption than bone formation, leads to better bone balance and a smaller remodelling space.[10] Thus, the antiresorptive agents increase bone density and mineralisation density and, as has recently been shown for the bisphosphonates, maintain skeletal microarchitecture.

The concept of an anabolic skeletal agent is based upon a therapeutic mechanism that is entirely distinct from the inhibition of bone resorption. The mechanism of anabolic agents is targeted to processes associated with bone formation. By stimulating bone formation to a greater extent, and earlier than bone resorption, anabolic agents have the potential to not only increase bone density but also to improve the microarchitecture of bone. Such actions even provide the potential for the reconstruction of the skeletal microarchitecture, an endpoint not shared by any of the antiresorptive agents.[11] The most promising skeletal anabolic agent to date, and the only one available throughout the world at this time, is parathyroid hormone (PTH). The first form of PTH to be studied and approved for the treatment of patients with osteoporosis was the amino-terminal fragment of human PTH [hPTH(1-34)]. This peptide is known generically as teriparatide. Teriparatide appears to contain all of the classical anabolic properties of the full-length molecule, PTH(1-84). Teriparatide can refer either to synthetic human PTH(1-34) or to the recombinant human form of PTH(1-34). Most of the reports summarised in this article have examined teriparatide. More recently, PTH(1-84) has been the subject of major clinical trials. When relevant, clinical data from these newer trials are summarised also. When reference is made to full-length PTH, the term PTH(1-84) is used. When comments are made to refer to any form of PTH, we simply use the term PTH.

1. Pharmacokinetics of Teriparatide in Humans

The pharmacokinetic profile of teriparatide is shown in figure 1. Data from the largest study in postmenopausal women show that serum calcium levels peak between 4 and 6 hours after injection, but remain within the normal physiological range, with the average increment being about 0.8 mg/dL. Serum calcium eventually returns to baseline levels prior to the next dose when administered once daily.[12] In the major phase III trial of teriparatide, there was a very small, insignificant incidence of hypercalcaemia when the approved 20μg dose was used.[12] The peak circulating concentration of teriparatide, equivalent to approximately 2- to 2.5-fold the usual circulating level of endogenous PTH, is reached 45–60 minutes after administration; complete disappearance of teriparatide occurs within 4–6 hours.[13,14] During the time that teriparatide is detectable in the circulation, PTH(1-84), the native secretory form of PTH, is not detected.[13] As the level of teriparatide falls, the level of endogenous PTH rises. The total amount of PTH to which a

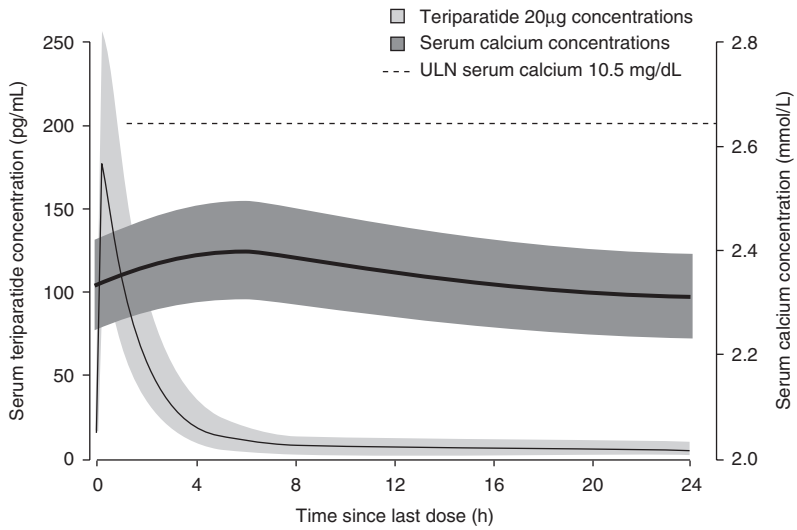

Fig. 1. Pharmacokinetic profile of teriparatide with resulting changes in serum calcium.[14] Mean ± 25th to 75th percentiles. **ULN** = upper limit of normal.

subject is exposed when receiving teriparatide is actually the same amount of PTH that would be secreted under normal circumstances over a 24-hour period.[13] Thus, the response to treatment is not due to a difference in the cumulative exposure to PTH, but rather to the changes in skeletal dynamics triggered by the intermittent, pulsatile administration of PTH.

PTH(1-84) has a longer half-life than teriparatide, with serum levels peaking at 120 minutes and disappearing from the circulation after 8 hours.[15,16] Recombinant PTH-related protein, PTHrP,[17] which is also being investigated as a potential therapy for osteoporosis, has a very short half-life, with serum levels peaking at 15 minutes and disappearing from the circulation after only 1–2 hours.[17] It is not known whether these differences in pharmacokinetics will be important in terms of any differences that might be appreciated in the clinical effects of teriparatide versus PTH(1-84) versus PTHrP.

2. Indications for Teriparatide

Teriparatide is approved in the US for the treatment of osteoporosis in postmenopausal women and in men with osteoporosis who are at high risk for fracture. These indications do not provide a specific definition for 'high risk for fracture'. Certainly, if a patient has already sustained a fragility fracture, there is greater probability for another fracture. One could also regard a low T-score to be a high-risk situation. Some have considered a T-score of less than −3 to be an indication for teriparatide therapy. Age is a factor in this discussion, because age itself is an independent risk factor for fracture: the older the patient for a given low T-score, the greater the risk for fracture. Indications for therapy are similar in other countries where teriparatide has been approved, but the demonstration of a previous fragility fracture is often required. The question of who is the ideal candidate for teriparatide therapy should take into account the specific indications for therapy, alternative treatments that might be appropriate, such as bisphosphonates, and cost. In some situations in which a bisphosphonate might be a reasonable choice, drug failure (defined by some as the occurrence of a fragility fracture or a significant reduction in bone mineral density [BMD] without an identifiable secondary cause while on therapy) or intolerance to other therapies could be regarded as appropriate reasons for considering teriparatide therapy in a patient with osteoporosis. PTH treatment is approved by the US FDA for 24 months;

however, one limiting feature of this therapy is its cost. The cost of teriparatide is approximately $US7000/year.[18]

3. Teriparatide as Monotherapy in Patients with Postmenopausal Osteoporosis

The seminal clinical trial performed by Neer et al.[12] examined daily subcutaneous injection of teriparatide 20 or 40μg in 1637 women with severe postmenopausal osteoporosis (i.e. low BMD and fractures) using a randomised, placebo-controlled, double-blinded protocol.[12] Median follow-up was 21 months. For the two doses of teriparatide, the increase in spine BMD averaged 10–14%. *Post hoc* analysis demonstrated that 96% of teriparatide-treated individuals had an increase above baseline in BMD of the spine and that 72% of patients had an increase of ≥5%.[19] The increase in femoral neck BMD was also significant but the change was smaller (approximately 3%) and it took longer to occur. At the 20 μg/day dosage, there was no change in cortical bone density (distal 1/3 radius site), but total body BMD increased significantly. As compared with placebo, teriparatide reduced the risk of one or more new vertebral fractures by 65% and 69% at the two doses, respectively. This decline in fracture incidence compares favourably with the relative risk reduction for fractures in women treated with bisphosphonates.[20] Among the women who sustained new vertebral fractures, mean loss in height was significantly greater in the placebo group (−1.1cm) than in the teriparatide 20 and 40 μg/day groups (−0.2 and −0.3cm, respectively; p = 0.002 vs placebo). The overall incidence of new non-vertebral fractures was reduced by 35% and 40%, respectively. When fragility fractures were considered separately from total fracture incidence, the reductions in new non-vertebral fractures were 53% and 54%, respectively. Hip fracture incidence was not analysed separately because the study was not sufficiently powered to examine this endpoint. The reduction in fracture incidence due to teriparatide was not related to the number of previous fractures or to the severity of previous fractures. The results were not dependent upon the site(s) of previous fragility fractures. Further *post hoc* analysis of this cohort demonstrated that the fracture risk reduction was largely independent of age and initial BMD.[21] The data also showed that, as expected, women with the highest pretreatment rate of bone turnover had the greatest risk of fracture.[22] However, the ability of teriparatide to reduce the fracture risk was independent of the baseline rate of bone turnover.

The clinical trial by Neer et al.[12] was not designed to closely monitor the time course of the effect of teriparatide on fracture incidence. To determine vertebral fractures, for example, radiographs were obtained at baseline and 18 months after treatment was started. Therefore, the only early fracture data captured was clinical events at non-vertebral sites. For clinical events, the time course of non-vertebral fracture incidence documents a reduction beginning after approximately 1 year of therapy. It is possible that fracture events are reduced at even earlier timepoints. Reasons for expecting that teriparatide might be associated with earlier reductions in the occurrence of fracture come from preclinical data in which rapid positive effects of teriparatide on bone geometry, microarchitecture and strength were seen.[23-29] Impressive effects of teriparatide on indicators of bone strength, such as trabecular connectivity and cortical width,[30,31] could possibly be expected to promote early fracture reduction as well, especially at the lumbar spine. Nevertheless, a clear chronology of antifracture efficacy has not been defined for teriparatide.

Adverse events were uncommon in the trial by Neer et al.[12] Back pain was significantly reduced in the teriparatide group. Nausea and headache occurred only in patients receiving the higher 40 μg/day dosage. Sustained increases in the occurrence of serum calcium levels above the normal range were significant only in the 40 μg/day dosage group (11%). The only adverse event that occurred more frequently in the teriparatide 20 μg/day dosage group than the placebo group was leg cramps (not thrombophlebitis). There was no increase in the incidence of hypercalciuria or urolithiasis at either dosage. However, postdose serum calcium levels

were at the upper limit of normal on at least one occasion in 11% of patients receiving teriparatide 20 μg/day. Following teriparatide treatment, there was a small and nonsignificant 30 mg/day increase in 24-hour urinary calcium excretion. However, it should be noted that patients with hypercalciuria or a history of renal calculi within the last 5 years were excluded from the study. Nausea was reported by 18% of women receiving teriparatide 40 μg/day and headache was reported by 13% of patients receiving this teriparatide dosage, whereas only 8% of women taking placebo reported each of these symptoms ($p < 0.001$ and $p = 0.01$, respectively). The frequencies of nausea and headache in the lower-dose PTH group were similar to those in the placebo group.[12]

In another randomised, double-blind placebo-controlled trial, teriparatide 40μg or alendronate 10mg was administered daily for 14 months to 146 postmenopausal women with osteoporosis.[32] The increases in BMD with teriparatide were twice as great than those with alendronate. Although the changes in bone density were much greater with teriparatide than with alendronate, inferences cannot be made about efficacy because of the poor relationship between increases in bone density and reductions in fracture risk.

PTH(1-84) has been the subject of a limited number of studies but is in active development as another anabolic skeletal agent for the treatment of osteoporosis. In a phase II trial, subjects were administered either placebo or one of three dosages of PTH(1-84) [50, 75 or 100 μg/day] for 12 months.[33] There were time- and dose-related increases in lumbar spine BMD with PTH(1-84); the 100 μg/day dosage was associated with the largest increase in BMD. Similar to the teriparatide studies, bone turnover markers rose quickly. Histomorphometric analysis of bone biopsy specimens confirmed the anabolic response to PTH(1-84) with regard to bone volume, trabecular number, thickness and separation.[34] In contrast to the patients in the study by Neer et al.,[12] in which the average number of fragility fractures per study subject was more than two, the incidence of baseline fragility fractures in the phase III PTH(1-84) study was only 19%. Nevertheless, a reduction in the occurrence of new vertebral fractures was seen with PTH(1-84) in women both with and without prior vertebral fractures (69% and 63%, respectively).[35]

4. Teriparatide in Men with Osteoporosis

The first randomised, controlled trial of PTH in men with idiopathic osteoporosis was carried out by

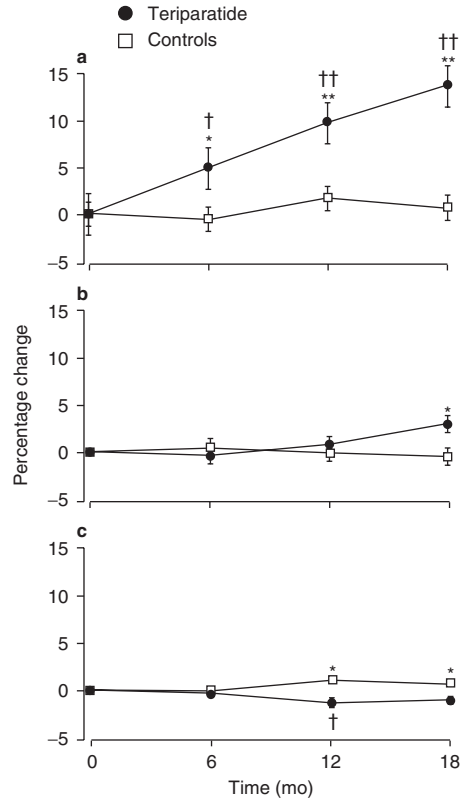

Fig. 2. Teriparatide increases bone mineral density at cancellous sites in men with osteoporosis and controls: (**a**) lumbar spine; (**b**) femoral neck; and (**c**) distal 1/3 radius. The cancellous bone of the lumbar spine responds to teriparatide therapy with a marked increase in bone density. In contrast, the distal 1/3 radius site does not change. The hip regions have an intermediate response. Data are shown as percentage changes from baseline ± SEM (reproduced from Kurland et al.,[36] with permission; © 2000, The Endocrine Society). * $p < 0.05$ for repeated measures analysis of between-group comparisons; ** $p < 0.005$ for repeated measures analysis of between-group comparisons; † $p < 0.05$ for repeated measures analysis of within-group comparisons between baseline and 6, 12 or 18 months; †† $p < 0.005$ for repeated measures analysis of within-group comparisons between baseline and 6, 12 or 18 months.

Kurland et al.[36] Twenty-three men (age 30–68 years) who had osteoporosis as defined by Z-scores less than −2.0 at the lumbar spine or femoral neck with no definable cause for bone loss, were randomised to teriparatide 400 U/day (equivalent to about 25 μg/day) or placebo in a double-blind experimental protocol with a duration of 18 months. The men who received teriparatide demonstrated a 13.5% increase in lumbar spine bone density (figure 2). Hip bone density increased, but was typically slower to change than lumbar spine bone density, and changes were not as robust, although significant. Cortical bone density at the distal radius did not increase compared with placebo. Bone turnover markers rose quickly and substantially in the men treated with teriparatide, with bone formation markers rising and peaking earlier than the bone resorption markers. Both sets of bone markers returned to or changed towards baseline by 18 months. In this, and virtually all other studies, the kinetics of change in bone markers were shown to be led by bone formation, followed thereafter by changes in bone resorption. These observations are consistent with the idea that PTH initially stimulates processes associated with bone formation, perhaps even excluding the bone remodelling cycle at first. This sequence of events, with the initial stimulation of bone formation by PTH, has given rise to the concept of the 'anabolic window', a period of time when PTH is maximally anabolic[37] (figure 3).

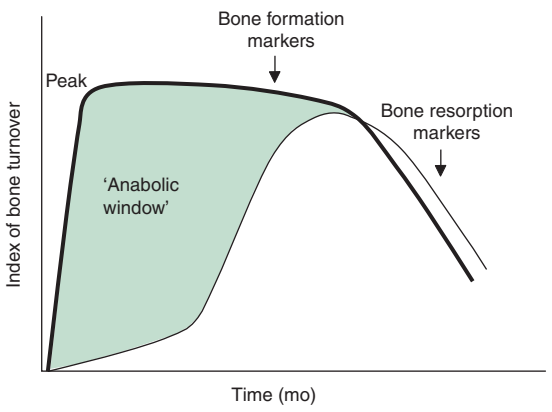

Fig. 3. The anabolic window. Parathyroid hormone (PTH) as an anabolic agent for bone: a kinetic model. Based upon the difference in kinetics of changes between bone formation and bone resorption markers, an 'anabolic window' is formed, during which the actions of PTH are believed to be maximally anabolic.

In the larger teriparatide study in men that was designed to be the counterpart to the study by Neer et al.[12] in postmenopausal women, Orwoll et al.[38] reported on 437 men with idiopathic or hypogonadal osteoporosis. The men were randomly assigned in a blinded fashion to either placebo or teriparatide 20 or 40 μg/day for a mean of 11 months.[38] BMD increased significantly at the lumbar spine in the active treatment groups by (6% and 9%, respectively), regardless of gonadal status. Over the 11 months of the study, the increases in bone density at the lumbar spine and hip closely resembled the time-dependent increase in bone density at those sites in the study of postmenopausal women by Neer et al.[12] Because of the short duration, the occurrence of fractures could not be assessed; however, fractures were assessed in a follow-up observational study in which 279 men from the original cohort were assessed by lateral thoracic and lumbar radiographs 18 months after the end of the treatment period. Between 25% and 30% of the men reported the use of an antiresorptive therapy during the follow-up period, with the men treated with placebo during the study utilising antiresorptive therapy to a greater extent than those who were treated with either dose of teriparatide (36% vs 25%). Nevertheless, the incidence of moderate-to-severe vertebral fractures was significantly reduced compared with the placebo group when the 20 and 40 μg/day dosage groups were combined (6.8% vs 1.1%; $p < 0.02$).[39]

5. Parathyroid Hormone (PTH) and Microarchitecture

Assessment of skeletal microarchitecture is not yet feasible in the clinical arena. Nevertheless, it is useful to review the beneficial effects of PTH on skeletal microarchitecture, because non-invasive imaging instruments are currently being developed to access this kind of information.[40,41] Microarchitectural deterioration, a common feature in osteoporosis, is an important contributor to increased fracture risk.[29] The increased osteoclast activity

that is associated with the high bone turnover states in postmenopausal women leads to perforation of cancellous plates, loss of trabeculae and trabecular discontinuity.[42] Since much of the strength of cancellous bone is derived from its microarchitectural organisation, loss of trabecular connectivity predisposes the individual to vertebral fracture. Preserving the trabecular network is even more important for bone strength than maintaining trabecular thickness.[43] When the trabecular network becomes discontinuous as a result of perforations, which are more likely to occur in the context of excessive remodelling, bone strength is affected, although bone density may not be.

Histomorphometric analysis of paired biopsies before and after treatment with PTH, using standard histomorphometry and 3-dimensional microcomputed tomographic analyses, have shown not only quantitative improvements in cancellous bone indices, but also major improvements in indices of connectivity.[44] There is increasing connectivity of trabeculae, thickening of trabeculae and conversion from a more rod-like to a more normal plate-like appearance.[44] Trabecular elements become connected or reconnected and marrow star volume is reduced, indicating PTH-enhanced connectivity.[45] Another potential mechanism by which PTH enhances connectivity is by increasing tunneling of thickened trabeculae, thus resulting in increased trabecular number and connectivity.[29] It is unclear whether PTH therapy stimulates the budding of new trabeculae *de novo* or, alternatively, leads to the thickening of trabeculae that are bifurcated by tunnelling resorption.[46,47]

6. PTH and Bone Geometry

Measurement of bone geometry as an index of PTH action is also not yet feasible in the clinical arena. However, as with assessments of microarchitecture, such measurements may become available clinically in the near future.

With PTH-driven increases in bone turnover, expectations of negative effects on cortical bone deserve specific consideration. It has been postulated that removal of cortical bone by PTH provides calcium to supply new trabecular bone during the initial period of therapy,[48] possibly through increases in cortical porosity. It is well established that PTH does not increase bone density at the distal 1/3 site of the radius. In some situations, there is a small decline in bone density at this site. This densitometric observation, combined with PTH-mediated increases in intracortical porosity, has raised concern that perhaps the cortical skeleton is at risk during PTH therapy. Nevertheless, there is no detrimental effect of PTH on the mechanical properties of cortical bone.[49] One reason to account for this observation is that PTH acts to favourably alter bone geometry. The inner endocortical surface of bone is a site of PTH-induced resorption and increased cortical porosity. When compensatory changes in the outer diameter of bone are induced by the actions of PTH that stimulate periosteal bone apposition, the net effect, a change in the ratio of the outer to inner diameter of bone, leads to increased, not decreased, bone strength. Moreover, in time, periosteal apposition actually leads to increases in cortical area and cortical thickness.[49] Thus, expansion of the inner diameter of tubular bone caused by PTH-induced endocortical remodelling[50] has little effect on calculated bending strength[49] because the effects are offset by an increase in both cross-sectional area and in cortical thickness, both of which are consequences of periosteal bone apposition.[27,29] The concept that PTH increases cortical thickness was confirmed when 101 postmenopausal women treated with PTH underwent peripheral quantitative computed tomography (pQCT) of the proximal radius to assess specific changes in cortical bone density after a median of 18 months of treatment.[31] PTH treatment resulted in significantly greater periosteal and endocortical circumferences and cortical area. These differences result in greater polar and axial moments of inertia and torsional bone strength index, which are all biomechanical indicators of skeletal resistance to bending and torsional loading.

These observations help to substantiate the densitometric observations made at a structural level, suggesting that PTH may improve the skeleton in ways that are distinctly different from the antire-

sorptive agents, and also helps to allay concerns that PTH may have adverse effects upon the cortical skeleton. Furthermore, fracture data from the study by Neer et al.[12] clearly indicate a substantial reduction in fractures of the non-vertebral skeleton. It is this observation by Neer et al.[12] that needs to be emphasised, even though the precise mechanisms by which PTH reduces non-vertebral fractures are not clear. It is apparent that changes in bone geometry account, at least in part, for these beneficial effects at non-vertebral sites.

7. Sequential and Combination Therapy with Teriparatide and an Antiresorptive Agent

In this section we consider three important questions that need to be addressed in connection with sequential and combination therapy.

7.1 Question 1: Does the Previous Use of an Antiresorptive Influence the Response to Teriparatide?

Many individuals who are going to be treated with teriparatide have previously been treated with a bisphosphonate or another antiresorptive agent. It is important to determine whether these individuals are as likely to respond to teriparatide – and what the nature of their response will be – compared with those who have never previously been treated with an antiresorptive agent.

Lindsay and colleagues[51] studied postmenopausal women who had been previously treated for at least 1 year with estrogen, who were then treated with teriparatide for 3 years. The group receiving teriparatide had significant increases in bone density of the spine (13%), hip (4.4%) and total body (3.7%). It is noteworthy that bone density in the vertebral spine began to increase with no delay and continued to increase in a linear fashion for the entire 3-year study. There was no significant change in bone density at the distal radius. Although the numbers were small, teriparatide significantly reduced the percentage of women who had a vertebral fracture (based on a reduction in loss of vertebral height). With the discordance between early changes in bone formation markers (osteocalcin) and later changes in bone resorption markers, as literally shown in all studies with teriparatide, there was a return of both sets of indices to baseline values within 2.5 years of initiation of treatment. It is of interest that the return of bone markers to baseline values was not associated with a reduction in the rate of the 3-year gain in BMD at the vertebral spine. Roe et al.[52] have obtained data from a study in postmenopausal women that was similar in design to the study of Lindsay and colleagues.[51] Women who were on estrogen replacement therapy for at least 1 year received either teriparatide or no further therapy except estrogen. This was not a blinded study because women in the placebo group did not receive an injection. Bone density at the lumbar spine increased by approximately 28% after 2 years. Using quantitative computed tomography (QCT), a technology that measures cancellous bone of the lumbar spine rather specifically, increases in vertebral BMD approached 80% after 2 years.[52] It is likely that pretreatment with estrogen does not impede the subsequent response to teriparatide.

Ettinger et al.[53] studied previous exposure to either raloxifene or alendronate followed by teriparatide. Both groups of subjects had been treated for an average of 28 months with the antiresorptive prior to being given teriparatide. In most respects, the subjects who had received raloxifene were similar to those who had received alendronate, despite not being part of a randomised matched cohort. However, women who had previously been treated with alendronate had much lower levels of bone turnover markers than those previously treated with raloxifene. After raloxifene treatment, the increase in BMD of the lumbar spine with teriparatide was linear and progressive, whereas after alendronate the increase in BMD of the lumbar spine in response to teriparatide was delayed for approximately 6 months. Those who had previously received alendronate actually had an initial decline in bone density at the hip for the first 6 months of teriparatide treatment. From these results, it is tempting to conclude that antiresorptive agents that do not have a profound effect on bone turnover permit teriparatide

to act promptly and in a robust manner, whereas more potent antiresorptive agents have an initial suppressive effect on teriparatide action. However, the results obtained by Cosman et al.[54,55] raise an additional point because in their study, women with postmenopausal osteoporosis who had been previously treated with alendronate for the same duration as those in the study by Ettinger et al.[53] responded with robust changes in BMD and biochemical markers. It is not clear why there is a discrepancy between these results, but it is distinctly possible that it is not so much the specific antiresorptive agent that is used prior to teriparatide that dictates the response but rather the extent to which bone turnover is reduced. Bone turnover marker levels appear to have been more markedly reduced in the study of Ettinger et al.[53] than in the study by Cosman et al.[55]

7.2 Question 2: Does Combination Therapy with Teriparatide and an Antiresorptive Agent Lead to Greater Effects than Either Drug Alone?

There is a theoretical basis for thinking that combination therapy with an antiresorptive agent and PTH would be more beneficial than monotherapy with either an antiresorptive or PTH. If bone resorption is inhibited and bone formation is stimulated, as would be the case with simultaneous combination therapy, the results might be much better than with either agent alone. Important data contrary to this reasoning have been provided by Black et al.[56] and Finkelstein et al.[57] These two groups independently completed trials with PTH alone, alendronate alone, or the combination of PTH and alendronate. The study by Black et al.[56] involved postmenopausal women treated with PTH(1-84) 100 μg/day (figure 4). The study by Finkelstein et al.[57] involved men treated with teriparatide 40 μg/day. Both studies utilised dual-energy x-ray absorptiometry (DEXA) and QCT to measure areal and volumetric BMD, respectively. With either measurement, the densitometric gains at the lumbar spine observed with PTH monotherapy exceeded those either with combination therapy or alendronate alone. In fact, measurement of trabecular bone by QCT showed that combination therapy was actually associated with substantially smaller increases in BMD than monotherapy with PTH(1-84). Levels of bone turnover markers followed the expected course for anabolic (increases) or antiresorptive (decreases) therapy alone. However, for combination therapy, bone markers followed the course of alendronate, not PTH, with reductions in bone formation and bone resorption markers, suggesting that the reduced response to combination therapy compared with PTH might be due to the dominating effects of the antiresorptive agent on bone dynamics (figure 5).

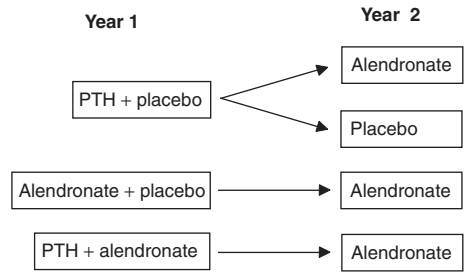

Fig. 4. The design of the PaTH (PTH and alendronate) study.[56] In the first year, the three groups were parathyroid hormone [PTH] (1-84) alone, alendronate alone or the combination of PTH(1-84) and alendronate; in the second year, the PTH alone arm was randomly divided into an alendronate or placebo alone arm.

Under other circumstances, combination therapy conceivably could be more beneficial than monotherapy. For example, in a short 6-month study, Deal et al.[58] reported that the combination of teriparatide and raloxifene has, in some respects, more beneficial effects than monotherapy with teriparatide alone. Bone formation, as assessed by levels of the N-terminal propeptide of type 1 collagen, increased similarly in both groups, but bone resorption as measured by levels of the C-terminal telopeptide of type 1 collagen was reduced in the combination group. BMD increased to a similar extent in the lumbar spine and femoral neck in both groups, but the increase in total hip BMD was significantly greater in the combination therapy group.

One reason why combination therapy with PTH and alendronate does not appear to provide more beneficial results than monotherapy with PTH alone

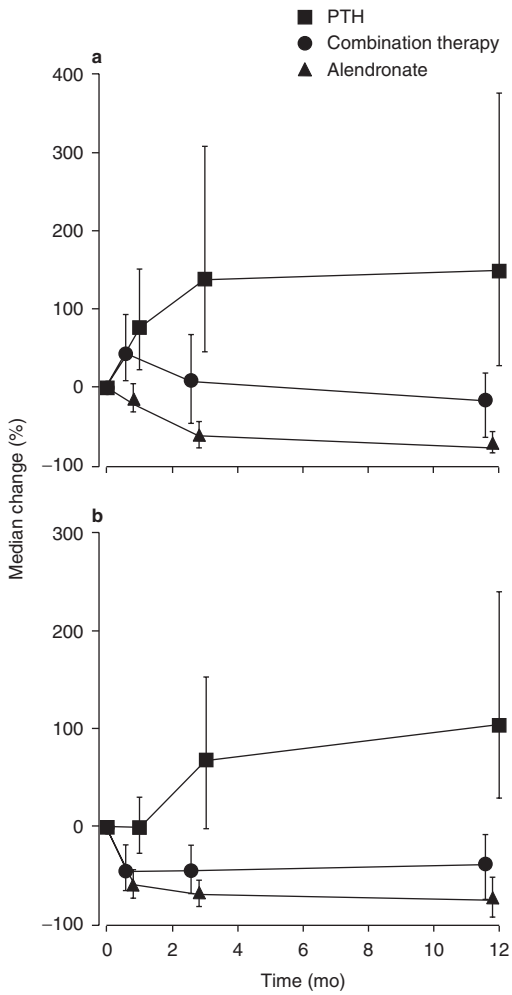

Fig. 5. The effect of combination therapy with parathyroid hormone [PTH] (1-84) and alendronate on bone turnover markers. The data show changes in serum concentrations of biochemical markers of (**a**) bone formation (N-terminal of propeptide type 1 collagen) and (**b**) bone resorption (C-terminal telopeptide of type 1 collagen) in response to therapy with PTH(1-84) or alendronate alone or together. The differences between the combination therapy group and the PTH group at 12 months and between the combination therapy group and the alendronate group at 12 months were significant ($p < 0.001$). Bars represent the interquartile ranges. Negative changes represent decreases (reproduced from Black et al.,[56] with permission. Copyright © 2003 Massachusetts Medical Society. All rights reserved).

may be related to the partial dependency of the bone formation effects of PTH on its ability to increase bone resorption. The effects of PTH may depend upon the bone remodelling cycle, in which there is a pool of committed osteoblasts. If bone turnover and bone formation are reduced, for example, as in the presence of a powerful antiresorptive agent, PTH may be less effective as it cannot access this pool of osteoblasts. This is consistent with the idea that some of the improvement in bone mass seen with PTH requires the release of insulin-like growth factor-1 and other growth factors from the skeleton by osteoclast action. Perhaps the reason why a less potent antiresorptive agent such as estrogen or raloxifene does not impede the responsiveness of bone to PTH is because bone resorption is not inhibited to the same degree with these agents as with alendronate, thus the necessary osteoblasts remain available. On the other hand, it is possible that alendronate itself has a direct effect that inhibits bone formation. Recent gene array studies suggest that alendronate may inhibit expression of bone formation marker genes[59] and the biochemical pathways utilised by PTH.[60]

Bearing this in mind, one can only speculate how previous or concomitant exposure to another bisphosphonate, risedronate, might affect the subsequent or concomitant response to PTH. It is possible that previous risedronate use may not impair the subsequent effects of teriparatide on BMD to the same extent as alendronate because risedronate does not reduce bone turnover to the extent that alendronate does. Risedronate may also be released from the bone surface after discontinuation more quickly than is the case with alendronate.[61] No clinical information currently exists regarding the interactions between risedronate or other bisphosphonates (excluding alendronate) and PTH. Animal data on the concomitant use of tiludronate (tiludronic acid), a different bisphosphonate, and PTH show a blunting of the skeletal anabolic effect of PTH,[62] similar to the clinical findings seen with alendronate and PTH.

It is most likely that it is the degree of bone turnover suppression prior to PTH treatment that dictates whether the anabolic effect of PTH will be compromised. The greater the suppression, the less likely that anabolic gains will ensue. It should also be considered that the data that are available with

regard to combination therapy utilise surrogate markers, such as BMD and levels of bone turnover markers. Whether combining PTH with an antiresorptive drug is more efficacious than PTH monotherapy for the prevention of fragility fractures remains to be seen.

7.3 Combination Therapy with Teriparatide and an Antiresorptive Agent in Glucocorticoid-Induced Osteoporosis

Glucocorticoid-induced osteoporosis (GIO) is characterised by prolonged suppression of bone formation and transient increases in bone resorption. A secondary increase in PTH is no longer considered by many to be of major pathophysiological importance in GIO.[63] Hence, the use of PTH in combination with an antiresorptive to treat GIO has an appealing rationale.

Lane et al.[64] conducted a 12-month, randomised controlled trial of 51 postmenopausal women who had previously received hormone replacement therapy and glucocorticoids (prednisone >5 mg/day). These women were randomised to either receive or not receive teriparatide for 1 year (placebo injections were not used). As measured by QCT and DEXA, vertebral bone density increased by 35% and 11%, respectively. Total hip BMD increased by 2% in the PTH group, while there was no difference in forearm BMD between groups. Levels of bone markers showed increased bone formation in the first 3 months of therapy, while resorption markers peaked later, at 6 months.[64] Buxton et al.[65] have implicated changes in receptor activator of nuclear factor-κβ ligand (RANK-L), osteoprotegerin, interleukin (IL)-6 and IL-6 soluble receptor (IL-6sR) in the processes that led to PTH-induced changes in both bone formation and resorption in the presence of glucocorticoids.

7.4 Question 3: What are the Consequences of Ending Teriparatide Therapy? Is an Antiresorptive Agent Necessary to Maintain the Gains Achieved with Teriparatide?

In the countries in which teriparatide has been approved for the therapy of osteoporosis, a short 18- to 24-month treatment period is recommended. Obvious concerns exist with regard to the consequences of discontinuing therapy. Most of the published data pertaining to this concern are observational trials.

The pivotal phase III trial of teriparatide[12] (see section 3) was followed by an observational, follow-up period in which study participants were given the option of switching to a bisphosphonate or not taking any further medications. Seventy-seven percent of the women in the original cohort in the Neer et al.[12] study were followed.[66] A majority (60%) were treated with antiresorptive therapy after discontinuation of teriparatide. Three groups were identified. One set elected to begin antiresorptive therapy immediately. In these individuals, the gains in bone density were maintained. A second group did not begin antiresorptive therapy until 6 months after discontinuation of teriparatide. In these individuals, there were major reductions in bone density during the 6 months prior to initiation of antiresorptive therapy, but as soon as antiresorptive therapy was instituted there were no further reductions in bone density. The third group elected not to take any therapy for the duration of the observational 30-month follow-up period. Reductions in bone density were progressive throughout follow-up in these subjects. Despite these data from bone mass measurements, the effect of previous therapy with teriparatide and/or subsequent therapy with a bisphosphonate for the prevention of fractures persisted for as long as 31 months after the discontinuation of teriparatide treatment.[66] Non-vertebral fragility fractures were reported by proportionately fewer women previously treated with teriparatide (with or without a bisphosphonate) compared with those treated with placebo ($p < 0.03$). Similarly, changes from baseline in lumbar spine BMD remained significantly higher in the original teriparatide-treated groups.[66] However, the data do not indicate whether the administration of a bisphosphonate was important in the subsequent maintenance of bone mass and fracture reduction. In a logistical regression model, bisphosphonate use for ≥12 months was shown to add little to overall risk reduction for new

vertebral fractures in this post-treatment period. It is hard to be sure of this conclusion because the data were not actually analysed separately in subjects who did or did receive antiresorptive therapy following teriparatide treatment.

In the post-treatment period of the PTH(1-84) study,[33] all subjects were treated with alendronate and either showed no change or an increase in BMD. Bone turnover declined but still remained above that of the original placebo group.[67] However, these studies did not have an arm in which the antiresorptive therapy was not administered. In addition, there were no fracture data available in the post-treatment period with PTH(1-84).

In the studies of Lindsay et al.[48,68] and Lane et al.,[69] the 3- or 1-year period of teriparatide therapy, respectively, was followed by continuation of estrogen use. Bone density was well maintained in the following year. Neither of these studies had a protocol that included a group of subjects in which estrogen therapy was withdrawn. Therefore, it is not certain that bone density would have been maintained had the antiresorptive agent been discontinued.

In the study by Kurland et al.,[70] men were given the choice to follow teriparatide therapy with or without an antiresorptive agent. Those who chose to receive the bisphosphonate showed further increases of 5% in bone density of the lumbar spine over the next 12 months. Those who chose no further treatment had progressive losses (up to 3.7%) in lumbar spine bone density. When the entire period of teriparatide therapy (18 months) and either bisphosphonate or no therapy (12 months) was reviewed, the changes between those who did or did not receive a bisphosphonate were even more dramatic. Among the men who followed teriparatide therapy with a bisphosphonate, the cumulative gain in bone density of the lumbar spine was >16%; in the men who did not follow teriparatide therapy with bisphosphonate treatment, the cumulative gain was reduced to only 4%.[70] Men who delayed the start of bisphosphonate therapy until 1 year after teriparatide discontinuation had gains in lumbar spine BMD over the year following bisphosphonate initiation, but these gains only matched the loss they had experienced in the previous year.

In a larger study of teriparatide in the treatment of male osteoporosis, 355 of the original cohort of 437 men who were treated with teriparatide 20 or 40 μg/day were followed up for 30 months.[39] The decline in BMD after teriparatide discontinuation was prevented by antiresorptive treatment. However, once again, it is difficult to know whether the post-teriparatide use of bisphosphonate was instrumental in demonstrating fracture prevention efficacy of teriparatide. The relatively small numbers of patients in the groups that either received bisphosphonate or did not precluded a specific analysis of the effect of bisphosphonate *per se*.

In all of the studies summarised in this section, the follow-up design was observational and, in many cases, control subjects who did not receive antiresorptive therapy during follow-up were either not available or not analysed separately. The PaTH (PTH and alendronate) study[71] has provided data in a rigorously controlled, blinded fashion to address the question of the need for post-PTH antiresorptive therapy. According to the prospective design, subjects who had received PTH(1-84) for 12 months were randomly divided into two groups. One group received alendronate 10 mg/day and the other group received placebo tablets for an additional 12 months. In the subjects who received alendronate, there was a further 4.9% gain in lumbar spine BMD, while those who received placebo experienced substantial declines in this parameter. By QCT analysis, the net change in lumbar spine bone density over 24 months was 31% among those who were treated with alendronate after PTH(1-84). In those who were given placebo after PTH(1-84), the net change in bone density was 14%.[71] The results of this study definitively establish the importance of following PTH therapy with antiresorptive treatment.

In the study of Black et al.[71] levels of bone markers fell in the post-PTH(1-84) period whether the subjects received placebo or alendronate. The reduction in bone turnover after PTH(1-84) was discontinued is probably based upon a different mechanism than the reduction in bone turnover

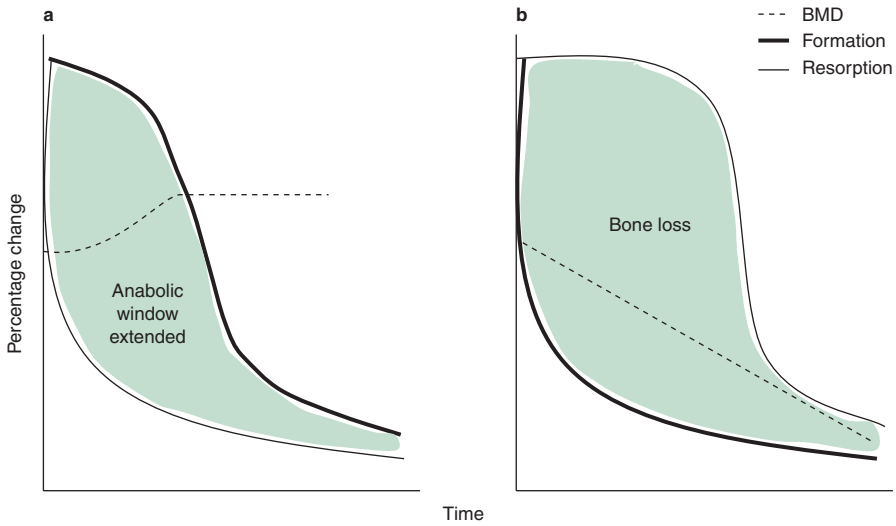

Fig. 6. Changes in bone density after parathyroid hormone (PTH) withdrawal. After therapy with PTH is discontinued, bone markers are reduced whether or not antiresorptive therapy is instituted. The diagram depicts the concept that (**a**) when PTH is discontinued with antiresorptive therapy, bone resorption markers fall more rapidly leading to an increase in bone mineral density (BMD); and (**b**) when PTH is not followed by antiresorptive therapy, bone formation markers fall more rapidly leading to a decrease in bone density.

when alendronate follows PTH(1-84). When bone turnover markers fall after PTH(1-84) in the presence of alendronate, it is likely that bone resorption falls more quickly than bone formation. This difference in time course should provide a post-PTH 'window' during which bone formation is favoured. On the other hand, when PTH is stopped without further antiresorptive therapy, it is likely that bone formation declines faster than bone resorption because PTH has been primarily driving processes associated with bone formation. Under these circumstances, bone resorption will predominate and BMD will fall. A depiction of this concept is shown in figure 6.

Further mechanistic explanations follow from the discussion of why the anabolic effects of PTH on bone mass acquisition are lost so quickly after the drug is discontinued. PTH stimulates bone formation, albeit with lower mineralisation density initially, enabling increased secondary mineralisation and maturation of new bone when a bisphosphonate is subsequently used. Without antiresorptive therapy, the bone that is formed in response to the actions of PTH is likely to be rapidly resorbed, particularly if bone resorption is still increased and is greater than bone formation in the post-PTH period. In patients treated with PTH, there is evidence that the new bone matrix is not yet fully mineralised because of the high rate of bone turnover.[72] Using quantitative backscattered electron imaging, Misof et al.[72] have shown that a greater than normal amount of matrix is found at lower mineralisation densities following PTH therapy because of the higher amounts of newly formed bone that have not yet had time to undergo complete secondary mineralisation. This observation is exactly opposite to the increases in mineralisation density observed using the same technique following treatment with an antiresorptive agent, such as alendronate. This is further illustrated by the resolution of cortical porosity that occurs after PTH withdrawal in ovariectomised cynomolgus monkeys.[49] This delay provides an explanation for the observation that apparent bone density, as measured by DEXA, increases following parathyroidectomy.[28] As the bone turnover rate is decreased, more time is available for secondary mineralisation, allowing for continued maturation of newly formed mineral that was rapidly deposited during ongoing PTH treatment but required further consolidation,[69] resulting in an increase in apparent bone density.

8. Safety of PTH

Teriparatide is generally well tolerated. Existing clinical trials with teriparatide indicate no major risk of hypercalcaemia when teriparatide is administered at the US FDA-approved dosage of 20 μg/day. In the pivotal study in postmenopausal women, serum calcium was above the upper limit of normal at least once in 11% of patients on teriparatide 20 μg/day.[12] Persistent elevation of serum calcium, necessitating a reduction of the teriparatide dose, occurred in only 3% of patients. Nevertheless, it is prudent to obtain a serum calcium level approximately 1 month after starting teriparatide therapy, with blood samples obtained prior to the next daily dose. On infrequent occasions, hypercalcaemia occurs within a few weeks after teriparatide initiation. In these instances, serum calcium levels usually return to normal within a few days of teriparatide discontinuation. Hypercalcemia does not recur once teriparatide is restarted if oral calcium intake is reduced by 500 mg/day. In most cases, the patient's original calcium intake can be resumed without hypercalcaemia recurring. Occasionally, allergic wheals have been observed at the teriparatide injection site. Headaches have also been reported, as have leg cramps. However, in the vast majority of patients, teriparatide is tolerated without significant adverse effects.

Contraindications for the use of teriparatide include any hypercalcaemic condition, osteosarcoma, metastatic bone disease, Paget's disease of bone, pregnancy, and x-ray therapy to the skeleton or to soft tissues in which a skeletal port is included. Use in children is also contraindicated. The US FDA label for teriparatide states that the drug should not be taken "if you have had radiation therapy involving your bones".[73] The intention of the FDA in this instance is to exclude therapeutic radiation, not diagnostic skeletal radiation.

8.1 PTH and Osteosarcoma

Long-term studies[74,75] with high-dose teriparatide administration to 6-week-old Fisher rats for 24 months demonstrate a dose-related appearance of osteogenic sarcoma. This effect is related not only to dose but also to the duration of use, consistent with lifetime exposure in a growing rodent (75 human-year equivalents). In a second rat toxicity study with teriparatide a 'no effect' dose was defined, which was still larger and provided greater drug exposure than any human will ever experience. No neoplasms were found when a 5 μg/kg treatment was initiated at 6 months of age and continued for up to 70% of the rat lifespan.[74] Osteosarcoma has also been reported in a similar carcinogenicity study of PTH(1-84). Although there was no difference in the occurrence of osteosarcoma between PTH(1-84) at the dosage of 10 μg/kg/day compared with controls, there was a dose-related incidence of osteosarcoma in the mid- (50μg) and high- (100μg) dose groups over 2 years.[76]

There is great uncertainty about whether this rodent model toxicity study[74,76] has relevance to human physiology. Vahle et al.[75] have reported the details of the experimental protocol for the toxicity studies with teriparatide and Tashjian and Chabner[77] have provided a comprehensive commentary on issues related to human safety of this drug. They point out that the rat responds to teriparatide with an exaggerated skeletal anabolic response, perhaps because the rat does not have an osteon remodelling system. In fact, the rat skeleton is in a constant state of modelling, with growth through open epiphyses occurring essentially throughout the lifespan.

To date, all nonhuman primate studies have not shown any evidence for osteogenic sarcoma in monkeys exposed to protocols that are similar to the rat toxicity studies. Moreover, among the millions of individuals who have been exposed to chronically elevated levels of PTH in primary or secondary hyperparathyroidism or even parathyroid cancer, there has been only a few reasonably well documented reports of osteogenic sarcoma.[78-80] Considering the millions of individuals worldwide who have primary hyperparathyroidism, it is surprising, in fact, that so few cases have been reported. One might have expected more, simply on the basis of a chance association alone. Admittedly, the model of chronic excess PTH syndromes, in which osteosarcoma is exceedingly rare, is not necessarily

analogous to the situation seen with intermittent PTH exposure. Bone cells exposed to chronically elevated levels of PTH respond differently than they do when exposure is intermittent. However, there have been no reports of osteogenic sarcoma among any of the patient cohorts in any of the clinical trials of PTH, amounting to exposure of >2500 patients.[81] It is reasonable to assume that teriparatide or PTH(1-84) is safe when administered to humans. However, the rat toxicity data have prompted a cautionary note by the US FDA in the form of a 'black box' warning on the use of the drug.[73] The black box warning is not a feature of the registration of teriparatide in other countries or regions, such as Europe, South Africa, Brazil, Australia and Hong Kong.

9. Future Considerations

In the future, PTH may be modified for easier and more targeted delivery; oral or transdermal delivery systems may become available. Preliminary data on a transdermal delivery system for teriparatide have recently been presented.[82] PTH has also been formulated for oral administration to provide systemic exposure in rats and cynomolgus monkeys.[83] An oral delivery formulation of teriparatide is being evaluated in a phase II clinical trial.[84] A bioactive recombinant PTH analogue has also been presented as potential future oral agent for the treatment of osteoporosis.[84]

Ostabolin [(hPTH)-(1-31)NH2] is a molecule that is believed to cause less hypercalcaemia compared with teriparatide[85] and this is currently undergoing evaluation. PTHrP (1-36) has also been the subject of early clinical trials.[86]

Less frequent administration of PTH, such as once weekly, might also be an effective treatment option.[87] It is also possible that repeated, shorter cycles of PTH treatment followed by bisphosphonate therapy while bone markers are still elevated (closer to the 1-year point, rather than the 3-year point) might be even more effective than the longer cycles.[55] Aside from forms and ways to administer exogenous PTH, Gowen et al.[88] have described an oral calcilytic molecule that antagonises the parathyroid cell calcium receptor, thus stimulating the endogenous release of PTH. This approach could represent a novel endogenous delivery system for intermittent PTH administration. The use of a calcilytic agent would have to meet the challenge of rapidly increasing the secretory rate of endogenous PTH for a very short period of time.

10. Conclusions

The advent of anabolic skeletal therapy in the form of teriparatide is revolutionising our approach to the therapy of osteoporosis. For the first time, a drug is available that not only improves bone density, features of bone turnover and reduces fracture incidence, but that also significantly improves the microarchitectural and geometric properties of bone. These changes in bone qualities are attractive when the goal of therapy for osteoporosis is considered, namely to improve the basic underlying abnormalities that give rise to skeletal fragility. Clearly, we are on the threshold of a new paradigm in the treatment of osteoporosis. We can look forward to a period of unprecedented further advances in our approach to a disease that is likely to affect us all, both women and men, if we live long enough.

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