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Review Article

Therapy of Osteoporosis in Men with Teriparatide

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Osteoanabolic therapy is an attractive therapeutic option for men with osteoporosis because it directly stimulates bone formation, an action not shared by any antiresorptive drug. Teriparatide (recombinant human PTH(1-34)) and PTH(1-84) are available in many countries but PTH(1-84) is not available in the United States. Only teriparatide is approved for the treatment of osteoporosis in men. It is also indicated in glucocorticoid-induced osteoporosis. Teriparatide is associated with major gains in bone density at the lumbar spine and, to a lesser extent, in the hip regions. Vertebral and nonvertebral fractures are reduced in postmenopausal women treated with teriparatide. Fracture reduction data in men are less secure because the number of study subjects is small and the studies have not been powered to document this endpoint. Nevertheless, observational data in men suggest a reduction in vertebral fractures with teriparatide. Attempts to show further beneficial effects of teriparatide in combination with antiresorptive agents have not been demonstrated yet to be superior to monotherapy with teriparatide alone. The duration of therapy with teriparatide is limited to 2 years. Thereafter, it is necessary to treat with an antiresorptive drug to maintain, and perhaps increase, densitometric gains. Teriparatide is well tolerated with a good safety profile.

1. Introduction

PTH(1-84) and its foreshortened variant, teriparatide (PTH(1-34)), represent the only available osteoanabolic therapies for osteoporosis. In contrast to antiresorptive therapies, which are the mainstay of osteoporotic treatment, these agents directly stimulate bone formation, and as a result, improve not only bone mass but also skeletal microstructure, including trabecular connectivity and cortical thickness.

Although postmenopausal women are the dominant cohort at risk for osteoporosis, men are not spared. Current figures show that men represent approximately 25% of all osteoporotic individuals [1]. Morbidity and mortality figures after a hip fracture in men are disproportionately higher than in women [2], perhaps because men are older when they develop their osteoporotic fractures and have, therefore, more comorbid conditions. Because men have not been the center of attention in this disease, the data supporting the use of teriparatide are not as secure as in postmenopausal women, a point that is also true for data related to the use of antiresorptive therapy in osteoporotic men. In this report, we summarize the available data on the use of osteoanabolic therapy in male osteoporosis.

2. Anabolic Activity of Parathyroid Hormone

Parathyroid hormone (PTH) has the interesting property of harboring both catabolic and anabolic proclivities in bone. The prototypical disease that illustrates best the catabolic disposition of PTH is primary hyperparathyroidism. It is of interest that the property to resorb bone in primary hyperparathyroidism is seen most in the cortical skeleton with cancellous bone being relatively spared [3]. In fact, microarchitectural studies of cancellous bone in primary hyperparathyroidism suggest that even under conditions of chronic excessive exposure to PTH, microstructure is maintained, if not enhanced [4]. This clue to the anabolic potential of PTH is realized by low-dose, intermittent administration of teriparatide or PTH(1-84). The mechanisms by which PTH induces an anabolic effect on bone are likely to be multifactorial, including a number of pathways such as

Wnt (via stimulating Wnt 10b [5], and inhibiting sclerostin [6]), Runx2, and insulin-like growth factor (IGF-I). The net effect of low-dose, intermittent PTH exposure is an initial recruitment of osteoblast progenitor cells and direct stimulation of mature osteoblasts [7].

In both men and women, PTH increases bone mineral density (BMD) in the lumbar spine, a site rich in cancellous bone (Figure 1). Increases in the hip region are more modest and PTH therapy reduces BMD at the distal 1/3 radius, a cortical site. The early effect of PTH is an initial rapid increase in bone formation markers subsequently followed by an increase in bone resorption markers (Figure 2). These changes in bone formation markers are accompanied by histomorphometric observations that confirm an effect of PTH to increase processes associated with bone formation without any early evidence for bone resorption (Figure 3). This effect is reminiscent of bone metabolism in growing children in whom bone *modeling* is dominant. Thereafter, teriparatide leads to an increase in bone resorption giving rise to the more typical characteristics of bone metabolism in adults, namely, bone *remodeling*. Approximately 30% of the overall effect of PTH is thought to be due to the early effect on bone modeling with the majority being the subsequent action of PTH to stimulate bone remodeling. The period of time when PTH stimulates bone formation directly, before bone remodeling is stimulated, is explained by the concept of the "anabolic window" [8] (Figure 4). Even after bone turnover is stimulated, there is more bone formation than bone resorption ongoing, thus maintaining the anabolic window at least for a finite period of time.

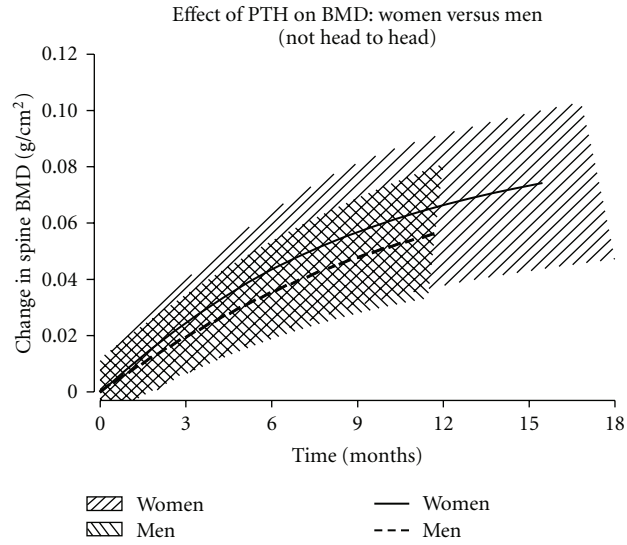

Figure 1: Changes in lumbar spine bone mineral density with teriparatide 20 μg daily. Although the figure does not show a head-to-head comparison, the increase in bone mineral density in men over the 11 months of the trial by Orwoll et al. tracks closely along the trajectory in bone mineral density women over the same period of time in the trial of Neer et al. (from Satterwhite et al. [26]).

3. Indications for Teriparatide Use

Teriparatide (PTH(1-34)) was approved by the United States Food and Drug Administration (FDA) in 2002 for the treatment of osteoporosis in men and postmenopausal women at high risk of fracture and in 2009 for the treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture. Hodsman et al. [9] proposed criteria to establish the condition of "high risk," including preexisting osteoporotic fractures, very low bone density (T-score ≤ -3.5), and/or an unsatisfactory response to antiresorptive therapy. An unsatisfactory response to antiresorptive therapy, or drug failure, could be argued in the context of an incident fracture during treatment or gastrointestinal or other intolerance to bisphosphonates.

4. Teriparatide in Male Osteoporosis

Although both teriparatide and PTH(1-84) are available widely for the treatment of postmenopausal osteoporosis, only teriparatide has been studied and is available in men. The results of clinical trials with teriparatide in men, while more limited and less conclusive than those in women, show nevertheless results that are similar to larger studies in postmenopausal women. Kurland et al. [10] performed the first randomized trial evaluating the use of PTH(1-34) in men with idiopathic osteoporosis. The double-blind, placebo-controlled trial included 13 controls and 10 men treated with teriparatide 400 IU daily (approximately equivalent to 25 μg daily) for 18 months. There was a 13.5% increase in BMD at the lumbar spine in the PTH-treated group compared with controls ($P < 0.001$). Femoral neck BMD in the treatment group increased, however, more slowly and to a lesser extent (2.9% at 18 months; $P < 0.05$), and there was no significant change in the 1/3 distal radius site. Markers of bone turnover increased rapidly in the teriparatide-treated cohort, with bone formation markers rising and peaking earlier than bone resorption markers. These data demonstrate that the concept of a PTH-induced anabolic window is valid for men as well as women.

In a larger clinical trial that was also randomized, double-blinded and placebo-controlled, Orwoll et al. [11] studied 437 men with idiopathic or hypogonadal osteoporosis. Men were assigned to placebo (147 men), teriparatide 20 μg daily (151 men), or teriparatide 40 μg daily (139 men). The trial was terminated prematurely, after only 11 months because of the rat osteosarcoma toxicity results (see Section 6). Lumbar spine and femoral neck BMD increased by 5.9% and 1.5% respectively ($P < 0.05$ in the 20 μg group versus placebo). There were even larger increases in BMD at the 40 μg group, but adverse events were more frequently encountered.

Individuals in the study by Orwoll et al. were followed for up to 30 months after teriparatide was discontinued as part of a safety study [12]. Radiographs were available for comparison between baseline and 18 months after treatment discontinuation in 279 of the 437 men. The risk of new vertebral fractures in men treated with teriparatide (20 and 40 μg groups were combined) was reduced by 51% versus placebo ($P = 0.07$). Absolute risk reduction was 6%, similar to the fracture reduction data in women [13]. When only

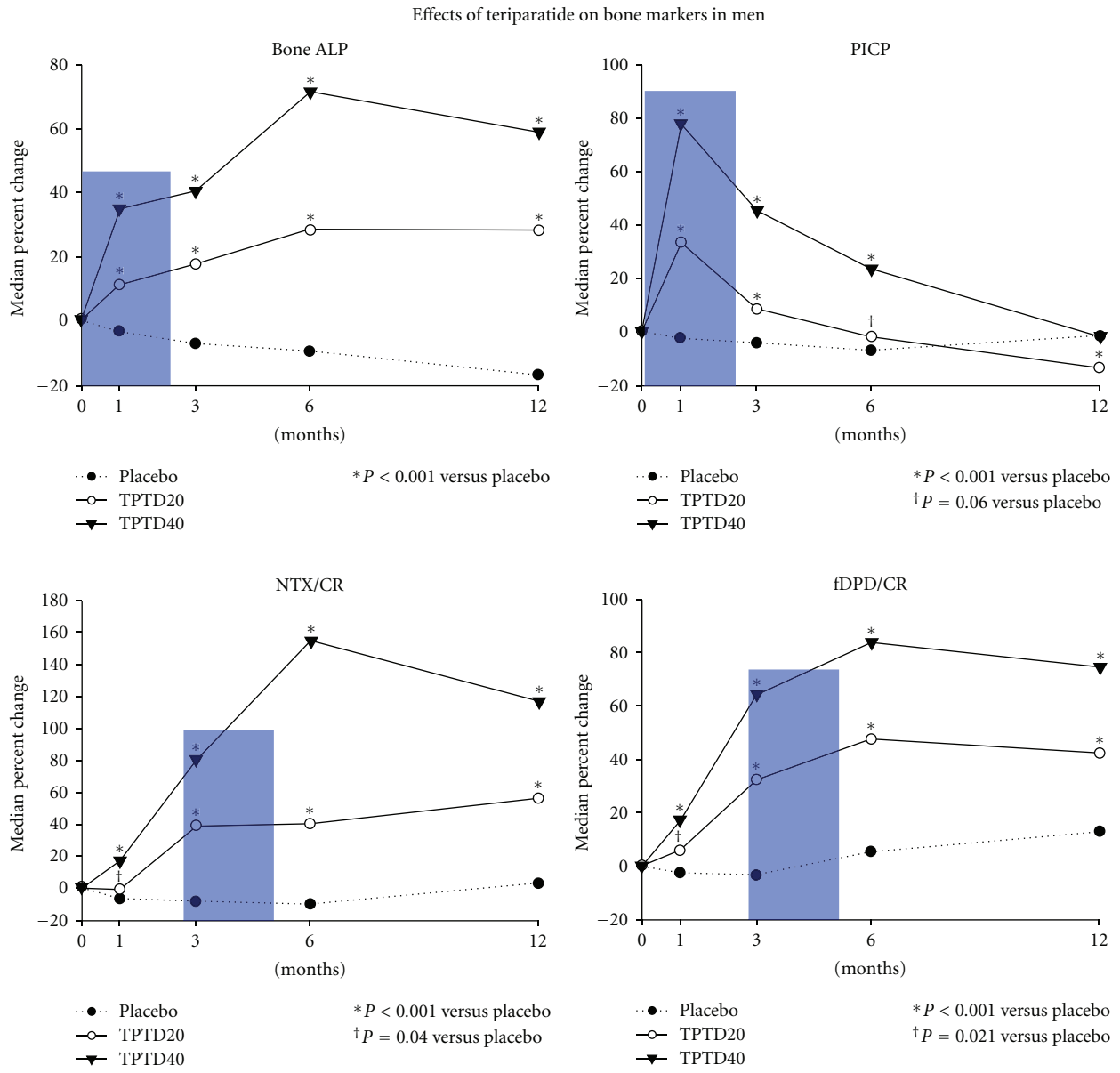

Figure 2: Changes in bone turnover markers after teriparatide administration to men with osteoporosis. Bone formation markers increase before bone resorption markers after men are exposed to teriparatide. Bone ALP, bone alkaline phosphatase; PICP, procollagen I carboxy-terminal; NTX/CR, urinary N-telopeptide/creatinine ratio; fDPD/CR, free deoxypyridinoline/creatinine ratio; TPTD20, teriparatide 20 μg; TPTD40, teriparatide 40 μg. From Orwoll et al. [11].

moderate or severe vertebral fractures were assessed, the difference from the placebo group reached significance (6.8% versus 1.1%; $P < 0.01$). In the 114 men who had a preexisting vertebral fracture at baseline, the absolute risk reduction for new vertebral fractures was 13.1%. In the follow-up period, other osteoporosis therapies were used, complicating the analysis and raising the possibility that subsequent treatment might have affected the fracture outcome data. More men in the placebo group received other treatment than those who received teriparatide (36% versus 25%; $P = 0.03$), suggesting that this confounding point might not be an issue. However, it is possible, if not likely, that those receiving further treatment after the clinical trial period had more severe osteoporosis. The greater use of osteoporosis therapy after the clinical trial was terminated was in the placebo group and thus, does not negate this confounder.

Glucocorticoid-induced osteoporosis (GIO) is the most common secondary cause of osteoporosis. Its major histomorphometric and dynamic element is reduced bone formation, a feature that may make GIO particularly well suited to an osteoanabolic approach. Saag et al. [14] compared alendronate and teriparatide in a head-to-head, randomized, double-blind, double-dummy trial of 83 men and 345 women with glucocorticoid-induced osteoporosis. All subjects had received 5 mg of daily prednisone, or the equivalent, for at least 3 months. In addition, enrollment

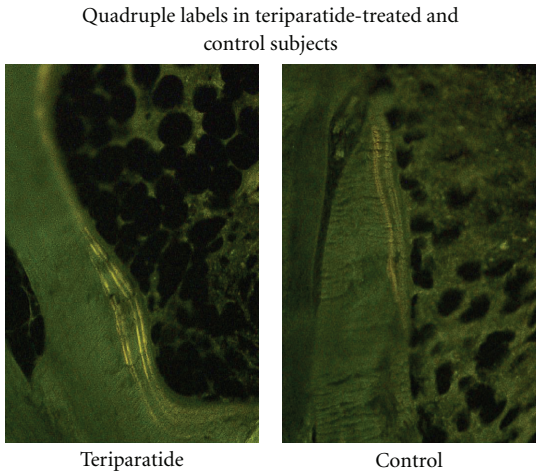

Figure 3: Early effects of teriparatide to increase bone modeling. Subjects were labeled before and 1 month after exposure to teriparatide. The control subjects did not receive treatment. The two sets of labels in the teriparatide-treated subject clearly demonstrate a marked increase in bone formation after teriparatide exposure. From Lindsay et al. [27].

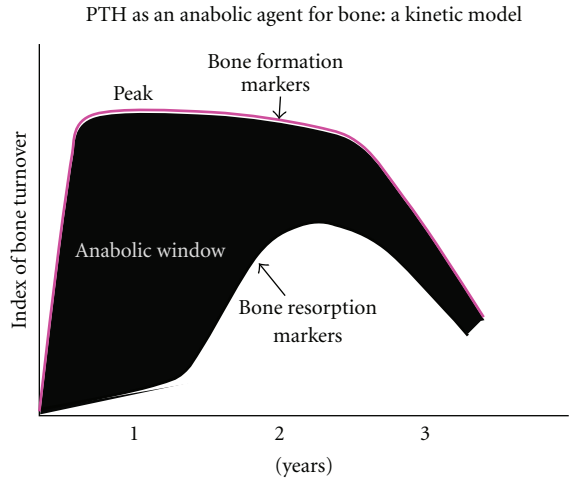

Figure 4: The anabolic window. The figure demonstrates the concept that bone formation is first stimulated by teriparatide or PTH(1-84) followed by an increase in bone resorption (adapted from [8]).

criteria included baseline lumbar spine or total hip T-scores ≤ -2.0 or ≤ -1.0 with at least 1 fragility fracture during glucocorticoid treatment. An equal number of subjects ($n = 214$) received either daily teriparatide 20 μg or daily alendronate 10 mg. The change in lumbar spine BMD (the primary end point) was greater in the teriparatide group, as early as 6 months after therapy was started, and by 18 months, the teriparatide group (+7.2%) was significantly greater ($P < 0.001$) than the alendronate group (+3.4%). When the men were analyzed separately from the women, the differences between teriparatide and alendronate were virtually identical to the combined data for men and women (7.3% versus 3.7%; $P = 0.03$) [15]. Total hip BMD in men increased significantly from baseline in the teriparatide group only. Although this study was not powered to detect a difference in fractures, they were captured as a reporting item. Notably, there were significantly fewer new vertebral fractures in the teriparatide group than in the alendronate group (0.6% versus 6.1%; $P < 0.01$). In the men, there were 4 new vertebral fractures in the alendronate group and none in the teriparatide group ($P = 0.05$).

This study was extended for an additional 18 months, with findings that continued to show major differences between those who were treated with teriparatide or alendronate. After 36 months, increases in lumbar spine and femoral neck BMD from baseline were significantly ($P < 0.001$) greater in the teriparatide group than in the alendronate group (11.0% versus 5.3% (lumbar spine); 6.3% versus 3.4% (femoral neck)) [16]. The major difference in fracture incidence was also maintained after 36 months when the teriparatide and alendronate groups were compared (1.7% versus 7.7%; $P = 0.007$).

5. Combination or Sequential Treatment with Teriparatide and Antiresorptive Therapy

5.1. Antiresorptive Therapy Prior to Teriparatide. Therapy with teriparatide typically follows a course of bisphosphonate or other antiresorptive therapy. In Europe, virtually all subjects who receive teriparatide or PTH(1-84) therapy have been previously treated with a bisphosphonate. Sequential therapy with an antiresorptive followed by teriparatide has only been studied in women, with the results suggesting that the potency of the antiresorptive drug to reduce bone turnover tends to determine whether or not there will be a delay in responsiveness to teriparatide. For example, bone markers in prior alendronate-treated patients increase later and peak at lower levels than in patients previously treated with raloxifene [17]. In a head-to-head comparison between risedronate and alendronate, the response to teriparatide was more rapid and greater in subjects previously treated with risedronate, but the results were not explained by the smaller effect of risedronate than alendronate to reduce bone turnover markers. These observations, made only in postmenopausal women, have not led to a general recommendation to wait for a period of time after bisphosphonate therapy before teriparatide is started. Eventually and rather soon after teriparatide therapy is started, bone turnover markers and BMD will begin to increase.

5.2. Combination Therapy. Finkelstein et al. [18] evaluated the simultaneous use of bisphosphonate and teriparatide in 83 osteoporotic men who were randomized to receive alendronate 10 mg (28 men), teriparatide 40 μg (27 men), or both (28 men) on a daily basis. Alendronate was given for 30 months, with teriparatide started at month 6 and continued for 24 months. The amount of daily teriparatide was twice the FDA-approved 20 μg dose. After 30 months, BMD at the lumbar spine increased to a greater extent in men treated with teriparatide alone than in the other groups (18.1% teriparatide versus 14.8% combination, or versus 7.9%

alendronate; $P < 0.001$). Femoral neck BMD also increased to a greater extent in the group treated with teriparatide alone (9.7% teriparatide versus 6.2% combination, or versus 3.2% alendronate; $P = 0.001$). Increases in vertebral trabecular BMD as determined by quantitative computed tomography (QCT) were markedly higher with teriparatide alone (48% teriparatide versus 17% combination, or versus 3% alendronate; $P < 0.001$). Bone turnover markers in the combination group were similar to those seen in the group treated with alendronate alone, namely, a rapid decrease in markers of both formation and resorption [19]. This lack of an effect of teriparatide in combination with alendronate to increase bone turnover markers confirms data in women who were evaluated with a protocol that differed only slightly (shorter time period; PTH(1-84) instead of teriparatide) [20]. Deal et al. [21] found that in women, the combination of teriparatide with raloxifene, a less potent antiresorptive agent, may enhance the bone-forming effects of teriparatide. In the study by Deal et al., bone formation markers increased with combination therapy to an extent similar to teriparatide alone while bone resorption markers did not increase to the same extent as teriparatide alone, suggesting that the anabolic window was greater with this approach to combination therapy. More recently, Cosman et al. [22] found that the combination of a single dose of zoledronic acid with daily teriparatide increased BMD after 6 months at the spine and hip to a greater degree than either drug alone. However, the major differences after 6 months were much less apparent at the end of the 12-month study.

5.3. Antiresorptive Therapy Following Teriparatide. Kurland et al. [10] were the first to show in men that when teriparatide is not followed by an antiresorptive agent, lumbar spine and hip bone density falls precipitously. In those whose teriparatide therapy is followed by alendronate, gains in lumbar spine and hip BMD are maintained [23]. Although not as clearly definitive, Kaufman et al. [12] also showed that lumbar spine and hip BMD tended to decline in men previously treated with teriparatide who received no subsequent treatment for osteoporosis. These results are similar to those observed in women [13]. Despite the lack of fracture outcome data, the results of these studies establish the importance of maintenance treatment with an antiresorptive following the recommended 2-year course of teriparatide therapy.

5.4. Teriparatide Retreatment. Subjects who completed the 30 month trial of Finkelstein et al. [18] comparing the effects of alendronate, teriparatide, or both on BMD and bone turnover were monitored for 12 months after therapy was discontinued and then randomized again to treatment with alendronate, teriparatide, or both for an additional 12 months [24]. Only the data for the group receiving teriparatide alone for 2 years, followed by 1 year of no therapy, then 1 year of teriparatide retreatment ($n = 21$) were presented. Not surprisingly, bone turnover markers and BMD fell when teriparatide was stopped. Teriparatide retreatment for 12 months resulted in an increase in lumbar spine BMD of 5.2%, compared with 12.5% during the first 12 months of treatment ($P < 0.001$). Bone turnover markers also increased more during the first 12 months of teriparatide treatment as compared to the 12 month retreatment period. The authors interpreted the data to reflect an attenuated response to teriparatide retreatment. The possibility remains that gains may have been greater if treatment had been continued beyond the first retreatment year.

6. Safety of PTH

Teriparatide is well tolerated in men and women. The FDA-approved treatment regimen is 20 μg daily for up to 24 months. Clinical trials have shown a very small risk of hypercalcemia at the 20 μg dose [11, 13]. In the postapproval period, the risk of hypercalcemia appears to be even lower than previously thought. Hypercalcemia is even less likely to occur if calcium supplementation is reduced by 500 mg/day when teriparatide is initiated. Teriparatide does not appear to significantly increase urinary calcium excretion [11, 12].

In the animal toxicity studies, male and female rats treated with teriparatide or PTH(1-84) at doses that were 3–60-times the equivalent dose to human subjects for 75 years of human equivalent time develop osteosarcoma [25]. This rat toxicity has not been seen in monkeys. With almost 9 years of clinical experience, the number of reported cases of osteosarcoma in patients is even less than expectations based upon epidemiological data of osteosarcoma in human subjects not treated with PTH. With no more than 3 cases reported among approximately 1.5 million subjects who have received teriparatide or PTH(1-84) worldwide, this toxicity does not appear to be a human one.

There are contraindications to the use of teriparatide, such as primary hyperparathyroidism. It should not be used in children with open epiphyses, in subjects at risk for osteosarcoma (Paget's disease of bone; previous external ionizing skeletal irradiation), or in subjects with a previous history of osteosarcoma. An unexplained elevation in the alkaline phosphatase is also a relative contraindication to teriparatide use.

7. Conclusions

Teriparatide, the only available osteoanabolic agent for men, is indicated for the treatment of osteoporosis when fracture risk is high. It is also indicated for the treatment of men with glucocorticoid-induced osteoporosis. The data for men in terms of increases in bone density and changes in bone turnover markers track virtually identically with the more extensive data that are available for postmenopausal women. Reduction in fracture incidence, although not conclusive, also appear to mirror the more extensive and conclusive data in women. Teriparatide is well tolerated for the recommended 2-year treatment period, and it should be followed by an antiresorptive drug to maintain increases in bone density. Combination therapy with antiresorptives has not been shown to be superior to monotherapy with teriparatide alone. Ongoing research, however, may offer

new insights into effective approaches to combination or sequential osteoanabolic and antiresorptive therapy.

Disclosure

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