Safety of Parathyroid Hormone for the Treatment of Osteoporosis

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Teriparatide (recombinant human 1-34 parathyroid hormone) has been registered for the treatment of postmenopausal osteoporosis and osteoporosis in men for more than 5 years, whereas 1-84 parathyroid hormone has just recently been registered in Europe for osteoporosis management. Therefore, more data are available regarding the long-term safety of teriparatide. The issues to be considered are the effects of the registered dose of teriparatide (20 μg/day) on the incidence of hypercalcemia, hypercalciuria, and hyperuricemia, and the US Food and Drug Administration's "black-box" warning regarding osteogenic sarcoma in the rat model. This review discusses these issues and provides the author's extensive clinical experience and advice on the use of teriparatide in clinical practice.

Introduction

Recombinant human (1-34) parathyroid hormone (teriparatide) was approved for the treatment of osteoporosis in postmenopausal women and in men at high risk for fracture on November 22, 2002 [1,2]. Teriparatide is the first anabolic agent approved by the US Food and Drug Administration (FDA) for this indication and soon will be registered for the treatment of glucocorticoid-induced osteoporosis [3••]. Parathyroid hormone (PTH; 1-84) has also been registered in Europe for osteoporosis management [4•]. Since the FDA registration of teriparatide, more than 600,000 patients have been treated, and several general reviews have been published regarding the clinical use of teriparatide [5,6•,7,8,9•] and its value in reducing fracture risk and back pain in patients with or at high risk for painful vertebral compression fractures [10–12]. There are multiple putative mechanisms of action, both cellular and biochemical, for the anabolic effect of teriparatide to improve bone mineral density as assessed by dual-energy radiographic absorptiometry or quantitative CT, bone size, and microarchitecture [13•,14–16,17•,18–22]. Suffice it to say, teriparatide is a novel therapy for osteoporosis and should be considered as first-line therapy in patients at high risk for fracture, or in patients in whom the physician is not satisfied with the effectiveness of other registered therapies [5,6•,9•].

As with any pharmacologic therapy that is administered to large populations of patients, safety is of primary concern. This article examines the evidence guiding clinicians considering PTH for the management of patients with osteoporosis. Specifically, the following issues are discussed:

1. Hypercalcemia—if and when to monitor?
2. Hypercalciuria—if and when to monitor?
3. Hyperuricemia—if and when to monitor?
4. Osteogenic sarcoma—what are the issues?

Hypercalcemia

PTH induces hypercalcemia. The fundamental mechanism of action of PTH is to increase bone turnover, which may mobilize skeletal calcium stores; increase renal production of 1,25-dihydroxyvitamin D, which increases gastrointestinal calcium absorption; and increase the renal tubular reabsorption of calcium (decrease urinary calcium excretion) [23,24]. The effects of PTH that may lead to hypercalcemia are seen in patients with sustained increases of PTH, especially primary hyperparathyroidism [25]. They may also be seen in patients with chronic kidney disease and in patients after renal transplantation [26,27]. However, PTH is used in the treatment of osteoporosis to induce an acute, transient elevation of PTH that is no longer measurable in serum 4 hours after the injection. What is the clinical significance of this short-term administration of PTH? In the pivotal clinical trial (registration) that led to the approval of teriparatide, hypercalcemia (above the upper limit of the normal range for total serum calcium [defined in the Fracture Prevention Trial as 10.6 mg/dL]) was seen in 11% of the patients administered the registered (20 μg/day) teriparatide dose, when the blood draw occurred 4 to 6 hours post-injec-

tion, and consecutive hypercalcemia was observed in 3% of this group [1]. The hypercalcemia was not sustained, and normocalcemia was observed in these 3% if the calcium supplementation was reduced by 500 mg/day. The serum calcium returned to normal in nearly all of the patients before the next dosing interval of teriparatide, and withdrawal of therapy due to persistent elevations of serum calcium was necessary in only one of 541 patients. Hence, hypercalcemia of clinical importance is rare in teriparatide administration to patients who receive 1000 mg/day of calcium supplementation. The FDA has no recommendations for monitoring the serum calcium in patients treated with teriparatide. However, there are a few pragmatic suggestions from those who have used teriparatide extensively [5,6•,9•]:

1. Avoid teriparatide in patients with primary hyperparathyroidism or unexplained hypercalcemia, a recommendation also in the FDA label.
2. Limit the calcium and vitamin D_3 intake to 1500 mg/day (total dietary and supplemental intake) and 800 IU vitamin D_3/day (unless measuring and monitoring serum 25-hydroxyvitamin D_3 levels; greater supplemental doses of vitamin D are needed to achieve a serum 25-hydroxyvitamin D_3 level of at least 30 ng/mL) [28,29].
3. Serum calcium should be checked at least once in the first month after starting teriparatide treatment. This recommendation is based on the broad clinical experience of many of us who use teriparatide extensively [5,6•]. Real-world patients are not as tightly regulated as clinical trial patients and are occasionally asymptomatic, yet potentially clinically significant hypercalcemia may develop, and the clinician must not miss it. This may be related to variable calcium intakes in clinical practice or reduced ability to increase urinary calcium excretion at even moderate reductions in renal function. The blood for serum calcium should be drawn 16 hours or longer after the administration of the teriparatide. I instruct all of my teriparatide patients to administer their PTH between 8 and 9 PM; then, a calcium measurement can be taken the next afternoon.

In my experience of starting more than 1000 patients on teriparatide, calcium levels greater than 11 mg/dL have been seen in about 5% of patients and more than 12 mg/dL in only five patients (range: 12–14.1 mg/dL). However, hypercalcemia can occur and may be related to calcium intakes that may be greater than instructed. Hence, for good clinical practice, it is advisable to obtain at least one serum calcium measurement within a month after starting teriparatide. Hypercalcemia does not develop late in the course of therapy if not seen early in treatment initiation. There are several pragmatic management suggestions if hypercalcemia develops: 1) repeat the calcium measurement in 1 to 2 days; 2) if persistent, ensure the calcium intake is about 1500 mg/day and that no other potential causes of hypercalcemia have been overlooked; 3) if persistent, reduce the calcium intake or stop the teriparatide, recheck serum calcium in 7 to 10 days, and, if normal, re-start the teriparatide or go back to the initial total calcium intake, checking the serum calcium again in 5 to 7 days; and 4) if hypercalcemia returns, consider reducing the calcium intake by 500 mg/day permanently or the teriparatide dose (eg, to every other day), although there is no evidence for any fracture efficacy with intermittent PTH administration or calcium intakes lower than those used in the registration clinical trial.

Hypercalciuria

The normal 24-hour urinary calcium excretion in patients with relatively normal renal function is about 4 mg/kg/day [30,31]. The upper limit of the normal range for absolute 24-hour urinary calcium excretion, not adjusted for body weight, is 300 mg/day. These limits are comparable to the 95th percentile of urinary calcium excretion (286 mg/day or 4.52 mg/kg/day) for estrogen-deprived, normal middle-aged white women with a dietary calcium intake of 500 to 1000 mg/day [31]. When normalized by body weight, data indicate that the upper limit of normal for 24-hour urinary calcium excretion is more than 4 mg/kg/day, with the definition of adjusted hypercalciuria more than 350 mg/day. Hypercalciuria per se may be a risk factor for kidney stone formation or loss of bone mineral density, since renal stone formation (or even "silent" nephrocalcinosis) often requires additional urine abnormalities, such as hypocitraturia or low urinary flow rates to induce stone formation; in addition, hypercalciuria may not necessarily be reflective of negative calcium balance [32]. Gastrointestinal calcium absorption may be the primary mechanism for the source of hypercalciuria, or gastrointestinal absorption may compensate for calcium emanating from bone storage. Hence, decisions regarding teriparatide effects on urinary calcium excretion and management of teriparatide-induced hypercalciuria must be interpreted in the context of the total clinical picture—not just in isolation.

In the pivotal teriparatide registration trials for women and men [1,2], patients were excluded if they had a history of renal stones in the 2 years before randomization or if they had hypercalciuria. The approach to consideration of teriparatide in patients with prior renal stones or hypercalciuria is more complex. The cause(s) of the renal stones from a metabolic standpoint must first be defined (hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia, and renal tubular acidosis) and corrected as a critical first step. In addition, the cause of hypercalciuria must also be defined and corrected before any teriparatide treatment

(renal, absorptive, primary hyperparathyroidism, renal tubular acidosis, and loop diuretics). In renal hypercalciuric patients, I perform a noncontrast CT of the kidneys, looking for silent nephrocalcinosis; the hypercalciuria has an entirely different and important clinical meaning in hypercalciuric patients with as opposed to without subclinical nephrolithiasis/nephrocalcinosis. Management of stones (clinical or silent) must first be accomplished before teriparatide initiation. In these cases, teriparatide must be considered only in high-risk patients and also requires more than the usual monitoring of serum and urinary calcium/kidney radiologic techniques suggested for teriparatide-treated patients without any preceding stone formation or hypercalciuria. In the teriparatide registration studies, urinary calcium excretion was assessed as a prespecified secondary endpoint safety analysis at baseline, 1, 6, and 12 months, and as a study endpoint after teriparatide initiation [1]. At baseline, 24-hour urine calcium excretion averaged 165 or 188 mg/24 hours, respectively, in the female and male studies. Teriparatide increased urinary calcium excretion significantly above baseline in both studies and compared with placebo at 6 and 12 months, with an average increase of 20 to 30 mg/day, even when adjusting for body weight [33•]. Although pre-existing hypercalciuria was an exclusion for randomization, 7% of the women and 18% of the men had 24-hour urinary calcium excretions at baseline measuring more than 300 mg/day. In addition, pre-existing hypercalciuria was correlated with continuous hypercalciuria. Clinical urolithiasis was seen in two women in the placebo group and two women in the treated group (20 µg/day), and "kidney pain" was reported in four women in the treated group; thus, it is possible that two women in the placebo group and six in the treated group had stones, although the specific cause of the kidney pain was not identified. In the male teriparatide study, there was one patient with kidney stones in the placebo group, two in the 20 µg/day group, and one in the 40 µg/day group [2]. Sustained hypercalciuria on repeated follow-up measurements was seen in 3% of study participants, and less than 1% of study participants required calcium intake adjustments (500 mg/day lower) or teriparatide dose adjustments due to hypercalciuria [33•].

What does all of this mean? In the study populations in the clinical trials, the risk of persistent hypercalciuria is small, and there is no greater incidence of renal stone formation. Should one monitor urinary calcium excretion? In patients with no history of renal stone formation or increased baseline urinary calcium excretion, FDA product labeling does not provide guidance. I do not monitor this because, in my opinion, mild increases in urinary calcium excretion per se are not associated with significant increased risk for stone formation [33•]. As previously stated, teriparatide management requires an entirely different approach in patients with pre-existing stone history or hypercalciuria.

Hyperuricemia

Increased serum uric acid is a risk factor for gout. In the Fracture Prevention Trial [1], serum uric acid rose above the upper limit of normal (range = 13% to 20% of the teriparatide-treated group) without any incidence of gout. In the glucocorticoid-induced trial [3••], increased uric acid was observed in three of 214 teriparatide-treated patients, and there was one case of gout. It is not the standard of care to monitor serum uric acid levels in patients treated with teriparatide or to treat asymptomatic increases of serum urate in patients on teriparatide with the hope of reducing the risk of an acute attack of gout.

The teriparatide clinical trial data do not provide guidance regarding management of patients with uric acid disorders (history of gout or urate kidney stones) who are being considered for teriparatide treatment. In these scenarios, individual clinical judgment must prevail. Most patients with a history of gout or uric acid–associated renal stones are already receiving treatment for their specific urate-associated disorders. Decisions regarding initiation of teriparatide for high-risk osteoporotic patients should not be altered by a pre-existing urate-associated disorder that is being appropriately managed.

Osteogenic Sarcoma

The pivotal registration trial for teriparatide was cut short from its planned (as required by the FDA) 3-year duration by the appearance of osteogenic sarcoma in 100% of the Fischer strain of rats receiving stratified doses of teriparatide [34,35]. The rats were given lifelong doses of teriparatide equivalent to 30 to 4500 µg/day in a 60-kg human. Osteosarcoma was seen at all dose levels, although it required a lifelong exposure (20 of 24 months). Osteogenic sarcoma did not result from long-term exposure in parallel studies of the cynomolgus monkey.

The rat almost exclusively models bone (eg, always forms new bone as opposed to remodeling bone and replaces old bone with new bone), has an exaggerated response to PTH, and nearly replaces the marrow space with bone [7]. Osteogenic sarcoma was also seen in the 1-84 PTH preclinical animal data in the rat, although there was a "no-dose" effect seen at the 10 µg/day dose. However, in the 1-84 PTH rat data, there was a dose-responsive increased incidence (50–100 µg/day) of osteosarcoma [36].

There is one case of osteogenic sarcoma related to teriparatide in humans. The case has been conscientiously reviewed and reported by the manufacturer of teriparatide (Eli Lilly and Company, Indianapolis, IN) [37]. The patient was a female smoker with a lung lesion that was thought to be osteogenic sarcoma after histologic biopsy. Autopsy was not performed, and thus the bone source (from which all osteogenic sarcomas originate) was not confirmed. Nevertheless, it is responsible to conclude that this was an osteogenic sarcoma in a patient receiving teriparatide. The natural background incidence rate of osteogenic

Table 1. Etiologies of an increase in bone-specific alkaline phosphatase

Hyperthyroidism
Hyperparathyroidism
Osteomalacia
Severe vitamin D deficiency
Recent large bone fracture
Paget's disease of bone
Metastatic cancer in bone
Immobilization
Space travel
Treatment with parathyroid hormone

sarcoma in the adult population is about 1/250,000/year [38]. Hence, because there are about 600,000 to 800,000 patients worldwide on teriparatide, it is plausible that the osteogenic sarcoma was not related to teriparatide. This case should not alter considerations regarding teriparatide for the treatment of postmenopausal, male, or glucocorticoid-induced osteoporosis. The osteogenic sarcoma rat data should be discussed with each patient before initiation of therapy and put it its proper perspective.

An important clinical issue is making certain that the alkaline phosphatase is not elevated before initiating teriparatide [5]. If the total alkaline phosphatase is elevated, then a bone-specific alkaline phosphatase (BSAP) measurement must be taken; if the BSAP is elevated, teriparatide should not be initiated without defining the cause of the increased BSAP. There are many potential etiologies of increased BSAP (Table 1). It is important to first exclude Paget's disease, metastatic cancer to bone, and osteomalacia. Patients with Paget's disease have a higher background incidence of osteogenic sarcoma than the general population. Hence, by FDA label, teriparatide is contraindicated in Paget's disease of bone.

The FDA label also states that teriparatide should be avoided in patients with prior skeletal radiation. It is implied, but not stated in the FDA label, that this warning applies to prior therapeutic and not prior diagnostic radiation (eg, chest radiography or dual-energy X-ray absorptiometry [DXA]). This warning is based on data showing osteogenic sarcoma of the sternum in a few patients who received high-dose mantle radiation of the chest for Hodgkin's disease or lymphoma, and observations of links between prior radiation and osteogenic sarcoma [39]. In clinical practice, the physician often must decide whether to use teriparatide for fragility fracture in high-risk patients who have had localized, narrow-beam therapeutic radiation (eg, for breast cancer). There are no firm guidelines to assist clinical judgment in these areas, and again, clinical judgment alone must prevail. I have used teriparatide in these superficial radiation–exposed cases, in which osteoporotic fractures that have not responded to prior therapy force the decision to consider a treatment with a completely different mechanism of action. There are data in the oncology literature that suggest a higher risk of osteogenic sarcoma in patients who have received narrow-beam skeletal radiation [40,41]. Nevertheless, if a physician decides that such a patient should receive teriparatide based on the high fracture risk, the physician should be clear about the use despite the FDA label, and the patient should be completely informed of the risk.

Conclusions

Teriparatide offers a unique opportunity that is not possible with any other osteoporosis treatments—the capacity to "make new bone" and increase bone strength by mechanisms totally different from antiresorptive agents. There are very few safety concerns, although a measurement of serum calcium should be obtained in the first month after teriparatide initiation in normocalcemic patients, and the alkaline phosphatase level should be normal before initiation of therapy. Teriparatide should not be used in patients with unexplained hypercalcemia, unexplained elevations of the BSAP, primary hyperparathyroidism, or an unfused epiphysis. Teriparatide use should be preceded by other evaluations and more careful monitoring in those with hypercalciuria or renal stones, a history of gout, or prior skeletal radiation.

Overall, teriparatide is very well tolerated and safe in most patients and should be the first-line therapeutic consideration in those with high risk for low-trauma fractures.

Disclosure

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References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Neer RM, Arnaud CD, Zanchetta JR, et al.: **Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis.** *N Engl J Med* 2001, **344**:1434–1441.
2. Orwoll ES, Scheele WH, Paul S, et al.: **The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis.** *J Bone Miner Res* 2003, **18**:9–17.
3. •• Saag KG, Shane E, Boonen S, et al.: **Teriparatide or alendronate in glucocorticoid-induced osteoporosis.** *N Engl J Med* 2007, **357**:2028–2039.

The pivotal clinical trial demonstrating the efficacy of teriparatide in glucocorticoid-induced osteoporosis.