# 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—whar 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-

(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 cur 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

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