



OSTEOPOROSIS

CLINICAL UPDATES

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PARATHYROID HORMONE: ANABOLIC THERAPY FOR OSTEOPOROSIS

The 1990s was a decade of tremendous growth and opportunity in osteoporosis research. In particular, great strides were made in our understanding of the pathophysiology of osteoporosis, and measurement of bone mineral density was refined such that familiarity and utilization allowed both consumers and healthcare providers the opportunity to identify high-risk individuals prior to fracture.

Probably the greatest advance occurred in the field of therapeutics. When the decade began, only estrogen and injectable calcitonin were approved for the treatment of osteoporosis. When it ended in 2000, alendronate and risedronate were being widely used to treat established disease, nasal calcitonin was approved, and raloxifene, the first of several estrogen agonist-antagonists (formerly called SERMs), was being employed as a preventive therapy in early postmenopausal women.

As the 21st century began, once weekly bisphosphonates were established therapies were being investigated. Most importantly, systematic reviews of large randomized placebo-controlled trials, confirmed the utility of these antiresorptives in the prevention and treatment of postmenopausal osteoporosis.

*Parathyroid hormone (PTH) as an injectable treatment for osteoporosis ushers in a new era in therapeutics: anabolic agents that do more than control bone loss, they actually stimulate new bone formation. In this issue of *Osteoporosis: Clinical Updates*, we will discuss PTH, its promise and its implications for patient care.*

CASE 1: 68-YEAR-OLD WOMAN

The first patient we will discuss is a 68-year-old woman with a history of osteoporosis. The patient had a hysterectomy at the age of 50 for significant bleeding around the time of menopause. Estrogen replacement therapy (ERT) was initiated at that time. Mammography results had been normal in the past. The patient has a history of GERD and GI complaints. Three years ago, after noting the patient's 3" loss in height, her physician recommended a DXA and spinal x-ray. The scan indicated T-scores of -2.0 BMD at hip and -2.7 at spine. The x-ray showed multiple vertebral fractures.

At that time, the patient's physician recommended that she increase her calcium intake to over 1200 mg/day in divided doses, which she did with diet and a daily supplement. In addition, she started on a vitamin D supplement of 400 IU/day.

The patient continued on ERT along with supplemental calcium and vitamin D for the next three years. In follow-up, her DXA is now repeated at

Osteosarcoma in Rats

Rats developed osteosarcomas in studies where they were given lifelong PTH (1-34) at doses higher than the human dose. Rats never close their epiphyses and continue to grow bone for life. It is therefore unclear if this has clinical relevance to older patients with low bone turnover, as their epiphyses have closed and they will only receive PTH for two years (not a lifetime).

Studies in monkeys show no such effects either.^{1,2} There has been one case of osteosarcoma in humans associated with teriparatide treatment and this is not higher than the background incidence in the normal population.³

1. Vahle JL, et al. Skeletal changes in rats given daily subcutaneous injections of recombinant human parathyroid hormone (1-34) for 2 years and relevance to human safety. *Toxicol Pathol.* 2002;30: 312–321.
2. Tashjian AHJ, Chabner BA. Commentary on clinical safety of recombinant human parathyroid hormone 1–34 in the treatment of osteoporosis in men and postmenopausal women. *J Bone Miner Res.* 002;17:1151–1161.
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the same facility. Despite taking ERT, calcium, and vitamin D, her bone mass has not remained stable. Her current T-scores are –3.2 at the spine and –2.6 at the total hip.

Is this patient a candidate for parathyroid hormone (PTH)?

She may be. The patient's T-score on DXA classifies her as having osteoporosis and, assuming there are no secondary problems, she may be a candidate for PTH. In her case, long-term ERT has not been helpful in maintaining her BMD. Due to her history of GI problems, she may not be a good candidate for bisphosphonates. Other FDA-approved alternatives to PTH include raloxifene, calcitonin nasal spray, or intravenous bisphosphonates.

Is it reasonable to start PTH at this time?

Possibly. However, before starting any additional therapy, the physician must rule out secondary causes of bone loss, particularly any conditions that could be exacerbated by PTH therapy. For example, if the patient has hyperparathyroidism, PTH would be contraindicated. A serum calcium and PTH level should therefore be checked. In addition, many older patients have mild vitamin D insufficiency, which leads to secondary hyperparathyroidism with normal calcium levels.

What laboratory tests should be checked?

Serum and ionized calcium, as well as albumin should be checked to rule out hyperparathyroidism. Serum PTH should also be checked to rule out primary hyperparathyroidism or secondary hyperparathyroidism (which is often associated with normal calcium levels). A 25-hydroxyvitamin D level would rule out vitamin D deficiency or insufficiency with mild secondary hyperparathyroidism. An alkaline phosphatase level would be the initial screen for active Paget's disease. (See figure page 4.)

The patient is very interested in considering PTH therapy. However, she currently feels well on ERT and is reluctant to discontinue it completely.

Should the patient discontinue ERT?

One arm of the Women's Health Initiative, a large multicenter trial involving over 16,000 postmenopausal women, examined hormone replacement therapy versus placebo. This arm of the study was terminated early because investigators found a 26% increased risk of breast cancer, a 29% increased risk of cardiovascular disease, and more than double the increased risk of venous thromboembolic events, despite a 34% reduction in hip and vertebral fractures and a 37% reduction in colon cancer.¹ The estrogen replacement versus placebo arm of the study was also halted for similar findings.

Because this patient continued to lose bone while on ERT, she should not continue ERT solely for the sake of her bone health.

The patient asks why PTH given by injection would improve bone mass when her friend, who has hyperparathyroidism, has been told that she is at risk for bone loss due to her elevated PTH level.

The dosing interval for PTH, like many other hormones, is responsible for different actions at the receptor site level. Intermittent PTH (i.e., small daily dose) leads to increased bone apposition. Both bone resorption and bone formation are increased, but bone formation is increased more than resorption for a net gain in bone mass. In contrast, continuous PTH delivery produces a greater increase in bone resorption than bone formation. This leads

to a net decrease in bone volume. Therefore, patients with the continuously elevated levels of PTH that are found with hyperparathyroidism (either primary or secondary) would be at risk for bone loss compared with patients taking a daily, intermittent, subcutaneous injection of PTH, which leads to an increase in bone mass and bone thickness.

CASE 2: 72-YEAR-OLD MAN

The second patient is a 72-year-old man who presents to the physician after experiencing acute, severe back pain upon lifting a suitcase.

Lumbar spine X-rays reveal a vertebral compression fracture at L2. DXA testing reveal that he had a T-score of -3.8 at the spine and -2.4 at the total hip (referenced to male data set) for a diagnosis of osteoporosis at the spine and borderline osteoporosis at the total hip.

Would this patient be a candidate for PTH therapy?

By clinical criteria alone, this patient should be diagnosed with osteoporosis. Therefore, he would be a candidate for bisphosphonate therapy or PTH.

What work-up would this patient need?

Because primary osteoporosis in men is less common and secondary causes of bone loss are more common, he needs a work-up to rule out secondary causes of bone loss. The most common causes of secondary bone loss in men include hypogonadism, glucocorticoid treatment, and alcohol abuse. In addition, patients can have vitamin D deficiency, hyperthyroidism, hyperparathyroidism, and all other secondary causes of bone loss found in women.

The patient denies any significant history of alcohol abuse and is not taking any glucocorticoids. He states that his libido is normal. Work-up reveals no evidence of secondary osteoporosis (see figure on page 4). It is therefore likely that he has idiopathic osteoporosis.

At this point, would it be reasonable to begin therapy with PTH?

Maybe. The patient's options include bisphosphonate therapy or PTH. However, this patient also reports a history of GERD. He currently has an active duodenal ulcer and has been on a proton pump inhibitor for a year. He is concerned about exacerbating his GERD with an oral bisphosphonate. However, he would be a candidate for intravenous bisphosphonates, although ibandronate and zoledronate are not currently FDA approved for men.

Will either therapy help relieve the patient's continuing back pain?

Possibly. Bisphosphonate studies have reported some reduction in pain, but the benefit is not widely ascribed to their use for acute vertebral fractures. Although a randomized, controlled clinical trial in osteoporotic women on PTH demonstrated a reduction in back pain compared to the control group, this was thought to be due to a reduction in vertebral fractures in the treatment group.

The patient begins teriparatide (PTH 1-34), calcium, and a multivitamin containing vitamin D. He also begins physical therapy and weight-bearing exercise to improve function and reduce pain. Three months later, he returns for a follow-up visit.

FORTEO™ (teriparatide, PTH ([1-34])

Dose: 20 mcg SQ daily for up to 24 months

Instructions for Use:

Forteo™ is administered as a subcutaneous injection into the thigh or abdominal wall. Patients and caregivers should receive appropriate training and instruction in the use of the pen-like injection device. Each pen can be used for up to 28 days and then discarded. It is stored under refrigeration at 36°–46° F (2°–8° C) at all times.

Indications:

- Forteo™ is indicated for the treatment of postmenopausal women with osteoporosis who are at high risk for fracture (history of osteoporotic fracture, multiple risk factors for fracture, or failed/intolerant of other osteoporosis therapy).
- Forteo™ is indicated to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture (history of osteoporotic fracture, multiple risk factors for fracture, or failed/intolerant to other osteoporosis therapy). The effects of Forteo™ on risk for fracture in men have not been studied.

Contraindications:

Forteo™ should not be given to patients with hypersensitivity to teriparatide or to any of its excipients.

Warnings:

The following categories of patients should not be treated with Forteo™:

- Patients with Paget's disease of bone.
- Pediatric patients or young adults with open epiphyses.
- Patients with a prior history of radiation therapy involving the skeleton.
- Patients with bone metastases or a history of skeletal malignancies.
- Patients with hypercalcemia, primary or secondary hyperparathyroidism.
- Patients with metabolic bone diseases other than osteoporosis.

¹FORTEO™ teriparatide (rDNA origin) injection 750 mcg/3 mL. [package insert]. Indianapolis, IN: Eli Lilly Company; 2003.

Work-up for Secondary Causes of Bone Loss

- BUN/creatinine
- Electrolytes
- Total or ionized calcium
- Albumin
- Phosphate
- Alkaline phosphatase
- 25-hydroxyvitamin D
- Parathyroid hormone
- TSH
- 24-hour urinary calcium and creatinine
- Testosterone (in males)
- 24-hour urinary cortisol or dexamethasone suppression test (Cushing's)
- Transglutaminase IgA/endomyseal/antigliadin antibodies (celiac)

Are laboratory values or bone density assessments necessary at this time?

Although bone mineral density changes were seen very early in PTH clinical trials, at this point, it is not reasonable to repeat a bone mineral density test. The DXA could be repeated in one to two years or when PTH is stopped. No specific laboratory tests must be performed for monitoring. If hypercalcemia is suspected, serum calcium should be assessed 16 to 24 hours following administration of PTH.

CASE 3: 60-YEAR-OLD POSTMENOPAUSAL WOMAN WITH ASTHMA

The third patient is a 60-year-old postmenopausal woman with a long history of asthma, requiring intermittent large boluses of oral steroids despite a daily maintenance dose of inhaled steroids and other medications. She underwent menopause at the age of 51 and has not taken hormone replacement therapy. She also takes a calcium supplement of 1000 mg/day in divided doses along with a multivitamin. She participates in a mild resistance training program at a gym twice per week.

The patient presents with acute back pain after picking up a grandchild. X-rays reveal a new vertebral compression fracture at T12 without obvious signs of any other pathology.

Would this patient be an appropriate candidate for PTH?

This patient likely has glucocorticoid-induced osteoporosis (GIOP). PTH is not yet FDA approved for treatment of this disorder. However, there are published studies in the literature about its use.² The bisphosphonates alendronate and risedronate are FDA approved for this purpose in the U.S., and etidronate is approved for GIOP in Canada. Unless contraindicated, these options should be tried before using a non-approved medication.

Although the patient is on preventive measures, including calcium, vitamin D, and exercise, she has an ongoing important risk factor for bone loss—use of glucocorticoid therapy. Glucocorticoids increase bone resorption and decrease bone formation by causing osteoblast apoptosis. In addition to glucocorticoid-induced bone loss, she could have another secondary cause of bone loss, such as vitamin D deficiency, hyperthyroidism, or hyperparathyroidism. Therefore, before beginning her on any additional therapy, it would be important to rule out these potential secondary causes.

A work-up reveals normal levels of serum calcium, PTH, TSH, and a vitamin D level of 15 ng/ml. How should this be addressed?

The patient's vitamin D level of 15 ng/ml suggests that she has vitamin D insufficiency. She should be treated with 50,000 units of vitamin D once weekly for 8 to 12 weeks. Her vitamin D level should then be rechecked, with a vitamin D level of 30 ng/ml or greater as the guide. After this, the patient should be put on a maintenance dose of 1000 IU/day vitamin D₃.

PTH IN THE TREATMENT OF OSTEOPOROSIS

During the 1990s small randomized trials with human recombinant parathyroid hormone (PTH) given in subcutaneous intermittent (i.e., once a day) doses demonstrated enhancement of bone mass and significant reduction in spine fractures in individuals already receiving estrogen

replacement.^{1,3,4}

Subsequent observational studies suggested that intermittent PTH, unlike continuously administered PTH, could dramatically stimulate new bone formation, while modestly increasing bone resorption.^{4,5}

Neer and colleagues completed a 20-month randomized, placebo-controlled, clinical trial of PTH (1-34) in postmenopausal women.⁶ The results were dramatic with respect to both the BMD effect (10–15% increase over 18 months) and the reduction in spine and non-spine fractures (50–60% relative risk reduction). In an 18-month, randomized, double-blind, placebo-controlled trial using intact PTH (1-84) in postmenopausal women with osteoporosis, Greenspan and colleagues reported that women treated with PTH (1-84) had a 58% reduction in new or worsened vertebral fractures and significant improvements in spine and hip BMD.⁷

PTH AND BONE

PTH therapy induces bone-forming cells, osteoblasts, to lay down new collagen and subsequently mineralize that tissue. The result is that it stimulates bone formation in excess of bone resorption. Early in treatment, PTH therapy raises markers of bone formation, in advance of any change in bone resorption. By nine months of therapy, PTH increases bone formation by as much as 200% in both men and women.^{4,5,8,9} Bone resorption is also activated, but this effect is not seen biochemically until several months into therapy. In this way, bone remodeling is uncoupled: formation increases more than resorption.

How exactly intermittently administered PTH does this remains to be fully characterized. Clearly, the mode of administration is important. In animal studies, the response of osteoblasts to PTH differs greatly, depending on whether they have short exposure or continuous exposure.^{4,5,8,10}

A series of bone-specific genes are turned on by intermittent PTH, but not by continuous treatment.^{4,5} This results in enhanced matrix generation and subsequent mineralization. Bone strength, as measured directly in animals and indirectly in humans, is remarkably enhanced. Thus, PTH has the advantage of not only building bone mass, but also strengthening bone's structural components, resulting in reduced skeletal fragility.

COMBINATION THERAPY

PTH has been given in combination with antiresorptive therapies in several trials. Some of the earliest studies with PTH included the use of PTH in women who were already on HRT.^{1,3,9} Studies have demonstrated that PTH provides an additional increase in bone mineral density of the spine and hip in postmenopausal women on HRT. Furthermore, research has found a significant increase in spinal trabecular bone as assessed by QCT in patients on PTH combination therapy.⁹ Currently, however, no study has specifically found that PTH works better in combination with HRT than it does alone. And, given the risks associated with the use of HRT, patients should be cautioned about continuing HRT for the purpose of preserving bone mass.¹¹

Combination therapy with PTH and alendronate does not appear to be more effective than PTH monotherapy.^{12,14} However, studies show that PTH followed by alendronate results in greater bone mass than PTH followed by placebo.¹⁵ Finally, PTH has been given in combination with

Contraindications for PTH

- Primary hyperparathyroidism
- Secondary hyperparathyroidism
- Vitamin D deficiency
- Paget's disease
- History of irradiation to bone
- Children and adolescents with open epiphyses
- History of bone cancer
- Substantial renal dysfunction
- Metastatic bone disease
- Multiple kidney stones
- Recent diagnosis of prostate or breast cancer

Special Considerations for Glucocorticoid-Induced Osteoporosis (GIOP)

- No data on combined bisphosphonates and PTH with GIOP
- PTH is not FDA approved for GIOP

PTH Study Results

1. Teriparatide (1-34): 20-month randomized, placebo-controlled, clinical trial in postmenopausal women

- 10-15% increased BMD
- Over 90% patients had an increase in BMD
- 50-60% reduction in total fracture risk

2. Parathyroidhormone (1-84) 18-month randomized, placebo-controlled, clinical trial in postmenopausal women:

- 2-7% increased BMD
- 58% reduction in vertebral fracture risk

PTH in Men

- 5.9-13.5% increase in spine BMD
- 1.5-3% increase in hip BMD
- Significant reduction in vertebral fracture risk

nasal calcitonin. Investigators found that there was no benefit to this combination over PTH alone.¹⁵

PTH FOR MEN

PTH has been shown to be an appropriate therapy for men with idiopathic osteoporosis. In one study, men with idiopathic osteoporosis and T-scores below -2.5 at the spine were treated with PTH (1-34), 1500 mg calcium, and 400 IU vitamin D for 18 months.^{8,16} Bone mineral density improved 13.5% at the spine and 3% at the femoral neck.

In a larger trial with 437 osteopenic men, bone mineral density increased 5.9% at the spine and 1.5% at the femoral neck in men receiving PTH (1-34) 20 mg/day over 11 months.¹⁷ Furthermore, following discontinuation of the therapy, men volunteered for an 18-month observation period.

In men treated with PTH, the relative risk of new vertebral fractures was decreased by 50%, but only trended to statistical significance. However, there was a significant reduction in moderate and severe fractures in the men treated with PTH versus placebo.¹⁸ Therefore, it appears that men with osteoporosis benefit from treatment with PTH.

SUMMARY

PTH has received approval by the U.S. FDA for treatment of osteoporosis (Forteo™). In clinical trials to date, teriparatide (PTH 1-84) is well tolerated. A few people develop mild hypercalcemia and leg cramps, nausea, dizziness, arthralgias, general weakness (all about 2% more than in placebo groups), increased uric acid, and increased blood and urine calcium (but no increase in kidney stones or gout).

There is no evidence that PTH has other long-term sequelae when administered over a 12–18 month period. It must be administered daily by subcutaneous injection. In addition, a potential increased risk for osteosarcoma has been suggested by PTH studies in rats, prompting the FDA to require warning language in Forteo™ product literature (see sidebar page 3). PTH is a valuable weapon in the battle against osteoporosis.

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