PTH and PTHrP Analogs

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Case Presentation

A 65-year-old woman was referred for evaluation of recently diagnosed osteoporosis. She sustained a left distal radius fracture 2 months prior in a fall from standing height onto a sidewalk. Subsequent bone density testing was significant for T-scores of −3.5 at the lumbar spine, −3.1 at the femoral neck, and −2.8 at the total hip. She had a history of thalassemia trait but no other significant past medical history and no history of radiation exposure. She had no previous personal history of fracture. Her mother had a history of osteoporosis, but there was no parental history of hip fracture. She had two servings of dairy per day and was taking a multivitamin with 300 mg of calcium and 1000 IU of vitamin D. She had no history of tobacco use and drank alcohol rarely. Her body mass index was 22 kg/m^2, and physical examination was otherwise unremarkable. Metabolic evaluation for secondary causes of bone loss was unremarkable, including normal serum calcium, PTH, and alkaline phosphatase levels. She was very interested in osteoanabolic therapy when discussed at the time of her visit.

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Assessment and Diagnosis

In contrast to antiresorptive agents, osteoanabolic therapies directly stimulate bone formation, improving not only bone mass but also bone microstructure [1]. Because bone formation and bone resorption are tightly coupled processes, osteoanabolic therapy will eventually stimulate bone resorption as well. The period of time when bone formation is greater than resorption is termed the anabolic window (Fig. 13.1) [2].

Parathyroid hormone has both anabolic and catabolic effects on bone. In patients with primary hyperparathyroidism, chronically elevated PTH levels have been associated with bone loss and increased fracture risk. In contrast, when PTH is given intermittently, with PTH levels rising and falling over a short period of time,

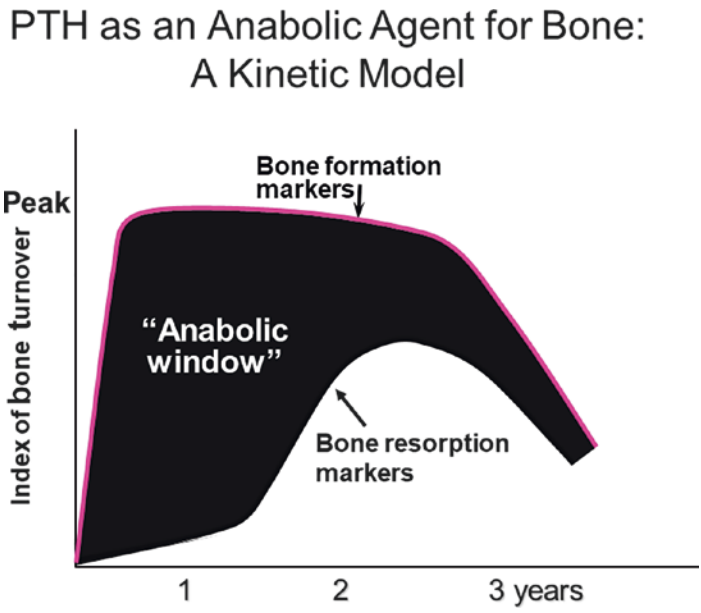

Fig. 13.1 Demonstration of the "anabolic window" concept that bone formation is first stimulated by an osteoanabolic agent followed by an increase in bone resorption [2]

there can be exuberant bone formation. The anabolic effects of PTH on bone are likely multifactorial, including pathways involving Wnt, Runx2, and insulin-like growth factor-1 (IGF-1) [1].

Teriparatide [PTH(1–34)] is the first 34 amino acids of the 84 amino acid parathyroid hormone protein. Abaloparatide is a functional optimization of parathyroid hormone-related peptide (PTHrP) based on amino acid substitutions between residues 22 and 34 [3].

Osteoanabolic therapy with teriparatide was approved by the Food and Drug Administration in 2002 for postmenopausal women and men at high risk for fracture and in 2009 for women and men with glucocorticoid-induced osteoporosis at high risk for fracture [4]. Per the approval, patients at high risk for fracture were defined as those who had experienced an osteoporotic fracture or patients with multiple risk factors for fracture. Teriparatide is used at a dose of 20 μg subcutaneously (SC) daily, typically for up to 24 months.

Abaloparatide was approved by the FDA in 2017 for treatment of osteoporosis in postmenopausal women at high risk for fracture or patients who have failed or are intolerant to other available osteoporosis therapy [5]. Abaloparatide is used at a dose of 80 μg SC daily, typically for up to 18 months.

The definitions of high fracture risk may differ, although there is general consensus encompassing patients who have already suffered a fracture. Hodsman and colleagues defined this group as patients with preexisting fractures, patients with a T-score of −3.5 or lower, and/or an unsatisfactory response to antiresorptive therapy [6]. Guidelines from the American Association of Clinical Endocrinology (AACE) [7] and Endocrine Society [8] recommend osteoanabolic therapy as first-line treatment for patients who are at very high risk for fracture. The AACE guidelines defined very high risk patients as patients with a fracture within 12 months, fractures while on approved osteoporosis therapy, multiple fractures, fractures while on drugs causing skeletal harm (e.g., glucocorticoids), very low T-score (<−3.0), high risk for falls or injurious falls, and very high fracture probability by FRAX (major osteoporotic fracture risk >30%, hip fracture >4.5%). Endocrine Society guidelines state very high risk patients include those with severe or multiple vertebral fractures.

In animal toxicity studies, male and female rats treated with PTH or PTH analogs were at an increased risk of osteosarcoma; however, this increased risk was not seen in monkeys [4]. Osteoanabolic therapy is contraindicated in patients at increased risk for osteosarcoma, including patients with open epiphyses, Paget's disease of bone or unexplained elevations of alkaline phosphatase, or prior external beam radiation therapy involving the skeleton.

Management

Osteoanabolic agents have been demonstrated to stimulate bone formation, improve bone density, and decrease vertebral and nonvertebral fracture risk. The pivotal trial leading to approval of teriparatide was a randomized, multicenter, double-blind, placebo-controlled trial in postmenopausal women that demonstrated an increase in bone density at the lumbar spine of +9.7% ($p < 0.001$) in the teriparatide 20 μg arm compared to placebo, +2.8% at the femoral neck ($p < 0.001$), and +2.6% at the total hip ($p < 0.001$) at a mean of 18 months of therapy [8]. There were relative risk reductions of 0.35 (95% CI, 0.22–0.55) for vertebral fracture and 0.47 (95% CI, 0.25–0.88) for nonvertebral fracture with the teriparatide 20 μg dose. Men were subsequently demonstrated to have similar improvements in bone density [9].

Teriparatide was compared to alendronate 10 mg PO daily in a randomized, multicenter, double-blind trial for women and men with glucocorticoid-induced osteoporosis [10]. There were significantly greater increases in bone density at the lumbar spine in the teriparatide versus alendronate group (+7.2% vs. 3.4%; $p < 0.001$) and at the total hip (3.8% vs. 2.4%; $p = 0.005$) at 18 months. Morphometric vertebral fractures were noted in 0.6% of patients in the teriparatide arm versus 6.1% in the alendronate arm ($p = 0.004$); there were no differences between groups in nonvertebral fractures. The study was extended for an additional 18 months, with findings that continued to demonstrate greater gains in bone density in the teriparatide over the alendronate arms

(11.0% vs. 5.3% at the lumbar spine; $p < 0.001$) as well as a decrease in fracture incidence (1.7% vs. 7.7%; $p = 0.007$) [11].

The pivotal trial leading to approval of abaloparatide was the Abaloparatide Comparator Trial in Vertebral Endpoints (ACTIVE), a randomized, multicenter, double-blind, placebo-controlled, active comparator (unblinded), 18-month trial in postmenopausal women with three arms: abaloparatide 80 μg SC daily, placebo SC, or teriparatide 20 μg SC daily [12]. Bone density at the lumbar spine increased similarly between the abaloparatide and teriparatide groups (+11.2% vs. +10.5%) and significantly greater than placebo (+0.63%; $p < 0.05$ compared to abaloparatide and teriparatide). Bone density at the femoral neck increased to a greater extent in the abaloparatide arm (+3.6%) compared to teriparatide (+2.7%; $p < 0.05$) and placebo (−0.43%; $p < 0.05$). Bone density at the total hip also increased to a greater extent in the abaloparatide arm (+4.2%) compared to teriparatide (+3.3%; $p < 0.05$) and placebo (−0.10%; $p < 0.05$). Vertebral fractures were similarly decreased in the abaloparatide (RR 0.14, 0.05–0.39) and teriparatide (0.20, 0.08–0.47) arms compared to placebo ($p < 0.001$ for both). Major osteoporotic fractures were decreased in the abaloparatide arm compared to both the teriparatide (HR 0.45 for abaloparatide versus teriparatide, 0.21–0.95; $p = 0.03$) and placebo groups (HR 0.30 for abaloparatide versus placebo, 0.15–0.61 $p < 0.001$).

Bone density at the spine and hip sites declines rapidly after osteoanabolic therapy is discontinued, and it is important to note that osteoanabolic therapy must be followed by antiresorptive therapy so that patients do not lose the bone that was gained [13].

Studies have investigated the combination of an antiresorptive and teriparatide therapy together. Oral or intravenous bisphosphonate therapy in combination with teriparatide has not been demonstrated to have significant additive effects, and in fact bisphosphonate therapy may attenuate the effect of teriparatide [14–16]. Combination of denosumab and teriparatide therapy was shown to increase bone density more than either agent alone; however, fracture data are not available [17]. It should be noted that combination therapy has not been approved.

The timing of therapy appears to be important. With oral or intravenous bisphosphonate therapy preceding treatment with teriparatide, there may be a delay in bone density gains, although it appears as if bone density may rise to a similar extent overall by the end of the treatment course [18]. When denosumab therapy precedes treatment with teriparatide, however, progressive or transient bone loss has been described [19].

Subcutaneous injections may not be acceptable to all patients or feasible for those with comorbidities that may affect motor function. Alternative delivery systems would be an attractive option, and there is a phase 3 trial of a transdermal abaloparatide patch (https://clinicaltrials.gov/ct2/show/NCT04064411). While it is important to consider osteoanabolic therapy for all patients at high fracture risk, antiresorptive therapy may be a better match for some patients.

Osteoanabolic therapy is well tolerated in women and men [9–12]. Hypercalcemia can occur and may prompt a reduction in calcium supplementation. In the pivotal trial of teriparatide, adverse events that were statistically greater in the teriparatide group included nausea and headache [8]. In the ACTIVE trial, hypercalcemia was less common in the abaloparatide arm compared to teriparatide; however, palpitations, nausea, and dizziness were greater in the abaloparatide compared to teriparatide and placebo arms [12]. A 15-year post-marketing surveillance study did not demonstrate an increased risk of osteosarcoma in adults treated with teriparatide [20]. While the black box warning for teriparatide to communicate serious risk was lifted by the Food and Drug Administration in January 2021, the use of teriparatide must still be avoided in patients with increased risk of osteosarcoma [4]. The black box warning for abaloparatide persists at this time.

Outcome

The patient was treated with abaloparatide 80 mcg SC daily for 18 months and recently transitioned to denosumab. Her bone density after completion of abaloparatide therapy was significant for

T-scores of −2.3 at the lumbar spine (+19.8%), −2.6 at the femoral neck, and −2.5 at the total hip (+5.3%). She has not experienced any other fractures during her treatment course. She is very satisfied with her bone density gains, and we expect further improvement with denosumab.

Clinical Pearls/Pitfalls

- Teriparatide and abaloparatide are approved osteoanabolic therapies administered as a daily subcutaneous injection.
- Osteoanabolic agents have been demonstrated to stimulate bone formation, improve bone density, and decrease vertebral and nonvertebral fracture risk.
- Osteoanabolic therapy should be considered for women and men at increased risk for fracture and for women and men with glucocorticoid-induced osteoporosis.
- Patients at high risk for fracture include those who have experienced an osteoporotic fracture, patients with very low T-scores, and patients with multiple risk factors for fracture.
- Osteoanabolic therapy must be followed by antiresorptive therapy to maintain bone density gains.
- Postmarketing surveillance has not demonstrated an increased risk of osteosarcoma in adults treated with teriparatide and the black box warning has been removed.

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