Bone Anabolic Therapy for Osteoporosis

Effective diagnosis and pharmacologic treatment of osteoporosis has prevented millions of fractures and the pain and disability that follow them. Antiresorptive agents that slow bone loss have proven effective in reducing fracture risk in many patients. However, more fractures still occur than are prevented.

While antiresorptives can slow loss of bone, they cannot rebuild bone that has already been lost. Stimulating new bone growth requires an anabolic agent. Currently, only one anabolic is FDA approved for treatment of osteoporosis, teriparatide, a recombinant form of endogenous human parathyroid hormone (PTH 1-34).

Since its approval in 2002, teriparatide (Forteo®) has been studied in multiple large-scale clinical trials, both alone and in conjunction with antiresorptive drugs. Data from this research demonstrate the remarkable potential of teriparatide and other variants of PTH for increasing bone density and strength.

Currently, insurers are reluctant to approve coverage for teriparatide. Prior authorization is required to support the need for teriparatide instead of antiresorptives.

In this issue of “Osteoporosis: Clinical Updates,” we will discuss PTH, its promise and its implications for patient care.

Editor-in-Chief, Angelo Licata, MD, PhD.

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Osteoporosis: Clinical Updates

Osteoporosis is a serious public health concern. In the U.S. alone, it is responsible for an estimated 2 million fractures a year and $17 billion in medical costs (2005 numbers). Osteoporosis-related fractures take a heavy toll, causing more than 432,000 hospital admissions, almost 2.5 million medical office visits and about 180,000 nursing home admissions annually in the U.S. As our population ages, this impact will only get worse.

In young healthy people, bone is maintained by a tightly coupled process of remodeling in which damaged old bone is removed (resorption) and replaced with new bone (formation). Advanced age, chronic disorders, hormone and nutrient deficiencies, and medications can unbalance the remodeling process so that bone resorption outpaces formation. The result is osteoporosis: progressive decline in bone mineral density (BMD), loss of bone resilience and mechanical strength, and increased incidence of fracture, primarily of the spine, forearm, and hip.

Restoring a more normal balance of bone remodeling can be achieved either by reducing resorption or increasing formation. Osteoporosis therapies fall into one or the other class: antiresorptives or osteoanabolics.

The most widely prescribed medications for osteoporosis are antiresorptive agents, primarily bisphosphonates, but also denosumab, selective estrogen receptor modulators, calcitonin, and estrogen.

Antiresorptives work by inhibiting the bone remodeling process, both resorption and formation. This effectively slows bone loss due to osteoporosis and can result in a relative increase or stabilization in BMD, reducing fracture risk. For fragile patients with severe osteoporosis, fracture risk is very high. No change or a slight increase

Activity Objectives

Upon completion of this CE material, the participant should be able to:

- Cite the indications for PTH in patients with osteoporosis.
- Cite the results of clinical trials of PTH in postmenopausal women.
- Recognize the contraindications for use of PTH.
- Discuss special considerations associated with PTH in patients with glucocorticoid-induced osteoporosis.
- Discuss the results of studies looking at the effect of PTH in combination with other drugs for osteoporosis.

Osteoporosis Clinical Updates is published to improve osteoporosis patient care by providing clinicians with state-of-the-art information and pragmatic strategies on prevention, diagnosis, and treatment that they may apply in clinical practice.

Overall Objectives

Upon completion of each issue of Osteoporosis Clinical Updates, participants should be able to:

- Recognize current concepts in osteoporosis research and clinical practice.
- Identify implications of these concepts for osteoporosis patient care.
- Adopt evidence-based strategies to study, prevent, and/or treat osteoporosis.
- Improve patient care practices by integrating new data and/or techniques.

Intended Audience

This continuing education activity is intended for health professionals who care for patients at risk for or suffering from osteoporosis practicing in primary care, endocrinology, geriatrics, gynecology, internal medicine, obstetrics, orthopedics, osteopathy, pediatrics, physiatry, radiology, rheumatology, and/or physical therapy. This includes physicians, nurse practitioners, registered nurses, pharmacists, physician assistants, technologists, researchers, public health professionals and health educators with an interest in osteoporosis and bone health.
in BMD may be insufficient to protect against fracture. A more effective option can be an anabolic agent that increases bone formation, either alone or in conjunction with an antiresorptive.

**Teriparatide and Bone**

The connection between endogenous parathyroid hormone and bone metabolism has long been recognized. Starting in the 1980s, randomized trials and observational studies with human recombinant parathyroid hormone given in subcutaneous intermittent doses was shown to dramatically stimulate new bone formation, while only modestly increasing bone resorption. The result was enhanced bone mass and significant reduction in spine fractures.2-7

In early animal studies, it was discovered that the response of bone to PTH differs greatly, depending on whether exposure is intermittent or continuous.

Intermittent PTH (e.g., small daily dose) leads to increased bone activation. Although both bone resorption and bone formation are increased, bone formation is increased more than resorption, leading to a net gain in bone density and volume.

In contrast, continuous PTH delivery produces a greater increase in bone resorption than bone formation, resulting in a net loss in density and volume. This is consistent with known effects of hyperparathyroidism, in which patients with the continuously elevated PTH experience bone loss and increased fracture risk.

Various forms of human parathyroid hormone have been studied: the intact molecule PTH (1-84), 34- and 31-amino-acid fragments (PTH [1-34], PTH [1-31]), and recently, the analog PTH (2-34). Of these, only PTH (1-34) has been developed into an FDA-approved drug. Teriparatide is the chemical name for the PTH (1-34) N-terminal fragment manufactured under the trade name Forteo™.

PTH (1-84) is approved for use in other countries, where it has been shown to significantly improve outcomes for elderly patients with pelvic fracture, a particularly difficult fragility fracture to treat. In a small Austrian study, daily PTH (1-84) started two days postfracture greatly improved healing rate (100% compared with 9.1%) and reduced healing time by ~60% (7.8 weeks compared with 12.6).8

The interval of activated bone formation with intact PTH or PTH analog is limited. The first 9 months of treatment is characterized by elevated bone formation.5 However, at 12-18 months, bone resorption begins rising toward baseline levels, outpacing formation. The interval of uncoupled bone turnover favoring formation is referred to as the *anabolic window.*9-12 Research is underway to enlarge this window and extend the utility of PTH beyond two years.13

Data from the pivotal 2001 teriparatide approval trial, conducted by Neer and colleagues, which enrolled 1650 postmenopausal women over a 21-month period, demonstrated significant improvements in both BMD and fracture risk. Compared with placebo, teriparatide accounted for a 10–15% increase in BMD and 50-60% reduction in relative risk of vertebral and nonvertebral fractures.14

Trabecular bone is more favorably affected by teriparatide than cortical bone. Trabecular bone is concentrated in the vertebral spine, while cortical bone is concentrated in the long bones. This physiologic distribution of bone may account for the smaller, though still enhanced bone mass and significant reduction in spine fractures.
significant, reduction of nonvertebral fracture seen with teriparatide.14

Combination Therapies

Studies have explored potential benefits of using teriparatide as an adjunct to antiresorptive therapy – either concurrently or sequentially, before or after antiresorptive treatment. A variety of approaches have been investigated that compare efficacy of PTH (1-34) alone and antiresorptive agents alone to:

• PTH concurrent with antiresorptive therapy
• PTH before antiresorptive therapy
• PTH following antiresorptive therapy

These combination therapeutics are largely investigational at this point. Many outstanding questions remain about their long-term safety and efficacy. Research is needed before they can gain widespread application in clinical practice.

Data from clinical trials indicate that PTH in combination with antiresorptive agents generally increases bone density more than treatment with either agent alone. The exception to this rule is alendronate, which has not been shown to produce greater increases in bone formation or BMD when combined with PTH (1-84) when given to treatment-naive individuals.15

Concurrent administration of raloxifene and teriparatide has been shown to improve total hip BMD to a greater degree than teriparatide alone in a six-month trial.16

Substantial gains in BMD of the spine and hip were seen with one year of PTH treatment in patients on prior raloxifene. When used after PTH is discontinued, raloxifene partially maintained PTH-induced BMD gains in the hip and spine.17

Due to the short duration and small size of these studies, fracture outcomes to confirm bone strength are not available.

Concurrent teriparatide-denosumab therapy was similarly shown to outperform single-drug therapy, in terms of BMD increase at hip and spine. Thsai, et. al., published results of a controlled clinical trial of 100 postmenopausal women randomized to 20 μg teriparatide daily, 60 mg denosumab every 6 months, or both taken concurrently. After 1 year, lumbar spine and hip BMD had increased more in the combination group than in either single-drug intervention.18 It should be noted that this study’s conclusions are also limited by the lack of fracture data due to its short duration.

The combination of teriparatide with zoledronic acid has also shown promise. Cosman, et. al., conducted a study comparing concurrent teriparatide-zoledronic acid, zoledronic acid alone, and teriparatide alone. Teriparatide was administered as a daily 20 μg subcutaneous injection, zoledronic acid as a single 5 mg infusion.19

Combination therapy provided the largest, most rapid increases in BMD, at both hip and spine at one year. Final hip BMD was increased 2.3%, 1.1%, and 2.2% in the combination, teriparatide, and zoledronic acid groups, respectively. BMD at spine had increased 7.5%, 7.0%, and 4.4% in the combination, teriparatide, and zoledronic acid groups, (p < .001 for combination and teriparatide versus zoledronic acid).19

Teriparatide used after discontinuation of antiresorptive therapy has been shown to produce positive effects on BMD and markers of bone formation in patients previously treated with alendronate,
etidronate, and risedronate.\textsuperscript{20}

The reverse, that is, antiresorptive therapy used after the discontinuation of teriparatide, has been shown to be beneficial in maintaining, but not increasing, BMD.\textsuperscript{21} Data from a study that assessed markers of bone turnover in patients who were prescribed raloxifene following 12 months of teriparadie found that markers of bone resorption were 60% lower in the teriparatide-followed-by-raloxifene group than in the teriparatide-only group. There was no significant difference between groups on markers of bone formation.\textsuperscript{22}

When added to existing alendronate therapy, PTH has been shown to mount an anabolic response, as indicated by increases in bone formation and BMD.\textsuperscript{24} Adding teriparatide to treatment of women currently taking estrogen therapy produced significant ($p < 0.001$) increases in spine BMD, total hip, and femoral neck. This increase was not seen at the distal radius, which was lower in the teriparatide cohort, as compared with the estrogen group.\textsuperscript{24}

There are currently no data-based or consensus recommendation for the concurrent or sequential use of PTH with other antifracture drugs.

<table>
<thead>
<tr>
<th></th>
<th>Spine</th>
<th>Total Hip</th>
<th>Femoral Neck</th>
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<tbody>
<tr>
<td>Estrogen-Teriparatide</td>
<td>14%</td>
<td>5.2%</td>
<td>5.2%</td>
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<tr>
<td>Estrogen Only</td>
<td>3%</td>
<td>1.6%</td>
<td>2%</td>
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\textbf{Figure 3.} Data showing comparison of estrogen alone versus estrogen plus teriparatide on BMD at spine, total hip, and femoral neck. (data from: Ste-Marie LG, et. al. J Bone Miner Res. 2006)

As data from longer-term studies become available, such as guidelines may be developed to support their use in clinical practice.

\textbf{PTH Treatment for Men}

Intermittent PTH has been shown to be an effective therapy for men with idiopathic or hypogonadal osteoporosis.\textsuperscript{21,22} Osteoporosis in men is characterized by low bone turnover. Because resorption is already low, inhibiting it further with an antiresorptive does very little to increase BMD.

An anabolic agent that increases formation can have a

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NOF depends on the generosity of individuals who recognize our important work educating the public and health professionals alike on how to prevent, diagnose and treat osteoporosis.

There are many ways to support NOF in its mission to defeat osteoporosis:

\textbf{Individual Giving}

Your gift will help us provide better care and support for the most vulnerable – those who have suffered a fracture – and to protect future generations from this debilitating disease.

\textbf{Recurring Gift}

By giving a little each month to sustain NOF throughout the year, you can make a big impact in our efforts to start conversations about bone health and family health history in order to elevate osteoporosis to an issue of national concern. Your support will help us reach our goals of better treating and ultimately preventing osteoporosis.

\textbf{Memorial and Tribute Gifts}

Give a tribute or memorial gift honoring the memory of friends and loved ones. For all gifts made, NOF will send appropriate notification to the honoree or to the family of the deceased on your behalf and you will receive acknowledgment of your gift either online or through the mail.

\textbf{Planned Giving}

NOF offers a variety of planned giving options. Planned giving allows supporters to leave gifts to NOF at death or to invest gifts during their lifetime. Investing during your lifetime allows you to receive the benefits while you are alive and bequest the remaining funds to NOF at the time of your death.

Visit \texttt{www.nof.org} today to make your tax-deductible donation.

The National Osteoporosis Foundation is a qualified 501(c)(3) tax-exempt organization and all donations to the organization are tax deductible.
greater impact. In one small study (23 participants), men with osteoporosis and T-scores below -2.0 were treated with PTH (1-34), 1500 mg calcium, and 400 IU vitamin D for 18 months. Bone mineral density improved 13.5% at the spine and 3% at the femoral neck. This study is obviously limited by its very small enrollment.

In a much larger trial of 437 men with low bone mass, BMD increased 5.9% at the spine and 1.5% at the femoral neck in men receiving teriparatide 20 μg/day over 11 months. Following discontinuation of the therapy, 350 study participants were followed for an additional 30-month observation period. In this group, the relative risk of all new vertebral fractures in men treated with teriparatide (20/40 μg/day) was 50% lower than in the placebo group. There was a significant reduction (80%) in moderate and severe vertebral fractures in the men treated with teriparatide versus placebo. BMD declined and markers of bone resorption increased towards baseline during this extension period, but were still better than baseline. In men who received antiresorptive therapy following discontinuation of teriparatide, BMD and bone resorption were both stable.

**PTH for Glucocorticoid-Induced Osteoporosis**

Intermittent parathyroid hormone has been shown to increase spine and hip BMD and reduce fracture risk in men and women with glucocorticoid-induced osteoporosis (GIOP).

In a 2007 randomized, double-blind trial designed to compare the effectiveness of alendronate to teriparatide, teriparatide was shown to increase BMD more than alendronate in GIOP patients. In the teriparatide group, the mean percent increase in BMD from baseline to endpoint (at 18 months) was 7.2% at the lumbar spine, 3.6% at the total hip, and 3.7% at the femoral neck (p<0.001 all sites). Mean BMD increase at lumbar spine for subjects in the alendronate arm was roughly half that of teriparatide, 3.4 percent. In a three-year extension of the original study, these gains from baseline in BMD were found to be significantly higher in the teriparatide group: 11.0% versus 5.3% for lumbar spine and 6.3% versus 3.4% for femoral neck. The teriparatide group experienced fewer new vertebral fractures than did alendronate subjects.
managed by having the patient lay down until the dizziness passes.

**PTH for Patients with Renal Disease**

Managing osteoporosis in patients with impaired renal function (chronic kidney disease, CKD) is a challenge. In addition to primary disease termed **renal dystrophy**, secondary osteoporosis is frequently seen. CKD itself is fracturing disease. Risk of bone loss increases as kidney function declines, marked by substantial elevation of intact PTH and alterations in serum levels of calcium and phosphorus.

Secondary analyses of teriparatide studies suggest that it may be possible to safely use teriparatide in patients with mild to moderate CKD (glomerular filtration rate [GFR] 30-79 ml/min; CKD stages 2-3), who have normal values for intact PTH, calcium, and phosphate, although clinical trial data are currently lacking. To date, trials of teriparatide have excluded patients with secondary hyperparathyroidism and vitamin D deficiency, both common in patients with CKD.

In patients with GFR <30 or who have pre-treatment hyperparathyroidism and/or hypocalcemia, teriparatide should not be considered and, if possible, nephrology consultation should be obtained for consideration of renal osteodystrophy care. (Guidelines for management of CKD-related bone disease have been published by KDIGO [Kidney Disease: Improving Global Outcomes] and are available at http://www.kidney.org.)

**Side Effects of PTH and Teriparatide**

In clinical trials, PTH has been well tolerated. A small percentage of people on teriparatide (2%) develop leg cramps, nausea, dizziness, arthralgias, general weakness, increased uric acid, and increased blood and urine calcium (but no increase in kidney stones or gout). A small number of teriparatide patients (5%) experience transitory orthostatic hypotension with their first few treatments. These episodes commonly resolve on their own and can be

Transient elevation of serum calcium can be seen in the 4-6 hours following injection. In the pivotal Neer study, mild hypercalcemia (calcium >10.6 mg/dL) was seen in 11% at the 20 μg dose and 28% at 40 μg dose (placebo 2%). (Note: clinical dose is 20 μg.) Serum calcium usually returns to normal concentrations without intervention. However, some patients develop persistent hypercalcemia. In the Neer study, persistent hypercalcemia was seen in 3% of those in the 20 μg group and 11% in the 40 μg dosing group (placebo <1%).

There are no data-based guidelines for managing hypercalcemia in such patients. However, it may be beneficial to limit calcium and/or vitamin D supplementation in patients with hypercalcemia following teriparatide treatment. For example, rather than the RDA intake recommendation of 1200 mg elemental calcium per day, the patient with hypercalcemia would be advised to get 1000 mg or less per day, the aim being to maintain serum calcium below 10 mg/dL.

Food sources of calcium are highly preferable to supplemental sources, which should be used only to reach target intake. Vitamin D could be supplemented only in patients with serum levels below 20 ng per milliliter.

A potential increased risk for osteosarcoma, suggested by toxicology studies in rats, prompted the FDA to require warning language in Forteo™ product literature. To date, there is no evidence that teriparatide treatment increases risk of osteosarcoma in humans.

<table>
<thead>
<tr>
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<th>Teriparatide</th>
<th>Oral rPTH</th>
<th>Placebo</th>
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<tbody>
<tr>
<td><strong>Number of Participants</strong></td>
<td>30</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td><strong>% Change From Baseline BMD Lumbar Spine Mean ± Standard Deviation</strong></td>
<td>5.07 ± 3.543</td>
<td>2.21 ± 2.503</td>
<td>-0.17 ± 2.739</td>
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**Figure 4.** Results from Phase 2 trial of 95 postmenopausal women comparing lumbar BMD change from baseline in women randomized to 20mg teriparatide, 5mg PTH oral analog, and placebo. (Source: U.S. National Institutes of Health. Pharmacodynamics, Pharmacokinetics, Safety and Tolerability of PTH Analog Tablets in Postmenopausal Women. ClinicalTrials.gov.)
In addition, analysis of population data has found no greater incidence of osteosarcoma in people with elevated endogenous PTH serum levels due to hyperparathyroidism. The Osteosarcoma Surveillance Study, a 15-year surveillance of ~1500 patients with osteosarcoma has found no evidence of an association between teriparatide treatment and incidence of osteosarcoma in humans.

Contraindications to teriparatide use include elevated pretreatment parathyroid hormone, hypercalcemia, and unexplained elevated bone-specific alkaline phosphatase (which could point to Paget’s disease of the bone). Also contraindicated would be pediatric and young adult patients who have open epiphyses, as well as anyone with a history of external beam radiation to the skeleton and/or internal radiation.

**In the Pipeline**

There are two significant barriers to the widespread adoption of teriparatide as an osteoporosis therapy as it currently exists: daily injection and high cost. Teriparatide is usually reserved for the most extreme cases: patients with severe osteoporosis and fractures that have not responded to other therapeutic options.

More practical and appealing methods for administering teriparatide are in development. The most promising and farthest along in development are micro-needle patch, oral teriparatide, and inhaled teriparatide preparations.

At this time, none of the investigational PTH preparations we discuss here are FDA approved or in commercial use in the US.

**Micro-Needle Patch.** To obviate the necessity of daily subcutaneous injection, a skin patch that delivers teriparatide via micro-needles is under development. This may prove to be a more convenient, patient-friendly mode of administration. Results from a six-month phase 2 dose-finding study of a daily micro-patch demonstrate anabolic benefits. In the study, daily 20 μg teriparatide injection was compared to 20 μg, 30 μg, or 40 μg dose micro-needle patch or a placebo patch.

All doses of teriparatide patch produced greater increases in total hip and spine BMD than placebo patch. Teriparatide patch groups showed dose-dependent increases in BMD at spine and total hip compared to both placebo patch and injection. The greatest increase was seen at the 40 μg dose: 4.9% at lumbar spine and 1.33% at total hip. No significant difference was seen in BMD at femoral neck or forearm between groups.

**Oral rPTH.** A recently completed phase II trial of 95 healthy postmenopausal women with osteoporosis investigated the efficacy of oral rPTH. The trial randomized participants to 5 mg daily oral preparation of rhPTH (1-31) NH (2), 20 mcg daily subcutaneous teriparatide rPTH (1-34), or placebo.

The oral route of administration produced changes in BMD at the lumbar spine that indicate anabolic bone formation. The percentage change from baseline was roughly half that seen in injectable teriparatide; however, it was significantly better than placebo (2.21% vs. -0.17). Data on long-term fracture outcomes as well as viability of absorption and cost remain to be addressed.

**Intranasal rPTH (1-34).** Another delivery method for rPTH (1-34) under investigation is an inhaled powder formulation. Animal studies have demonstrated bioavailability of rPTH (1-34) with pulmonary administration. One small (10 people) phase 1 study was done that confirmed what was seen in animal studies: inhaled rPTH (1-34) produces serum levels comparable to injected teriparatide. In addition, inhaled rPTH (1-34) reaches maximal concentrations more rapidly than the injected form. More research is required to explore fracture and BMD outcomes in larger cohorts of people.

**Other Bone Anabolics**

Research is ongoing to identify other bone anabolics, including a parathyroid hormone analog PTHrP (BA058) and agents targeting other pathways governing bone remodeling, such as Wnt signaling.

Phase 2 trials of the parathyroid hormone analog PTHrP (BA058) are currently underway. In early results from phase 2 trials, PTHrP has been shown to increase spine BMD and markers of bone formation significantly more than teriparatide at 12 months of administration.
**Patient Cases: Teriparatide in Clinical Practice**

In the following case studies, we will discuss potential clinical applications for teriparatide in typical patients.

**Case 1: 67-Year-Old Woman with multiple vertebral fractures and GERD**

The first patient we will discuss is a 67-year-old woman with a history of osteoporosis. The patient had a natural menopause at age 55 after which she experienced severe hot flashes, sleeplessness, and uterine bleeding, which eventually necessitated hysterectomy at the age of 57. At that time daily oral estradiol .5 mg/day was initiated. Mammography results had been normal in the past. The patient has a history of GERD and borderline Barrett’s Esophagus.

*At age 65, she had a baseline DXA. Her BMD T-scores were -2.7 at hip and -2.8 at spine.*

The patient’s physician recommended that she stay on estrogen and 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.

**Should the patient have a follow-up DXA?**

Two years have passed since her baseline DXA. It is appropriate to repeat the test. DXA is now repeated on the same device as her baseline for comparison.

Baseline BMD
- Hip: 0.73 g/cm²; T-score -2.7
- Lumbar spine: 0.72 g/cm²; T-score -2.8

Current BMD (2 Years from Baseline)
- Hip: 0.70 g/cm²; T-scores -3
- Lumbar spine: 0.68 g/cm²; T-score -3.2

**Is this patient a candidate for osteoporosis treatment?**

Yes. The patient’s T-scores indicate worsening osteoporosis and high risk of future fracture. Despite taking estrogen, calcium, and vitamin D, her bone mass has not remained stable. She needs to start on a medication to reduce her fracture risk, either an antiresorptive or an anabolic agent. However, before starting a therapy, the physician must rule out secondary causes of bone loss.

**What lab work should be done for this patient?**

It may be helpful to check serum and/or ionized calcium, serum PTH to evaluate for primary (high serum calcium) or secondary hyperparathyroidism (normal or low). A 25-hydroxyvitamin D level would rule out vitamin D deficiency or insufficiency and mild secondary hyperparathyroidism. An alkaline phosphatase level could rule out active Paget’s disease.

An evaluation of her kidney and liver function should be done to exclude renal or liver disease as well as a CBC or protein electrophoresis to rule out myeloma. Urinary calcium excretion should also be considered. Serum antibody testing should also be done.
Estrogen therapy is not recommended for long-term use solely to preserve bone mass.\textsuperscript{44} If the patient has stayed on estrogen for other benefits, her alternatives include topical and/or low-dose preparations that treat specific estrogen-related disorders, such as vaginal or urinary symptoms.

This patient is 10 years past menopause. An assessment of her risk of stroke and CVD would help inform the decision.

What osteoporosis treatment options should the clinician discuss with the patient?

The patient is eligible for a wide range of effective osteoporosis therapeutics. With her history of gastroesophageal problems, she is not be a good candidate for a daily oral bisphosphonate. Other FDA-approved alternatives include teriparatide, raloxifene, denosumab, and intravenous zoledronic acid. Additionally, the patient may require additional calcium via supplements to reach her daily recommended target.

Is it reasonable to start teriparatide at this time?

Although she could probably benefit from teriparatide, it is likely not the best option for her, given its high cost and need for daily injection. Antiresorptive agents would be a better initial choice.

The patient decides to start with yearly injection of zoledronic acid. If she continues to fracture or show further decline in BMD, the option of teriparatide can be reconsidered.

Case 2: 78-Year-Old Man with Severe Osteoporosis

The second patient we will discuss is a 78-year-old man who presents to the physician after experiencing acute, severe back pain upon lifting a suitcase. The patient lives in a retirement community with on-site medical support.

The patient has a history of GERD. He currently has an active duodenal ulcer and has been on a proton pump inhibitor for a year. He reports that he is considerably shorter than in his youth. Six months ago, he broke his wrist in a fall from standing height. He has never had a bone density test.

to exclude celiac disease, which can lead to calcium malabsorption.

The patient currently feels well on estrogen therapy and is reluctant to discontinue it completely.

Should the patient continue estrogen therapy? Not if it is for the sole purpose of preserving bone. Although estrogen therapy has been shown to reduce fracture risk, data from the Women’s Health Initiative linked it to increased risk of stroke in women who were 10 years or more post menopause. (Subanalysis as well as subsequent studies suggest that timing of initiation of therapy may be key in determining cardiovascular risk for both estrogen and estrogen-progestin therapy.\textsuperscript{42,43})

Estrogen therapy is not recommended for long-term use solely to preserve bone mass.\textsuperscript{44}
Lumbar spine X-rays reveal a vertebral compression fracture at L2.

He is referred for a bone density scan. His DXA results indicate significantly low bone mass: T-score of -3.8 at the spine and -3.4 at the total hip (referenced to male data set). Given his T-scores and history of fracture, the patient is diagnosed with severe osteoporosis.

Would this patient be a candidate for teriparatide therapy?

Possibly. There are multiple medications FDA approved for treatment of osteoporosis in men. Before deciding on a specific treatment, the patient should be worked up for any cause of secondary osteoporosis.

What work-up would this patient need?

Because primary osteoporosis in men is uncommon, he needs a work-up to rule out secondary causes of bone loss. The most common of these include hypogonadism, glucocorticoid treatment, and alcohol abuse. His work up should also rule out any conditions that could be exacerbated by teriparatide therapy.

For example, if the patient has hyperparathyroidism, teriparatide would be contraindicated. A serum calcium and intact PTH level should therefore be checked. In addition, vitamin D deficiency, hyperthyroidism, hyperparathyroidism, impaired renal and liver function, celiac disease, and myeloma need to be ruled out.

For the purpose of establishing baseline levels, the patient’s markers of bone turnover, both resorption and formation, are measured. This will be used as a benchmark for future comparison.

The patient’s labs come back unremarkable for causes of secondary osteoporosis.

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

Possibly. The patient’s options include antiresorptive therapy or teriparatide.

What treatment options should be considered?

We would want to avoid daily oral bisphosphonates, which could exacerbate his GERD and ulcer conditions.

Weekly oral preparations of alendronate and risedronate are available, as is monthly oral ibandronate. However, given the severity of his gastroesophageal
conditions, an injectable antiresorptive drug would probably be a better option. Yearly zoledronic acid or twice yearly denosumab have both been proven to slow bone loss and reduce fractures in men.

What advantages would teriparatide have over antiresorptives at this point?
Teriparatide is his best option for getting the biggest BMD gain in the shortest time. This patient has had prior vertebral fracture and is at very high risk of additional fractures. Because he has access to onsite healthcare providers, he is able to have daily injections without leaving his retirement community.

The patient begins teriparatide injections daily.
At the same time he begins a daily supplementation regimen to ensure he consumes 1200 mg calcium per day and 400 IU vitamin D.

He is urged to get as much calcium as possible from his diet and supplement only when needed to get him up to the daily target. He also begins physical therapy and weight-bearing exercise to improve function, reduce pain, and help mitigate fall risk. Three months later, he returns for a follow-up visit.

Are laboratory values or bone density assessments necessary at this time?
Although BMD changes were seen very early in teriparatide clinical trials, at this point, it is not reasonable to repeat a BMD test. The DXA can be repeated in one to two years or when teriparatide is stopped. Instead, the clinician requests measure of markers of bone turnover now and again in six months.

Changes in markers of bone formation (e.g., osteocalcin or bone specific alkaline phosphatase) above baseline will indicate response to teriparatide treatment. (Ensure the same marker measured at baseline is measured here.)

What is the long-term plan following teriparatide treatment?
At the end of two years treatment with teriparatide, the patient will be prescribed an antiresorptive drug to retain the BMD gains made on teriparatide. In order to avoid oral bisphosphonates, his options would be once-yearly zoledronic acid, quarterly injectable ibandronate, or twice-yearly denosumab.

Case 3: 60-Year-Old Postmenopausal Woman with Asthma
The third patient we will discuss is a 60-year-old postmenopausal woman with a long history of asthma, requiring intermittent large boluses of oral corticosteroids in addition to a daily maintenance dose of an inhaled corticosteroids and other medications.

The patient underwent menopause at the age of 51 and has not taken hormone therapy. She consumes 700 mg of calcium in her diet and takes a daily 500 mg calcium supplement and a 1000 IU vitamin D supplement. She participates in a mild resistance-training program at a gym twice a 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. She has never had a DXA measurement of bone density.

The patient has a DXA scan. Her BMD T-scores are -3.0 at the spine and -2.4 at the total hip. She is diagnosed with osteoporosis.

Would this patient be an appropriate candidate for teriparatide?
Possibly. This patient likely has primary osteoporosis due to postmenopausal bone loss as well as glucocorticoid-induced osteoporosis (GIOP). GIOP causes secondary damage to bone quality in addition to the thinning of trabeculae seen in primary postmenopausal osteoporosis. This puts this patient at a greater risk for fracture than if she simply had bone loss due to menopause. Teriparatide is FDA approved for treatment of GIOP. Research has shown teriparatide to increase BMD and reduce new vertebral fractures better than alendronate in GIOP patients.27

The patient could have another secondary cause of bone loss, such as vitamin D deficiency, hyperthyroidism, or hyperparathyroidism or any of the aforementioned causes. 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 indicates
vitamin D deficiency. She can be treated with 50,000 units of vitamin D$_3$ 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 D$_3$.

**What treatment would be appropriate to manage this patient's osteoporosis?**

If the patient is willing and able to give herself daily injections and if her insurance carrier can be persuaded to cover it, teriparatide would probably be the best option for increasing her BMD and avoiding fracture. Two years on teriparatide could then be followed up with an antiresorptive.

If the patient is unable or unwilling to self-administer daily injections or if her insurance refuses to cover teriparatide, an antiresorptive agent could be initiated. Teriparatide can be added to her therapy in the future if her bone health continues to deteriorate. Her markers of bone turnover are measured to provide a baseline for future comparison (e.g., NTX, CTX, pyridinoline).

**The patient expresses unwillingness to give herself daily injections.**

She is prescribed annual zoledronic acid injection and followed with markers of bone resorption after six months, ensuring the marker measured at baseline is followed with markers of bone resorption after six months, ensuring the marker measured at baseline is measured here.

**SUMMARY**

Bone anabolics are sure to play a larger part in osteoporosis patient care in the future, both those based on parathyroid hormone and those that harness other metabolic pathways involved in the regulation of bone formation. Some day soon, researchers may develop a pure anabolic, one that activates formation with no offsetting increase in resorption. Until that time, teriparatide, alone or in conjunction with antiresorptives, will continue to offer patients with severe osteoporosis their best chance at avoiding fracture and maintaining their quality of life.

**REFERENCES**

FORTEO® INDICATIONS AND USAGE

FORTEO® is recombinant human parathyroid hormone analog (1-34), [rhPTH(1-34)] indicated for:

• Treatment of postmenopausal women with osteoporosis at high risk for fracture
• Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture
• Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture

DOSAGE AND ADMINISTRATION

• Recommended dose is 20 mcg subcutaneously once a day
• Administer as a subcutaneous injection into the thigh or abdominal wall
• Administer initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur
• Use of the drug for more than 2 years during a patient’s lifetime is not recommended

DOSAGE FORMS AND STRENGTHS

• Multi-dose prefilled delivery device (pen) containing 28 daily doses of 20 mcg

CONTRAINDICATIONS

• Patients with hypersensitivity to teriparatide or to any of its excipients

WARNINGS AND PRECAUTIONS

• Patients with Paget’s disease of bone, pediatric and young adult patients with open epiphyses, and patients with prior external beam or implant radiation involving the skeleton: Should not be treated with FORTEO®
• Treatment duration: Use of FORTEO® for more than 2 years during a patient’s lifetime is not recommended.
• Patients with bone metastases, history of skeletal malignancies, metabolic bone diseases other than osteoporosis, or hypercalcemic disorders: Should not be treated with FORTEO®
• Laboratory alterations: FORTEO® may increase serum calcium, urinary calcium, and serum uric acid
• Urolithiasis: Use with caution in patients with active or recent urolithiasis because of risk of exacerbation
• Orthostatic hypotension: Transient orthostatic hypotension may occur with initial doses of FORTEO®

ADVERSE REACTIONS

• Most common adverse reactions (>10%) include: arthralgia, pain, and nausea. To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-545-5979 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

• Digoxin: Use FORTEO® with caution in patients receiving digoxin. Transient hypercalcemia may predispose patients to digitalis toxicity

USE IN SPECIFIC POPULATIONS

• Pregnancy: Based on animal studies, may cause fetal harm
• Nursing Mothers: Discontinue nursing or FORTEO®, taking into account the importance of treatment to the mother
• Pediatric Use: FORTEO® should not be used in pediatric and young adult patients with open epiphyses due to increased baseline risk of osteosarcoma.

WARNING: POTENTIAL RISK OF OSTEOSARCOMA

In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20-mcg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, prescribe FORTEO® only for patients for whom the potential benefits are considered to outweigh the potential risk. FORTEO should not be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with Paget’s disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy involving the skeleton).

Osteoporosis International

Osteoporosis International is the leading scientific journal for clinical research in osteoporosis and related bone diseases. Published monthly, the journal is an international, multi-disciplinary joint initiative of NOF and the International Osteoporosis Foundation.

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This brochure will help you better understand your osteoporosis treatment options. It provides information on the osteoporosis medicines approved by the U.S. Food and Drug Administration (FDA), discusses factors to consider when making a treatment decision and the issues you may face in staying with a treatment plan.

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