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# Recombinant human PTH 1-34 (Forteo): An anabolic drug for osteoporosis

## ABSTRACT

Forteo (teriparatide of rDNA origin), a genetically engineered fragment of parathyroid hormone, is the first of a new class of drugs to treat osteoporosis. The drug's anabolic action increases bone turnover, stimulating osteoblasts to a greater extent than osteoclasts, and reducing both vertebral and nonvertebral fractures. However, a number of issues about its use remain unanswered.

## KEY POINTS

The drug is indicated for people with osteoporosis at high risk for fracture, although the definition of "high risk" is left to the treating physician.

Although Forteo comes with a warning about osteosarcoma based on rat studies, the risk in humans appears to be very small.

Data are limited on how to use Forteo appropriately in combination with current antiresorptive agents.

The drug is contraindicated in patients with open epiphyses (ie, children, adolescents), Paget disease of the bone, prior radiation therapy involving the skeleton, bone metastases or skeletal malignancies, metabolic bone diseases other than osteoporosis, or preexisting hypercalcemia.

\*The author has indicated that he serves as a consultant for and is on the speaker's bureau of Eli Lilly and Company.

**W**E NOW HAVE an important new drug for treating osteoporosis, derived from nature's own molecule for regulating calcium: parathyroid hormone (PTH).

In a large placebo-controlled trial, the new drug, called Forteo, increased bone density significantly, reduced the incidence of fractures by more than half, and caused minimal side effects.

Forteo's mechanism of action is distinct from that of the antiresorptive drugs such as estrogen, selective estrogen receptor modulators, bisphosphonates, and calcitonin, which all increase bone mass by inhibiting osteoclastic bone resorption. Forteo, in contrast, increases bone turnover, stimulating osteoblasts to a greater extent than osteoclasts.

Although the US Food and Drug Administration (FDA) has approved Forteo as safe and effective, a number of issues remain to be resolved, notably:

- Who should get Forteo? The official indication of "high risk for fracture" is based on physician assessment. Exactly which patients constitute this high-risk group is not defined and is thus subjective.
- How should it be used in conjunction with antiresorptive agents?
- Who will pay for it? Forteo costs approximately \$600 per month, and as with many other new, expensive, genetically engineered drugs, its use may be limited by formulary and pharmacy benefit committees and by a patient's ability to pay.

This paper reviews Forteo's pharmacology and efficacy, and unresolved issues.

FIGURE 1

**Not available for online publication.  
See print version of the  
*Cleveland Clinic Journal of Medicine***

**Daily PTH  
injections  
paradoxically  
increase bone  
mass**

#### ■ DEFINITIONS

**Native PTH** is a protein composed of 84 amino acids (FIGURE 1). A recombinant human formulation of PTH (rhPTH 1-84, Preos) is under development.

**Teriparatide** is the generic name for the 34-amino acid N-terminal fragment of the PTH molecule. Teriparatide has the same binding affinity as does native PTH for the surface receptors that mediate its activity.

- **Synthetic teriparatide** is a synthetic version of teriparatide (hPTH 1-34), which has been used in a number of clinical trials.
- **Forteo** (teriparatide of rDNA origin) is the brand name for teriparatide of recombinant DNA origin manufactured by Eli Lilly and Company.

For the sake of clarity, in this paper we refer to the drug by its brand name.

#### ■ HOW PTH REGULATES CALCIUM

Native PTH regulates calcium and phosphate metabolism in the bones and kidneys. The bones are the major reservoir of calcium available to keep serum calcium levels in the normal range.

Decreases in serum calcium levels stimulate PTH production, which stimulates bone turnover and release of bone-bound calcium,

which in turn increases serum calcium levels. PTH also promotes renal retention of calcium and excretion of phosphate and 1-alpha hydroxylation of 25-hydroxyvitamin D, which increases gastrointestinal absorption of calcium.<sup>1</sup>

Osteoblasts have receptors that affect bone remodeling, including receptors for PTH. The increase in bone resorption induced by PTH is mediated through the stimulation of osteoblasts and the interaction of the receptor activator of NF- $\kappa$ B (RANK) ligand on their surfaces with RANK on the surface of osteoclasts.

#### **The PTH paradox:**

##### **PTH can cause bone resorption or formation**

The pattern of exposure to PTH determines its skeletal effects. Chronic elevation of PTH, as in primary hyperparathyroidism, results in a greater degree of osteoclastic bone resorption and thus depletion of calcium from bone, leading to osteoporosis. In contrast, intermittent administration of PTH, using daily injections of short-lived PTH preparations, has the seemingly paradoxical effect of increasing bone mass.

When Forteo is given by injection, it reaches peak serum concentrations in approximately 30 minutes and declines to nondetectable levels within 3 hours. Given in this manner, it stimulates new bone formation by stimulating osteoblast activity to a greater extent than osteoclast activity (FIGURE 2).

#### ■ KEY CLINICAL TRIALS OF FORTEO

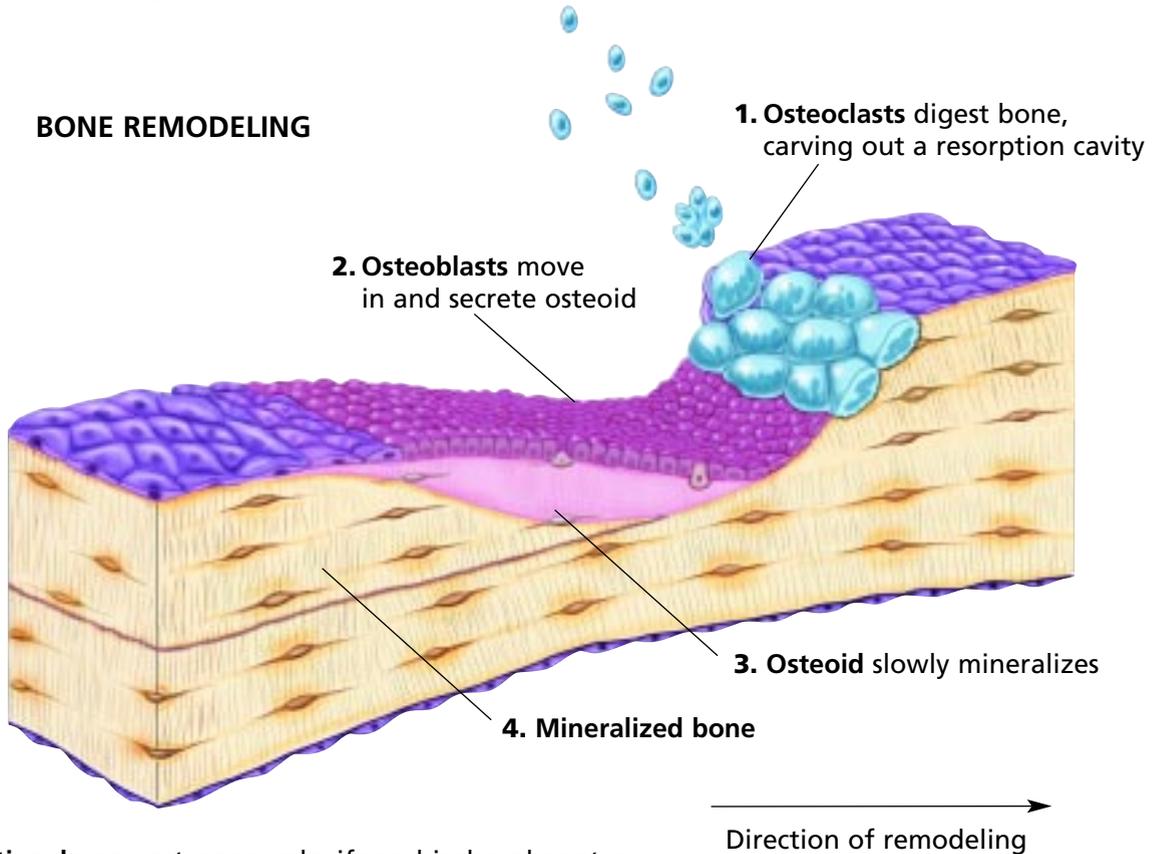
In a trial funded by Eli Lilly and Company, Neer et al<sup>2</sup> evaluated Forteo in two dosages (20  $\mu$ g and 40  $\mu$ g daily) vs placebo in postmenopausal women with low bone mass (mean lumbar spine T score  $-2.6$ ) and prior vertebral fractures (mean of 2.3 fractures). In all, 1,637 women were treated for a median of 19 months.

##### **Bone density increased**

In the Forteo 20- $\mu$ g group, lumbar spine density increased by 9.7%, compared with 1.1% in the placebo group ( $P < .001$ ). Femoral neck density increased by 2.8% in the Forteo 20- $\mu$ g group but decreased 0.7% in the placebo group



## ■ Antiresorptive and anabolic drugs: Two strategies for building bone



**Antiresorptive drugs**—estrogen, raloxifene, bisphosphonates—  
inhibit osteoclasts and decrease bone turnover, resulting in a  
net increase in bone density

**Anabolic PTH-type drugs** increase both osteoclast and  
osteoblast function and bone turnover, but once-a-day doses  
of short-acting preparations affect osteoblasts more, resulting  
in a net increase in osteoid and, ultimately, more bone

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**FIGURE 2**

( $P < .001$ ). The increases were greater with the 40- $\mu\text{g}$  dose (TABLE 1).

In all, 96% of patients treated with Forteo had an increase in bone mass, and 44% had an increase that was greater than 10%.

### Fracture risk decreased

New vertebral fractures occurred in 5% of the Forteo 20- $\mu\text{g}$  group, compared with 14.3% of the placebo group, for a relative risk of 0.35

(95% confidence interval [CI] 0.22–0.55). The number of patients that would need to be treated to prevent one fracture (“number needed to treat”) was 12. The relative risk in the 40- $\mu\text{g}$  group was 0.31 (95% CI 0.19–0.50). Vertebral fractures were defined as a reduction in vertebral height of 20% or more on radiography.

New nonvertebral fragility fractures occurred in 3% of the two Forteo groups and in 6% of the placebo group, for a relative risk

TABLE 1

**Effect of Forteo on osteoporosis: 21-month data**

MEASURE	PLACEBO	FORTEO 20 $\mu$ G	FORTEO 40 $\mu$ G
Change in lumbar vertebral density	1.1%	9.7%	13.7%
Change in femoral neck density	-0.7%	2.8%	5.1%
Incidence of vertebral fractures	14.3%	5%	4%
Incidence of nonvertebral fragility fractures	6%	3%	3%

DATA FROM 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.

of 0.47 with Forteo 20  $\mu$ g (95% CI 0.25-0.88) and 0.46 with Forteo 40  $\mu$ g (95% CI 0.25-0.86). The number needed to treat was 38 for both groups.

**Antifracture effect persists**

After the trial ended, 77% of the study patients enrolled in an 18-month observational extension.<sup>3</sup> The findings suggest that the antifracture effect of Forteo persists after the drug is stopped.

In the 18-month extension, vertebral fractures occurred in 11.2% of the patients who had received Forteo compared with 19.5% of the patients who had received placebo. Moreover, of the patients with an incident fracture during the randomized trial, 15.8% of those who had received Forteo had another vertebral fracture in the 18-month follow-up compared with 44.7% of those who received placebo.

Approximately 54% of patients in each group were on antiresorptive agents at the end of the 18-month observational study.

**Side effects of Forteo:****More hypercalcemia, but not serious**

Women who received Forteo had slightly higher rates of leg cramps, nausea, dizziness, and hypercalcemia than those in the placebo group.<sup>2</sup>

Although 11% of the patients on Forteo 20  $\mu$ g had a single episode of hypercalcemia, serum calcium levels were measured 4 to 6 hours after dosing, which maximized the chance of finding hypercalcemia. The half-life of the drug is approximately 1 hour, and its effect on serum calcium begins at 2 hours and is maximal at 4 to 6 hours.

Serum calcium was measured 5 to 6 times during the study in each patient, and only one third of patients who had a high serum calcium value had a subsequent high value on retesting.

Clinically significant hypercalcemia was rare with the 20- $\mu$ g dose (the dose approved for marketing), and resulted in discontinuation in only 1 of the 544 patients in this group.

If a patient develops hypercalcemia while taking Forteo, it would be appropriate to reduce oral calcium intake by 50%. The package insert does not recommend routine monitoring of serum calcium.

The only other side effects that were significantly increased in the Forteo-treated patients were dizziness (8% vs 5.4%) and leg cramps (2.6% vs 1.3%).

**Study in men**

A trial in 437 men<sup>4</sup> was stopped at a median treatment period of 11 months, after toxicology studies in rats revealed an excess number of osteosarcomas (see below). However, it also included an 18-month observational extension.<sup>4</sup>

Although the study was not of sufficient duration or size to evaluate efficacy in preventing fractures, in the approximately 30 months of the study and follow-up, vertebral fractures occurred in 12% of the men in the placebo group vs 6% in the treated group ( $P = .086$ ).

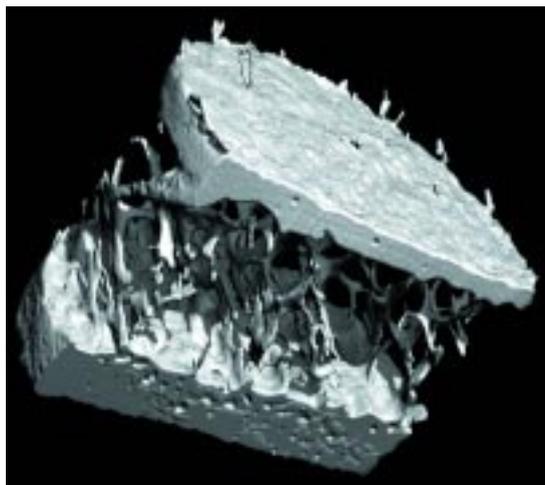
**■ WHAT ABOUT OSTEOSARCOMA?**

A toxicology study showed a dose-dependent increase in the occurrence of osteosarcoma in Forteo-treated rats.<sup>5</sup>

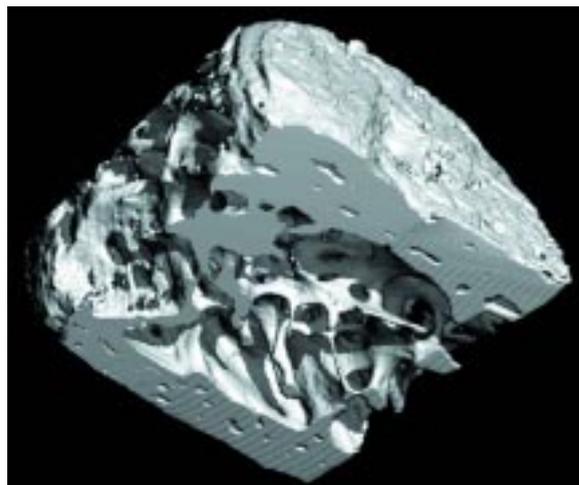
**Clinically significant hypercalcemia was rare in the study**

## Effect of teriparatide 20 µg on skeletal architecture

### Baseline



### Follow-up



**FIGURE 3.** Left, microcomputed tomographic scan of a biopsy specimen from the iliac crest of a 65-year-old woman at baseline. Right, repeat biopsy from the same patient after 21 months of therapy with Forteo 20 µg/day, showing increased trabecular and cortical thickness.

PHOTOS COURTESY ELI LILLY AND COMPANY

### Risk of osteosarcoma with Forteo appears very low

After thoroughly reviewing this issue, the FDA approved the drug but required a black box warning in the package insert noting this finding. The FDA and an expert panel felt that the findings of the rat study were unlikely to predict the development of bone tumors in patients who receive Forteo.

The risk of osteosarcoma in humans would appear to be very small, based on the following.

#### High doses in susceptible rats

Forteo was tested in Fischer 344 rats, which grow throughout their lives, have open epiphyses, and are more susceptible to osteosarcoma. The spontaneous rate of osteosarcoma in this rat strain is 1 to 3 in 1,000; in contrast, the rate in humans is 4.5 in 1 million.

Furthermore, the rats received Forteo in doses of 5, 30, or 75 µg/kg—3 to 60 times higher than the dose approved in humans—for more than 70% of their lives. In a 70-kg patient, a dose of 20 µg is 0.3 µg/kg. The approved 2-year treatment period in humans is about 2.5% of a human lifespan.

In a second study, no cases of osteosarcoma occurred when mature (6-month-old) Fischer 344 rats were treated with 5 µg/kg for 6 or 20 months.<sup>6</sup>

#### No human cases of osteosarcoma reported

No cases of osteosarcoma have been observed in approximately 2,000 patients treated with Forteo.

Indirect evidence for the safety of Forteo regarding osteosarcoma comes from the Swedish Cancer Registry database of 12,644 women and men with a history of hyperparathyroidism,<sup>7</sup> in which no cases of osteosarcoma have been reported.

Analogously, in studies in animals, long-term use of thyroid-stimulating hormone has led to follicular cancer,<sup>8</sup> and proton pump inhibitors have led to neoplasia of enterochromaffin cells by elevation of gastrin,<sup>9</sup> but neither has caused neoplasia in humans.

Forteo is not genotoxic, based on standard tests: the Ames test for bacterial mutagenesis, the mouse lymphoma assay for mammalian cell mutation, the chromosomal aberration assay in Chinese hamster ovary cells, and the in vitro micronucleus test in mice.<sup>10</sup>

#### ■ ANTIRESORPTIVE VS ANABOLIC DRUGS

The mechanism of action of Forteo is different from that of antiresorptive drugs. The difference has implications for measuring the efficacy of therapy.



## **Anabolic drugs build bigger bone, not just denser**

Antiresorptive drugs inhibit osteoclast function, decrease turnover and remodeling, and decrease the remodeling space (the portion of bone where osteoclasts have carved out a resorption cavity). Anabolic drugs, in contrast, increase osteoblast and osteoclast function (stimulating osteoblasts more than osteoclasts), increase turnover and remodeling, and increase the remodeling space (FIGURE 2).

Therefore, anabolic drugs may prevent fractures not only by increasing bone mass: they may also change the geometry of bone (FIGURE 3).<sup>11-13</sup> Treatment with these drugs enlarges bone by increasing periosteal and endosteal apposition of bone, creating a mechanically stronger bone by increasing its size.

## **DXA may underestimate the effect of anabolic drugs**

This increase in bone size results in a smaller apparent increase in bone mass when measured by dual-energy x-ray absorptiometry (DXA), which measures density as mass per unit *area*, than by quantitative computed tomography (CT), which measures mass per unit *volume*. This increase in bone volume does not occur with antiresorptive agents.

In patients treated for 6 months with Forteo 20 µg daily or with alendronate (Fosamax; a bisphosphonate) 10 mg daily, bone density as measured by DXA increased 4.7% in Forteo-treated patients and 3.2% in alendronate-treated patients.<sup>14</sup> Measured by quantitative CT, the increase in bone mass was 14.6% with Forteo and 2.9% with alendronate. The marked increase in volumetric bone mass is consistent with both an increased size of bone and a substantial increase in bone formation.

Since antiresorptive agents reduce bone turnover, a greater proportion of osteoid is mineralized. This increase in mineral results in a higher measured bone mass. The slower turnover allows the remodeling space to fill, also resulting in higher bone mass. With anabolic drugs, osteoid is produced at an accelerated rate, which would leave more osteoid unmineralized. A portion would mineralize at a later time. DXA does not measure unmineralized osteoid, and this later mineralization

may result in a continuing increase in bone mass for a time after PTH or teriparatide is discontinued. In addition, the remodeling space may be increased with anabolic drugs.

## **Even by DXA, anabolic drugs seem to increase density more**

Nonetheless, even as measured by DXA (which may underestimate their effect), anabolic drugs seem to increase bone density more than the bisphosphonates or raloxifene (Evista).

In the trial of Neer et al,<sup>2</sup> 19 months of Forteo treatment increased lumbar spine density by 9.7%. In contrast, in the Fracture Intervention Trial (FIT),<sup>15</sup> alendronate-treated patients had a mean increase of 8.8% at 36 months.

Body et al<sup>16</sup> treated patients with Forteo 40 µg (double the approved dose) or alendronate 10 mg daily. At the end of 1 year, lumbar spine density (measured by DXA) had increased 12.2% in the Forteo group vs 5.6% in the alendronate group.

## **Long-term increase in mass with anabolic drugs**

The slope of the increase in bone mass with antiresorptive agents is greatest in the first 6 to 12 months but slows thereafter. In the study of Neer et al,<sup>2</sup> the rate of increase in bone density with Forteo was greatest in the first 6 months but the rates of increase were equal in months 6 to 12 compared with months 12 to 18. We do not have data on the rate of increase in months 18 to 36, since this trial was stopped at a median follow-up of 19 months.

The only 3-year trial of an anabolic drug used teriparatide (synthetic hPTH 1-34), not Forteo, and was conducted in patients previously treated with estrogen.<sup>17,18</sup> (Patients in the Neer cohort had not received bone-active agents for 2 to 24 months.) The increase in lumbar spine density with hPTH 1-34 was 13.4% at 36 months, and the rate of increase in bone mass did not appear to slow in months 24 to 36. In contrast, with antiresorptive drugs the increases in bone mass slow markedly after 12 months.

## **Does more bone mean fewer fractures?**

The relationship between the magnitude of the increase in bone mass with therapy and

**Anabolic drugs may prevent fractures by changing the geometry of bone**

the degree of fracture reduction is controversial. The important question is whether the larger gains in bone mass seen with anabolic drugs result in greater fracture reduction than with antiresorptive agents.

Since no head-to-head studies have compared an anabolic drug with an antiresorptive agent with fracture as an end point, the question cannot be answered at this time.

Recent reviews indicate that changes in bone density can explain only a portion of the antifracture efficacy of antiresorptive agents.<sup>19,20</sup> For example, raloxifene and the bisphosphonates reduce the incidence of vertebral fractures by a similar amount, although raloxifene induces a much smaller increase in bone mass.<sup>15,21,22</sup>

The factors other than bone density that reduce fractures are not known but may include drug effects on bone turnover, microarchitecture, quality, and geometry, and local cellular effects. These factors may be quite different with anabolic drugs than with antiresorptive drugs.

In the study of Neer et al,<sup>2</sup> lumbar spine density increased by 9.7% in the Forteo 20- $\mu$ g group and 13.7% in the 40- $\mu$ g group. The additional gain in bone mass in the 40- $\mu$ g group did not significantly change the magnitude of vertebral fracture reduction (65% in the 20- $\mu$ g group and 69% in the 40- $\mu$ g group).

Antiresorptive agents reduce the 12-month incidence of vertebral fractures by more than 60%,<sup>21</sup> and the 36-month incidence by 40% to 50%. Is the fracture reduction with Forteo significantly better, and if so, is it enough to justify the added expense of this agent? Would the fracture reduction at 36 months have been greater with Forteo than with antiresorptive agents?

### ■ CLINICAL USE OF FORTEO

Forteo is given as a daily injection using a pen injector similar to the one used to deliver Humalog and Humulin, insulin preparations made by Eli Lilly and Company.

Each pen (ordered as “Forteo pen, 750  $\mu$ g, 3 mL”) is preloaded with a 28-day supply of drug and must be kept refrigerated. The needles, either 29-gauge or 31-gauge ultrafine pen needles, have to be ordered separately. The

pen delivers the approved dose of 20  $\mu$ g after a priming step.

The approved duration of treatment is 24 months (the trial of Neer et al was planned to continue for 36 months).

### ■ WHO SHOULD GET FORTEO?

The package insert states that Forteo is indicated for postmenopausal women and men at high risk for fracture, based on physician assessment. The definition of high risk is thus left to the treating physician but could include:

- Patients who continue to have fractures while on antiresorptive therapy
- Patients who continue to lose bone mass while on antiresorptive therapy
- Patients who cannot take oral bisphosphonates because they have esophageal strictures or motility disorders—although intravenous bisphosphonates are a non-FDA-approved option), or who have a history of blood clots that precludes the use of estrogen or raloxifene
- Patients whose bone mass remains very low (T scores lower than  $-2.5$  or  $-3.0$ ) despite antiresorptive therapy. For instance, a patient who began antiresorptive therapy with a T score of  $-4.0$  and improved to a T score of  $-3.0$  after several years of treatment could be an appropriate Forteo candidate
- Never-treated patients at high risk for fractures (ie, those who have prevalent fractures or low bone mass with additional risk factors)
- Glucocorticoid-treated patients who have fractures.

### ■ WHO SHOULD NOT RECEIVE FORTEO?

The following are contraindications to Forteo:

**Open epiphyses.** A peak of osteosarcoma incidence occurs in children, and since there is concern about treatment in growing humans with open epiphyses, Forteo is not recommended for use in children, teenagers, or young adults. An NIH-sponsored trial of teriparatide (not Forteo) in children with hypoparathyroidism was stopped after the rat toxicology study.

Cost will be an issue in who gets Forteo



**Paget disease** causes increased bone turnover, and an agent that further increases turnover would not be appropriate. In addition, patients with Paget disease are at increased risk for osteosarcoma.

**Unexplained elevations of alkaline phosphatase.** (This would not include explained elevations such as in rheumatoid arthritis, in which alkaline phosphatase is an acute-phase reactant, or in liver or gall bladder disease.)

**Metabolic bone diseases** other than osteoporosis, eg, vitamin D deficiency or osteomalacia.

**Primary hyperparathyroidism.** It is probably prudent to measure serum calcium before starting Forteo. If the calcium level is high, it would be appropriate to measure the serum PTH and 25-hydroxyvitamin D levels as well.

**History of osteosarcoma** or any bone cancer, either primary or metastatic to bone.

**Prior radiation therapy** that includes the skeleton. (These patients are at increased risk for bone malignancy.)

**Pregnancy or breast-feeding.** No information is available in humans on the effects of Forteo on the fetus or concentrations in breast milk.

**Renal impairment.** Patients with a creatinine clearance lower than 30 mL/minute have an increase in Forteo plasma concentrations. Efficacy studies have not been done in patients with end-stage renal disease.

## ■ UNRESOLVED ISSUES AND THE AUTHORS' BOTTOM LINE

### Should we stop antiresorptive drugs when starting Forteo?

The patients most likely to receive Forteo will be those who continue to have fractures while on antiresorptive therapy. Should Forteo be added to ongoing antiresorptive therapy in this situation, or should the antiresorptive agent be stopped?

Although no randomized trial has been done in these patients, it is hoped that the addition of an anabolic agent will further reduce the risk for fracture.

Lindsay et al<sup>17</sup> and Cosman et al<sup>18</sup> added synthetic teriparatide (hPTH 1-34) to ongoing estrogen treatment (average 5 years of conjugated equine estrogens) in patients with

a T score lower than  $-2.5$  and preexisting vertebral fractures. Patients treated with synthetic teriparatide and estrogen had fewer vertebral fractures than patients treated with estrogen alone (37.5% vs 8.3%,  $P < .002$ ).

The AAA (Anabolic After Antiresorptives) trial<sup>23</sup> is assessing the effect of previous antiresorptive therapy on the response to Forteo. Preliminary data (at 6 and 12 months) showed attenuated bone mineral density response to Forteo in the spine with a slight decline in hip density in patients who had been on alendronate for at least 18 months (prior to Forteo treatment). Patients on raloxifene (which is a less potent antiresorptive agent than alendronate) had a response to Forteo similar to that of treatment-naive patients. The difference in bone density response seen at 6 months narrowed at 12 months.

These findings raise the concern that Forteo may be less effective in preventing fractures in patients who have received bisphosphonates, although the clinical importance of these is not known.

If bone formation must always be preceded by bone resorption (as proposed by Frost<sup>24</sup>), the effect of anabolic drugs could be blunted by pretreatment with an antiresorptive agent. However, anabolic drugs may initiate bone formation at surfaces that are not undergoing resorption. The AAA trial is planned to continue for 24 months.

Bisphosphonates have long half-lives—years for alendronate; thus, stopping them is unlikely to have an immediate effect on bone turnover. This is confirmed by a study in which patients were treated with alendronate for 5 years, stopped the drug, and were followed for an additional 5 years. Markers of bone turnover continued to be suppressed at 2 and 5 years.<sup>25,26</sup> Thus, the effect on bone turnover produced by stopping bisphosphonates when starting Forteo is likely to be small.

**Bottom line.** We, along with many experts, recommend stopping the antiresorptive agent before starting Forteo, although studies in estrogen- and raloxifene-treated patients do not appear to show any blunting of effect. If a patient needs estrogen because of ongoing menopausal issues, it may not have the same effect on attenuation of Forteo response as do bisphosphonates.

**We recommend stopping antiresorptive agents when starting Forteo, except perhaps estrogen and raloxifene**

In patients previously treated with bisphosphonates for several years, the effect of the drug on bone turnover would be expected to persist perhaps for years after stopping the drug because of the very long half-life of this class of agents.

As a practical matter in these patients, if the clinician measures bone density 12 months after starting Forteo, the increase may be much smaller than expected. Physicians should not assume that the patient is not responding to Forteo or that he or she is not taking it as directed.

### Should untreated patients with low bone mass and fractures get Forteo first?

Patients with low bone mass (T scores lower than  $-2.5$ ) with prevalent fractures have a significant residual risk of fracture with antiresorptive therapy. The rationale for using Forteo before antiresorptive agents in this situation is the belief that Forteo is more effective. However, while studies showed greater increases in bone mass in patients treated with Forteo than with alendronate,<sup>14,16</sup> there are no head-to-head studies that compared efficacy for preventing fractures.

In randomized controlled trials,<sup>15,21,22</sup> patients with previous vertebral fractures had significantly *fewer* fractures if they received antiresorptive drugs—but they still had fractures. In the FIT study,<sup>15</sup> 8% of such patients treated with alendronate had vertebral fractures during 3 years, compared with 15% of placebo-treated patients. In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial,<sup>22</sup> 14.7% of patients treated with raloxifene had vertebral fractures in 3 years, vs 21.2% of placebo-treated patients.

All the patients in the study by Neer et al<sup>2</sup> had low bone mass and prevalent vertebral fractures. Is the vertebral fracture reduction of 65% seen in this trial significantly different than the fracture reduction seen with antiresorptives?

**Bottom line.** Until there are head-to-head studies, this issue will not be resolved. In the meantime, physicians will need to make their best judgment about which patients to treat. In general, the greater the risk a patient will suffer another fracture, the more likely we will be to prescribe Forteo first. That is, in a patient

with very low bone mass and multiple risk factors for further fracture (such as low body weight, smoking) we would be more likely to prescribe Forteo first, followed by an antiresorptive drug. Still, this a major gray area.

### Should untreated patients get an antiresorptive drug after Forteo?

Alendronate has an additive effect on bone mass when given after a course of teriparatide or rhPTH 1-84, but no fracture data have been published.<sup>27</sup>

**Bottom line.** Based on the AAA trial, most experts would use Forteo as initial therapy for 2 years (the FDA-approved interval) in high-risk patients, followed by an antiresorptive agent to maintain and further the increase in bone mass achieved with Forteo.

### Should Forteo be used in patients with very low bone mass but no fractures?

No data are available on fracture reduction with Forteo in patients with low bone mass without prevalent fractures.

The fracture rate is lower in patients without prevalent fractures. In the FIT 2 study,<sup>28</sup> patients with a T score less than  $-2.5$  without a prevalent vertebral fracture had a 3-year risk of vertebral fracture of 5.8%.<sup>28</sup>

It is reasonable to think that using Forteo for 2 years followed by an antiresorptive would be more effective than either agent used alone.

In a trial of combination therapy, Ste-Marie et al<sup>29</sup> used estrogen and Forteo 40  $\mu\text{g}$  for 15 months. Patients treated with both Forteo and estrogen from the outset had an increase in lumbar spine density of 16.9% compared with 11.2% in patients who had Forteo added to ongoing estrogen therapy. It would appear that the effects of the two agents given together are additive and that estrogen does not inhibit the anabolic response to Forteo.

Rittmaster et al<sup>27</sup> used rhPTH 1-84 followed by alendronate and also demonstrated additive effects of combination therapy on bone density. Neither trial was large enough to evaluate fracture efficacy between the two agents.

**Bottom line.** What degree of osteopenia or osteoporosis warrants the use of this more expensive agent? We would use it in patients

**Most experts would use Forteo as initial therapy for 2 years in patients at very high risk**

with very low bone mass (T score < -3.0) and multiple risk factors that make the likelihood of fracture very high (5% or more in the next 3 years). Risk factors include increasing age, low body weight, family history of osteoporosis, smoking, and high bone turnover.

### Use Forteo in glucocorticoid-treated patients who have had fractures?

There are no data with Forteo in steroid-treated patients, but a study is currently in the enrollment phase. Fifty-one steroid-treated patients showed significant increases in bone mass after treatment with synthetic hPTH 1-34.<sup>30,31</sup>

**Bottom line:** The same rationale outlined above for high-risk patients could guide Forteo use in this population. Forteo could be used in glucocorticoid-treated patients who have fractures while on antiresorptive therapy or in untreated patients with low bone mass and risk factors that put them at high risk for fractures.

### OTHER UNANSWERED QUESTIONS

**Can patients receive more than one course of Forteo?** After Forteo is used for 2 years and the gains are maintained with antiresorptive agents, can it be used again at some future time to give the skeleton another anabolic stimulus? Will the increase in bone mass during the second course be as robust as in the first course? If so, is it possible to “normalize” bone density in some patients with repeated courses of PTH drugs? Might other dosing regimens (eg, treatment for less than 24 months or doses every other day) also reduce fracture risk?

**What is the appropriate interval to measure bone density?** Since Forteo treatment is limited to 24 months, should bone density be measured at 12 months to assess response? Will insurance companies pay for earlier bone density measurement? In Medicare patients,

the Bone Mass Measurement Act allows for a bone density measurement 12 months after starting a new therapy.

**Do patients with larger increases in bone density enjoy greater protection against fractures?** Preliminary analysis of the trial by Neer et al<sup>2</sup> shows no relationship between bone density response and fracture efficacy (personal communication).

**Are markers of bone formation a good surrogate for bone density response?** Markers of bone formation rise more rapidly (peaking at 1 month) with teriparatide treatment than do markers of resorption (which peak at 6 months). It appears that PINP (terminal peptide of type 1 collagen) may be the best formation marker to use, since levels rise quickly and remain elevated while on Forteo. Many of the markers return to baseline at 12 to 24 months.<sup>17</sup>

### HOW WILL COST INFLUENCE THE USE OF FORTEO?

Forteo costs about \$20 per day or about \$600 per month. The Eli Lilly company has an assistance program for patients who have no drug coverage and cannot afford the drug. However, patients with drug coverage that does not include Forteo as an approved drug, or that includes Forteo but with a large co-pay or cap, are not eligible for the program.

Lilly will assess insurance coverage: call 1-866-436-7836.

Since the drug is much more expensive than antiresorptive agents, its use will be restricted to patients at high risk. The definition of high risk is physician-determined, but in reality the use of Forteo will be restricted by the patient's ability to pay and his or her insurance drug coverage. It is likely that pharmacy benefits committees will develop guidelines for the use of Forteo—not a surprise, since this is common for other expensive drugs. 

What degree of osteoporosis warrants the use of this more expensive agent?

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