OVERVIEW

Osteoporosis can be defined as a systemic skeletal disease characterized by low bone mass, microarchitectural deterioration of bone tissue, and increased bone fragility and susceptibility to fracture.\(^1\) It most commonly affects older populations, primarily postmenopausal women.

The prevalence of osteoporosis poses a serious health problem. The National Osteoporosis Foundation has estimated that 44 million people are experiencing the effects of osteoporosis or osteopenia.\(^2\) By the year 2010, osteoporosis will affect more than 52 million people and, by 2020, more than 61 million people. The prevalence of osteoporosis is greater in Caucasians and Asians than in African-Americans, perhaps because African-Americans have a higher peak bone mass. Women are affected in greater numbers than men because bone turnover increases, resulting in accelerated bone loss because of the lack of estrogen after menopause.

The effects of osteoporosis or osteopenia.\(^2\) The National Osteoporosis Foundation has estimated that 44 million people are experiencing the effects of osteoporosis or osteopenia.\(^2\) By the year 2010, osteoporosis will affect more than 52 million people and, by 2020, more than 61 million people. The prevalence of osteoporosis is greater in Caucasians and Asians than in African-Americans, perhaps because African-Americans have a higher peak bone mass. Women are affected in greater numbers than men because bone turnover increases, resulting in accelerated bone loss because of the lack of estrogen after menopause.

The goal of pharmacological treatment is to maintain or increase bone strength, to prevent fractures throughout the patient’s life, and to minimize osteoporosis-related morbidity and mortality by safely reducing the risk of fracture. The medications that have been used most commonly to treat osteoporosis include calcium and vitamin D, estrogen (with or without progestin), bisphosphonates, selective estrogen receptor modulators (SERMs), and calcitonin.

Parathyroid hormone (PTH) has recently emerged as a popular osteoporosis treatment. Unlike other therapies that reduce bone resorption, PTH increases bone mass, which results in greater bone mineral density (BMD). In November 2002, the U.S. Food and Drug Administration (FDA) approved teriparatide injection (Forteo®, Eli Lilly) for the treatment of osteoporosis. As a PTH derivative, teriparatide has proved effective in increasing bone formation, augmenting bone mass, and reducing fracture rates.

PHARMACOLOGY

A strain of Escherichia coli, modified by recombinant DNA technology, is used to manufacture teriparatide. The drug contains recombinant human PTH (rhPTH 1-34) and has a sequence that is identical to that of the 34N-terminal amino acids (the biologically active region) of the 84-amino acid human PTH.\(^3\)

PTH, the primary regulator of calcium and phosphate metabolism in bones, has many functions. It can initiate bone turnover by the stimulation of osteoclasts. This stimulation results in net resorption of bone or directly activates bone formation by initiating osteoblastic activity. The continuous exposure to PTH results in bone resorption; therefore, administration of intermittent doses of PTH leads to bone formation. Intermittent PTH treatment has been shown to increase bone formation and bone mass, leading to improved compressive strength.

Compared with other standard therapies for osteoporosis, teriparatide increases BMD and restores bone architecture and integrity. Bisphosphonates increase BMD and reduce bone resorption.

Body and colleagues compared the effects of teriparatide and the bisphosphonate alendronate (Fosamax®, Merck) on BMD, the incidence of non-vertebral fracture, and bone turnover in postmenopausal women with osteoporosis.\(^4\) The women were given once-daily subcutaneous (SQ) injections of 40 mcg of teriparatide or oral doses of 10 mg of alendronate. The BMD of the lumbar spine increased by 12.2% in the women receiving teriparatide and by 5.6% in the women receiving alendronate. Teriparatide increased femoral neck BMD and total-body BMD significantly more than did alendronate. The incidence of nonvertebral fracture was significantly lower in the teriparatide group than in the alendronate group.\(^4\)

PHARMACOKINETICS

Teriparatide is absorbed extensively after SQ injection; its absolute bioavailability is approximately 95%, and its half-life in serum is approximately one hour when it is given by SQ injection. The metabolism and excretion of teriparatide have not yet been formally studied, but the peripheral metabolism of PTH is believed to occur by nonspecific enzymatic mechanisms in the liver, followed by excretion via the kidneys.

Suzuki et al. found that when PTH was given in pulses to rats, the serum level exhibited three peaks, with each peak appearing at the end of the 30-minute application period.\(^5\) The maximal concentration (\(C_{max}\)) values decreased gradually after repeated application (Table 1).
ADVERSE EFFECTS

The FDA has issued a black-box warning because of the drug’s association with an increased incidence of osteosarcoma (a malignant bone tumor) in male and female rats. The effect was dependent on the dose and treatment duration and was observed at systemic exposures to teriparatide ranging from three to 60 times the exposure in humans who were given a 20-mcg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, teriparatide should be prescribed only when the potential benefits are considered to outweigh the potential risks for each patient. It should not be prescribed for patients who are at increased risk for osteosarcoma at baseline, including those with Paget’s disease of bone or unexplained elevations of alkaline phosphatase, open epiphyses, or previous radiation therapy involving the skeleton.

Adverse drug events (ADEs) associated with teriparatide use include—but are not limited to—headache, asthma, neck pain, hypertension, angina pectoris, syncope, nausea, constipation, dizziness, depression, insomnia, vertigo, hyperuricemia, and hypercalcemia. ADEs appear to increase with higher dosages. According to the study by Body et al., significantly fewer patients taking teriparatide (5.5%) had new or worsened back pain compared with patients taking alendronate (19.2%), although six patients taking teriparatide and none taking alendronate reported leg cramps. In this study, 28 women taking teriparatide and two receiving alendronate had elevated four-hour to six-hour post-dose serum calcium levels at least once, and one woman discontinued teriparatide treatment because of increased serum calcium levels after injection. The women with elevated serum calcium levels were asymptomatic, and these increases were not associated with clinically significant adverse outcomes.

In a study by Neer et al., 94 of 1,637 women withdrew because of ADEs. Dosages of 20 mcg and 40 mcg were administered by SQ injection. Eighteen percent of the women reported nausea, 13% reported headache, 9% reported dizziness, and 3% reported leg cramps. The investigators also noticed an increase in circulating antibodies to PTH, which occur more often in higher doses of teriparatide (40 mcg) and had no apparent effect on any of the measurements.

DOsing

The manufacturer recommends a dose of 20 mcg SQ once daily, given in the thigh or abdomen, for a maximum of two years. Upon the initiation of treatment, patients should be observed for signs and symptoms of orthostatic hypotension.

The clear, colorless liquid is available in a 3-ml pen injector containing 750 mcg of teriparatide. The pen must be refrigerated and can be reused for 28 days.

The safety and efficacy of teriparatide have not been evaluated beyond two years of treatment.

DRUG INTERACTIONS

Teriparatide appears to have no significant drug–drug interactions. In a study of nine healthy people and 17 patients with mild, moderate, or severe renal insufficiency (with a creatinine clearance of 13–72 ml/minute), coadministration of intravenous furosemide (20–100 mg) with 40 mcg of teriparatide resulted in small elevations in serum calcium levels (2%). Twenty-four-hour urine calcium (37%) responses to teriparatide did not appear to be clinically important.

In a study of 20 healthy people, the coadministration of teriparatide plus hydrochlorothiazide (HCTZ) 25 mg did not affect the serum calcium response to teriparatide 40 mcg. The 24-hour urine excretion of calcium was reduced by a clinically unimportant amount (15%). The effect of a higher dose of HCTZ administered with teriparatide on serum calcium levels has not been studied.

In a study of 15 healthy individuals who received digoxin (Lanoxin®, GlaxoSmithKline) daily to a steady state, a single teriparatide dose did not alter the effect of digoxin on the systolic time interval. However, sporadic case reports have suggested that hypercalcemia might predispose patients to digitalsis toxicity. Because teriparatide temporarily causes elevated serum calcium levels, it should be used with caution in patients taking digitalsis.

CLINICAL EFFICACY

Horwitz et al. demonstrated that SQ PTH in high doses for only three months appeared to be a potent anabolic agent, producing a 4.7% increase in lumbar spine BMD. This compares favorably with available antiresorptive drugs for osteoporosis and is similar to the increases in BMD reported for PTH at this early point in time. Despite the high
Montvale, NJ: Medical Economics.

Drugs Used in the Treatment of Osteoporosis or vertebral osteoporosis. It is possible that this drug has anabolic effects on bone mass and bone structure, leading to the formation of a substantial amount of new bone.15

**COST**

The average wholesale prices (AWPs) of teriparatide and other agents are listed in Table 2.16 A cost of $515.79 for a month’s supply puts teriparatide at the top of the list as the most expensive osteoporosis drug. All of the other drugs, such as the bisphosphonates, SERMs, and calcitonin, are similar to one another in price (approximately $65 per month). Teriparatide is eight times more expensive than the other drugs, and its route of administration is a cause for concern. It must be given daily as an SQ injection, which can be an inconvenience to the patient. Calcitonin is the only other medication listed that must be injected by the SQ route, but it is given every other day with a much lower monthly cost ($155.16) than teriparatide.

In the end, it is up to patients to choose the therapy they prefer. Will it be the one that is said to work best in preventing bone loss and rebuilding BMD, or will it be the cheapest therapy that prevents bone resorption only? Price is not the only concern; the ease of the route of administration is also a consideration. With few patients willing to give themselves an injection once a day, perhaps new formulations are needed to help foster patient compliance.

**CONCLUSION**

Teriparatide is the newest option for the treatment of postmenopausal osteoporosis. It is effective when used as a single agent and in conjunction with alendronate to increase bone density.17 It is well tolerated, with an ADE profile similar to that of placebo, except for the incidence of dizziness and leg cramps.

Teriparatide has a place in therapy as an alternative treatment for osteoporosis, although no current studies have demonstrated its safety or efficacy after two years of use.

**REFERENCES**


3. CenterWatch: Clinical Trials Listing Service. Drugs Approved by the FDA. Available at: drugstore.com, as of January 27, 2003. Cost of two 2-ml bottles with at least 14 doses each.

mcg = microgram; mg = milligram; IU = International Unit; IM = intramuscular; PO = orally; SQ = subcutaneous.


<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroid hormone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teriparatide (Forteo®, Eli Lilly)</td>
<td>20 mcg SQ daily</td>
<td>$516</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alendronate (Fosamax®, Merck)</td>
<td>10 mg PO daily</td>
<td>$65</td>
</tr>
<tr>
<td></td>
<td>or 70 mg PO weekly</td>
<td>$64</td>
</tr>
<tr>
<td>Risedronate (Actonel®, Procter &amp; Gamble)</td>
<td>5 mg PO daily</td>
<td>$63</td>
</tr>
<tr>
<td></td>
<td>or 35 mg PO weekly</td>
<td>$62</td>
</tr>
<tr>
<td>Selective estrogen receptor modulator</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raloxifene (Evista®, Eli Lilly)</td>
<td>60 mg daily</td>
<td>$67</td>
</tr>
<tr>
<td>Calcitonin-salmon (Miacalcin Injection®, Novartis)</td>
<td>100 IU SQ every other day</td>
<td>$155</td>
</tr>
<tr>
<td></td>
<td>or 100 IU IM every other day</td>
<td></td>
</tr>
<tr>
<td>Calcitonin-salmon (Miacalcin Nasal Spray®, Novartis)</td>
<td>200 IU intranasal daily</td>
<td>$64†</td>
</tr>
</tbody>
</table>

* Approximate retail cost to the patient for 30 days’ treatment, based on listings at drugstore.com, as of January 27, 2003.

† Cost of two 2-ml bottles with at least 14 doses each.

In a study by Rittmaster and coauthors, observed that the sequential treatment of osteoporosis with PTH and alendronate resulted in an increase in vertebral BMD that was considerably more than had been reported with alendronate or estrogen alone.13 It is possible that this drug combination might be a useful approach to maximizing the BMD in women with vertebral osteoporosis.


