Summary

✔ In the US, teriparatide is indicated for the treatment of patients with osteoporosis who are “at high risk for fracture.”

✔ Although placebo-controlled trials show that teriparatide can reduce fractures, there is little information on its efficacy compared to available alternatives.

✔ In the US, the Food and Drug Administration highlighted concerns about teriparatide’s carcinogenic effects in rats. Company-sponsored studies have been voluntarily stopped.

The Technology

The active principle of teriparatide injections is recombinant human parathyroid hormone [rhPTH(1-34)]. Its amino acid sequence is identical to the 34 N-terminal amino acid sequence of human parathyroid hormone (hPTH). Its physiological actions include regulation of bone metabolism, renal tubular reabsorption of calcium and phosphate and intestinal calcium absorption. The intermittent administration of hPTH at optimal doses stimulates bone formation and increases bone mass and strength. In animal studies, the administration of high doses of hPTH causes bone resorption and decreases bone mass. In the human body, teriparatide produces similar biological effects by binding to PTH receptor sites.

Regulatory Status

Teriparatide (rDNA origin) injections (Forteo™, Eli Lilly and Company) have been approved in the US by the Food and Drug Administration (FDA) for use by post-menopausal women with osteoporosis and by men with primary or hypogonadal osteoporosis, who are at high risk of fractures. On June 17, 2003, the European Union approved teriparatide for marketing in 15 countries. Teriparatide is still unavailable in Canada.

Patient Group

Osteoporosis is a skeletal disorder in which reduced bone strength predisposes a person to an increased risk of fracture. Bone strength reflects the integration of bone mineral density (BMD) and bone quality. Fractures of the spine, hip and wrist are the most clinically significant osteoporotic fractures. Hip fractures are costly to repair and cause more disability than the other types. Since hip fractures are mainly treated in hospital, they can be counted and compared among countries. Vertebral fractures may be clinically significant, but they may also be occult and asymptomatic.

Current Treatments

For the treatment of osteoporosis in post-menopausal women, several agents are marketed: estrogens; selective estrogen-receptor modulators (e.g. raloxifene); bisphosphonates (e.g. etidronate, alendronate, risedronate); calcitonin and vitamin D. For the treatment of osteoporosis in men, bisphosphonates, calcitonin, calcium and vitamin D are recommended. No available agent, however, restores normal bone mass and strength.

Assessing the Evidence

The briefing documents developed for the FDA’s review of teriparatide focused on three phase III trials, which were also reported in peer-
reviewed journals. All trials were voluntarily suspended because of an unexpected skeletal finding in rats. Osteosarcoma occurred in 26% of the rats exposed to different doses of teriparatide over 17 to 20 months (most of a rat’s life span).

**Teriparatide versus alendronate in women:** In a double-blind randomized controlled trial (RCT) over two years, teriparatide 40 µg SC (double the recommended dose) was compared to alendronate 10 mg PO in 146 post-menopausal women with lumbar spine or femoral neck bone mineral density at least 2.5 standard deviations (SD) below the mean for young adult women. The median exposure to treatment was 14 months. The fracture data were reported as a secondary endpoint. The proportion of patients with non-vertebral fractures in the teriparatide and alendronate groups was not significantly different [4.1% (3/73) versus 13.7% (10/73)] (Table 1). Non-vertebral fractures were not only defined as those of the ribs and ankles, but also of the toes and feet, which some do not consider to be osteoporotic fractures. The proportions of patients who withdrew because of adverse events in the teriparatide and alendronate groups were 19.2% (14/73) and 9.6% (7/73) respectively. Only 55% of screened patients were included in the study.

**Teriparatide versus placebo in women:** The efficacy and safety of teriparatide 20 µg SC once daily (n=541), 40 µg SC once daily (n=552) and placebo (n=544) were compared in post-menopausal women with previous vertebral fractures in a three-year multi-centre RCT. After a median follow-up of 21 months, new vertebral fractures occurred in 5.0% (22/444) of those receiving teriparatide 20 µg, 4.4% (19/434) of those receiving 40 µg and 14.3% (64/448) of those receiving placebo injections. The proportions of women with new non-vertebral fractures were 6.3% (34/541), 5.8% (32/552) and 9.7% (53/544) respectively. Teriparatide significantly reduced the risk of fractures in post-menopausal women compared with placebo (Table 1). Data from 19% of the patients with a vertebral fracture were excluded in the analysis, as follow-up radiographs were unavailable. The flat dose response curve of teriparatide leads to the question of whether a dosage of 10 µg/day or lower should be studied. Fractures of the ribs, feet and ankles were included as non-vertebral osteoporotic fractures. There were no significant differences among the three groups with respect to the number of deaths and hospitalizations or the number of women in whom cardiovascular disorders, bladder stones or gout developed during the study. Only 21% of screened patients were included in the study.

**Table 1: Comparisons of teriparatide with alendronate and placebo**

<table>
<thead>
<tr>
<th>Study and Patient Population</th>
<th>Comparators</th>
<th>Median Exposure (months)</th>
<th>RRR (95% CI) of Vertebral and Non-vertebral Fractures</th>
<th>NNT (95% CI)</th>
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<tr>
<td><strong>Post-menopausal women with osteoporosis</strong></td>
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<td>Body et al., 2003</td>
<td>Teriparatide 40 µg versus alendronate 10 mg</td>
<td>14</td>
<td>Non-vertebral fractures 71 (-5; 91)</td>
<td>10 (5; 1074)</td>
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<tr>
<td>Neer et al., 2001</td>
<td>Teriparatide 20 µg versus placebo</td>
<td>21</td>
<td>Vertebral fractures 65 (45; 78) Non-vertebral fractures 35 (2; 57)</td>
<td>11 (8; 18)</td>
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<tr>
<td></td>
<td>Teriparatide 40 µg versus placebo</td>
<td></td>
<td>Vertebral fractures 69 (50; 81) Non-vertebral fractures 40 (9; 61)</td>
<td>10 (7; 16)</td>
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<td><strong>Men with osteoporosis</strong></td>
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<td>FDA report</td>
<td>Teriparatide 20 µg versus placebo Teriparatide 40 µg versus placebo</td>
<td>10</td>
<td>Vertebral fractures 52 (-32; 72) Vertebral fractures 48 (-41; 81)</td>
<td>–</td>
</tr>
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SC=subcutaneous, PO=oral, RRR (95% CI)=relative risk reduction with 95% confidence interval, NNT (95% CI)=number needed to treat with 95% confidence interval.
Teriparatide versus placebo in men: A double-blind two-year RCT in men with osteoporosis (BMD<2 SD below the average for healthy young men), about half with low serum testosterone levels, compared teriparatide 20 µg SC once daily (n=151), 40 µg SC once daily (n=139) and placebo (n=147).10,11,13 The median time on the drug was 10 months. Fracture data were reported as a secondary endpoint. The proportions of patients with new vertebral fractures after 30 months of follow-up were 5.7% (5/87), 6.2% (5/81) and 11.9% (12/101) in the respective groups.10 Teriparatide did not significantly protect against vertebral fractures (Table 1). This information was limited by the number of patients lost to follow-up. No significant difference was observed in the number of deaths and the number of patients reporting at least one serious adverse event. Only 45% of screened patients were randomized.

In all the reports of patients with cancer treated with teriparatide, no cases of osteosarcoma were found.10 Nausea, dizziness, leg cramps and headache were the most common adverse effects. Transient mild hypercalcemia and hypercalciuria were also reported.

Dosage and Potential Cost: The recommended dose of teriparatide is 20 µg SC once daily (thigh or abdomen) for a maximum of two years.1 The drug is available in 3 mL pen injectors containing 750 µg of teriparatide. The pen must be refrigerated and can be re-used for 28 days. In the US, the retail price of a 3 mL syringe (equivalent to one month of treatment) is US$515.96.16

Projected Rate of Diffusion

Teriparatide is a proposed hormone therapy for osteoporosis. There is little information on its comparative efficacy and effectiveness versus alternatives. There is also concern about long-term safety. Despite this, endorsement in newer consensus guidelines may promote its use.5 Anti-resorption agents, such as bisphosphonates, inhibit PTH’s bone-forming effect.17,18 Since bisphosphonates bind to bone for a long time, their antagonizing effect on PTH efficacy may continue after bisphosphonate therapy ceases. More comparative clinical trials are needed to define teriparatide’s role.

Concurrent Developments

Clinical studies show that hPTH (1-34) is effective in the treatment of gonadotropin-releasing-hormone induced bone loss and glucocorticoid-induced osteoporosis.19,20 Since teriparatide and hPTH(1-34) are chemically the same, but come from different sources, teriparatide may potentially be used for these indications.

Implementation Issues

Because of safety concerns and the lack of efficacy and effectiveness data, it is difficult to define teriparatide’s role in the treatment of osteoporosis. This is compounded by the possible long-term antagonizing effect of bisphosphonates on teriparatide’s bone-forming properties. Teriparatide may also be an expensive drug.

References


