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Abaloparatide (Tymlos®): A New Agent to Prevent Vertebral Fractures in Women with Osteoporosis

Jonathan Ramnauth, PharmD Candidate

Osteoporosis affects an estimated 44 million Americans or 55% of people 50 years of age or older.[1,2] Another 34 million Americans are estimated to have low bone mass placing them at an increased risk for osteoporosis. This disease affects more women than men, putting women at a higher risk for hip, wrist, and spine fractures.[1] The prevalence of osteoporosis in postmenopausal women increases with age from 46.3% of those aged 45-64 to 68.7% for those aged 75 and over. Many risk factors are associated with the development of low bone mineral density (BMD) leading to osteoporotic fracture including: lean body mass, low peak bone mass, hormonal factors, the use of certain drugs (e.g., glucocorticoids), cigarette smoking, low physical activity, low intake of calcium and vitamin D, race, small body size, Caucasian and Asian race, and a personal or a family history of fracture.[3]

The American Association of Clinical Endocrinologist supports treatment of osteoporosis with lifestyle changes, calcium and vitamin D supplementation, as well as several different medication classes such bisphosphonates, hormonal based therapies, selective estrogen receptor modifiers (SERMs), calcitonin, recombinant human parathyroid hormone (PTH), and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors.[2] Recently, a new agent, abaloparatide (Tymlos®) was granted approval by the FDA for the treatment of postmenopausal women with osteoporosis at high risk for fracture.[4]

The FDA's approval of abaloparatide for the treatment of osteoporosis was based on the results of the 18 month Abaloparatide Comparator Trial in Vertebral Endpoints (ACTIVE) trial and first six months of ACTIVExtend trial.[4] The purpose of this article is to review abaloparatide in the treatment to prevent vertebral fractures in postmenopausal women with osteoporosis including a review of pharmacology, pharmacokinetics, pharmacodynamics, clinical trials, adverse events, and dosing.

Clinical Pharmacology

Mechanism of Action

Abaloparatide is a synthetic 34 amino acid peptide that acts as an agonist at the PTH1 receptor (PTH1R). Of the 34 residues, 22 of them are identical to the parathyroid hormone-related protein (PTHrP) and the other 11 were made to improve stability.[4,5] After it binds to the receptor, it then increases cyclic adenosine monophosphate (cAMP) concentrations within the target cells. Abaloparatide has an anabolic effect on bone by increasing BMD and bone mineral content (BMC) which correlates with increases in bone strength at vertebral and nonvertebral sites. It has 41% homology to hPTH (human parathyroid hormone) and 76% homology to hPTHrP (human parathyroid hormone-related peptide).[5]

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Treatment with abaloparatide increases the bone formation marker serum -procollagen type I N-propeptide (PINP) and osteocalcin.[4,6] The PINP levels peak after one month of treatment, which then decrease over time but stay above the initial baseline for the remainder of the treatment. Serum collagen type I cross-linked C-telopeptide (sCTX) is a biomarker used to assess bone resorption. For example, an elevated sCTX level indicates increase in bone resorption. Clinical data suggests sCTX levels by month 3 increase by 43% above baseline of 0 ($P< 0.001$) and by month 18, it trend down towards 20% above baseline of 0 ($P= 0.27$).[5]

Pharmacokinetics

Abaloparatide achieves a max concentration (t_{max}) 30 minutes after a subcutaneous injection of 80 mcg with a bioavailability of 36% in healthy women.[4] Abaloparatide peptides are eliminated in the kidneys with a half-life of 1.7 hours. Studies have shown its metabolism is consistent with proteolytic degradation into smaller peptide fragments. It appears that this medication does not inhibit or induce cytochrome P450 enzymes when studied in vitro and no related drug interactions are currently known.

Special Populations

No age-related differences were observed in the pharmacokinetic properties of abaloparatide in postmenopausal women ranging from 49 to 86 years of age.[4] In comparison to subjects with normal renal function, the C_{max} increased 1.0-fold for mild, 1.3-fold for moderate, and 1.4-fold for severe renal impairment. Compared to healthy subjects with normal renal function, the abaloparatide AUC increased 1.2-fold in mild, 1.7-fold in moderate, and

2.1-fold in severe renal impairment. Despite these changes, there are no current recommendations for dose adjustment in renally impaired patients. Pregnant patients or patients undergoing dialysis were excluded from the studies.

Clinical Trials

Phase II

A phase II randomized, parallel group, multicenter, dose-finding, double blind, placebo controlled trial was completed to determine the efficacy and safety of abaloparatide on bone mineral density.[5] Patients were randomized 1:1:1:1:1 ratio into the following groups: abaloparatide subcutaneous injections dosed at 20 mcg, 40 mcg, and 80 mcg, teriparatide 20 mcg subcutaneous injections, and matching placebo injection. Teriparatide is currently the only available anabolic agent available for treatment of osteoporosis and acts by a similar mechanism to abaloparatide that involves stimulating new bone formation. The primary efficacy endpoints were BMD changes from baseline to 24 weeks and bone turnover markers, verified by dual x-ray absorptiometry and biochemical markers of bone turnover from baseline to 24 weeks. Baseline characteristics were similar between the treatment groups which consisted of healthy postmenopausal women between the ages of 55 to 85 years.

In order to be included in the study, patients had to meet the following criteria:

1. Postmenopausal female aged 55-85 years with the following criteria: Dual x-ray absorptiometry (DXA) –derived BMD T-score <-2.5 at the lumbar spine, femoral neck or total hip
2. DXA-derived BMD T-score <-2.0 with a history of forearm, humerus, vertebral, sacral, pelvic, hip, femoral, or tibial fracture within the past 5 years.
3. DXA- derived BMD T-score <-2.0 with an additional osteoporosis risk factor such as at least 65 years of age or strong maternal history of osteoporosis (defined as a fracture related to osteoporosis or osteoporosis itself determined by BMD criteria).
4. BMI: 18.5-33 kg/m^2; normal levels of serum Ca, PTH (1-84), normal 25-hydroxy vitamin D, phosphorous, alkaline phosphatase levels, and normal cardiac parameters (systolic blood pressure between 100 mmHg and 155 mmHg and diastolic blood pressure between 40 and 95 mmHg).

Patients were excluded from the study if they had any of the following: history of osteosarcoma or other bone diseases, radiation therapy, malabsorption, nephrolithiasis, urothiasis; renal dysfunction, or any other medical conditions that could interfere with the study; hip replacement; spine dysfunction; treatment with calcitonin, estrogens, estrogen derivatives, selective estrogen receptor modulators, tibolone, progestins, anabolic steroids, or daily glucocorticoids in the past 6 months; if they received bisphosphonates or strontium in the past 5 years or if they had ever received PTH or its analogs, fluoride, gallium nitrate or denosumab.

The primary endpoint results from this study found no statistically significant increases in BMD between teriparatide and abaloparatide subjects in the lumbar spine and femoral neck groups. However, differences were seen when compared to placebo, as seen in **Table 1**. When comparing the two active groups, this study did find a significant increase in BMD of total hip with the abaloparatide-treated women of 37% versus 16% compared to those treated with teriparatide (P <0.2) and those treated with placebo at 15% (P<0.04, abaloparatide vs placebo).

The authors reported 164 treatment emergency adverse events (TEAEs) from the 221 subjects (74% of patients experienced ≥1 TEAE) . The percentage of patients in each group experiencing TEAEs were 71%, 72%, 74%, 76%, and 78% in patients treated with placebo, abaloparatide 20-, 40-, and 80-mcg, and teriparatide groups respectively. No statistical difference was seen between the treatment groups in occurrence or severity of TEAE. Patients in the abaloparatide treatment groups had a numerically higher incidence of headaches at 40 mcg (14%) and 80 mcg (13%) compared with placebo (7%), abaloparatide 20 mcg (5%) and was similar to teriparatide 20 mcg (13%). Injection-site reaction rates were similar amongst the abaloparatide, placebo, and teriparatide groups. A total of 8 patients reported severe events.

Phase III

The Abaloparatide Comparator Trial in Vertebral Endpoints (ACTIVE) study was a phase III, double blind, randomized controlled trial lead by Paul and colleagues.[7] The study objective was to determine the safety and efficacy of abaloparatide 80 mcg vs. placebo for prevention of new vertebral fracture in postmenopausal women at risk of osteoporotic fracture. The study enrolled 2463 women that were randomized in a 1:1:1 ratio to one of the three treatment groups to receive daily subcutaneous injections of abaloparatide 80 mcg, placebo or teriparatide 20 mcg subcutaneous injection for 18 months. The women in each treatment group had similar baseline characteristics.

The subjects were eligible if they had BMD by DXA T-score of ≤−2.5 and >−5.0 at the lumbar spine or femoral neck together. Additional criteria were radiologic evidence of at least 2 mild vertebral fractures, or at least 1 moderate vertebral fracture, or history of a low-trauma fracture of the forearm, humerus, sacrum, pelvis, hip, femur, or tibia within the past 5 years. Women older than 65 years who met fracture criteria but had a T-score of ≤−2.0 or

Table 1 | Mean in Bone Mineral Density after 24 weeks of injections[5]

Treatment	Lumbar spine BMD[a]	Femoral neck BMD[a]	Total hip BMD[a]
Placebo	1.6 ± 3.4%	0.8 ± 4.8%	0.4 ± 3.1%
Abaloparatide 20 mcg	2.9 ± 2.6%	2.7 ± 4.0%	1.4 ± 2.6%
Abaloparatide 40 mcg	5.2 ± 4.5%[b]	2.2 ± 4.4%	2.0 ± 3.7%
Abaloparatide 80 mcg	6.7 ± 4.2%[b]	3.1 ± 4.2%[c]	2.6 ± 3.5%[d]
Teriparatide	5.5 ± 4.1%[b]	1.1 ± 4.6%	0.5 ± 3.9%

Data represent mean change ± standard deviation
BMD: bone mineral density; **a:** changes in (BMD) after 24 weeks of injections; **b:** p <0.001 compared to placebo; **c:** p = 0.36 compared to placebo; **d:** p = 0.007 compared to placebo

>−5.0 were eligible. Women >65 years were eligible without fracture criteria if either BMD or T-score was ≤−3.0 and >−5.0. Eligibility required normal serum values for calcium, intact parathyroid hormone, phosphorus, and alkaline phosphatase and a vitamin D level of greater than 15 ng/mL (37.5 nmol/L).

Subjects were excluded if they had more than 4 mild vertebral fractures, 4 moderate vertebral fractures, or any severe vertebral fractures; fewer than 2 evaluable lumbar vertebrae; or if hip BMD was un-evaluable. Participants were ineligible if they had evidence of metabolic bone disease, malabsorption, or were taking any medications that would interfere with bone metabolism. Women were also excluded if they used bisphosphonates for more than 3 months in the past 5 years or denosumab within the past year. Women with a history of osteosarcoma were also excluded.

The primary efficacy end point was the percentage of patients with ≥1 incident of new morphometric vertebral fracture. Both anteroposterior and lateral radiographs of the lumbar and thoracic spine were obtained at baseline and at the end of treatment (18 months). Each woman's vertebrae were graded with a semiquantitative technique defining a decrease in height of 20 to 25% as mild, 26 to 40% as moderate, and >40% as severe. The primary efficacy outcome occurred in 0.58% (n = 4) of the abaloparatide group and in 4.22% (n = 30) of those in the placebo group (relative risk [RR] = 0.14; 95% CI, 0.05 to 0.39). In the teriparatide group, the primary efficacy endpoint occurred in 0.84% (n = 6) of patients (compared to placebo, RR = 0.20; 95% CI, 0.08 to 0.47).

Secondary endpoints included nonvertebral fractures (excluding fractures of the spine, sternum, patella, toes, fingers, skull, and face) and changes in baseline BMD for total hip, femoral neck, and lumbar spine each at 6, 12, and 18 months. Additional secondary endpoints were concentrations of serum markers of bone turnover (collagen type I N-terminal propetide [s-PINP]) and carboxy-terminal cross-linking telopeptide of type I collagen (s-CTX) measured at months 1, 3, 6, 12, and 18 in select patients.

Event rates for the secondary outcome of nonvertebral fracture were 2.7% in the abaloparatide group compared to 4.7% in the placebo group (hazard ratio [HR] = 0.57; 95% CI, 0.32 to 1.00). BMD changes 18 months were greater in the abaloparatide group compared to placebo for total hip (4.18% vs. -0.10; difference = 4.25%; 95% CI, 3.90% to 4.59%), femoral neck (3.60% vs -0.43%; difference = 4.01%; 95% CI, 3.58% to 4.45%), and lumbar spine (11.20% vs. 0.63%; difference = 10.37%; 95% CI, 9.75% to 10.98%). In addition to the improvements in BMD, the authors found higher levels of s-PINP, a bone formation marker, in the first month of use between the abaloparatide and teriparatide groups; however, at 3 months, a decrease was shown in s-PINP within the abaloparatide group compared with the teriparatide group from a baseline of 80%. On the contrary, there was an increase in s-CTX in the teriparatide group compared to the abaloparatide group along with an increase in hypercalcemia in the teriparatide group (P <0.001) from 3 to 18 months.

Of the 824 randomized to receive subcutaneous abaloparatide injections, 821 randomized to receive placebo, and 818 randomized to receive teriparatide subcutaneous injections; 218, 184, and 160 were lost to follow up, respectively. The discontinuation rate for the abaloparatide group was 9.9% and mostly involved mild to moderate adverse events related to nausea (1.6%), dizziness (1.2%), headache (1.0%), and palpitations (0.9%). More severe adverse events were consistent among both abaloparatide and teriparatide.

ACTIVExtend trial

The Abaloparatide Comparator Trial in Vertebral Endpoints Xtend (ACTIVExtend) trial was a preplanned extension of the ACTIVE trial that aimed to assess the efficacy of abaloparatide for an additional 6 months of therapy.[8] This study was an extension of the ACTIVE trial[7]; therefore, only eligible patients at the end of the ACTIVE trial were enrolled in the ACTIVExtend trial. The eligible patients were split into 2 treatment arms including alendronate 70 mg orally weekly plus either placebo (n=581) or abaloparatide 80 mcg subcutaneous injections (n=558). Consistent with the ACTIVE trial, the ACTIVExtend primary end point was the percentage of participants who sustained 1 or more new morphometric vertebral fractures between the baseline of ACTIVE and 6 months after the initiation of alendronate 70 mg tablets (25 months total treatment). An additional exploratory end point evaluated the percentage of patients with one or more morphometric vertebral fractures between baseline of ACTIVExtend and 6 months into the extension trial. Secondary end points included the ACTIVE trial endpoints of incidence and time to first event for nonvertebral, major osteoporotic, and clinical fractures. There was a one-month gap allowed between studies to obtain patient consent. Baseline characteristics were the same in each group and similar to those in the ACTIVE trial vs the ACTIVExtend other than the improved T-scores. At baseline, the abaloparatide plus alendronate group had a mean lumbar spine BMD baseline T-score of -2.11 and a mean total hip baseline T-score of -1.63. The mean lumbar spine BMD baseline T-score was -2.87 in the placebo group and -1.93 in the abaloparatide group.

Once a patient was deemed eligible for the ACTIVExtend trial, the patients underwent additional safety evaluations. The safety evaluations included physical examinations, electrocardiograms, and clinical laboratory tests after 6 months of alendronate as well as monitoring and reporting of adverse events at each study visit. The patients were withdrawn from the study if any of the following occurred: BMD deterioration was >7% decrease

Table 2 | Primary Outcome Results of ACTIVE and ACTIVExtend[7,8]

Trial	Treatment	Primary Outcome	Results
ACTIVE[8]	ABL-SC (n=606) vs Placebo (n=637)	Percentage of patients with new morphometric vertebral fractures after 18 months of therapy	0.58% vs 4.22%; RR=0.14 (95% CI, 0.05 to 0.39)
	Teriparatide (n=658) vs Placebo (n=637)		0.84% vs. 4.22%; RR=0.20 (95% CI, 0.08 to 0.47)
ACTIVExtend[9]	ABL-SC/ALN (n=558) vs Placebo/ALN (n=581)	Percentage of patients with new morphometric vertebral fractures after 25 months of therapy	0.55% vs. 4.40%; RR=0.13 (95% CI, 0.04 to 0.41)

ABL-SC: abaloparatide 80 mcg subcutaneous daily; **ALN:** Alendronate 70 mg orally once weekly; **RR:** relative risk; **95% CI:** 95% confidence interval

from baseline, there was treatment related serious adverse events, the patient refused further treatment, were unable to complete the treatment, or were lost to follow up.

The primary efficacy outcome occurred in 4.4% of the placebo/alendronate group compared to 0.55% of the abaloparatide/alendronate group (RR = 0.13; 95% CI, 0.04-0.41) (**Table 2**). Notably, 7 new events occurred in the placebo/alendronate group in the 6 months of the ACTIVExtend trial, and 0 events occurred in the abaloparatide/alendronate group.

Also reported were average gains in BMD, during the 25 months of treatment over both studies. These percentages were all statistically significant at either lumbar spine (12.8% in study group vs 3.5% in the placebo group), total hip (5.5% in study group vs 1.4% in the placebo group), or femoral neck (4.5% in the study group vs 0.5% in the placebo group) sites; thus demonstrating the combination of the two therapies improved BMD versus placebo (P <0.001) at each site.

Adverse Events and Contraindications

Abaloparatide (Tymlos®) is not recommended in patients at increased risk of osteosarcoma including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, open epiphyses, bone metastases or skeletal malignancies, hereditary disorders predisposing to osteosarcoma, or prior external beam or implant radiation therapy involving the skeleton.[4] Cumulative use of abaloparatide and parathyroid hormone analogs for more than 2 years during a patient's lifetime is not recommended. Some common side effects are orthostatic hypotension, hypercalcemia, hypercalciuria and urolithiasis.

Dosing and Administration

The recommended dose of abaloparatide is 80 mcg subcutaneous once daily for treatment of osteoporotic fractures for women who are at a high risk for fracture.[4] Supplemental calcium and vitamin D should be administered if dietary intake is inadequate. Guidelines recommend calcium 1,200 mg/day for women over the age of 51 years and 1,000 International Units/day of vitamin D for women over the age of 50 years.

Abaloparatide injection is a sterile, colorless, clear solution in a pre-assembled disposable glass cartridge.[4] The pen can deliver 30 once-daily doses of 80 mcg in 40 mcL. Each cartridge contains 1.56 mL of the drug solution.

Conclusion

Abaloparatide is a novel synthetic peptide analog of PTH-related protein that was selected to retain potent anabolic activity with decreased bone resorption, less calcium mobilizing potential, and improved room temperature stability. Clinical trials have demonstrated abaloparatide as an effective agent for decrease in vertebral fractures compared to current agents on the market in postmenopausal women. The findings supported early anabolic therapy as a potential treatment option for qualified postmenopausal women with osteoporosis.

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