Abaloparatide and the Spine: A Narrative Review

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Abstract: Osteoporosis is a common and debilitating condition characterized by diminished bone mass and architecture leading to bone fragility. Antiresorptive medicines like bisphosphonates (and less commonly denosumab) are the typical first-line agents for the medical treatment of osteoporosis. However, newer anabolic agents have been shown to improve bone mass and architecture, as well as reduce fracture risk, to a greater degree than traditional antiresorptive therapies. Teriparatide (human recombinant parathyroid hormone (PTH) 1–34, Forteo, Ely Lilly, Indianapolis, IN), which was the first in class to be approved in the United States, is the most widely used anabolic osteoporosis medicine and has shown significant benefit over traditional antiresorptive therapies. However, abaloparatide (synthetic parathyroid-related peptide (PThrP), Tymlos, Radius Health, Waltham, MA), the second drug in this family, has recently become available for use. In this narrative review, we review the mechanism, effects, and benefits of abaloparatide compared to alternative treatments as well as discuss the current literature in regard to its effect on osteoporosis-related complications in the spine.

Keywords: abaloparatide, Tymlos, anabolic, osteoporosis, spine, teriparatide

Introduction

Osteoporosis is a common, debilitating condition characterized by diminished bone mass and architecture leading to bone fragility. It is estimated that over 10.2 million Americans have osteoporosis with an additional 43.4 million living with osteopenia.1–3 Approximately 16% of men and 30% of women older than 50 years have osteoporosis.3 Osteoporosis places patients at a significant risk of sustaining fractures most commonly involving the hip, wrist, and thoracolumbar spine with over 2 million osteoporosis-related fractures per year.1,2,4 Further, there is a 20% incidence of vertebral compression fracture in osteoporotic patients.5 Osteoporosis and osteoporotic fragility fracture are associated with significant complications including decreased quality of life, reduced independence, risk of additional fracture and increased mortality.1,4,6,7

Antiresorptive medicines like bisphosphonates (and less commonly denosumab) are the typical first-line agents for the medical treatment of osteoporosis.1,4 However, newer anabolic agents have been shown to improve bone mass and architecture, as well as reduce fracture risk, to a greater degree than traditional antiresorptive therapies. Teriparatide (human recombinant parathyroid hormone (PTH) 1–34, Forteo, Ely Lilly, Indianapolis, IN), which was the first in class to be approved in the United States, is the most widely used anabolic osteoporosis medicine and has shown significant benefit over traditional antiresorptive therapies.8–19 However, abaloparatide (synthetic parathyroid-related peptide (PThrP), Tymlos, Radius Health, Waltham, MA), the second drug in this family, has recently become available for use.
The purpose of this review is two-fold. First, we will review the mechanism, effects and benefits of abaloparatide compared to alternative treatments. Second, we will review the current literature regarding the effect of abaloparatide on osteoporosis-related complications in the spine.

**Basic Science**

Abaloparatide is a synthetic 34-amino acid peptide analogue of PTHrP. PTHrP is a protein with similar function to PTH that is expressed in almost all human tissues and has many regulatory functions. While not normally detectable under physiologic conditions (except in pregnancy and lactation), PTHrP can be detected in malignancy where it is associated with humoral hypercalcemia of malignancy.20,21

PTH and PTHrP influence bone turnover via the receptor activator of nuclear factor kappa-β ligand (RANKL) pathway in osteoblasts. In this pathway, PTH and PTHrP stimulate PTH receptors in osteoblasts, inducing cyclic adenosine monophosphate (cAMP) activation, osteoblastic bone formation, and later osteoclast activation. However, there are differences in activation between PTHrP and PTH. The PTH receptor has at least 2 conformations that activate the RANKL pathway: R⁰ and RG. R⁰ is a G-protein independent receptor that is the primary target of teriparatide (Forteo). The R⁰ receptor binds PTH with high affinity and results in prolonged binding and activation leading to an initial burst of bone formation followed by bone resorption due to downstream osteoclast activation. On the contrary, RG, a G-protein dependent receptor targeted by abaloparatide, reversibly binds to PTHrP with high affinity resulting in transient activation that maximizes initial bone formation while limiting late bone resorption and osteoclast differentiation [Figure 1].22,23

The effectiveness of abaloparatide has been demonstrated in multiple rodent and primate studies. Varella et al demonstrated that long-term daily administration of abaloparatide resulted in dose-dependent gains in bone mass, bone architecture, and up to 2.7-fold greater peak load to failure over controls in the lumbar spine of ovariectomized osteopenic rats.24 Similarly, Berhardsson et al confirmed these findings and further showed increases in

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**Figure 1** Model of parathyroid hormone (PTH)/teriparatide and PTH-related peptide (PTHrP/abaloparatide activation of parathyroid hormone type 1 receptor (PTH1R)).
bone formation markers without associated increases in bone resorption factors associated with hypercalcemia.\textsuperscript{25} In orchiectomy-induced osteoporotic male mice, Chandler et al showed reversal of osteoporosis with 8-weeks of abaloparatide therapy.\textsuperscript{26} Doyle et al translated the rodent model to primates and showed that 16 months of abaloparatide treatment resulted in increased whole body bone mass and greater lumbar vertebral strength in ovariection-mized monkeys.\textsuperscript{27} Moreover, Sahbani et al compared the effects of abaloparatide and teriparatide in wild-type female mice. His findings showed an increase in bone formation marker, P1NP, and decrease in bone resorption marker, TRAcP-5b when compared to teriparatide. Additionally, although the study showed that abaloparatide demonstrated an increase in cortical thickness when compared to teriparatide, it is not known whether the increase in cortical thickness was due to the difference in endocortical resorption or in periosteal bone formation.\textsuperscript{28}

**Clinical Results**

The beneficial effects of abaloparatide in human studies have been consistent with those demonstrated in animal models. Additionally, while teriparatide has been shown to significantly improve bone mineral density and architecture when compared to placebo and bisphosphonates therapy, abaloparatide therapy has shown superior clinical results. In a multi-center, multi-national, double-blind placebo-controlled clinical trial, Leder et al observed lumbar BMD increases up to 6.7% over 24 weeks with abaloparatide vs only 5.5% and 1.6% in the teriparatide and placebo groups, respectively (\(p = 0.001\)).\textsuperscript{29} The increase in lumbar BMD tripled increased in hip BMD. Similarly, Bilezikian et al, in a Phase 2 randomized control trial of postmenopausal women aged 55–85 years, demonstrated consistently greater dose-dependent improvements in lumbar trabecular bone score by 12 weeks with abaloparatide when compared to teriparatide and placebo.\textsuperscript{6} Improvement in lumbar TBS indicates improvement in bone microarchitecture and corresponds to decrease risk of fracture and improvement in pedicle screw strength.\textsuperscript{30,31}

Abaloparatide therapy increases biomechanical strength and bone-formation, which results in a substantial reduction in fragility fractures. The ACTIVE randomized control trial (RCT) compared the clinical effects of abaloparatide to teriparatide and placebo. This trial was an 18-month double-blinded RCT in 2463 patients with osteoporosis. Subjects were randomized to receive daily injections of 80 micrograms of abaloparatide, 20 micrograms of teriparatide, or placebo (both the abaloparatide and teriparatide dosages are the standard recommended dosages for these medications). The primary endpoint of the study was new vertebral compression fractures which occurred in 0.58%, 0.84%, and 4.22% in the abaloparatide, teriparatide, and control groups, respectively (\(p = 0.001\)). Both active treatments had a significantly lower risk than placebo. Subjects in the abaloparatide group showed a significantly greater improvement of BMD in the lumbar spine, femoral neck, and total hip compared to teriparatide and placebo at all time points beginning at 6 months a significantly lower incidence of hypercalcemia in the abaloparatide group (3.4%) versus teriparatide group (6.4%) (\(p = 0.01\)). Overall, Miller and colleagues concluded that abaloparatide treatment reduced the risk of new vertebral and non-vertebral fractures over 18 months compared to placebo. However, the study was inadequately powered to make a definitive claim regarding comparison between abaloparatide and teriparatide.\textsuperscript{32,33}

Additional post hoc studies have shown that teriparatide therapy is also beneficial in special populations. McClung et al demonstrated a 12% increase in BMD at 12 months with abaloparatide therapy which was similar to the results found in younger patients.\textsuperscript{34} Cosman et al further demonstrated those with high risk of osteoporotic fracture including those with T-score \(< -3.0\), history of non-vertebral osteoporotic fracture, and age >75 years had significantly greater major osteoporotic fracture risk reduction with abaloparatide vs teriparatide (78% reduction with abaloparatide vs 23% with teriparatide) (\(p = 0.007\)).\textsuperscript{35} She concluded that abaloparatide results in improvement in BMD across all age groups and risk factors. Additionally, Reginster et al added that abaloparatide is potentially a more effective therapy than teriparatide based on the number needed to treat comparisons showing that the NNT for ABL in ACTIVE was 28 for vertebral, 55 for non-vertebral, 37 for clinical, and 34 for major osteoporotic fracture. NNT for these fracture types for teriparatide in ACTIVE were 30, 92, 59, and 75, respectively.\textsuperscript{36}

While studies have shown that anabolic therapy provides substantial benefit in BMD and fracture risk, these therapies can result in loss of bone mass soon after they are discontinued, particularly if an antiresorptive agent is not subsequently administered. Leder et al showed BMD decreases of \(-4.2 \pm 4.3\)% in the femoral neck, \(-4.5 \pm 3.6\)%
Table 1  Summary of Study Characteristics

| Author                | Study Type                                      | Abaloparatide & Comparison Group(s) & ("n" & dosage) | Follow-up (mo) | Female (%) | Age (Mean, SD, Range) (y) |
|-----------------------|-------------------------------------------------|------------------------------------------------------|----------------|------------|--------------------------|
| Miller et al. 33       | RCT (ACTIVE Trial)                              | 824 (80 µg) PBO (821) TPTD (818)                      | 18             | 100%       | ABL (68.9 ± 6.5) TPTD (68.8 ± 6.6) PBO (68.7 ± 6.5) |
| Bone et al. 38         | RCT: ACTIVExtend (Extension of ACTIVE trial)    | 558 (80 µg) PBO (551) Addision of 24 months ALN      | 100%           |           | ABL/ALN (70.2 ± 6.54) PBO/ALN (70.1 ± 6.29)          |
| Leder et al. 45        | RCT:ACTIVE & ACTIVExtend post-hoc comparison of ABL vs. ALN | 606 (80 µg) PBO/ALN (from ACTIVExtend) (581)         | 18             | 100%       | ABL (66.6 ± 6.5) ALN (70.1 ± 6.29)                  |
| McCloskey et al. 67    | RCT:ACTIVE trial post-hoc analysis in subgroup of women at baseline high risk for fracture based on FRAX probabilities (10-year risk of major osteoporotic fracture > 10% or hip fracture > 5%) | 459 (80 µg) PBO (468) TPTD (473)                      | 18             | 100%       | ABL (69.9 ± 6.67) TPTD (69.9 ± 6.37) PBO (70.0 ± 6.27) |
| McClung et al. 34      | RCT: ACTIVE trial post-hoc analysis in patients age > 80 years | 51 (80 µg) PBO (43)                                  | 18             | 100%       | ABL (81.7 ± 1.4) PBO (81.9 ± 1.5)                    |
| Bilezikian et al. 6    | RCT: post-hoc of ACTIVE trial                   | 24 (80 µg); 25 (40 µg) PBO (29) TPTD (31)            | 6              | 100%       | 20 µg ABL (68.1 ± 6.3) 40 µg ABL (65.4 ± 6.9) 80 µg ABL (64.3 ± 6.9) TPTD (66.2 ± 7.3) PBO (66.7 ± 7.6) |
| Cosman et al. 35       | RCT: ACTIVE trial post-hoc analysis in varying baseline risk groups | 558 (ABL 80 µg /ALN) PBO/ALN (581) Subgroup analysis of the following groups: Lumbar T-score ≤ -2.5 vs. > -2.5 Lumbar T-score ≤ -3.0 vs. > -3.0 Total Hip T-score ≤ -2.5 vs. > -2.5 Total Hip ≤ -3.0 vs. > -3.0 Femoral Neck T-score ≤ -2.5 vs. > -2.5 Femoral Neck T-score ≤ -3.0 vs. > -3.0 History of nonvertebral fracture History of vertebral fracture Age < 65 vs. 65 to <75 vs. ≥ 75 years | 18             | 100%       | —                                                      |

(Continued)
in the hip, and −10 ± 5.4% in the spine of patients 1–2 years after completing a 24-month course of abaloparatide therapy. Leder and colleagues also found that subjects who were treated with denosumab for 1–2 years after completion of abaloparatide did not show the same loss of BMD with only −0.6 ± 2.7% in the femoral neck, −0.8 ± 3.1% in the total hip, and −1.2 ± 4.7% in the spine. A summary of the study characteristics is included in Table 1, and a summary of the study findings is included in Table 2.

### Initiating Abaloparatide (Tymlos)
Abaloparatide is currently approved by the FDA for the treatment of postmenopausal women with osteoporosis who are at high risk for fracture. “Risk” factors that qualify patients for the use of abaloparatide include a history of previous osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. The typical dosing regimen is 80 micrograms/day subcutaneous injection for up to 18 months. Prior to initiation of therapy and calcium and vitamin D replenishment is recommended. Abaloparatide undergoes renal metabolism so dosing may need to be adjusted for patients with renal impairment.

There are multiple contraindications to abaloparatide therapy. The most concerning to patients may be related to its dose-dependent increase in the incidence of osteosarcoma in F344 rats that are predisposed to osteogenic sarcoma. Of note, this relationship was observed at dosages 4–28 times the 80 mcg/day dose given to humans.
### Table 2 Summary of Study Findings

| Author          | Lumbar BMD Outcomes | Vertebral Fracture Outcomes | Bone Turnover Markers | Other                  |
|-----------------|---------------------|-----------------------------|-----------------------|------------------------|
| Miller et al    | 6.58% increase in lumbar spine BMD in ABL group vs TPTD and 0.60% with PBO at 6 months (p < 0.001) | New vertebral fracture in 0.58% of ABL group vs 0.84% in TPTD and 4.22% in PBO groups (Risk difference: 3.64 (RR 0.14 (0.05, 0.39) (p < 0.001)) | S-P1NP (bone formation marker) effects: Initial increases in month #1 were similar, but s-P1NP began to decrease in the ABL group compared to the TPTD group after month #1. s-CTX (bone resorption marker) effects: Lower magnitude of increases in the ABL group than in TPTD | —                     |
| Bone et al      | Absolute increase 0.265 ± 0.0451 with ABL/ALN | 0.9% of patients with new vertebral fracture (ABL/ALN) vs 5.6% (PBO/ALN) RRR 84% (p < 0.001) | —                     | —                     |
| Cosman et al    | Percent increase in lumbar spine BMD treated with ABL/ALN vs PBO/ALN in the following subgroups: | Relative risk of fracture in patients treated with ABL/ALN vs PBO/ALN in the following subgroups: Lumbar spine T-score ≤ −2.5 (RR = 0.14) vs > −2.5 (RR = 0.13) (p = 0.960) | —                     | Hazard ratio of fracture in patients in patients treated with ABL/ALN vs PBO/ALN in the following subgroups: Lumbar spine T-score ≤ −2.5 (HR = 0.58) vs > −2.5 (HR = 0.53) (p = 0.879) | —                     |
|                 | Lumbar spine T-score ≤ −2.5 (8.90%) vs > −2.5 (8.28%) (p = 0.361) | Lumbar spine T-score ≤ −3.0 (9.95%) vs > −3.0 (8.56%) (p = 0.534) | Total hip T-score ≤ −2.5 (RR = 0.10) vs > −2.5 (RR = 0.16) (p = 0.699) | Lumbar spine T-score ≤ −3.0 (HR = 0.34) vs > −3.0 (HR = 0.98) (p = 0.082) |
|                 | Lumbar spine T-score ≤ −3.0 (8.95%) vs > −3.0 (8.56%) (p = 0.534) | Total hip T-score ≤ −3.0 (9.84%) vs > −3.0 (8.75%) (p = 0.864) | Total hip T-score ≤ −3.0 (RR = 0.48) vs > −3.0 (RR = 0.48) (p = 0.86) | Total hip T-score ≤ −3.0 (HR = 0.58) vs > −3.0 (HR = 0.56) (p = 0.968) |
|                 | Total hip T-score ≤ −3.0 (8.94%) vs > −3.0 (8.75%) (p = 0.366) | Femoral neck T-score ≤ −2.5 (9.62%) vs > −2.5 (8.41%) (p = 0.063) | Femoral neck T-score ≤ −2.5 (RR = 0.19) vs > −2.5 (RR = 0.11) (p = 0.588) | Femoral neck BMD T-score ≤ −3.0 (HR = 0.48) vs > −3.0 (HR = 0.61) (p = 0.707) |
|                 | Femoral neck BMD T-score ≤ −3.0 (9.53%) vs > −3.0 (8.68%) (p = 0.404) | Femoral neck T-score ≤ −3.0 (RR = 0.19) vs > −3.0 (RR = 0.16) (p = 0.403) | Femoral neck T-score ≤ −3.0 (RR = 0.19) vs > −3.0 (RR = 0.16) (p = 0.403) | Femoral neck BMD T-score ≤ −3.0 (HR = 0.10) vs > −3.0 (HR = 0.10) (p = 0.61) |
|                 | History of vertebral fracture (8.35%) vs No history of vertebral fracture (8.86%) (p = 0.49) | History of vertebral fracture (RR = 0.07) vs No history of vertebral fracture (RR = 0.20) (p = 0.371) | History of vertebral fracture (RR = 0.07) vs No history of vertebral fracture (RR = 0.20) (p = 0.371) | History of vertebral fracture (HR = 0.44) vs No history of vertebral fracture (HR = 0.62) (p = 0.622) |
|                 | Presence of any prior nonvertebral fracture (8.23%) vs No history of any prior nonvertebral fracture (9.26%) (p = 0.075) | History of any prior nonvertebral fracture (RR = 0.14) vs No history of any prior nonvertebral fracture (RR = 0.13) (p = 0.984) | History of any prior nonvertebral fracture (RR = 0.14) vs No history of any prior nonvertebral fracture (RR = 0.13) (p = 0.984) | History of any prior nonvertebral fracture (HR = 0.60) vs No history of any prior nonvertebral fracture (HR = 0.60) (p = 0.790) |
|                 | Age < 65 years (7.62%) vs age 65 to <75 years (8.86%) vs age ≥ 75 years (9.53%) (p = 0.170) | Age < 65 (RR = 0.13) vs age 65–75 (RR = 0.06) vs age > 75 (RR = 0.48) (p = 0.209) | Age < 65 (RR = 0.13) vs age 65–75 (RR = 0.06) vs age > 75 (RR = 0.48) (p = 0.209) | Age < 65 (HR = 0.35) vs age 65–75 (HR = 0.90) vs age > 75 (HR = 0.29) (p = 0.230) |

(Continued)
Table 2 (Continued).

| Author         | Lumbar BMD Outcomes | Vertebral Fracture Outcomes | Bone Turnover Markers | Other                     |
|----------------|---------------------|----------------------------|-----------------------|--------------------------|
| Leder et al    |                     | Rate of new vertebral fracture 0.47 per 100 patient-years with ABL vs 1.66 per 100 patient-years with ALN (p = 0.027) | —                     | —                        |
| Leder et al    | percent increase in lumbar spine BMD treated with ABL/ALN vs PBO/ALN in the following subgroups: | Relative risk of fracture in patients treated with ABL/ALN vs PBO/ALN in the following subgroups: | —                     | —                        |
| Leder et al    |                     | Lumbar spine BMD T-score ≤ -2.5 (3.72%) vs > -2.5 (3.68%) (p = 0.952) | Lumbar spine BMD T-score ≤ -2.5 (RR = 0.16) vs > -2.5 (RR = 0.18) (p = 0.896) | —                        |
| Leder et al    |                     | Lumbar spine BMD T-score ≤ -3.0 (3.73%) vs > -3.0 (3.68%) (p = 0.938) | Lumbar spine BMD T-score ≤ -3.0 (RR = 0.14) vs > -3.0 (RR = 0.21) (p = 0.686) Total hip BMD T-score ≤ -2.5 (RR = 0.12) vs > -2.5 (RR = 0.18) (p = 0.682) | —                        |
| Leder et al    |                     | Total hip BMD T-score ≤ -2.5 (3.88%) vs > -2.5 (3.65%) (p = 0.680) | Total hip BMD T-score ≤ -3.0 (RR = 0.56) vs > -3.0 (RR = 0.14) (p = 0.277) Femoral neck BMD T-score ≤ -2.5 (RR = 0.24) vs > -2.5 (RR = 0.14) (p = 0.574) | —                        |
| Leder et al    |                     | Total hip BMD T-score ≤ -3.0 (4.19%) vs > -3.0 (3.66%) (p = 0.588) | Femoral neck BMD T-score ≤ -2.5 (RR = 0.06) vs No history of vertebral fracture (RR = 0.30) (p = 0.115) History of vertebral fracture (RR = 0.06) vs No history of any prior nonvertebral fracture (RR = 0.10) vs No history of any prior nonvertebral fracture (RR = 0.26) (p = 0.320) | —                        |
| Leder et al    |                     | Femoral neck BMD T-score ≤ -3.0 (4.81%) vs > -3.0 (3.57%) (p = 0.113) | History of any prior nonvertebral fracture (RR = 0.06) vs No history of any prior nonvertebral fracture (RR = 0.10) vs No history of any prior nonvertebral fracture (RR = 0.26) (p = 0.320) Age < 65 (RR = 0.13) vs age 65 to <75 (RR = 0.06) vs age > 75 (RR = 0.42) (p = 0.222) | —                        |
| Leder et al    |                     | History of vertebral fracture (3.94%) vs No history of vertebral fracture (3.62%) (p = 0.552) | History of vertebra fracture (RR = 0.06) vs No history of any prior nonvertebral fracture (RR = 0.10) vs No history of any prior nonvertebral fracture (RR = 0.26) (p = 0.320) Age < 65 (RR = 0.13) vs age 65 to <75 (RR = 0.06) vs age > 75 (RR = 0.42) (p = 0.222) | —                        |
| Leder et al    |                     | History of any prior nonvertebral fracture (3.72%) vs No history of any prior nonvertebral fracture (3.70%) (p = 0.950) Age < 65 years (3.72%) vs age 65 to <75 years (3.68%) vs age > 75 years (3.91%) (p = 0.976) | History of any prior nonvertebral fracture (RR = 0.06) vs No history of any prior nonvertebral fracture (RR = 0.10) vs No history of any prior nonvertebral fracture (RR = 0.26) (p = 0.320) Age < 65 (RR = 0.13) vs age 65 to <75 (RR = 0.06) vs age > 75 (RR = 0.42) (p = 0.222) | —                        |
| McCloskey et al| 0.5% with new vertebral fracture in ABL group vs 1.4% in TPTD group and 5.6% in PBO group RRR 91% vs placebo. “Not statistically significant” vs TPTD (p value not given) | —                     | —                        |
| McClung et al  | 12.1% increase in lumbar spine BMD with ABL (p < 0.001) | 0% fractures in ABL vs 5.9% fractures in PBO “not statistically significant” (p value not given) | —                     | —                        |
| Author          | Lumbar BMD Outcomes | Vertebral Fracture Outcomes | Bone Turnover Markers | Other |
|-----------------|---------------------|----------------------------|-----------------------|-------|
| Miller et al    | —                   | —                          | —                     |       |
| Bilezikian et al | —                   | —                          | —                     |       |
| Leder et al     | +1.6 ± 3.4% in PBO group; TPTD +5.5 ± 4.1%; 20µg +2.9 ± 4.5%; 40µg 5.2 ±4.5%; (p < 0.001); 80microgram 6.7 ±4.2%; (p < 0.001). | —                          | —                     |       |

At 48 weeks, lumbar spine BMD increased by 0.7 in PBO vs 5.1 in ABL (20 µg), 9.8 in ABL (40µg), 12.9 in ABL (80 µg), and 8.6% in TPTD groups. Not statistically significant given small numbers of the extension study.

Percentage of patients with >3% increase in BMD at all anatomic sites:
- 19.1% of patients in ABL vs 6.5% in TPTD and 0.9% in placebo groups at 6 months (p<0.001)
- 33.2% of patients in ABL group vs 19.8% in TPTD and 1.5% in placebo groups at 12 months (p<0.001)
- 44.5% of patients in ABL group vs 32% in TPTD and 1.8% in placebo groups at 18 months (p<0.001)

Percentage of patients with >6% increase in BMD at all anatomic sites:
- 33.2% of patients in ABL vs 19.8% in TPTD and 1.5% in placebo groups at 12 months (p<0.001)
- 2.3% of patients in ABL group vs 0.3% in TPTD and 0% in placebo groups at 18 months (p<0.002)
- 8.5% of patients in ABL vs 2.9% in TPTD and 0% in placebo groups at 12 months (p<0.002)
- 13.4% of patients in ABL vs 7.0% in TPTD and 0.2% in placebo groups at 18 months (p<0.002)

BMD increased +1.6 ±3.4% in PBO group; TPTD +5.5 ± 4.1%; 20µg +2.9 ± 4.5%; 40µg 5.2 ±4.5%; (p < 0.001); 80microgram 6.7 ±4.2%; (p < 0.001).

Trabecular Bone Score (TBS) changes at 24 weeks:
- TBS Increased 2.27% in ABL 20 µg (P = 0.91)
- Increased 3.14% in ABL 40 µg group (p = 0.42)
- Increased 4.21% in ABL 80 µg groups at 24 weeks (p < 0.03)
- TBS Increased 2.21% in TPTD group at 24 weeks
- TBS decreased by 1.08% in PBO group at 24 weeks (p < 0.0001 vs all groups)

P1NP (bone formation) increased by week 1.
- Increased by median 55% at 24 weeks in ABL 40 and 52% in ABL 80, and 98% in TPTD group.
- Decreased by 20% in PBO group (all groups p < 0.001 when compared to placebo).
- CTX (bone resorption) not apparent increased until week 12.
- Increased by 33% at 24 weeks in ABL40 group; 23% in ABL80 group, but 76% in the TPTD group and 7% in the PBO group. (P < 0.003 in all ABL groups compared to TPTD.)

Abbreviations: ABL, abaloparatide; PBO, placebo; TPTD, teriparatide; RR, relative risk; RRR, relative risk reduction; HR, hazard ratio.
While it is unknown if abaloparatide will cause osteosarcoma in humans at clinically relevant doses, it is not recommended for patients at increased risk for osteosarcoma. This includes those with Paget’s disease, unexplained elevations of alkaline phosphatase, open epiphyses, bone metastases or other skeletal malignancies, hereditary disorders predisposing to osteosarcoma, or prior external beam radiation or implant radiation of the skeletal system.

Patients should be informed of the possible side effects of abaloparatide. Orthostatic hypotension occurs in approximately 4% of patients on abaloparatide therapy. Because it typically occurs within 4 hours of injection, patients are advised to sit or lie during and immediately after administration to minimize this side effect. Additional side effects include dizziness (10%) and tachycardia (2%). While drug site reactions including redness (58%), edema (10%), and pain (9%) are common, severe reactions are rare and generally do not limit its use. Abaloparatide therapy may also cause laboratory abnormalities. Increase in serum uric acid is common (25%) but is not associated with increases in gout or arthralgia. Hypercalcemia, defined as albumin-corrected serum calcium ≥10.7 mg/dL, occurs in approximately 3% of patients but rarely causes discontinuation of therapy.33,39

Based on the wholesale acquisition cost for one abaloparatide pen-injection, the monthly cost of abaloparatide therapy is approximately $1721.40 While these costs are substantial and potentially burdensome for some patients, it is about one-half the monthly cost of teriparatide therapy (approximately $3295). Le and colleagues performed a cost-effectiveness analysis comparing abaloparatide and teriparatide. Using a discrete event simulation (DES) model and ACTIVE trial outcomes, the authors concluded that ABO/ALN therapy afforded patients 10-year average total discounted per-patient cost of $26,837 vs $46,783 for TPTD/ALN. Overall ABL/ALN provided a greater value, with higher quality-adjusted life-years at lower costs than for TPTD/ALN in general ($333,266/QALY vs $951,016/ QALY) and high risk ($188,891/QALY vs $537,998/ QALY) subgroups.40 Hiligsman performed a similar study with consistent results confirming that ABL/ALN therapy was more cost-effective than TPTD/ALN.41

Use in Spine Surgery

Osteoporosis plays a significant role in outcomes of spine surgery as successful spinal fusion requires adequate bone stock for implant fixation and bone physiology to support fusion. Numerous cadaveric and clinical studies have shown increased implant failure in patients with compromised BMD, which leads to complications such as pseudoarthrosis, progressive kyphosis, fracture, and implant subsidence and/or pullout.42,43 On the contrary, studies have shown general consensus regarding the benefits of anabolic osteoporosis medications, specifically teriparatide, on spinal fusion outcomes. These benefits include shorter time to fusion, higher insertional torque, pull-out strength, and lower rates of screw pullout and proximal junctional kyphosis.5,8,10-19 Additionally, Kong et al found that patients receiving teriparatide for 12 months after percutaneous kyphoplasty had a lower risk of new vertebral compression fracture and greater improvements in pain and quality of life than placebo at all time points up to 24 months after surgery.44 While published data has only evaluated teriparatide use in spinal surgery, similar work is ongoing and needed to demonstrate the clinical benefits of abaloparatide.

Conclusion

Abaloparatide is a second-generation anabolic therapy used for the treatment of osteoporosis. It differs from the 1st generation anabolic therapy, teriparatide, in that it reversibly binds to the RG configuration PTH receptor with high affinity resulting in transient activation of osteoblasts that maximizes initial bone formation while limiting late bone resorption and osteoclast differentiation. Animal and human studies have shown the beneficial effects to BMD, bone architecture, and fracture protection. Additional benefits to abaloparatide therapy are its relatively mild side effect profile and economic cost. Additional studies are needed to determine exhibit the effect of abaloparatide on spinal surgery outcomes.

Disclosure

Dr Paul A Anderson reports personal fees from Radius Medical, Amgen, Titan spine, Medtronic, Regeneration Technologies inc, outside the submitted work. The authors report no other conflicts of interest in this work.

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