Abaloparatide

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Summary

Abaloparatide is an investigational analog of human PTHrP (1-34) being developed for the treatment of osteoporosis. The amino-acid sequence of abaloparatide is identical to that of PTHrP in the first 20 amino-acids, while over half of the remaining amino-acids are different. Some studies in animals and in humans reported that abaloparatide presented a potent anabolic activity with reduced effects on bone resorption as compared to that observed with teriparatide. This may be due to a more transient signaling response of abaloparatide related to differing affinities of the two drugs to the specific conformations of the PTH1 receptor. In the ACTIVE study, a phase 3 fracture prevention trial, 2460 postmenopausal osteoporotic women at high risk for fracture were randomized to receive 18-months of either daily abaloparatide 80 µg s.c., placebo or teriparatide 20 µg s.c. The reduction in vertebral fracture rate with respect to placebo was 86% in the abaloparatide group and 80% in the teriparatide group. Abaloparatide also produced a significant 43% reduction in the rate of nonvertebral fractures (2.7 *vs* 4.0% with placebo, p=0.04) whereas teriparatide determined a 28% reduction (2.9 *vs* 4.0% with placebo, p=NS). Abaloparatide or teriparatide showed similar increases in BMD at lumbar spine, while the patients of the abaloparatide group showed significantly greater increases in BMD at both total hip (4.18 *vs* 3.26%) and femoral neck (3.60 *vs* 2.66%). Therefore, if the preliminary data of the ACTIVE study is confirmed, abaloparatide may become an important option for the anabolic treatment of postmenopausal osteoporosis.

KEY WORDS: abaloparatide; PTHrP analogs; anabolics; osteoporosis.

Introduction

Osteoporosis is a common multifactorial systemic skeletal disease, characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and in susceptibility to fracture (1). Fractures related to osteoporosis are currently considered a public health problem since they significantly increase the morbidity and mortality of affected patients, especially in the case of hip fracture. It is expected that 42-56% of all women and 27-29% of all men will develop osteoporotic fractures after the age of 50 years and, due to aging populations, it is predicted that the number of fractures will increase by 4% *per annum* (2, 3). Osteoporosis is treated with agents that diminish osteoclastic bone resorption or increase osteoblastic bone formation or both. The most commonly used medications for treatment of osteoporosis are antiresorptive agents, including the bisphosphonates, selective estrogen receptor modulators, and denosumab. The antiresorptive agents increase bone density by decreasing the number of bone remodeling units and allowing for mineralization of osteoid. In doing so they, particularly the bisphosphonates and denosumab, significantly reduce the risk of vertebral fractures in osteoporotic patients by about 40-70% and hip or non-spine fractures by 20-40% (2, 3). Although antiresorptive drugs are able to partially correct disruption in bone architecture, the principal bone quality defect in osteoporosis, they cannot restore mechanical bone integrity because of the absence of anabolic effect. Thus, new agents are required which can increase bone mineral density (BMD) and reduce fracture beyond the levels achievable using antiresorptives. In contrast to the antiresorptive agents, anabolic agents can directly stimulate osteoblastic formation of new bone. Several agents have been investigated regarding their osteoanabolic potential, including fluoride, growth hormone, insulin growth factors and parathyroid hormone (PTH) analogs. Among these PTH analogs are regarded as the most efficacious and the only category currently available for clinical use (4). It is well known that chronically sustained elevations of PTH, as in hyperparathyroidism, exert a catabolic effect on the skeleton, whereas intermittent PTH administration increases bone formation and BMD, especially at skeletal sites where trabecular bone prevails. The parathyroid hormone (1-34) (PTH 1-34), or teriparatide is the only anabolic agent currently used in the United States and in Europe. The full-length recombinant human parathyroid hormone (PTH 1-84), is also available for treatment of postmenopausal osteoporosis in many European countries but has not yet received the FDA approval. Treatment of osteoporosis with both PTH 1-34 and PTH 1-84 is currently limited to 18-24 months, since this hormone administered for this time period in several rat strains, at doses >40-fold above those used in humans, increased the incidence of osteosarcoma (5). Teriparatide is the most powerful anabolic drug currently available for clinical use and its introduction has substantially changed the treatment of osteoporosis. In fact, teriparatide increases cancellous and endocortical bone formation, mainly at sites undergoing active bone remodeling, but has limited effect on periosteal bone formation and increases cortical porosity (6). In women with osteoporosis, the

treatment with teriparatide compared with placebo, decreased the risk of vertebral and nonvertebral fractures by 65 and 58%, respectively. Nevertheless, teriparatide has two important limitations which are represented by the necessity to be administered via daily subcutaneous injections, and by the fact that in prolonged treatments teriparatide in parallel with new bone formation also stimulates bone resorption, resulting in a gradual reduction in the anabolic effect. This has stimulated the search for other PTH and parathyroid hormone-related protein (PTHrP) analogs that would be purely anabolic, thus stimulating bone formation without stimulating bone resorption (4, 7). The PTHrP, produced by the same gene of PTH, acts by binding to the same receptor of PTH (PTH1R) and has a marked similarity to PTH in the aminoterminal amino-acid sequence (5). Parathyroid hormone-related protein (PTHrP) is widely expressed in normal tissues throughout development, although it does not normally appear in circulation except during lactation. PTHrP is required for normal bone development and acts as a paracrine and autocrine factor to regulate cellular growth, differentiation, development, and cell death as well as epithelial calcium transport in cartilage, bone, mammary glands, and a variety of other tissues (7, 8).

PTHrP analogs and bone

It is well known that chronically sustained elevations of PTHrP, as in humoral hypercalcemia of malignancy, exert a catabolic effect on the skeleton, whereas intermittent PTHrP administration has been found to increase bone formation and BMD in both rodents and humans (9, 10). PTHrP exhibits high homology to PTH in its N-terminal first 36 amino-acids. In an initial clinical trial 16 healthy postmenopausal women with osteoporosis were randomized to receive daily subcutaneous injections of synthetic human PTHrP 1-36 or placebo for 3 months. Lumbar spine BMD increased by 4.7% from baseline in patients on PTHrP 1-36. Markers of bone formation were increased whereas markers of bone resorption were unchanged, suggesting that PTHrP 1-36 might have purely anabolic effects on bone (10). A more recent 3-month study carried out on postmenopausal osteoporotic women compared daily subcutaneous injections of synthetic human PTHrP 1-36 (at 400 and 600 µg doses) with PTH 1-34. While PTH induced a greater increase in bone markers, there was no significant difference in BMD changes between groups at any site (11). However, the fact that the PTH 1-36 needs to be administered at a much higher dosage compared to teriparatide and produces an increased number of episodes of hypercalcemia, has moved the interest of researchers towards a novel synthetic analog of human PTHrP 1-34 (BA058 or abaloparatide) which is currently being assessed as a new treatment for osteoporosis. Figure 1 shows the amino-acid sequence of abaloparatide which appears to be identical to that of PTHrP in the first 20 amino-acids, while over half of the remaining amino-acids are different. The growing interest for abaloparatide is based on results of some studies in animals and in humans which reported that abaloparatide presented a potent and rapid anabolic activity with reduced effects on bone resorption as compared to that observed with teriparatide and improved room temperature stability (12-14). In particular, in a human osteoblastic cell line abaloparatide and teriparatide increased RANKL and M-CSF mRNA expression level, but these effects were rapidly reversed after removal of abaloparatide from the culture media, while those in teriparatide-treated cells were sustained (15). Moreover, studies carried out in animals have demonstrated marked bone anabolic activity of abaloparatide with complete reversal of bone loss in ovariectomy-induced osteopenic rats and monkeys (12, 13). The molecular mechanisms underlying the differences between abaloparatide and teriparatide are unknown, but may relate to differing affinities of the two drugs to the specific conformations of the PTHR1 (14, 16). Some years ago Ferrandon et al. reported that the PTH-PTHR1 complex moves intracellularly and results in sustained cAMP generation, while PTHrP-PTHR1 complex remains at the plasma membrane and produces more transient cAMP elevations (17). Recent studies have reported that PTH or PTHrP analogs can distinguish between two high affinity PTHR1 conformations, R0 and RG, and that an efficient binding to R0 results in prolonged signaling responses in cells and prolonged calcemic responses in animals, whereas the binding to RG results in more transient responses (4, 14). Hattersley et al. recently reported that abaloparatide binds more selectively to the RG *versus* to the R0 PTHR1 conformation than teriparatide does, and thus induces more transient signaling responses in cells. The high RG selectivity (or lower R0 affinity) hypothesized for abaloparatide is supported by the observation that the cAMP signaling responses induced by abaloparatide are more transient in duration, as compared to those induced by similar concentrations of teriparatide (14). Therefore, the selective binding of abaloparatide to the RG conformation of PTHR1 may mediate more transient cAMP responses in PTHR1 expressing cells and account for the favorable anabolic effect of abaloparatide on bone. Recently, a novel microneedle based transdermal technology (sMTS) has been developed and a study carried out on cynomologus monkeys has reported that the patch abaloparatide formulation presented a pharmacokinetic profile comparable to subcutaneous injections (18).

Abaloparatide: clinical studies

The effects of abaloparatide on bone metabolism and BMD have been recently evaluated in a randomized, double-blind, placebo-controlled, dose-finding, phase 2 study carried out on postmenopausal women with osteoporosis and conducted at 30 centers in the US, India, Argentina and UK (19). In this study 222 women were randomized to receive 24-weeks of treatment with daily subcutaneous injections of placebo, abaloparatide 20, 40 or 80 µg, or teriparatide 20 µg. All patients received supplemental calcium and vitamin D per local practice. Concerning bone turnover markers, in both abaloparatide and teriparatide groups P1NP, marker of bone formation, began to increase from week 1. After 24 weeks, the median of P1NP had increased by 55% in the 40µg abaloparatide

	1	34
PTH (1-34)	SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNF	$-(NH_2)$
PTHrP (1-36)	AVSEHQLLHDKGKSIQDLRRRFFLHHLIAEIHTAEI	$-(NH_2)$
ABL	AVSEHQLLHDKGKSIQDLRRRELLEKLLXKLHTA	$-(NH_2)$

Figure 1 - Amino-acid sequence of the NH_2 terminal chain of PTH (1-34), PTHrP (1-36) and abaloparatide (ABL).

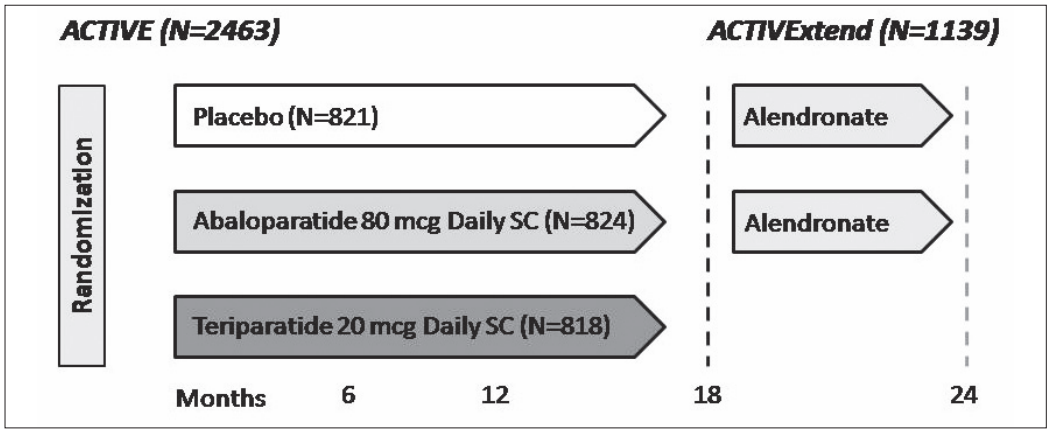

Figure 2 - Study design of the ACTIVE and ACTIVExtend phase 3 trial.

group, 52% in the 80 µg abaloparatide group and by 98% in the teriparatide group. Moreover, CTX increased significantly more in the teriparatide group than in any of the abaloparatide groups. In fact, after 24 weeks the median of CTX had increased by 23% in the 80 µg abaloparatide group and by 76% in the teriparatide group. At 24-weeks, abaloparatide and teriparatide had similarly increased BMD at lumbar spine (5.2, 6.7 and 5.5% for abaloparatide 40 µg, abaloparatide 80 µg and teriparatide, respectively). Femoral neck BMD increased by 2.7, 2.2, and 3.1% in abaloparatide, 20-, 40-, and 80-µg groups, respectively, and by 1.1% in the teriparatide group. The increase in femoral neck BMD with abaloparatide, 80 µg was significantly greater than placebo (0.8%). Total hip BMD increased by 1.4, 2.0, and 2.6% in the abaloparatide, 20-, 40-, and 80-µg groups, respectively. The total hip increases in the 40- and 80-µg abaloparatide groups were greater than both placebo (0.4%) and teriparatide (0.5%). Concerning safety, during the 24-week treatment period, the proportion of patients who experienced adverse effects was similar across treatment groups. Also most injection site reactions were of mild intensity and similar in the abaloparatide and teriparatide groups. Instead the incidence of hypercalcemia, observed 4-hours post-dose, was slightly greater ($p<0.01$) in the teriparatide group than in the abaloparatide groups (19). In the ACTIVE (Abaloparide Comparator Trial in Vertebral End-points) double-blind, placebo-controlled, phase 3 fracture prevention trial, 2460 postmenopausal osteoporotic women at high risk for fracture were randomized to receive 18-months of either daily abaloparatide 80 µgs.c., placebo or open label teriparatide 20 µgs.c. (Figure 2). All patients received calcium and vitamin D supplements, and 1901 participants completed the trial. The groups were well matched for baseline demographics. The patients had a mean age of 68.8 years and mean BMI of 25.1Kg/m^2; moreover, 16.3% of patients had 1 vertebral fracture, 28.2% had 2 or more vertebral fractures and 46.8% had at least 1 non-vertebral fracture. The mean spine, femoral neck and total hip baseline T-scores were -2.90, -2.14 and -1.90, respectively. Preliminary results of the ACTIVE study were presented at the 2015 meetings of the Endocrine Society (San Diego, CA, March 5-8) and the American Society of Bone and Mineral Research (Seattle, WA, October 9-12).On the primary endpoint, among the 2118 patients who had baseline and post-therapy X-rays, the rate of new vertebral fracture among those receiving abaloparatide (n=690) was 0.58%, representing a reduction of new incident vertebral fractures by 86% as compared to placebo treated patents [n=711, fracture rate 4.22%; ($p<0.0001$)]. In the teriparatide the fracture rate of 0.84% (n=717) was reduced by 80% ($p<0.001$ *versus* placebo (20). Abaloparatide also produced a significant 43% reduction in the rate of nonvertebral fractures (2.7 *vs* 4.0% with placebo, p=0.04) whereas teriparatide determined a 28% reduction (2.9 *vs* 4.0% with placebo, p=NS). Moreover, wrist fractures were lower in the abaloparatide group compared with teriparatide (0.5 *vs* 2.0%, p=0.014) (20). At the end of the 18-month study period the patients treated with either abaloparatide or teriparatide showed similar increases in BMD at lumbar spine (11.20 and 10.49%, respectively) while the patients of the abaloparatide group showed significantly greater increases in BMD at both total hip and femoralneck with respect to those in the teriparatide group (4.18 *vs* 3.26% and 3.60 *vs* 2.66%, respectively) (20). In the ACTIVExtend trial, subjects enrolled in the ACTIVE trial, who completed 18 months of treatment with either abaloparatide or placebo, and who were deemed eligible, were offered up to 6 additional months of treatment with alendronate (70 mg per week). Also in the ACTIVExtend trial the patients previously treated with abaloparatide showed a lower rate in both vertebral and nonvertebral fractures with respect to those in the placebo group (21). The overall incidence of hypercalcemia based on albumin corrected serum calcium measured pre and post injection (4 hours) were 0.37, 3.41 and 6.36% for the placebo, abaloparatide and teriparatide groups, respectively. Hypercalcemia was significantly less frequent inabaloparatide treated group than in the teriparatide group (p=0.0055).

In conclusion, abaloparatide has shown a similar effect to teriparatide regarding the increase of BMD at lumbar spine and the reduction of vertebral fracture risk, whereas it has demonstrated a higher increased in BMD at femoral sites and distal radius. Also, abaloparatide has shown a higher reduction in non vertebral fractures respect to teriparatide. Therefore, if the preliminary data of the ACTIVE study is confirmed, abaloparatide may become an important therapeutic option for the anabolic treatment of osteoporosis.

Conflict of interest

C. Caffarelli and S. Gonnelli declare that they have no conflict of interest.

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