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Abaloparatide: Future Projects

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Short Communication

After fifteen years of studies, in 2017 the Food and Drug Administration approved a new osteoanabolic drug, Abaloparatide (ABL), with the indication of the treatment of post-menopausal osteoporosis in women at high risk of fracture, i.e. with history of fragility fracture, multiple risk factors or unable to assume other anti-osteoporosis drugs for intolerance or inefficacy [1]. Abaloparatide is recombinant human parathyroid hormone-related peptide 1–34 [rhPTH (1-34)], developed by Radius Health, with 71% homology with Parathyroid Hormone-related Peptide (PTHrP) (1-34) and 41% homology to PTH (1-34) [1-3]. Compared to PTH and PTHrP ligands, ABL presents a higher affinity and greater selectivity for the G protein-dependent receptor conformation of PTHR1 [3]. This provides Abaloparatide particular pharmacodynamic features with a stronger anabolic effect and a modest stimulation of bone resorption compared to its analogous teriparatide (TPTD) [1]. The FDA approval of Abaloparatide derives from the results of ACTIVE (Abaloparatide Comparator Trial in Vertebral Endpoints, trial registration NCT 01343004) and ACTIV Extend trials. The ACTIVE phase 3 trial [1], assessing the efficacy and safety of Abaloparatide (80 μg daily subcutaneous) vs. placebo during 18 months in postmenopausal osteoporosis, showed that Abaloparatide increases bone mineral density and reduces major osteoporotic fractures better and with a more rapid onset of action than TPTD (20 μg daily subcutaneous), which was used as an open label active comparator (i.e. a drug that this currently marketed for managing PMO) [2]. The ACTIVE showed that ABL reduced new vertebral and non-vertebral fractures by 86% and 43% respectively, compared to placebo, and it decreased major osteoporotic fractures significantly more than teriparatide, with faster and higher BMD gains and a lower increase in s-CTX and a lower incidence of hypercalcemia compared to TPTD. Bone biopsies were obtained from a total of 105 subjects (35, 36, and 34 for the placebo, abaloparatide, and teriparatide groups, respectively) after 12-18 months of treatment, in order to evaluate the effects of ABL on bone safety through histological and histomorphometric analysis. No evidence of abnormalities in osteoid, marrow fibrosis, mineralization was found in ABL-treated group, which reported a lower eroded surface than the control group, as expected [4]. The ACTIV Extend trial (NCT01657162) enrolled patients who completed 18 months of ABL or placebo in ACTIVE to receive up to 24 additional months of open-label Alendronate (ALN). A pre-planned 6-months interim analysis reported, in the ABL/ALN group, compared to placebo/ALN, a risk reduction of new morphometric vertebral fractures 87%, non - vertebral fractures 52%, major osteoporotic fractures 58%, and clinical fractures 45%. As observed for TPTD followed by antiresorptive therapy such as zoledronic acid or denosumab, the sequential therapy with ABL/ALN is a promising strategy to maintain the osteoanabolic effects of ABL [5]. As regards safety, these trials reported a similar proportion of adverse events across ABL, TPTD and placebo groups, in particular headache, dizziness, dyspepsia were reported as probably related to treatment in 30% of patients. Preclinical studies in rats confirmed the potential risk of bone proliferative changes, mostly osteosarcoma, for prolonged treatment with ABL, as observed for TPTD [6]. Therefore, the history of bone tumors represents a contraindication for these anabolic products, and their recommended period of use is within 24 months.

Commentary and Perspectives

Abaloparatide is a promising osteoanabolic agent showing the ability to consistently reduce fracture risk and increase BMD at lumbar spine and hip, with room - temperature stability, a safety similar to teriparatide, a lower incidence of hypercalcemia, and lower bone resorption stimulation. Recently approved for the treatment of postmenopausal osteoporosis, it could represent a potential new approach for the therapy of men, young women and Glucocorticoid-induced or other secondary osteoporosis at high risk of fracture. Its anabolic effect could be prolonged by sequentially administering an antiresorptive agent.

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