DRUG REVIEW

Odnanactib: New Targets in Treatment of Postmenopausal Osteoporosis

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Cathepsin K is a key enzyme involved in the degradation of organic bone matrix by osteoclasts. Odanacatib is a powerful, reversible nonpeptidic biaryl slective inhibitor of cathepsin K that inactivates the proteolytic activity of cathepsin k. In preclinical studies, ODN showed substantial inhibition of bone resorption markers along with increase in bone mineral density. Significant differences have been observed in the effects of ODN treatment compared with those of other antiresorptive agents such as bisphosphonates and denosumab. ODN displays compartment-specific effects on trabecular versus cortical bone formation, with treatment resulting in marked increase in periosteal bone formation and cortical thickness whereas trabecular bone formation has been shown to reduce. Furthermore, osteoclasts remain viable.

Phase I and II studies conducted in postmenopausal women showed ODN to be safe and well tolerated. After 5 years, women who received ODN, 50 mg weekly continuously from year 1, showed BMD increase from baseline of 11.9% at the lumbar spine, 9.8% at the femoral neck, 10.9% at the hip trochanter, and 8.5% at the total hip (1).It is orally available and effective in a once-weekly dose. After 5 years, women who received ODN 50 mg weekly showed significant BMD increases at the lumbar spine and total hip (2,3). Available data suggests that cathepsin K inhibition could be a promising intervention to treat osteoporosis. Ongoing studies are expected to provide information on the long-term efficacy in fracture reduction and safety of prolonged treatment with ODN. Postmenopausal osteoporosis is a disease of high bone remodeling, with an imbalance of bone resorption over bone formation, resulting in decreased bone mineral density and disruption of bone microarchitecture. In a trial looking into safety and tolerability of the drug, adverse experience with single dose of ODN were transient and considered to be mild to moderate with exception of one adverse event of gastroenteritis which was severe in nature (4).

In 2 year , phase 2 dose ranging trial, postmenopausal women with BMD T Score -2 to -3.5 at spine or hip receiving combination ODN over a range of (10-50 mg) with vit D 3 & calcium showed a gain of BMD at spine and hip. Discontinuation of ODN resulted in reversal of the treatment effect.Treatment with ODN was generally well tolerated upto 5 years (5).

With our improved understanding of the molecular and cellular regulators and mediators of bone remodeling, new targets for therapeutic intervention have been identified. However, large adequately powered fracture reduction trials shall guide us more to establish role of biological options as one of important group for treatment of postmenopausal steoporosis.

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