METABOLIC BONE DISEASES

Cathepsin K inhibition for osteoporosis

The 24-month results of a study in postmenopausal women with low bone mineral density (BMD) indicate that odanacatib progressively increases BMD with only modest effects on bone turnover.

Odanacatib is a selective and orally bioavailable inhibitor of cathepsin K, a cysteine protease that is predominantly expressed in osteoclasts and has a key role in bone resorption. Unlike other commonly used antiresorptive agents that broadly suppress osteoclast activity, cathepsin K inhibitors specifically target the role of osteoclasts in the degradation of bone matrix.

In a proof-of-concept, multicenter phase II study, 399 postmenopausal women aged 45–68 years with low BMD were randomly allocated to receive weekly treatment with placebo or 3 mg, 10 mg, 25 mg or 50 mg odanacatib. Weekly treatment with 10 mg, 25 mg or 50 mg odanacatib resulted in improvements from baseline in lumbar spine and femoral BMD, which increased with increasing dose. At 2 years, treatment with the 50 mg dose increased lumbar spine and total hip BMD by 5.5% and 3.2%, respectively; by contrast, BMD at these sites was more or less unchanged from baseline in the placebo group (–0.2% and –0.9%, respectively).

> “...odanacatib warrants further study as a treatment for osteoporosis”

Consistent with the mechanism of action of odanacatib, changes from baseline in markers of bone remodeling were modest and dose-related. The observed decreases in markers of bone resorption reflect an antiresorptive effect of the drug, and decreases in markers of bone formation were transient. Notably, levels of tartate-resistant acid phosphatase 5b (TRAP5b), a marker of osteoclast viability, were similar in the treatment and placebo groups at 24 months.

Treatment with odanacatib was generally well tolerated: the rate of adverse events was similar in the treatment and placebo groups, and bone biopsy samples obtained from 32 women near the end of the study revealed no abnormalities.

The results suggest that odanacatib warrants further study as a treatment for osteoporosis, which might also be used in combination with other agents given its distinct mechanism of action. A phase III trial using a dose of 50 mg odanacatib weekly, selected on the basis of the above study, is fully enrolled and ongoing.

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