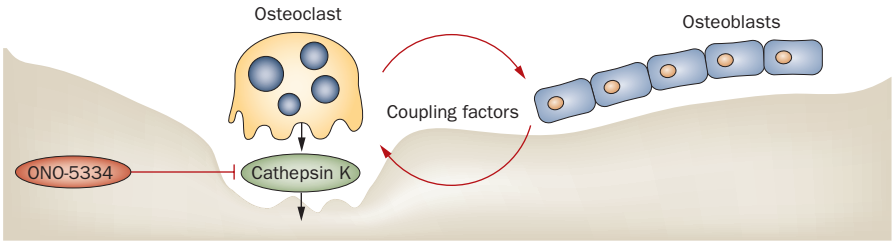
METABOLIC BONE DISEASES

Cathepsin K inhibition halts bone destruction, while remodeling merry-go-round runs merrily on

Targeting cathepsin K to treat osteoporosis could be a step closer to the clinic, after publication of 12-month data from a 2-year trial of the latest cathepsin K inhibitor, ONO-5334, in postmenopausal women with the disease. Cathepsin K is a cysteine protease secreted by osteoclasts to degrade the organic matrix of bone. "After the odanacatib efficacy and safety results, this is a second positive clinical study with an oral, apparently safe and dose-dependent but structurally different cathepsin K inhibitor," says Dieter Brömme of the University of British Columbia, who studies proteases as targets in rheumatic conditions, and is not involved in the trial.

Following on from successful studies *in vitro*, in monkeys, and in healthy women, the trial (published in the *Journal of Bone and Mineral Research)* is the first proof-of-concept study to investigate the efficacy and safety of ONO-5334 in 295 postmenopausal women with osteoporosis. Patients were randomly assigned to one of five treatment arms: ONO-5334 50 mg twice daily, 100 mg daily or 300 mg daily, alendronate or placebo. The study was powered to directly compare ONO-5334 with placebo, but not with alendronate, and the primary outcome measure was mean bone mineral density (BMD) at the lumbar spine. The researchers also measured several markers of bone turnover.

All doses of ONO-5334 were effective, with 300 mg producing the greatest gains in BMD; for example a 5.1% (±0.49%) increase from baseline BMD, at the lumbar spine, at 12 months. ONO-5334 50 mg twice daily performed better than 100 mg daily, suggesting that development of a slow-release formulation might reduce the optimum dose by mitigating troughs in serum levels of the inhibitor. Levels of bone resorption markers were suppressed by ONO-5334 or alendronate at the first time point (1.5 months) and thereafter, but whereas alendronate also had a clear suppressive effect on markers of bone formation, ONO-5334 did not.



Although the effect of ONO-5334 on bone resorption in osteoporosis was thus similar over 12 months to that produced by the most frequently prescribed existing therapy, alendronate, what really has experts excited about targeting cathepsin K is the ability to uncouple bone resorption and formation, potentially increasing therapeutic benefit in the long term. "It is highly encouraging that bone formation parameters such as bone-specific alkaline phosphatase, osteocalcin and procollagen were less affected by ONO-5334 than by alendronate," continues Brömme, explaining that inhibiting the enzyme could outclass existing approaches to osteoporosis, which all destroy the cellular communication network that regulates the balance between bone formation and resorption.

"Levels of bone formation and bone resorption markers usually change in parallel," agrees Richard Eastell, lead author of the study, "and the observation that with this treatment they do not raises the possibility of greater effects on bone density and bone structure in the long term, at 3 years and beyond."

Existing therapies in osteoporosis are either antiresorptive, including bisphosphonates such as alendronate, or anabolic, such as teriparatide. Bisphosphonates interfere with osteoclast function, whereas teriparatide boosts bone formation by increasing osteoblast numbers. Nevertheless, neither is ideal as a long-term therapy. In general, the effects of drugs for osteoporosis are undermined by the dynamic nature of bone remodeling; over time, feedback mechanisms kick in to balance suppressed bone resorption by increasing bone formation, and *vice versa*. It is this long-term therapeutic inadequacy that Eastell and colleagues hope ONO-5334 might redress.

Although, as a preliminary trial, this study was too short to assess long-term efficacy, the observed lack of suppression of bone-formation markers after ONO-5334 treatment is a positive sign that blocking cathepsin K impedes osteoclast function without disrupting cellular activity, or at least, without doing so enough to trigger the 'corrective' feedback cycle.

The researchers are currently analyzing the final data from their trial, and are considering the best dose and formulation for a large, anti-fracture, 3-year phase III efficacy study. How this treatment performs in direct comparison with alendronate, or with the other cathepsin K inhibitor currently in development, odanacatib, remains to be seen.

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