EDITORIAL

Sclerostin Inhibition for Osteoporosis — A New Approach

Carolyn B. Becker, M.D.

Effective new therapies are still needed for people with osteoporosis. In 2002, the introduction of teriparatide, or recombinant parathyroid hormone (PTH [1-34]), opened a promising chapter in osteoporosis care.[1] For the first time, there was an anabolic agent that significantly increased bone mineral density (BMD), reduced fracture risk, and restored bone architecture back to, or close to, normal. However, despite an impressive track record of both safety and efficacy, teriparatide has had a limited clinical reach as compared with other agents, largely owing to its requirement for daily subcutaneous injection, a black-box warning about osteosarcoma in rats, and its high cost. Since antiresorptive therapies do not restore bone architecture and have a number of other limitations, finding new treatments for osteoporosis has been a high priority.

The results of the study by McClung et al.[2] now reported in the *Journal* represent a potential breakthrough in osteoporosis therapeutics. The study introduces romosozumab, a humanized monoclonal antibody directed against the osteocyte-derived glycoprotein known as sclerostin. Humans with genetic deficiencies of sclerostin and mice with knockout of the sclerostin gene (*Sost*) have high bone mass, increased bone strength, and resistance to fracture. Sclerostin works by inhibiting the Wnt and bone morphogenetic protein signaling pathways that are critical for osteoblast proliferation and activity. By inhibiting sclerostin, romosozumab should enhance osteoblastic function.

This phase 2 study was a randomized, placebo-controlled trial that included two comparator drugs. Participants were healthy postmenopausal women with osteopenia, randomly assigned to one of eight study groups — romosozumab administered subcutaneously either monthly or every 3 months at various doses; oral alendronate at a dose of 70 mg weekly; subcutaneous teriparatide at a dose of 20 μg daily; or placebo injections given monthly or every 3 months. Primary and secondary end points included changes in BMD as compared with placebo, changes in markers of bone metabolism, and comparisons of the study drug with alendronate and teriparatide.

The results were impressive. As compared with baseline, BMD was significantly improved for all doses of romosozumab and at all sites except at the distal third of the radius, which remained essentially unchanged. At the highest monthly dose of romosozumab, increases in BMD at the spine and hip were rapid and robust, surpassing the BMD values with alendronate and teriparatide at 6 months and remaining significantly higher than the BMD values with either comparator by the end of the trial.

If the changes in BMD for a presumed anabolic agent were predictable, the changes in bone-turnover markers were not. Levels of bone-formation markers increased rapidly after the first dose of romosozumab but then declined. By month 6, the bone-formation markers were nearly back to baseline levels, despite continued administration of the drug. In contrast and perhaps most surprising, markers of bone resorption declined in the first week and remained suppressed for the duration of the trial.

The pattern of brief anabolic stimulation coupled with chronic suppression of bone resorption seen with romosozumab is unprecedented among current therapies for osteoporosis. Potent antiresorptive agents such as bisphosphonates and denosumab suppress both bone-resorption and bone-formation markers. Teriparatide increases levels of bone-formation markers early

on but, after a delay, stimulates bone-resorption markers as well. The so-called anabolic window opened by teriparatide may be prematurely closed by this effect on resorption, blunting the bone-strengthening properties of the drug. PTH-related protein, another potential anabolic agent, was recently shown to act similarly to PTH.[3] Odanacatib, a cathepsin K inhibitor, initially suppresses both bone-formation and bone-resorption markers, but the levels of bone-formation markers increase back to baseline values by 1 year.[4]

Can we reproduce the effect of romosozumab on bone remodeling with existing osteoporosis therapies? Results from small studies suggest that perhaps we can. Combination therapy with teriparatide and potent but intermittently dosed antiresorptive agents such as zoledronic acid[5] or denosumab[6] administered one or two times per year shows promising results. Shorter courses of PTH followed sequentially or cyclically by oral bisphosphonates may increase bone formation without stimulating resorption.[7,8]

Many questions about romosozumab remain. Will changes in BMD translate into potent antifracture efficacy? Will it be safe over time? In the current study, there were no clinically significant adverse events other than injection-site irritation. Will longer administration (>1 year) cause bony complications such as cranial-nerve palsies or spinal stenosis? What duration of treatment is associated with the highest rate of response? Why did BMD not improve at the wrist? A phase 3 clinical trial of romosozumab is under way in a cohort of postmenopausal women with osteoporosis (ClinicalTrials.gov number, NCT01631214) and may answer some of these questions. For now, more than a decade after the introduction of teriparatide, we may at last have a sequel to the anabolic story.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From Brigham and Women's Hospital, Boston.

This article was published on January 1, 2014, at NEJM.org.

1. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001;344:1434-41.
2. McClung MR, Grauer A, Boonen S, et al. Romosozumab in postmenopausal women with low bone mineral density. N Engl J Med. DOI: 10.1056/NEJMoa1305224.
3. Horwitz MJ, Augustine M, Kahn L, et al. A comparison of parathyroid hormone-related protein (1-36) and parathyroid hormone (1-34) on markers of bone turnover and bone density in postmenopausal women: the PrOP study. J Bone Miner Res 2013;28:2266-76.
4. Brixen K, Chapurlat R, Cheung AM, et al. Bone density, turnover, and estimated strength in postmenopausal women treated with odanacatib: a randomized trial. J Clin Endocrinol Metab 2013;98:571-80.
5. Cosman F, Eriksen EF, Recknor C, et al. Effects of intravenous zoledronic acid plus subcutaneous teriparatide [rhPTH(1-34)] in postmenopausal osteoporosis. J Bone Miner Res 2011;26:503-11.
6. Tsai JN, Uihlein AV, Lee H, et al. Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial. Lancet 2013;382:50-6.
7. Cosman F, Nieves J, Zion M, Woelfert L, Luckey M, Lindsay R. Daily and cyclic parathyroid hormone in women receiving alendronate. N Engl J Med 2005;353:566-75.
8. Schafer AL, Sellmeyer DE, Palermo L, et al. Six months of parathyroid hormone (1-84) administered concurrently versus sequentially with monthly ibandronate over two years: the PTH and Ibandronate Combination Study (PICS) randomized trial. J Clin Endocrinol Metab 2012;97:3522-9.

DOI: 10.1056/NEJMe1315500