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PHARMACOTHERAPY

Novel antibody therapy demonstrates potential for building bone in osteoporosis

Targeting a naturally occurring inhibitor of bone formation could signal a new direction for osteoporosis care. Findings from an international phase II clinical trial reported in the *New England Journal of Medicine* indicate that administering romosozumab—a humanized monoclonal antibody directed against sclerostin—increases BMD among individuals with low bone mass.

Sclerostin is an osteocyte-derived glycoprotein that acts through the Wnt and bone morphogenetic protein signalling pathways to inhibit osteoblast function; as a consequence, bone formation is decreased. Patients with mutations in the gene encoding sclerostin (*SOST*) are characterized by high bone mass and reduced incidence of fracture. As expression of *SOST* is restricted to the skeleton, inhibition of sclerostin represents an ideal candidate for targeted therapeutic intervention. Preclinical work previously demonstrated that using antibodies to block the activity of sclerostin in rats and monkeys with osteoporosis led to marked increases in bone formation, with restoration of bone mass, structure and strength. Furthermore, a phase I first-in-human study of single-dose injections of romosozumab showed promise for increasing BMD among healthy volunteers.

To further characterize the efficacy and safety of romosozumab, researchers from 28 centres in Europe, North America and South America conducted a phase II randomized controlled trial in which the primary outcome measure was the percentage change from baseline in BMD at the lumbar spine. Secondary end points included percentage changes in BMD at other anatomical sites and in biochemical markers of bone turnover.

The study group evaluated the effects of five different dosing regimens of romosozumab (administered by subcutaneous injection) over a 12-month period among 419 postmenopausal women (mean age 67 years) with osteopaenia or osteoporosis. Responses to romosozumab were weighed against those observed with placebo injections and two active comparators, alendronate and teriparatide. "This methodology was typical for a phase II dose-ranging study," explains lead clinical investigator Michael McClung of the Oregon Osteoporosis Center (Portland, USA), "the active comparators were included to provide a clinical reference to the magnitude of responses observed."

The researchers found that all doses of romosozumab markedly increased BMD in the spine and hip. Notably, with the largest dose of romosozumab (210 mg administered each month), the increase in lumbar spine BMD at 12 months (11.3%) was significantly greater than the response to either alendronate (4.1%) or teriparatide (7.1%). By contrast, participants assigned to the placebo group experienced a 0.1% decrease in BMD at the lumbar spine during this timeframe.

Biochemical indices of bone formation increased during the first 6 months of romosozumab administration but then dropped back to baseline levels thereafter, whereas levels of a bone resorption marker were modestly decreased from baseline during the full 12 months of romosozumab therapy.

Injection-site reactions occurred more frequently among the groups receiving romosozumab than the placebo group; however, these effects were generally mild and did not exhibit a dose-response relationship. The incidence of serious adverse effects was 7% with romosozumab and 14% with placebo.

The novelty of the study findings for driving future targeted treatment of osteoporosis is confirmed by Carolyn Becker (Brigham and Woman's Hospital, Boston, USA), an expert in bone disease. Writing in an accompanying editorial, Becker states "The pattern of brief anabolic stimulation coupled with chronic suppression of bone resorption seen with romosozumab is unprecedented among current therapies for osteoporosis."

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This phase II study has already been extended to evaluate the effect of long-term treatment with romosozumab, as well as the effects of stopping treatment, of following romosozumab treatment with another antibody-based osteoporosis drug (denosumab) and of providing additional rounds of romosozumab. The investigators are also planning phase III studies to appraise the efficacy of romosozumab for reducing fracture risk among women with postmenopausal osteoporosis.

"If phase III studies are successful, the availability of drugs that inhibit sclerostin may provide an important new approach to treating patients with severe osteoporosis in need of skeletal reconstruction," McClung concludes.

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Original article McClung M. R. *et al.* Romosozumab in postmenopausal women with low bone mineral density. *N. Engl. J. Med.* doi:10.1056/NEJMoa1305224