Nature Reviews Drug Discovery | AOP, published online 14 March 2014; doi:10.1038/nrd4282

TRIAL WATCH

Bone-building antibody outshines current treatments in osteoporosis trial

A monoclonal antibody that targets sclerostin — a key regulator of bone growth — outperformed two approved osteoporosis drugs in a recently published Phase II trial (*N. Engl. J. Med.* **370**, 412–420; 2014). Importantly, romosozumab increased bone formation, an effect that is lacking from many current therapies.

Carolyn Becker, a clinician the Division of Endocrinology, Diabetes and Hypertension at the Brigham and Women's Hospital, Boston, Massachusetts, USA, highlights that there is a pressing need for osteoporosis therapies that build bone. "We have only had one anabolic drug on the market for osteoporosis since 2002 (teriparatide) [a recombinant form of parathyroid hormone]. New therapies that build bone could change our entire approach to the care of patients with osteoporosis, particularly those with extremely low bone density and/or who have had multiple fractures."

Sclerostin is a glycoprotein that is secreted by osteocytes (bone cells) and inhibits canonical WNT signalling — a pathway that is involved in cellular growth and differentiation — in bone. Inhibition of WNT then decreases bone formation and increases bone resorption. A key advantage of inhibiting sclerostin is that it has a restricted expression pattern. "Sclerostin appears to be a very specific product of osteocytes," says David Goltzman, Director of the McGill Centre for Bone and Periodontal Research, McGill University, Montreal, Quebec, Canada. "Consequently, a pharmaceutical that targets sclerostin should localize the modulation of the WNT system to bone and minimize off-target effects on WNT signalling outside of bone."

The trial assessed the effects of romosozumab in 419 postmenopausal women aged 55 to 85 years who had low bone mineral density. Patients received romosozumab once a month (subcutaneous 70 mg, 140 mg or 210 mg) or once every 3 months (subcutaneous 140 mg or 210 mg), placebo or an open-label active comparator. The comparator drugs were the bisphosphonate alendronate (Fosamax (Merck); oral 70 mg weekly) or teriparatide (Forteo (Eli Lilly); subcutaneous 20 µg daily).

All doses of romosozumab met the primary end point: a significant increase in bone mineral density at the lumbar spine after 12 months. The largest effects were seen in patients who received 210 mg once a month, who had an increase in bone mineral density of 11.3%, compared to a decrease of 0.1% with placebo and increases of 4.1% with alendronate and 7.1% with teriparatide. Romosozumab also induced transient increases in the levels of bone formation markers and a sustained decrease in a marker of bone resorption.

Goltzman notes that the results of this trial indicate that sclerostin inhibition simultaneously increases bone formation and inhibits bone resorption. "This combined action could theoretically provide a greater bone mass than any agent yet available, including parathyroid hormone," he says.

Aside from mild injection-site reactions with romosozumab, adverse events were similar among treatment groups. The promotion of bone growth could plausibly, for example, cause overgrowth of the skull and face, leading to cranial nerve compression, or worsening of spinal stenosis, says Becker. "But this is theoretical and has not been shown in studies so far," she notes.

Secondary end points of the trial included changes in bone mineral density in other areas of the body. Patients who received 210 mg of romosozumab once a month had an increased bone mineral density of 4.1% at the hip and 3.7% at the femoral neck, which were again larger than the increases observed with alendronate or teriparatide.

Because patients with osteoporosis have low bone mass, they have a greatly increased risk of fracture, which was not studied in the current trial. "It will be crucial to determine if romosozumab reduces not just vertebral but also non-vertebral and hip fractures [which are common in patients with osteoporosis]," says Becker. Indeed, the incidence of fracture will be assessed in ongoing Phase III trials. Becker notes that it will also be important to determine what the optimal duration of therapy is, as well as what happens to bone density, markers of bone turnover and fracture risk after administration of the drug is stopped.

Romosozumab is currently in four Phase III trials, and initial results are anticipated in the first half of 2016. "The success of romosozumab would be a huge boon for the treatment of a disease that is having a major personal, social and economic impact as the population ages," concludes Goltzman.

Charlotte Harrison

PhotoDisc/Getty Images/TRBfoto/EyeWire/ Nature Publishing Group