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COMMENTARY

Inhibition of sclerostin in the management of osteoporosis: results of a phase 2 clinical trial meet expectations

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Commentary on: McClung MR, Grauer A, Boonen S, Bolognese MA, Brown JP, Diez-Perez A, Langdahl BL, Reginster JY, Zanchetta JR, Wasserman SM, Katz L, Maddox J, Yang YC, Libanati C, Bone HG. Romosozumab in postmenopausal women with low bone mineral density. *N Engl J Med* 2014;**370**(5):412–420.

Current therapies of osteoporosis, with the exception of parathyroid hormone, decrease the risk of osteoporotic fractures by reducing bone resorption and preserving its architecture but cannot stimulate bone formation. Studies of rare human bone disorders and genetically modified animal models led to the identification of signaling pathways that regulate bone formation, which provided targets for the development of novel therapeutics for bone diseases.[1] Of particular importance have been studies of two rare bone sclerosing dysplasias, sclerosteosis and van Buchem disease, characterized by increased bone mass due to sclerostin deficiency.[2] Sclerostin, a glycoprotein produced in the skeleton by osteocytes, is a negative regulator of bone formation.[3] The restricted expression of sclerostin in the skeleton, the markedly increased bone mass and bone strength of patients and mice with sclerostin deficiency, and the lack of extraskeletal complications in patients made sclerostin a very attractive therapeutic target in osteoporosis.[4] Consequently, animal studies showed that exogenously administered antibodies to sclerostin increase bone formation at all skeletal envelopes, maintain or decrease bone resorption and increase bone mineral density (BMD) and bone strength.[4] Furthermore, in phase 1 human studies, increases in bone formation and decreases of bone resorption associated with significant increases in BMD were reported after administration of single doses of two different humanized antibodies, romosozumab (Amgen (Thousand Oaks, CA, USA), UCB (Brussels, Belgium)) and blosozumab (Eli Lilly, Indianapolis, IN, USA).[5,6]

McClung *et al.*[7] recently reported the results of a phase 2 clinical trial on the efficacy and tolerability of romosozumab in 419 postmenopausal women with low bone mass. This was a typical phase 2 study that compared different doses and dosing intervals of subcutaneous injections of romosozumab with placebo, oral alendronate, 70 mg weekly, and subcutaneous teriparatide, 20 μg daily. The primary efficacy point of the study was the change of spine BMD after 12 months. All doses of romosozumab induced significant increases in BMD. The highest dose of romosuzamab used, 210 mg monthly, increased BMD at the spine (11.3%), total hip (4.1%) and femoral neck (3.7%). These increases were significantly higher than those observed in women treated with either alendronate or teriparatide. For example, the corresponding increases at the spine were 4.1% for alendronate and 7.1% with teriparatide after 12 months. No significant differences in BMD of the distal third of the radius were observed at 12 months between any of the romosozumab groups and the placebo, alendronate or teriparatide groups. Adverse events were similar among all groups of studied women except for mild reactions at the injection sites of romosozumab.

These results meet the expectations raised by genetic, animal and phase 1 human studies and establish sclerostin inhibition by romosozumab as a potential new bone building therapy for osteoporosis, particularly for women with low bone mass at increased risk of fractures. Phase 3 clinical studies are currently investigating the anti-fracture efficacy and tolerability of monthly subcutaneous injections of romosozumab in patients with osteoporosis. Results also raised questions, which are mainly related to the mechanism of action of romosozumab at the bone tissue and consequently to its optimal use in clinical practice.

In their study, McClung *et al.*[7] also reported sequential measurements of biochemical markers of bone turnover that revealed a remarkable but difficult to explain pattern that was different from the well-established changes induced by alendronate and teriparatide. Overall, romosozumab increased bone formation and decreased bone resorption consistent with the results of the phase 1 studies with this sclerostin inhibitor and with blosozumab.[5,6] The pattern of response was, however, intriguing, showing an early rapid increase in bone formation markers followed by a progressive decline with time (**Figure 1**), which was not due to the development of

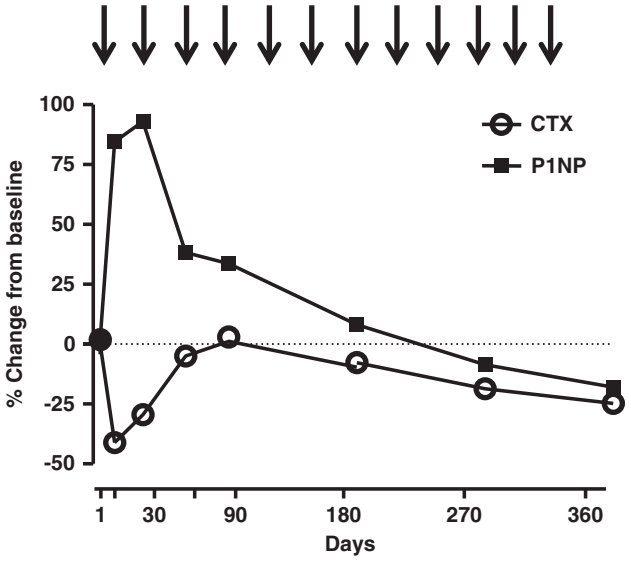

Figure 1 Percent changes (median values) of serum P1NP and CTX during treatment of postmenopausal women with low bone mass with monthly subcutaneous injections of romosozumab 210 mg. Arrows indicate the time of injections. Adapted from data reported by McClung *et al.*[7]

neutralizing antibodies. Similar results were reported with multiple injections of blosozumab, illustrating that this is a general phenomenon of sclerostin inhibition in humans.

An explanation of the pattern of changes of bone turnover markers with romosozumab treatment is not readily available. On the basis of studies of patients with genetically determined sclerostin deficiency, we hypothesized earlier that the long-term response to exogenously administered inhibitors of sclerostin may be more complex and different from that observed in short-term studies of animals and humans.[8] The stabilization of the clinical course of sclerosteosis and van Buchem disease in adulthood and the negative relationship between serum P1NP and age in patients and disease carriers suggested that in sclerostin deficiency bone formation is not elevated to the same extent throughout life and that the lack of sclerostin does not stimulate bone formation at the same rate with time.[8,9] This may be due to the available pool of osteoblasts (high in the growing skeleton and lower in the mature skeleton), as sclerostin is produced at late stages of the mineralization process. These observations raise the question of whether prolonged treatment with a sclerostin inhibitor will be associated with a sustained anabolic effect on bone or whether the stimulatory effect on bone formation will be attenuated with time.

The progressive decrease in stimulation of bone formation observed by McClung *et al.* is consistent with the latter notion but a study of the changes in BMD and bone markers during the second year of treatment is needed to confirm or reject the hypothesis. Furthermore, available results showed that the initial rapid effect on bone formation following sclerostin inhibition is associated with decreased bone resorption, possibly through an effect on the production of RANKL/OPG by the osteocytes.[10] With treatment prolongation, however, it appears that the antibody acts as a mild inhibitor of bone resorption and remodeling. It may, therefore, be that the initial very positive bone balance induced by treatment is followed by a mild reduction of the remodeling space.

The findings of McClung *et al.* establish romosozamab as a novel treatment for postmenopausal osteoporosis, the full efficacy and tolerability of which should await the results of the phase 3 clinical studies. Additional short- and long-term pharmacodynamic studies are clearly warranted. Such studies are not only of theoretical interest in understanding the mechanism of action of sclerostin inhibitors but can also help to determine the optimal period of administration of the antibodies.

Conflict of Interest

Dr Papapoulos is a member of an Advisory Board of Amgen and UCB.

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