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Salvatore Minisola

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EXPERT OPINION

Romosozumab: from basic to clinical aspects

Salvatore Minisola
"Sapienza" Rome University, Department of Internal Medicine and Medical Disciplines, Rome, Italy

The Wnt pathway has an important role in bone formation. Inactivation of sclerostin, an inhibitor of this pathway, has been associated with increased bone mass both in animal experiments and in human clinical trials. Romosozumab is a humanized monoclonal antibody targeting sclerostin. Preclinical studies showed that this antibody primarily increases bone formation resulting in increased bone mineral density. Initial studies carried out in humans are in line with data obtained in animals. If these results are confirmed in larger studies with fracture end-points, this monoclonal antibody with its anabolic action, will become a key drug in the treatment of osteoporosis.

Keywords: anabolic therapy, osteoporosis, romosozumab, sclerostin

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1. Introduction

Osteoporosis, with its complication of fractures, represents a significant clinical concern in terms of both morbidity and mortality. Treatment and prophylaxis of this disease has mainly relied until a few years ago on antiresorptive agents. These drugs (such as estrogens, bisphosphonates and, more recently, denosumab) reduce the rate of bone resorption followed by a decrease in the rate of bone formation due to the coupling between these two processes and after about 6 months a new equilibrium between the two phases of bone remodeling is reached at a lower rate. These changes are associated with moderate increases in bone mineral density and maintenance or some improvement of structural and material properties of bone leading to reduction of bone fragility [1]. Long-term increases in bone mass are largely secondary to an increase in mineralization density, a result of reduced bone turnover.

Recently, the attention has been focused on pharmacological interventions not limiting bone resorption (acting on osteoclast) but augmenting skeletal formation (acting on osteoblasts). Anabolic drugs have the capacity to increase bone mass to a greater extent than traditional antiresorptive agents. Indeed, they are able to improve bone quality and strength; these effects may be derived by favorable changes in microarchitectural features such as connectivity, density and geometric properties. Currently, anabolic therapy is limited to the use of parathyroid hormone (PTH) 1 – 34; the entire molecule is approved for the treatment of osteoporosis in Europe but is no more commercialized.

Some new anabolic drugs under development act in part through stimulation of the Wnt signaling pathway, an important metabolic route to drive osteoblast proliferation and commitment. An important component of this pathway is represented by sclerostin; this is a glycoprotein mainly secreted by osteocytes (and to a lesser extent by cementocytes and mineralized hypertrophic chondrocytes), which is a potent inhibitor of osteblastogenesis. Sclerostin secreted from osteocytes reaches the bone surface through the canaliculi where it binds to co-receptors LRP5 and LRP6; it prevents co-receptor colocalization with frizzled protein and Wnt, thereby reducing osteoblastogenesis and bone formation [2].

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There are two important very rare genetic diseases that help us to better understand the link between sclerostin and bone formation. Loss of function mutations in sclerostin is associated with an autosomal-recessive disorder termed sclerosteosis, which is characterized by progressive bone overgrowth and high bone mass; this disease has been mainly diagnosed among Afrikaners in South Africa [3] and in a few individuals and families in other parts of the world. Another, somewhat milder high bone mass genetic disease (van Buchem disease) was determined to be caused by a deletion downstream of the SOST gene (which encodes the sclerostin protein); this deletion results in a significant reduction in sclerostin expression. Patients with this disease are most uniquely found in a Dutch fishing village.

In addition, genetic studies have demonstrated that polymorphism in the SOST gene is associated with low bone mineral density (BMD) in older men and women, further suggesting a causal relationship between modified SOST expression and BMD. Finally, some authors [4,5] suggested that the effects of parathyroid hormone therapy in humans are mediated, at least in part, by a decrease in sclerostin.

2. Preclinical studies

Given the naturally occurring diseases showing the crucial role of sclerostin in bone heath, it was intuitive to explore the pharmacological inhibition of sclerostin by a monoclonal antibody in various animal models of bone disease, including conditions of bone loss, osteogenesis imperfecta and other bone diseases. The data obtained show a consistent effect of sclerostin antibody (Scl-Ab) to increase bone formation, bone mass and bone strength at different skeletal sites.

Some of the effects of Scl-Ab (romosozumab) on bone formation and resorption in animal models deserve, in our opinion, particular consideration. Specifically, Scl-Ab determined an increase of bone formation rate/bone surface on trabecular, endocortical and periosteal surfaces in aged ovariectomized rats. These increases derived from increases in bone mineral apposition rate and mineralizing surfaces, suggesting that this antibody increases both the number and the activity of osteoblasts [6]. Contrary to the results obtained on the formation side, the effect on bone resorption is not uniform. Indeed, tartrate-resistant acid phosphatase, considered to be a marker of osteoclast number [7], was reduced or unchanged by treatment in rodent experiments, while serum C-terminal telopeptide of type I collagen (CTx-1) was not affected by such a treatment. However, while there was such a variability in the response of systemic biomarkers of bone resorption, there was a uniform reduction of such markers at tissue level.

It is important to observe that Scl-Ab treatment of ovariectomized rats and adolescent male monkeys was able to increase trabecular bone formation on quiescent surfaces, suggesting that Scl-Ab/romosozumab stimulates modeling-based bone formation without the need of prior activation of bone resorption as it occurs in bone remodeling. Furthermore, Scl-Ab can also extend the new bone formation to cover over the quiescent surfaces near the pre-resorptive surface [8].

Preclinical investigations performed with antisclerostin therapy in monkeys are of highest implication since they constitute the basis for the evaluation of romosozumab in humans. One of these studies [9] was carried out in gonadal-intact adolescent female cynomolgus monkeys, by administering two once-monthly doses of the antibody in three different dosages. Bone formation markers increased significantly in a dose-dependent manner without clear changes in bone resorption markers. Histomorphometric parameters confirmed the positive effect on bone formation without detrimental effect on bone resorption. These data obtained following only two doses of Scl-Ab are consistent with increased recruitment, activation and survival of osteoblasts [2]. Finally, in a model of fibular osteotomy in monkeys, Scl-Ab treatment resulted in an increase in callus size and an increase in both bone mass and strength at the site of fracture and in nonfractured bone [10].

3. Effects of Scl-Ab in humans

The first study was carried out in healthy men and postmenopausal women. A single administration of Scl-Ab increased in a dose-dependent manner markers of bone formation while decreasing the circulating levels of CTx-1 [11]. These findings are of particular importance because they indicate the possibility of having a pharmacological option that simultaneously increases bone formation and decreases bone resorption. This pattern is different from the behavior of biochemical markers of bone turnover following PTH 1 – 34 [1] and is consistent with the histomorphometric data obtained in animal models. Subsequent to this initial investigation, a Phase II randomized, placebo-controlled study has been recently published [12]. The main findings of this study indicate that all the doses of romosozumab investigated (70, 140, 210 mg monthly or 140 and 210 mg every 3 months) were associated with significant increases of BMD at the lumbar spine, total hip and femoral neck. The largest gains were observed with the 210 mg monthly dose of romosozumab, with mean increases from baseline to 12 months of 11.3% at the lumbar spine, 4.1 at the total hip and 3.7% at the femoral neck. Of note, these increases were significantly greater than those observed in the group treated with alendromate or teriparatide. The BMD of the distal third of the radius remained essentially unchanged during all the treatment period. Interestingly markers of bone formation increased very rapidly after the first dose and then declined; by month 6, markers of bone formation declined to basal values despite continuous treatment with romosozumab. Markers of skeletal resorption decreased in the first week of treatment and remained suppressed as long as the drug was administered [13]. As we outlined before, this behavior is unique and profoundly differs from what is

observed with current anabolic and antiresorptive therapies; furthermore, these atypical changes of bone turnover markers were accompanied by continuous sustained increase at both hip and lumbar sites.

Recently, a paper has been published in which different doses of romosozumab were administered, every 2 or 4 weeks The authors demonstrated that mean serum romosozumab exposure increased approximately in a dose-dependent manner; then they were also able to confirm the biochemical and densitometric data of previous papers. Importantly, the development of neutralizing antibodies had no discernible effects on pharmacokinetics, pharmacodynamics or safety [14].

4. Expert opinion

There are a number of factors that should be kept in mind when prescribing a drug in patients with osteoporosis. Among these, the most important are the efficacy in reducing the incidence of vertebral, hip and nonhip nonvertebral fractures; the modalities and schedule of administration in order to facilitate adherence; the absence of side effects and the cost. At this point in time, we do not have all the abovementioned parameters to fully judge romosozumab. However, from the published studies, we know that administration is once monthly or every three months [12,14], a schedule that can be considered very promising. Furthermore, side effects have been reported to be similar between patients treated with the antibody or placebo, even though the small number of subjects treated for a short interval of time preclude definitive conclusions; understanding the safety of romosozumab must await the results of the larger Phase III clinical trials. Concerning reduction of fractures, data on bone mineral density are very promising and it is hoped that such important increases obtained in a very short period of time might be translated into a reduced incidence of fractures. In this context, data of biochemical markers of bone turnover are particularly intriguing since this agent might be the first that positively uncouples the processes of bone formation and resorption. The two Phase III studies that are underway will give us conclusive data on the reduction of fracture. Concerning the cost, it is premature to argument this issue; however, this should be considered a key referent parameter if a large utilization is anticipated in a condition often regarded as an 'epidemic disease'. Finally, other aspects are ill-defined at present (i.e., duration of treatment, side effects on the long term, etc.); in addition, the drug should be tested in specific subgroups as has also reported for other compounds [15], in those who have been already exposed to other bone active drugs or in those with particularly disabling forms of osteoporosis, such for example glucocorticoid-induced osteoporosis, an ideal field for an anabolic drugs [16,17].

We are at the beginning of the history as far as human studies are concerned. However, if BMD data are paralleled by fracture data and safety profile proves to be reassuring in the long term, this drug will represent a cornerstone of treatment in subjects with reduced bone strength.

Declaration of interest

S Minisola served as speaker for Abiogen, Amgen, Bruno Farmaceutici, Eli Lilly, Italfarmaco, Merck Sharp & Dohme. He also served in the advisory board of Eli Lilly and Merck Sharp & Dohme. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Affiliation

Salvatore Minisola
"Sapienza" Rome University, Department of Internal Medicine and Medical Disciplines, Via del Policlinico 155, 00161 Rome, Italy
Tel: +39 06 49978388;
Fax: +39 06 49978365;
E-mail: salvatore.minisola@fastwebnet.it