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MINIREVIEWS

Effects of sclerostin antibody on bone healing

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Abstract

Promoting bone healing after a fracture has been a frequent subject of research. Recently, sclerostin antibody (Scl-Ab) has been introduced as a new anabolic agent for the treatment of osteoporosis. Scl-Ab activates the canonical Wnt (cWnt)-β-catenin pathway, leading to an increase in bone formation and decrease in bone resorption. Because of its rich osteogenic effects, preclinically, Scl-Ab has shown positive effects on bone healing in rodent models; researchers have reported an increase in bone mass, mechanical strength, histological bone formation, total mineralized callus volume, bone mineral density, neovascularization, proliferating cell nuclear antigen score, and bone morphogenic protein expression at the fracture site after Scl-Ab administration. In addition, in a rat critical-size femoral-defect model, the Scl-Ab-treated group demonstrated a higher bone healing rate. On the other hand, two clinical reports have researched Scl-Ab in bone healing and failed to show positive effects in the femur and tibia. This review discusses why Scl-Ab appears to be effective in animal models of fracture healing and not in clinical cases.

Key Words: Canonical Wnt-β-catenin pathway; Fracture healing; Osteoporosis; Romosozumab; Sclerostin antibody

Core Tip: Sclerostin antibody (Scl-Ab) has been recently introduced for the treatment of osteoporosis. Several researchers have reported on the effects of Scl-Ab in bone fracture healing because of its rich osteogenic potential. In this review, we describe the latest reports of preclinical and clinical studies on the bone-healing effects of Scl-Ab.

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INTRODUCTION

Achieving robust bone healing is the ultimate goal in the treatment of bone fractures. The development of methods to promote fracture healing has been a frequent subject of research. Recently, the safety of several osteoporosis drugs has been established in large-scale clinical trials, and it is expected that these drugs could be converted to fracture treatment. In experimental studies, some agents used to treat osteoporosis have had a positive effect on the promotion of bone healing, including parathyroid hormone (PTH), bisphosphonates, and sclerostin antibody (Scl-Ab).

Romosozumab, an Scl-Ab for humans, which recently has been developed for the treatment of osteoporosis, is an anabolic agent that stimulates bone formation. The difference between Scl-Ab and PTH_{1-34} (teriparatide), a former anabolic agent, is that teriparatide increases both bone formation and resorption *via* PTH-PTH receptor signaling, whereas Scl-Ab increases bone formation and simultaneously decreases bone resorption *via* canonical Wnt (cWnt)-β-catenin signaling[1]. This difference shows that the bone formation by PTH_{1-34} is primarily "remodeling-based" and that by Scl-Ab is primarily "modeling-based"[2,3].

In this review, we describe how Scl-Ab effects the cWnt-β-catenin pathway to stimulate bone formation and then discuss the current experimental and clinical evidence in bone healing.

SCLEROSTIN AND THE CANONICAL WNT/BETA-CATENIN PATHWAY IN BONE METABOLISM

The cWnt-β-catenin pathway plays an important role in bone metabolism, including skeletal development and homeostasis and bone remodeling[4]. The pathway is activated by the binding of Wnt proteins to receptor complexes composed of frizzled receptors and co-receptors of the low-density lipoprotein receptor-related protein (LRP) family, LRP5 and LRP6. This event increases the level of β-catenin and induces its translocation to the nucleus and activates the transcription of gene; it further accelerates the differentiation of osteoblast precursors and promotes the maturation of osteoblast and their survival, leading to osteogenesis by the increased and activated osteoblasts. On the other hand, the increased level of β-catenin results in an increased expression of osteoprotegerin, which binds to RANKL as a decoy receptor, preventing the binding of RANKL and RANK. Osteoclast activation and differentiation, which lead to bone resorption, occurs in the presence of RANKL-to-RANK binding. Thus, the activation of this pathway leads to increased bone formation by the increased and activated osteoblasts and to decreased bone resorption due to the disturbed binding of RANKL to RANK[5-7].

In the regulation of the cWnt-β-catenin pathway, osteocytes play an important role as producers and targets of Wnt ligands and as secretors of molecules that regulate Wnt action[8]. One regulation mechanism is the secretion of sclerostin, a potent antagonist of Wnt signaling. Sclerostin is a protein encoded by the *SOST* gene primarily expressed by mature osteocytes, but not by early osteocytes or osteoblasts [9]. Sclerostin binds to the Wnt co-receptors LRP5/LRP6, antagonizing downstream signaling in the cWnt-β-catenin pathway[10]. Thus, when the stoichiometry levels of sclerostin overwhelms the levels of the Wnt ligands, the signals will not be activated, leading to β-catenin degradation, lower bone formation, and higher bone resorption. On the other hand, when the stoichiometry levels favor in Wnt ligands than sclerostin, Wnt-β-catenin signaling will be activated, leading to stabilized β-catenin for translocation to the nucleus and the activation of target genes to increase bone formation and decrease bone resorption[2]. In addition, not only LRP 5 and 6, but also LRP4 was associated with bone homeostasis by interacting with sclerostin; mutation of LRP4, impairing interaction with sclerostin was found in patients suffering from bone overgrowth[11]. Thus, sclerostin is established as a bone formation inhibitor, though the molecular mechanisms are not fully understood.

In humans, the absence of sclerostin expression or secretion causes an abnormally high bone mass. These conditions have been seen in the rare hereditary diseases sclerosteosis and van Buchem disease. Sclerosteosis was first described by Truswell as osteopetrosis with syndactyly and is mostly seen in patients in South Africa; van Buchem disease was described by van Buchem as hyperostosis corticalis generalisata familiaris and is mostly found in patients in the Netherlands[12,13]. In both diseases, the *SOST* gene encoding sclerostin was identified as the gene responsible; a loss-of-function mutation occurs in sclerosteosis, and the downregulation of the expression of the *SOST* gene occurs in van Buchem disease[14]. Bone mineral density (BMD) and bone strength are significantly higher in patients with these diseases than those in the general population[15,16]. In experimental reports using mice, genetic deletion of the *SOST* gene or neutralizing antibodies for sclerostin duplicated the high bone mass found in humans lacking sclerostin[17-19]. Conversely, sclerostin overexpression leads to a decrease in bone mass[20-22].

SCLEROSTIN ANTIBODY THERAPY AND OSTEOPOROSIS

As the mechanisms of sclerostin and the cWnt-β-catenin pathway were elucidated, improvement in bone mass became the expected outcome of inhibiting the action of sclerostin. In a study using a model of ovariectomized rats with postmenopausal osteoporosis treated with Scl-Ab, researchers found a significant increase in bone formation on the trabecular, periosteal, endocortical, and intracortical surfaces. Furthermore, osteoblast and mineralizing surfaces increased, while the osteoclast surface decreased. These results suggest that the use of Scl-Ab increased bone formation and decreased bone resorption for osteoporosis[23]. In another study evaluating the effects of the osteoblast lineage in young rats with Scl-Ab and PTH_{1-34}, the osteoblastic surface and estimated total number of osteoblasts increased to similar levels in both the Scl-Ab and PTH_{1-34} groups at week 4. However, both parameters decreased in the Scl-Ab group while maintaining in the PTH_{1-34} group at week 26. Similarly, the osteoprogenitors increased to similar levels in both groups at week 4, and only those in the Scl-Ab group decreased at week 26. Interestingly, the percentage of labeled perimeter of the periosteal surface of the femur diaphysis was higher in the Scl-Ab group at both weeks 4 and 26, and the percentage of labeled perimeter of the endocortical surface was at the same level at week 4 and was higher in the Scl-Ab group at week 26. These results suggest that Scl-Ab strongly increases the differentiation induction of osteoprogenitors to osteoblasts, while increase of osteoprogenitors are only seen in the early stages of administration. While, PTH_{1-34} increases both the differentiation induction of osteoprogenitors to osteoblasts and the number of osteoprogenitors at similar levels throughout the administration period, although the level of bone formation was similar or even higher in Scl-Ab than in PTH_{1-34}[24].

In cynomolgus monkeys, treatment with Scl-Ab led to increase in BMD and bone strength just like in the rats. No increase in bone resorption markers was noted, while a significant increase in bone formation markers was demonstrated, also suggesting the distinct effects of modeling-based bone formation associated with Scl-Ab, differing from remodeling-based bone formation by PTH_{1-34} in which osteoblast-mediated bone formation follows osteoclast-mediated bone resorption[25]. Summarizing the difference between Scl-Ab and PTH, with Scl-Ab, bone formation is seen with no increase or even some decrease of bone resorption. The effect of bone formation is stronger in the early stages of administration and decreases with longer administration due to lack of osteoprogenitors after the strongly accelerated differentiation to osteoblasts. With PTH, bone formation is also seen with increase of bone resorption (relatively higher formation than resorption). Bone formation is similar in any stage of administration due to increase in both number of osteoprogenitors and differentiation to osteoblasts.

Romosozumab, a Scl-Ab agent for humans, has recently become commercially available for clinical use. A phase III clinical trial has shown that romosozumab strengthened osteoporotic bone by increasing BMD and decreased the incidence of new fractures. The Fracture Study in Postmenopausal Women with Osteoporosis trial evaluated the 12-month efficacy of romosozumab as compared with the placebo. The risk of vertebral fracture was reduced by 73% at 12 mo (incidence, 0.5% in the romosozumab group *vs* 1.8% in the placebo group, $P < 0.001$), and the risk of clinical fracture was reduced by 36% at 12 mo (incidence, 1.6% in the romosozumab group *vs* 2.5% in the placebo group, $P = 0.008$). The percentage of change in BMD from baseline was 13.3% greater in the lumbar spine, 6.9% greater in the total hip, and 5.9% greater

in the femoral neck in the romosozumab group than in the placebo group. An increase in the bone formation marker P1NP was seen in the romosozumab group, and a decrease in the bone resorption marker β-CTX was seen early in treatment, suggesting modeling-based bone formation[26]. Similar results of increased bone formation and strength, decreased fracture risk, and increased levels of bone formation markers with decreased levels of bone resorption markers have been shown in other phase III trials (ARCH trial, romosozumab *vs* alendronate; STRUCTURE trial, romosozumab *vs* teriparatide)[1,27].

SCLEROSTIN ANTIBODY THERAPY AND BONE HEALING

Preclinical evidence

Bone healing is a complex process controlled by numerous cellular signaling pathways regulated by factors expressed in a time and concentration-dependent manner. The cWnt-β-catenin pathway is one of the most critical signaling pathways involved in bone healing[28-30]. The peak of upregulation was from 7 to 14 d in rat models[31,32]. Upregulating and/or controlling the cWnt pathway along with the levels of β-catenin have the potential of accelerating bone healing. Bone healing occurs in two different mechanisms; intramembranous or endochondral bone formation. Marsell *et al*[33] reported Wnt-responsive cells were not observed near the marrow cavity but seen over the periosteal callus, presuming that the cWnt-β-catenin pathway associates with endochondral bone formation rather than intramembranous bone formation. Liedert *et al*[34] suggested that Wnt inhibitors play a role in delayed union and Montjovent *et al* [35] demonstrated non-rigid fixation of femoral defects caused increase levels of inhibitors of Wnt proteins. In non-rigid fixation, endochondral bone formation becomes the main healing process. Inhibiting the inhibitors of Wnt proteins and activating the cWnt-β-catenin pathway may help bone healing in such fractures.

The efficacy of Scl-Ab for bone healing has been demonstrated in several reports with animal models (Table 1). In a mouse tibial-shaft osteotomy model, both the sclerostin knockout and wild-type groups showed an increase in bone mass at the osteotomy site when Scl-Ab was administered[36]. Ominsky *et al*[37] observed in a rat femur fracture model that an increase in bone mass and mechanical strength at the fracture site occurred after 7 wk in the Scl-Ab group. The other researchers also reported similar positive effects of Scl-Ab for a rat femur fracture or osteotomy model [38,39]. Virdi *et al*[40] also observed that in a rat femoral bone ablation model with intramedullary fixation, there was a 1.9-fold increase in fixation strength at week 4 and a 2.2-fold increase at week 8 in the Scl-Ab group compared to the vehicle group. Furthermore, Yee *et al*[41] reported in a type 1 diabetes mellitus (T1DM) mouse model, administration of Scl-Ab mitigates inhibition of osteoblast differentiation caused by the diabetic state. They found a significant benefit in callus bone volume, increase in callus size and a reverse of lower mineralization seen in T1DM mouse model. Studying the mechanisms for the fracture healing effect of Scl-Ab, Feng *et al* reported an increase in the proliferating cell nuclear antigen score and bone morphogenetic protein (BMP)-2 expression at weeks 1 and 2 in a femur osteotomy model in young rats. Furthermore, cartilage decreased and BMD and the mechanical strength of the callus associated with accelerated fracture healing increased at weeks 4 and 6[42].

As an evaluation outside the long tubular bone fracture model, Agholme *et al*[43] inserted screws into the proximal tibia of young rats and measured the pull-out strength; the Scl-Ab-treated group showed a 50% increase after 2 and 4 wk compared with the saline-treated group. They conducted the same experiment comparing with PTH, and the PTH group showed significant higher pull-out strength in the metaphyseal, while Scl-Ab significantly increased femoral cortical and vertebral strength[44]. In a rat model of distraction osteogenesis, no difference occurred in the rate of bone union between the Scl-Ab and control groups, but mechanical strength and bone mass increased in the Scl-Ab group, suggesting that the optimal effect of Scl-Ab treatment is achieved in the later stages of distraction osteogenesis[45]. In addition, in a rat critical-size femoral-defect model with a 6-mm femoral defect, 24% of the Scl-Ab-treated group had healed after 12 wk compared with no cases of healing in the control group[46]. Furthermore, in the treated group, systemic Scl-Ab administration plus local BMP-2 administration resulted in significantly more robust healing of critical-size femoral defects than did BMP-2 alone[47].

On the other hand, Kruck *et al*[48] negatively reported on the effects of Scl-Ab on bone healing. The author created rigid and semirigid fixation models for femoral osteotomy in rats. All groups showed an increase in bone mass, but no difference in

Table 1 The efficacy of sclerostin antibody for bone healing has been demonstrated in several reports with animal models

Animal model	Bone	Bone injury model	Dosage, frequency	Major findings	Ref.
Mouse	Tibia	Osteotomy	100 mg/kg, 1/wk	BV/TV↑, strength↑	[36]
Rat	Femur	Fracture	25 mg/kg, 2/wk	Callus↑, BMC↑, BV/TV↑, strength↑	[37]
Cynomolgus monkey	Fibula	Osteotomy	30 mg/kg, 1/2 wk	Callus↑, BMC↑, strength↑	[37]
Rat	Femur	Ablation	25 mg/kg, 2/wk	Fixation strength↑, cortical thickness↑, BV/TV↑	[40]
Rat	Femur	Fracture	25 mg/kg, 2/wk	BMD↑, BV/TV↑, strength↑, MS/BS↑, BFR/BS↑	[38]
Rat	Femur	Osteotomy	25 mg/kg, 2/wk	Callus↑, BMD↑, BV/TV↑, strength↑, bone area↑, cartilage↓	[39]
Mouse	Femur	Fracture	25 mg/kg, 2/wk	BV/TV↑, BMC↑	[41]
T1DM mouse	Femur	Fracture	25 mg/kg, 2/wk	BV/TV↑, BMC↑	[41]
Rat	Femur	Osteotomy	25 mg/kg, 2/wk	Mature callus↑, BMC↑, BMD↑, strength↑	[42]
Rat	Tibia	Metaphyseal screw	25 mg/kg, 2/wk	Pull-out strength↑, bone volume surrounding screw↑	[43]
Rat	Femur	Distraction osteogenesis	25 mg/kg, 2/wk	Union rate→, (united bones) strength↑, bone volume↑	[45]
Rat	Femur	Critical defect	25 mg/kg, 2/wk	Union rate↑, bone formation markers↑	[46]
Mouse	Femur	Osteotomy rigid fix	25 mg/kg, 2/wk	Periosteal and/or intracortical bridging→, endosteal bridging↑	[48]
Mouse	Femur	Osteotomy semi-rigid fix	25 mg/kg, 2/wk	Periosteal and/or intracortical bridging→, endosteal bridging↑	[48]

T1DM: Type 1 diabetes mellitus; BV/TV: Bone volume to total bone volume ratio; BMC: Bone mineral content; BMD: Bone mineral density; MS/BS: Mineralizing surface rate; BFR/BS: Bone formation rate.

delayed healing occurred with semirigid fixation between the Scl-Ab and control groups. In rigid fixation, Scl-Ab had more bridging of the endosteum, which adversely affected late healing, suggesting delayed callus remodeling and marrow reconstitution at the time of fracture. These results suggest that Scl-Ab promotes bone formation in the early stages of healing, but not in the advanced stages of fracture callus remodeling [48].

Clinical evidence

Two phase II clinical trials have reported the efficacy of romosozumab in adult fresh fractures. Bhandari *et al*[49] reported the efficacy of romosozumab in 402 patients with fresh unilateral tibial diaphyseal fractures (median age, 40 years; range, 18−82 years) who underwent fracture fixation with intramedullary nails. Patients were randomized to a placebo (n = 103) or one of nine different romosozumab groups (n = 299), with three different doses and frequencies of administration (doses: 70 mg, 140 mg, and 210 mg; administration: twice, postoperative day 1 and week 2; three times, postoperative days 1 and 2 and week 6; and four times, postoperative days 1 and 2 and weeks 6 and 12). The percentage of patients with a radiological cure, defined as the bridging of three of the four cortices as shown on the radiographs, which ranged from 63.2% to 84.7% at week 24 and from 83.4% to 96.7% at week 52 in the romosozumab group and from 76.1% at week 24 and 87.1% at week 52 in the placebo group. The estimated median time to radiological cure ranged from 14.4 to 18.6 wk in the romosozumab group and 16.4 wk in the placebo group. Thus, no significant difference occurred between both groups. In addition, no significant difference occurred in the time to clinical healing (defined as the ability to bear weight without pain at the fracture site) between the groups. Furthermore, the authors found no treatment effects of romosozumab on the incidence of unplanned revision surgery, physical function scores, or adverse events. The study concluded that romosozumab did not promote the healing of tibial fractures in this patient population.

Schemitsch *et al*[50] reported on a trial of romosozumab for the treatment of hip fractures in 332 patients (median age, 78 years; range 55−94 years). Patients were randomized to groups receiving a placebo (n = 89) or romosozumab at three different doses (70 mg, 140 mg, and 210 mg). Patients received subcutaneous romosozumab

injections on postoperative days 1, 2, 6, and 12, and the percentage of patients with radiographic evidence of healing ranged from 66.2% to 78.6% at week 24 and from 89.1% to 93.2% at week 52, with no significant difference between the treatment groups. In addition, no significant difference occurred in the estimated median time to radiographic evidence of healing neither between the groups nor in functional mobility assessment, radiographic fracture healing assessment, and hip pain scores. Similar to the results with patients with tibial fractures, romosozumab did not improve fracture healing in patients with hip fractures.

It is unclear why bone healing was not accelerated in humans. In both studies, romosozumab was administered starting on postoperative day 1. Since romosozumab promotes the differentiation of osteoblasts from osteoprogenitors with little increase in osteoprogenitors[24], it is possible that administering romosozumab early in the fracture healing process period is not ideally timed. Yukata *et al*[51] reported that *SOST* gene expression were more abundant in the hard callus in the later stages of bone repair than in the soft callus in the early stages in a mouse tibia fracture model, and PTH administration upregulated *SOST* expression as the hard callus increased. These suggest the need to change the starting point of administration and to consider the combination of romosozumab and PTH, which has the effect of increasing immature cells. Additionally, in both studies the patients were treated at sites for high surgical standards of care and they received rigid fixation. The quality of the surgery and care may out-weighed the effects of romosozumab on fracture healing[49,50]. Future studies may focus on healing of serious fractures, which could only accomplish relatively un-rigid fixation.

CONCLUSION

Despite the preclinical success of Scl-Ab in promoting fracture healing in animals, currently, no clinical evidence exists for the positive effects of Scl-Ab for bone healing in humans. As an osteogenic agent in osteoporosis, Scl-Ab offers promising effects supported by reliable evidence. Although the drug targets the same bone tissue, further research is needed on the differences in the pathogenesis of osteoporosis and fracture, spatio-temporal expression pattern of *SOST* according to bone healing process, and corresponding timing and interval of drug administration.

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