Published in final edited form as:

Curr Opin Rheumatol. 2014 July ; 26(4): 447–452. doi:10.1097/BOR.0000000000000073.

Inhibitors of Sclerostin – Emerging Concepts

Matthew T. Drake, M.D., Ph.D.^{1,*} and Joshua N. Farr, Ph.D.¹

Matthew T. Drake: Drake.Matthew@mayo.edu; Joshua N. Farr: Farr.Joshua@mayo.edu

¹Division of Endocrinology, Metabolism, Nutrition and Diabetes, Department of Medicine; Mayo Clinic, Rochester, MN, 55905, USA

Abstract

Purpose of review—Recent data suggest that inhibitors of sclerostin, an osteocyte-produced Wnt signaling pathway antagonist, can stimulate bone formation. This review provides rationale and summarizes recent evidence supporting this novel approach to skeletal anabolism.

Recent findings—Data from numerous pre-clinical models in rodents and monkeys consistently demonstrate that anti-sclerostin monoclonal antibody (Scl-Ab) treatment leads to improvements in bone mass and strength, as well as enhanced fracture repair. Delivery of Scl-Ab therapy either subcutaneously or intravenously in phase 1 and 2 human clinical trials demonstrates short-term anabolic responses in excess of those seen with teriparatide, the only currently available anabolic skeletal agent. Gains have been primarily at central (spine and hips) versus peripheral (wrist) sites. Strikingly, Scl-Ab treatment appears to both stimulate bone formation and inhibit bone resorption in humans. If proven, Scl-Ab would be the first pharmacologic agent with such dual properties. Data on fractures are not yet available.

Summary—Scl-Ab therapy represents a novel pharmacologic approach to skeletal anabolism. Although many questions remain before Scl-Ab treatment can be introduced into clinical practice, phase 3 human clinical trials are currently underway and could provide the necessary data to bring this exciting class of skeletal anabolic agents to patient care.

Keywords

sclerostin; monoclonal antibody; anabolic therapy; osteoporosis; bone formation

Introduction

Osteoporosis is a common skeletal disorder characterized by diminished bone mass and progressive microarchitectural deterioration. Collectively, these changes lead to decreased bone strength and result in an increased likelihood of fracture. As found in clinical practice, osteoporosis frequently reflects variable contributions from an array of factors such as aging, sex steroid deficiency, underlying disease, supraphysiologic corticosteroid dosing, or other pharmacologic insults. At the tissue level, such factors lead to a relative imbalance of

*Corresponding Author: Matthew T. Drake M.D., Ph.D., Division of Endocrinology, Metabolism, Nutrition and Diabetes, Department of Medicine; Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA; Drake.Matthew@mayo.edu; Tel: 507-266-0500; Fax: 507-293-3853.

Disclosure Statement: Neither author has a conflict to disclose.

osteoclast-mediated bone resorption and osteoblast-mediated bone formation, with disruption of normal skeletal homeostasis – consequently bone loss ensues.

Current pharmacologic approaches to the care of osteoporosis

To date, pharmacologic approaches for the treatment of osteoporosis have primarily focused on efforts to limit osteoclast-mediated bone resorption. The most commonly used agents are the nitrogen-containing bisphosphonates, pyrophosphate analogs which preferentially disseminate to skeletal sites of increased bone turnover where they are selectively endocytosed by osteoclasts during the resorptive process, ultimately inducing osteoclast apoptosis. Additional agents which act primarily to limit osteoclast activity include calcitonin, estrogen, and selective estrogen-receptor modulators, as well as the most recently approved anti-resorptive agent denosumab, a humanized monoclonal antibody against receptor-activator of nuclear factor kappa-b ligand (RANKL), which functions to inhibit osteoclast formation.

In the United States, a single approved anabolic skeletal agent (teriparatide) stands as a counterbalance to this armada of anti-resorptive agents. However, that may soon change. Indeed, as detailed in the remainder of this review, recent pre-clinical studies and early clinical trials examining therapies against sclerostin, an osteocyte secreted molecule only recognized to play a central role in bone metabolism within the past decade (Figure 1), may soon lead to the unveiling of a new anabolic skeletal agent to our pharmacologic armamentarium.

Sclerostin as an endogenous inhibitor of Wnt signaling

Much work over the past two decades has laid bare the central role of the Wnt/ β -catenin signaling pathway in osteoblast differentiation, proliferation, survival, and ultimately bone formation. Like many regulatory networks, Wnt signaling is modulated by a complex array of endogenous agonists and antagonists, the relative actions of which determine whether Wnt signaling (and thus bone formation) is stimulated or inhibited. Sclerostin was identified only about a decade ago as an osteocyte-secreted cysteine knot glycoprotein inhibitor of Wnt signaling whose loss of function produced skeletal dysplasias marked by high bone mass and increased bone formation rates [1]. Interestingly, in humans with heterozygous inactivating sclerostin mutations, serum sclerostin levels are roughly half of normal levels, but bone formation rates are significantly increased. Such findings immediately suggested that reduction of endogenous sclerostin levels may be a viable method to increase bone mass, and therefore quickly brought sclerostin to the forefront of efforts to identify the next anabolic skeletal agent.

Pre-clinical models of anti-sclerostin treatment on skeletal outcomes

Multiple studies performed over the past five years have used various models of skeletal disease to convincingly demonstrate that sclerostin inhibition by treatment with anti-sclerostin monoclonal antibodies can improve bone mass and bone strength, and enhance repair of fractures as well as both non-critical and critical size skeletal defects in mice and rats [2–7]. Likewise, a study which provided a humanized sclerostin-neutralizing

monoclonal antibody (Scl-Ab) subcutaneously to gonad-intact female cynomolgus monkeys demonstrated a clear dose-dependent anabolic effect on the skeleton, with increases in bone formation on trabecular, endocortical, intracortical, and periosteal surfaces [8], without negatively impacting bone matrix quality [9]. Interestingly, histomorphometric analyses in both rodents and monkeys demonstrate that Scl-Ab treatment increases modeling-based bone formation (occurring directly on quiescent surfaces) rather than remodeling-based bone formation (in response to bone resorption) [10]. Notably, this mechanism is in contrast to that seen with teriparatide treatment, in which both bone formation and resorption are both increased. Collectively, these pre-clinical data demonstrated a consistent anabolic skeletal effect of sufficient magnitude to justify the initiation of clinical trials to determine whether similar skeletal responses also occur in humans in response to Scl-Ab treatment.

Human studies with sclerostin-neutralizing monoclonal antibodies

While numerous studies in animal models have clearly demonstrated that pharmacological inhibition of sclerostin by administration of Scl-Ab leads to increased bone formation rates as well as significant improvements in bone mineral density (BMD) and bone structural strength [2–14], comparatively few studies in humans have been reported to date. In the first such human study [15], either placebo or a humanized monoclonal antibody to sclerostin (AMG 785 – later branded “romosozumab” by Amgen/UCB) was administered at various doses [i.e., subcutaneously (0.1, 0.3, 1, 3, 5, or 10 mg/kg) or intravenously (1 or 5 mg/kg)] to 72 healthy men and postmenopausal women (age range, 45 to 59 years) in a phase 1, single-dose, double-blind, placebo-controlled, randomized controlled trial. After 85 days of follow-up, no deaths or study discontinuations occurred, and only a single treatment-related serious adverse event (non-specific hepatitis) was reported. Thus, AMG 785 was generally well-tolerated and had minimal side effects.

Further, the single-dose effects of AMG 785 on bone metabolism and BMD were impressive [15]. Analyses of serum markers of bone turnover revealed dose-dependent increases in bone formation and decreases in bone resorption. Together, these divergent effects on bone metabolism created robust osteogenic responses as evidenced by significant increases in areal BMD derived from dual-energy X-ray absorptiometry (DXA) scans of the lumbar spine and hip in both men and women. Importantly, these findings suggest that Scl-Ab treatment is the first pharmacological approach with the ability to simultaneously stimulate bone formation and inhibit bone resorption in humans. Given the previously noted anabolic actions of Scl-Ab administration in various animal models [2–14], the observed increases in serum bone formation markers were expected. However, the latter finding of reduced serum levels of bone resorption markers was surprising given that the specific mechanism(s) responsible for this action is not known. Nevertheless, with these provocative findings, the stage was set to explore the utility of Scl-Ab treatment to prevent bone loss in longer duration studies.

The most convincing data to date demonstrating that pharmacological inhibition of sclerostin with Scl-Ab enhances bone health in humans come from a very recently published phase 2, multicenter, international, placebo-controlled, randomized controlled trial of the dose-related effects of romosozumab (AMG 785) on efficacy and safety over a 1-year period

in 419 postmenopausal women (age range, 55 to 85 years) [16]. In this study, women with low areal BMD (T-scores between -2.0 and -3.5 at the lumbar spine, total hip, or femoral neck) were randomized to one of eight groups: subcutaneous romosozumab once monthly (70 mg, 140 mg, or 210 mg) or every 3 months (140 mg or 210 mg), placebo injections every 3 months, or active comparator drugs at standard clinically used doses and schedules – an anabolic agent (teriparatide; 20 μ g once daily) or an anti-resorptive agent (alendronate; 70 mg once weekly). The primary and secondary study outcomes included safety, side effects, and changes in areal BMD and serum markers of bone turnover in the romosozumab-treated subjects as compared to subjects treated with placebo or the two active comparator drugs.

The study results were particularly noteworthy [16]. With the exception of mild injection-site reactions in response to subcutaneous romosozumab, side effects and adverse events were minimal and did not differ among groups. Thus, continuous administration of varying doses of romosozumab appears to be safe in humans, at least for up to 1 year. Further, in findings which virtually mirrored the previously studied single-dose regimen [15], significant increases in bone formation with simultaneous decreases in bone resorption were observed in subjects assigned to romosozumab. It is important to point out, however, that the early rapid peak in bone formation was only temporary (serum bone formation markers returned to baseline levels by 6 months), whereas the decrease in bone resorption was moderate, yet more sustained. The net result of these divergent effects was a strong positive balance in bone turnover. Consequently, all doses of romosozumab resulted in significant 1-year increases in DXA-derived areal BMD at the lumbar spine, with the higher doses appearing to be most effective (largest gain of 11.3% with the 210-mg monthly dose). Similar increases in areal BMD were observed at the total hip and femoral neck, but not at the wrist, in the groups randomized to romosozumab. By contrast, lesser changes were found in the placebo, alendronate, and teriparatide groups – consistent with their expected response profiles. Taken together, compared to placebo or active comparator agents, 1-year of romosozumab therapy was associated with a significant widening of the bone balance window, albeit only transiently, as well as impressive gains in DXA-derived areal BMD at the hip and lumbar spine in postmenopausal women with low bone mass [16].

Given the inability of DXA to measure bone structure or to distinguish between cortical and trabecular skeletal compartments, the effects of romosozumab on these parameters have been the subjects of additional recent research [17]. Indeed, in the same cohort of 419 postmenopausal women with low areal BMD described above [16], analysis of hip and lumbar spine quantitative computed tomography (QCT) scans revealed significantly increased volumetric (three-dimensional) BMD at both skeletal sites in women randomized to romosozumab as compared to those receiving either placebo or teriparatide [17]. The improvements in cortical and trabecular volumetric BMD at the hip and lumbar spine observed in these women lend further support to the continued investigation of romosozumab, as well as other Scl-Ab agents, in human clinical studies.

Given these impressive findings, it is of interest whether additional Scl-Ab drugs can be developed with similar success. Thus far, competition to romosozumab has been limited, although another humanized monoclonal antibody (branded “bloszumab” by Eli Lilly) has recently been developed to target and inhibit sclerostin. The first two phase 1 clinical studies

of this drug in humans were recently conducted to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of single and multiple escalating doses (administered intravenously or subcutaneously) [18]. Blosozumab was well-tolerated with no safety concerns, and dose-dependent increases were observed in serum markers of bone formation and in lumbar spine areal BMD at day 85. Thus, similar to romosozumab, blosozumab appears to be safe and exhibited anabolic effects on bone density, lending further support to investigation of this drug as an alternative anabolic skeletal therapy.

This study also tested the important question of whether prior/current exposure to bisphosphonate therapy would alter the response to Scl-Ab treatment [18]. Indeed, many in the target osteoporotic population will have taken bisphosphonates, which can remain buried in the skeleton for many years, and previous data suggest the anabolic skeletal effects of teriparatide are blunted in patients with prior anti-resorptive exposure [19]. Interestingly, prior bisphosphonate use did not appear to significantly impact blosozumab-mediated effects on bone formation and BMD responses [18]. Nevertheless, because these data are preliminary, future studies will be needed to fully address this issue.

The effects of subcutaneous administration of blosozumab have also been examined in postmenopausal women (mean age 62 years) with low areal BMD (lumbar spine T-score between -2.0 and -3.5) in a phase 2, double-blind, placebo-controlled, randomized, multicenter, 1-year dosing study with four treatment groups (all of which received concomitant calcium and vitamin D supplementation): 1) placebo; 2) blosozumab 180 mg every 4 weeks; 3) blosozumab 180 mg every 2 weeks; or 4) blosozumab 270 mg every 2 weeks [20]. The primary and secondary study endpoints were changes in estimates of hip and lumbar spine strength as determined by finite element analysis of QCT images. Despite the relatively small sample size ($n = 42$), blosozumab increased bone strength at both the hip and lumbar spine in postmenopausal women with low BMD, with a statistically significant positive dose-response effect at both skeletal sites [20]. In addition, adverse events were similar across groups, with the exception of mild injection-site reactions which were more frequently observed in subjects randomized to blosozumab versus placebo.

Open questions regarding anti-sclerostin therapies

Notwithstanding these promising results from human studies, many important questions about Scl-Abs as pharmacologic agents remain unresolved [21]. For example, will it be safe for patients to take these agents for longer periods of time given that the longest study duration reported thus far has only been one year [16]? Will additional side effects (such as cranial nerve impingement due to the robust bone formation that occurs) emerge with longer duration of use given that in the short-term studies reported, side effects and adverse events have been minimal [15,16,18]? What are the ramifications of the transient increase in bone formation with regard to a dosing regimen and to any potential long-term changes in bone strength? Why are central skeletal sites (spine and hip) responsive, whereas peripheral sites (wrist) unresponsive, during one year of treatment with romosozumab, and does blosozumab have this same property [16]? Does Scl-Ab treatment effect bone structural parameters or the ability to restore bone microarchitecture? Will long-term (>1 year) changes in bone be maintained longitudinally? Finally, will the noted changes in skeletal parameters translate

into anti-fracture efficacy? These as well as many other questions will undoubtedly serve as the focus of ongoing and future clinical studies. Indeed, a phase 3 randomized controlled trial is currently underway to examine both the safety and anti-fracture efficacy of romosozumab in postmenopausal women with osteoporosis (ClinicalTrials.gov number, NCT01631214).

Potential role for Scl-Ab therapies in other disorders with skeletal effects

The findings of these relatively short-term studies in humans certainly hold promise for preventing age-associated osteoporosis and reducing the burden of fractures. It is important to ask, however, whether a role for Scl-Ab therapies may exist for patients with other medical disorders which routinely affect the skeleton. Although this answer remains unknown, the long-term effects of Scl-Ab on bone health and anti-fracture efficacy in patients with conditions that negatively affect the skeleton (i.e., prolonged immobilization, corticosteroid treatment, diabetes, malignancy, etc.) should be the focus of future research efforts. Importantly, a phase 3 clinical trial examining the effects of Scl-Ab treatment on bone turnover, skeletal parameters, and fracture outcomes is currently ongoing in patients with chronic renal insufficiency (ClinicalTrials.gov number, NCT01833754). We anticipate the conduct of such studies will broaden the clinical applicability of Scl-Ab treatments, while providing further evidence regarding anti-fracture efficacy, optimal dosing and duration of treatment, and long-term safety in humans.

Conclusion

In summary, the exciting pre-clinical and early human clinical trial data presented herein clearly pinpoint sclerostin as a promising target for new anabolic bone therapeutics [22]. As shown in studies in both animals and humans, sclerostin inhibition with Scl-Ab (Figure 1) results in significant improvements in bone health owing to simultaneous increases in bone formation and decreases in bone resorption. It is particularly noteworthy that no previous single pharmacologic agent has demonstrated these divergent effects on bone metabolism. Importantly, this unprecedented widening of the bone balance window permits additional new bone to be deposited – thereby potentially allowing for restoration of the complex microarchitecture, and biomechanical integrity, of the skeleton late in life. Although the mechanism(s) responsible for these unique changes remain largely unclear [22], Scl-Ab therapy has emerged as a potential breakthrough approach for slowing and potentially reversing age-related bone loss. However, before this class of agents can be introduced into clinical practice, additional studies are needed to provide answers to important unresolved questions regarding the long-term efficacy and safety of Scl-Ab therapies for the treatment of osteoporosis and other skeletal disorders.

Acknowledgments

Grant Support: The authors are supported by the following grants: NIH K08 AR059138 (M.T.D), and NIH T32 DK007352 (J.N.F).

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest

- of outstanding interest

1. Williams BO. Insights into the mechanisms of sclerostin action in regulating bone mass accrual. *J Bone Miner Res.* 2014; 29:24–28. [PubMed: 24285419]
2. Li X, Warmington KS, Niu QT, et al. Inhibition of sclerostin by monoclonal antibody increases bone formation, bone mass, and bone strength in aged male rats. *J Bone Miner Res.* 2010; 25:2647–2656. [PubMed: 20641040]
3. Ominsky MS, Li C, Li X, et al. Inhibition of sclerostin by monoclonal antibody enhances bone healing and improves bone density and strength of nonfractured bones. *J Bone Miner Res.* 2011; 26:1012–1021. [PubMed: 21542004]
4. Hamann C, Rauner M, Hohna Y, et al. Sclerostin antibody treatment improves bone mass, bone strength, and bone defect regeneration in rats with type 2 diabetes mellitus. *J Bone Miner Res.* 2013; 28:627–638. [PubMed: 23109114]
5. Spatz JM, Ellman R, Cloutier AM, et al. Sclerostin antibody inhibits skeletal deterioration due to reduced mechanical loading. *J Bone Miner Res.* 2013; 28:865–874. [PubMed: 23109229]
6. Virk MS, Alaei F, Tang H, et al. Systemic administration of sclerostin antibody enhances bone repair in a critical-sized femoral defect in a rat model. *J Bone Joint Surg Am.* 2013; 95:694–701. [PubMed: 23595067]
7. Agholme F, Macias B, Hamang M, et al. Efficacy of a sclerostin antibody compared to a low dose of PTH on metaphyseal bone healing. *J Orthop Res.* 2014; 32:471–476. [PubMed: 24243768]
8. Ominsky MS, Vlasseros F, Jolette J, et al. Two doses of sclerostin antibody in cynomolgus monkeys increases bone formation, bone mineral density, and bone strength. *J Bone Miner Res.* 2010; 25:948–959. [PubMed: 20200929]
9. Ross RD, Edwards LH, Acerbo AS, et al. Bone matrix quality following sclerostin antibody treatment. *J Bone Miner Res.* 2013 Jan 28. Epub ahead of print Edited by. 10.1002/jbmr.2188
- 10. Ominsky MS, Niu QT, Li C, Li X, Ke HZ. Tissue level mechanisms responsible for the increase in bone formation and bone volume by sclerostin antibody. *J Bone Miner Res.* 2013 Nov 19. doi. 1002/jbmr.2152 [Epub ahead of print] Study using histomorphometry to demonstrate that the increase in bone parameters that occurs with Scl-Ab treatment primarily reflects bone formation on quiescent surfaces (bone modeling) rather than bone remodeling (in which bone formation occurs in response to bone resorption).
11. Li X, Ominsky MS, Warmington KS, et al. Sclerostin antibody treatment increases bone formation, bone mass, and bone strength in a rat model of postmenopausal osteoporosis. *J Bone Miner Res.* 2009; 24:578–588. [PubMed: 19049336]
12. Eddleston A, Marenzana M, Moore AR, et al. A short treatment with an antibody to sclerostin can inhibit bone loss in an ongoing model of colitis. *J Bone Miner Res.* 2009; 24:1662–1671. [PubMed: 19419292]
13. Tian X, Jee WS, Li X, Paszty C, Ke HZ. Sclerostin antibody increases bone mass by stimulating bone formation and inhibiting bone resorption in a hindlimb-immobilization rat model. *Bone.* 2011; 48:197–201. [PubMed: 20850580]
14. Marenzana M, Greenslade K, Eddleston A, et al. Sclerostin antibody treatment enhances bone strength but does not prevent growth retardation in young mice treated with dexamethasone. *Arthritis Rheum.* 2011; 63:2385–2395. [PubMed: 21484764]
15. Padhi D, Jang G, Stouch B, Fang L, Posvar E. Single-dose, placebo-controlled, randomized study of AMG 785, a sclerostin monoclonal antibody. *J Bone Miner Res.* 2011; 26:19–26. [PubMed: 20593411]
- 16. McClung MR, Grauer A, Boonen S, et al. Romosozumab in postmenopausal women with low bone mineral density. *N Engl J Med.* 2014; 370:412–420. First phase 2 randomized controlled

trial of anti-sclerostin monoclonal antibody on efficacy and safety in postmenopausal women showing divergent effects on bone metabolism. [PubMed: 24382002]

17. Genant, HK.; Boonen, S.; Bolognese, MA., et al. ASBMR. Oct 6. 2013 Effect of romosozumab on lumbar spine and hip volumetric bone mineral density (vBMD) as assessed by quantitative computed tomography (QCT).
- 18. McColm J, Hu L, Womack T, Tang CC, Chiang AY. Single- and multiple-dose randomized studies of blosozumab, a monoclonal antibody against sclerostin, in healthy postmenopausal women. J Bone Miner Res. 2013 Aug 31. Epub ahead of print. First phase 1 study of blosozumab on safety and tolerability, pharmacokinetics, bone turnover markers, and bone mineral density in humans. 10.1002/jbmr.2092
19. Boonen S, Marin F, Obermayer-Pietsch B, et al. Effects of previous antiresorptive therapy on the bone mineral density response to two years of teriparatide treatment in postmenopausal women with osteoporosis. J Clin Endocrinol Metab. 2008; 93:852–860. [PubMed: 18160462]
20. Keaveny, T.; Myers, S.; Chiang, A., et al. ASBMR. Oct 5. 2014 Effects of blosozumab on estimated spine and hip strength in postmenopausal women with low bone mineral density: finite element analysis of a phase-II dosing study.
21. Becker CB. Sclerostin inhibition for osteoporosis--a new approach. N Engl J Med. 2014; 370:476–477. [PubMed: 24382003]
- 22. Ke HZ, Richards WG, Li X, Ominsky MS. Sclerostin and Dickkopf-1 as therapeutic targets in bone diseases. Endocrine Reviews. 2012; 33:747–783. More detailed summary of the underlying mechanisms mediating anti-sclerostin monoclonal antibody actions in bone. [PubMed: 22723594]

Key points

1. Inhibition of sclerostin, an osteocyte secreted antagonist of the Wnt signaling pathway within osteoblasts, increases bone mass and strength in pre-clinical (rodent and monkey) models.
2. Recent phase 2 randomized clinical trial data examining humanized sclerostin-neutralizing monoclonal antibodies demonstrate robust skeletal anabolic effects at central (hips and spine) sites, with minimal side effects.
3. Anti-sclerostin monoclonal antibody treatment appears to be the first pharmacologic approach in humans to simultaneously stimulate bone formation and inhibit bone resorption.
4. A large phase 3 international, double-blind, randomized controlled clinical trial examining the safety and anti-fracture efficacy of anti-sclerostin monoclonal antibody therapy in postmenopausal women with osteoporosis is currently underway, with estimated study completion in early 2017.

Figure 1.

In the presence of sclerostin-neutralizing monoclonal antibodies (Scl-Ab), the osteocyte-produced Wnt signaling pathway antagonist sclerostin is prevented from binding to the Wnt co-receptor LRP5/6. Sclerostin sequestration allows the Wnt signaling pathway agonist Wnt to bind to the Frizzled-LRP5/6 complex, thereby stimulating Wnt pathway signaling within osteoblasts to increase osteoblast activity and ultimately promote increased bone formation.