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CORR Insights®: Does Sclerostin Depletion Stimulate Fracture Healing in a Mouse Model?

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Where Are We Now?

Pathologic and traumatic bone fractures would greatly benefit from a safe and consistent pharmacological agent. While most

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pharmacologic approaches exclusively target osteoclast activity (bisphosphonates and denosumab), sclerostin-neutralizing monoclonal-antibody (Scl-Ab) injections are gaining traction as a potential anabolic treatment to improve bone-healing and increase bone mass [5, 6, 8, 10]. Deficiency of sclerostin, which is secreted by osteocytes to target the Wnt pathway in osteoblasts, augments bone formation and strength in rodents and monkeys [4, 9]. In Phase I and II clinical trials, Scl-Ab treatment (romosozumab [Amgen/UCB, Thousand Oaks, CA, USA] and blosozumab [Eli Lilly & Co, Indianapolis, IA, USA]) [1, 6, 10] also increases bone formation with minimal side-effects, other than mild reactions at the injection site. However, as stated by Alzahrani et al. [1], “Fracture healing has been reported to be improved with the Scl-Ab, but the degree of sclerostin depletion with this modality has yet to be determined.”

The most substantial contribution from Alzahrani et al. [1] is a direct comparison of the extent to which Scl-Ab injections (100 mg/kg/wk) improve murine fracture healing compared to the extreme case of Sclerostin depletion by genetic ablation. Ten-week-old

sclerostin KO and wild-type mice were subjected to tibial fracture and analyzed for up to 5 weeks. After each weekly injection that began 1 week after the fracture (n = 5/group/wk), calluses were analyzed for morphology by microCT and biomechanical properties by three-point bending. For the most part, Scl-Ab injections and sclerostin gene (SOST) deletion engendered a greater callus bone volume to total volume (BV/TV) and biomechanical properties than saline injections in wild-type mice 2 weeks after the fracture. Additionally, the morphological and mechanical properties between the experimental groups were not different after 2 weeks. By contrast, while the BV/TV of the callus was maintained high until week 5 in both the Scl-Ab and sclerostin knockout (SOST KO) groups, the mechanical benefits after the third week through to the fifth week were larger in the SOST KO group than the Scl-Ab group, with ~150% greater ultimate force. These data suggest that while the injection dose used here was promising at vastly improving the structure and strength of the healed fracture, there is room to improve its efficacy by increasing the dosage to levels used in healthy men and postmenopausal women [11].

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Where Do We Need To Go?

There are many remaining questions that this interesting study and others have yet to resolve. For instance, age is a major factor contributing to osteoporosis-related fractures and while old age impairs bone formation [2], few studies have explored the interaction of age and injection dosage on fracture healing and its mechanisms. Next, the current study injects Scl-Ab a week after the fracture, which may have undercut the beneficial effectiveness of the treatment during the first week of healing. Delayed injection post fracture of a different monoclonal antibody of a negative regulator of the Wnt pathway, DKK1, impaired its benefit compared to injections immediately postfracture [3]. Therefore, what are the consequences of early as well as late Scl-Ab treatment? For example, Morse et al. [7] show that the genetic knockout of SOST increases bone volume of the fracture callus by removing the fibrocartilage earlier than the wild-type mice. Also, it would be interesting to determine whether this differential rate would occur with Scl-Ab injections. Next, lumbar, total hip and femoral neck bone-mineral density remains elevated 1 year after discontinuing a year-long/biweekly regiment of blosozumab injections [12]. Does this benefit persist beyond a year? The

wrist is a common site of fracture but limited changes were observed after 1 year of romosozumab injections and for unknown reasons [6]. Lastly, Scl-Ab injections in clinical trials are both anabolic and antiresorptive [6, 10], whereas anabolic in lower-order species [8]. Therefore, conclusions from studies in lower-order species must be interpreted cautiously.

How Do We Get There?

In order to address the age/dosage concern, injections should first be tested in adult mice between the ages of 4 months and until at least 18 months of age; peak bone mass occurs at approximately 4 months of age and old age begins at approximately 18 months. The injection dose used in the current study, is on par compared to clinical trials—of course without fracture—but since bone gain is observed with increasing Scl-Ab dosage, it may be helpful to use a higher dosage (> 100 mg/kg/wk) in aged mice with a fracture. Reducing the frequency of the injection to a biweekly injection of 200 mg/kg or monthly injection of 400 mg/kg may help institute a more manageable injection regiment, requiring fewer visits.

Several studies [7] demonstrate that bone formation may occur in a sclerostin-independent manner, which may

suggest that including another agent may result in a superimposed benefit. One of those additional agents may be DKK1-antibody, but delay in its injection weakens its effectiveness. Therefore, before a potential study can address its combinatorial effectiveness on bone formation under varying dosages and frequencies, the benefit of injecting Scl-Ab or Dkk1-Ab alone should be assessed immediately or days after a fracture. In the same potential study, the speed with which the fibrocartilage is replaced by bone under varying injection combinations or timing should be determined by histology or estimated by microCT. Further, the effectiveness of healing specific fracture sites would also be an interesting study, where the hip, spine, or wrist can be fractured in a SOST KO mice or animals supplied Scl-Ab. Researchers would then note the progression of the healing. In particular, the bone mass at the wrist does not improve demonstrably with romosozumab injections [6]. It is possible that since the site does not sustain the same level and variety of mechanical loads as the hip or spine and since bone is a highly load-sensitive tissue, a clinical trial may include a group where the wrist is subjected to a mechanical stimulus, such as resistive exercise, during Scl-Ab injections to increase bone mass.

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Scl-Ab administration is a promising countermeasure to osteoporosis and enhances fracture healing, but further studies must assess their safety following long-term use. Other musculoskeletal tissues, such as articular cartilage and intervertebral discs, have been reported to be sensitive to altered Wnt signaling, leading to a cascade of degeneration and may also require vigilance during long-term Scl-Ab use [13, 14]. Here, Scl-Ab may be applied during the course of a few weeks and the outcomes from the knees and spines may include mechanical testing to note functional changes, histology to note structural changes, and gene expression to note changes in biomarkers of degeneration.

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