Effects of Anti-Sclerostin Antibody in a Rat Model of Ischemic Osteonecrosis

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INTRODUCTION:
Osteonecrosis of the femoral head (ONFH) is an intractable disease characterized by ischemic necrosis of the femoral head, which often leads to its collapse. The etiology of ONFH is not fully understood, and currently, no effective pharmacological treatment is available to prevent the onset or progression of collapse. Anti-sclerostin antibody (Scl-Ab), a therapeutic agent for osteoporosis, promotes bone formation by activating the Wnt/β-catenin pathway. Given its proven efficacy in promoting bone formation for osteoporosis, Scl-Ab may hold therapeutic potential for ONFH, where reinforcing bone structure is critical. Therefore, the objective of this study was to investigate the therapeutic effects of Scl-Ab in a rat model of ischemic osteonecrosis.

METHODS: All animal experiments were conducted with the approval of our Institutional Animal Care and Use Committee. Ischemic osteonecrosis was induced in the distal femur of 12-week-old male Sprague-Dawley rats via vascular cauterization. A separate group of animals underwent a sham operation consisting of surgical exposure without cauterization. The rats were then randomly assigned to one of four experimental groups (n=4 per group): 1) Sham + Vehicle (Sham+Veh), 2) Sham + Scl-Ab (Sham+Scl-Ab), 3) Osteonecrosis + Vehicle (ON+Veh), and 4) Osteonecrosis + Scl-Ab (ON+Scl-Ab). Histological assessment using Hematoxylin and Eosin (H&E) staining was performed at 1 and 4 weeks post-surgery to quantify the percentage of empty lacunae. At 4 and 8 weeks, micro-computed tomography (micro-CT) was used to evaluate trabecular bone architecture (trabecular thickness, Tb.Th; trabecular number, Tb.N; trabecular separation, Tb.Sp) and epiphyseal collapse, which was quantified by the total epiphyseal volume. Statistical analysis was performed using a two-way ANOVA followed by a Tukey's post-hoc test for multiple comparisons. $P<0.05$ was considered significant.

RESULTS SECTION:
Histological analysis revealed early signs of osteonecrosis at 1 week, with the percentage of empty lacunae significantly elevated in the ON+Veh group (89.9±6.2%) compared to the Sham+Veh group (2.5±0.9%; $p<0.05$). At 4 weeks, the ON+Veh group continued to show extensive osteonecrosis (71.4±5.1% empty lacunae) compared to the Sham+Veh group (2.2±0.3%; $p<0.05$). Scl-Ab treatment significantly reduced the percentage of empty lacunae in the ON+Scl-Ab group (47.0±2.3%) compared to the ON+Veh group ($p<0.05$).

At 4 weeks, micro-CT analysis showed that trabecular thickness (Tb.Th) of the Sham+Scl-Ab group (244.2±31.3 μm) was significantly greater than that of the Sham+Veh group (183.9±13.7μm; $p<0.05$). Likewise, the Tb.Th of the ON+Scl-Ab group (232.9±6.0 μm) was significantly greater than that of the ON+Veh group (169.4±19.8μm; $p<0.05$). In contrast, no significant differences were observed among the four groups for trabecular number (Tb.N) or trabecular separation (Tb.Sp).

By 8 weeks, the total epiphyseal volume was significantly reduced in the ON+Veh group (33.7±16.0mm³) compared to the Sham+Veh group (64.9±10.1mm³; $p<0.05$), indicating epiphyseal collapse. The total epiphyseal volume of the ON+Scl-Ab group (55.0±10.3mm³) was significantly larger than that of the ON+Veh group ($p<0.05$).

DISCUSSION:
In this rat model of ischemic osteonecrosis, anti-sclerostin antibody (Scl-Ab) did not prevent the initial development of osteonecrosis. However, Scl-Ab treatment significantly increased trabecular thickness within the necrotic lesion. This structural enhancement of the trabecular architecture likely provided the mechanical support necessary to mitigate subsequent epiphyseal collapse. The primary limitation of this study is the use of a rodent model, which may not fully replicate the complex pathophysiology of human ONFH. Our findings indicate that the therapeutic benefit of Scl-Ab in this context is derived from its bone anabolic effect, reinforcing the compromised bone structure rather than reversing the ischemic insult.

SIGNIFICANCE/CLINICAL RELEVANCE: (1-2 sentences):
This study introduces a potential paradigm shift in the pharmacological management of ONFH, focusing on preventing joint collapse by enhancing bone structure rather than targeting the initial ischemic event. Anti-sclerostin antibody could represent a promising, novel therapeutic agent for joint preservation in patients with early-stage osteonecrosis.

IMAGES AND TABLES: