Combination Sclerostin Antibody and Zoledronic Acid Treatment Outperforms Either Treatment Alone in a Mouse Model of Osteogenesis Imperfecta

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Introduction: Osteogenesis Imperfecta (OI) is a genetic disorder involving bone fragility and decreased bone mass. As there is no cure, current therapies aim to reduce fracture risk and increase bone strength. Bisphosphonate treatment has been the mainstay of medical management of OI for over 10 years. Bisphosphonates in children with OI work by reducing bone catabolism and relying on normal growth to form new bone [1]. A novel anabolic treatment, Anti-Sclerostin Antibody (Anti-SOST Ab), has shown positive effects in one pre-clinical model of pediatric OI [2] but almost no effect in another [3]. We hypothesized that as one therapy is anabolic and the other anti-catabolic that combined treatment may produce superior outcomes. We examined this approach in a mouse model of OI and wild-type littermates.

Methods: Female Col1a2 G610C mice and their wild type littermates (WT) were subjected to treatment from week 5 to week 9 of life to either saline treatment (control), zoledronic acid (ZA) given 0.025 mg/kg sc weekly, Anti-SOST Ab given 50 mg/kg IV weekly (Anti-SOST), or a combination of both interventions (ZA Anti-SOST). During the 4 week treatment period weekly DEXA measurements were made with a GE Lunar PIXImus (Lunar Piximus Corp, Madison, WI, United States). After 4 weeks treatment mice were culled and tibias harvested. Micro-computed tomography (µCT) was used to assess mineral and microstructural parameters. Samples were scanned at 12 µm pixel resolution on a SkyScan 1174 (Kontich, Belgium) using a 0.5mm aluminum filter, 50 kV X-ray voltage, and 800 µA tube electric current. Quantification was performed using CTAnalyser software (Version 1.13.5.1). Mechanical testing was performed on the tibiae using 4 point bending with an Instron 5944 (Massachusetts, USA) with displacement at 0.5 mm/min until fracture. For statistical analyses, data were analyzed with one-way ANOVA (SPSS v11).

Results: Increases in areal Bone Mineral Density (BMD) of the tibia were seen over time in all groups (Fig 1). Anti-SOST treatment alone had no notable effect on BMD while ZA and combination ZA Anti-SOST treatments produced significant increases in areal BMD from weeks 1-4 (P<0.05). By week 4, ZA treatment resulted in an increase in BMD of 16%, while ZA Anti-SOST increased BMD by 27% (P<0.01). MicroCT analysis demonstrated increases in Tissue Mineral Density and Cortical Thickness for combined treatment over their respective control.

Four point bending revealed that only the combined treatment (ZA Anti-SOST) yielded a significant increase in strength and energy to failure in OI mice (Fig 2). Bone strength for Col1a2 G610C mice treated with ZA Anti-SOST were restored to the equivalent of normal (untreated) WT values.
Discussion: This study was performed in young animals, in line with our goal to investigate the effects of treatment in the growing skeleton. We saw larger increases in bone density and strength in WT mice than in Col1a2 G610C mice in response to ZA Anti-SOST co-treatment. We speculate that this was due to the additional bone being produced in Col1a2 G610C mice still being of a substandard quality. Notably, no significant effect was found in any parameter in Col1a2 G610C mice treated with Anti-SOST Ab alone. Similarly, Roschger et al reported minimal effect in the more severe Col1a1(Jrt)/+ mouse model3. In contrast, large effects were noted with just 2 weeks treatment in 8 week-old Brtl/+ mice treated with Anti SOST Ab, leading to increase in bone size and strength. In a follow up study, adult Brtl/+ mice were treated for 5 weeks, resulting again in increases in size and strength of the bone on an anabolic basis [4].

Significance: A combination of Zoledronic Acid and Anti-Sclerostin antibody treatment increases size and strength of the tibia in the Col1a2 G610C model of osteogenesis imperfecta. Further studies of this combination treatment are required in alternate mouse models of OI to confirm efficacy across different models, and thus to predict possible efficacy across the heterogeneous population of OI patients.