A CNP Analog as Adjuvant Treatment for the Growing Osteogenesis Imperfecta Mouse: A Pilot Study

Seide, K.[1]; Mulcrone, J.[1]; Carter, E[1]; Pleshko, N.[2]; Raggio, C.[1]

[1]Hospital for Special Surgery, New York, NY; [2]Temple University, Philadelphia, PA

Contact: Cathleen L. Raggio, MD. Email: raggioc@hss.edu. Phone: (212) 606-1339

Introduction: Osteogenesis imperfecta (OI) is a heterogenous type 1 collagenopathy characterized by bone fragility. Bisphosphonates decrease fracture incidence and are utilized to manage moderate to severe forms of OI in children. C-type natriuretic peptide (CNP) is produced in the growth plate and positively regulates linear bone growth. This study aims to evaluate if the addition of a CNP Analog to standard bisphosphonate (alendronate (ALN)) therapy will reduce fracture incidence, improve growth, increase bone mineral density (BMD), and/or improve bone strength in a growing *oim/oim* mouse model of moderate to severe OI.

Methods: Starting at 2 weeks of age, growing *oim/oim* mice (N=17) were divided into 4 groups, saline-treated (controls, N=8), and treated *oim/oim* mice where all received weekly ALN and one of 3 CNP dosages: 20 ug/kg 5days/week (20x5) (N=3), 20 ug/kg 3 days/week (20x3) (N=3), or 10 ug/kg 3 days/week (10x3) (N=3). Faxitron images were taken at 2 and 14 weeks (sacrifice) to evaluate fracture incidence. Femurs and vertebrae (L3-L6) were analyzed post-sacrifice to assess femoral length, vertebral height, and other bone microstructural parameters by microcomputed tomography (micro-CT) analysis.

Results: This study was approved by IACUC. At sacrifice, all of the mice in 20x5 group had no new fractures, in comparison to one fracture in one mouse in both the 20x3 and 10x3 groups and 1.57 +- 1.33 fractures in the untreated *oim/oim* mice. All three treatment groups had increased femoral lengths in comparison to the untreated *oim/oim* mice (Figure 1); the greatest increase was in the 20x5 group with the 20x3 and 10x3 having similar increases. All treated groups also had an increase in vertebral height; both the 20x5 and 10x3 groups had higher vertebral heights than the 20x3 group, but were not different from each other. In comparison to untreated *oim/oim* mice, all three dosage groups had increased cortical bone tissue mineral density (TMD), cortical bone mineral density (BMD), cortical bone thickness, trabecular bone volume fraction (BVF), trabecular TMD, trabecular BMD, and trabecular bone number. Furthermore, all three dosage groups had decreased trabecular bone separation (Figure 2). Overall, small N values and variability preclude seeing any statistical significance between treatment groups and the vehicle control. As such, these reported differences are qualitative.

Discussion: In this preliminary pilot study, it appears that the adjuvant treatment with a CNP analog results in an overall increase in both femoral and vertebral heights without compromising fracture reduction. In addition, the combination treatment appears to have an additive beneficial effect on both trabecular and cortical bone, the latter of which was not seen with bisphosphonates alone. Continued enrollment will yield the best dosage to maximize the positive bone effects. Continued enrollment of *oim/oim* mice should increase significance of our preliminary findings and will yield the best dosage to maximize the positive bone effects.

Significance/Clinical Relevance: If the aims of this research project are achieved, the optimal dose of the CNP analog will prove a promising adjuvant treatment with ALN therapy to reduce fracture incidence and improve bone growth, quality, and strength in pediatric patients that are suffering from OI.

Acknowledgements: We would like to thank BioMarin for their grant support in this project.

Figure 1: Graph of the femoral lengths of left *oim/oim* femurs with and without treatment

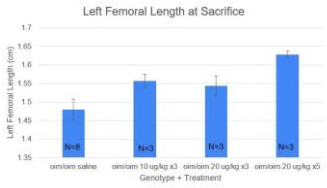

Figure 2: Micro-CT 3D images of the female *oim/oim* trabecular bone with and without treatment