P-038 - EVALUATION OF EZETIMIBE AND PRANLUKAST AS PHARMACOLOGICAL CHAPERONES FOR MORQUIO A

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INTRODUCTION: Morquio A syndrome (MPS IVA) is caused by mutations in gene encoding for the lysosomal enzyme N-acetylgalactosamine-6-sulfate sulfatase (GALNS). Although the enzyme replacement therapy (ERT) has shown some clinical improvements, it has limited effects on skeletal, corneal, and heart valvular complications, along with issues of immunogenicity, short half-life, and high cost. In this sense, it is necessary to explore alternatives that improve ERT or design new therapeutic approaches. Pharmacological chaperone therapy has been experimentally tested for several lysosomal storage diseases including MPS II, IIIC, and IVB, but not for MPS IVA. OBJECTIVE: In this study, we describe the in-vitro characterization of two pharmacological chaperones for human GALNS.

MATERIALS AND METHODS: Compounds were identified in-silico against a set of drugs approved for human use. Interaction with the active cavity of the enzyme was evaluated using a recombinant GALNS. Efficacy was evaluated using Morquio A skin fibroblasts with different mutations. In addition, the selected drugs were tested in chondrocytes and cardiomyocytes differentiated from induced pluripotent stem cells (iPSC) from Morquio A patients. RESULTS: Through a molecular docking-based virtual screening, we identified ezetimibe and pranlukast as potential pharmacological chaperones for GALNS. These compounds bound to the GALNS active cavity and increased thermal stability of the enzyme in experiments. Both compounds increased the enzyme activity of recombinant GALNS produced in bacteria, yeast, and HEK293 cells. MPS IVA fibroblasts treated with these molecules exhibited increases in GALNS proteins and enzyme activity, and reduction in lysosomal mass. The abnormalities of autophagy pathway found in the patient cells were also ameliorated after treatments with these two compounds. Noteworthy, combination treatment of recombinant GALNS with ezetimibe or pranlukast exhibited an additive effect on reduction of the enlarged lysosomal mass. Reduction in lysosomal mass was also observed in MPS IVA chondrocytes and cardiomyocytes differentiated iPSC. CONCLUSIONS: The results demonstrate that ezetimibe and pranlukast can be used in the production process of recombinant GALNS. Ezetimibe showed the potential to be used as a monotherapy for Morquio A treatment. Noteworthy, ezetimibe and pranlukast may be used in combination with ERT to improve the therapeutic efficacy for MPS IVA patients.