O-001 - INHIBITORS OF C-ABL KINASE FOR THE TREATMENT OF THE NEURODEGENERATIVE NIEMANN-PICK TYPE A DISEASE

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INTRODUCTION: Niemann-Pick type A (NPA) disease is a fatal lysosomal neurodegenerative disorder characterized by the deficiency in acid sphingomyelinase (ASM) and accumulation of sphingomyelin and cholesterol in lysosomes and autophagy alterations. We have described that c-Abl kinase is activated in other neurodegenerative diseases and recent studies show a role for c-Abl in autophagy and cellular clearance. Although there are several c-Abl inhibitors approved by the FDA, most of them are poorly selective and present low CNS penetration. ***OBJECTIVE:*** Our aims were: i) to evaluate c-Abl participation in the autophagy alterations and neuronal pathology in Niemann-Pick type A (NPA) disease and ii) to test the effect of the in vivo treatment of a NPA model mice with the new c-Abl inhibitor ABLy-1, designed by our group, with high selectivity and greater CNS penetration than other inhibitors. ***MATERIALS AND METHODS:*** In in-vitro NPA models we evaluated c-Abl activation, autophagy flux and cell viability. Then we evaluated the gene-expression profile in the human NPA fibroblasts treated with Imatinib, a c-Abl classic inhibitor. In the NPA mice we evaluated c-Abl pathway activation in cerebellum and the effect of c-Abl inhibition with Imatinib on locomotor function, Purkinje cell loss, inflammation, autophagy markers. Currently we are using a diet supplemented with Nilotinib and ABLy-1 a new c-Abl inhibitor, and evaluating their effect on disease progression. ***RESULTS:*** We found autophagy flux alterations and autophagosome accumulation around nucleus in NPA cellular models. Moreover, we found progressive neurodegeneration, inflammation, an impairment locomotor function and increment in autophagy markers in NPA animal model. In-vitro as well as in-vivo NPA models showed activation of the c-Abl pathway. c-Abl inhibition improved the autophagy flux, revealed differentially expressed genes involved in the disease pathogenesis, decreased number and changed distribution of autophagosomes and reduced neuronal death and improved locomotor function in the NPA mouse model. ***CONCLUSION:*** c-Abl is activated and relevant in NPA neurodegeneration and autophagy alterations, supporting the potential use of c-Abl inhibitors for clinical treatment of NPA patients. FONDECYT: 1150186(SZ), 1161065(AA) CARE-UC Projecto Basal AFB170005, CONICYT-PCHA/Doctorado Nacional/2015-150038, MSCA-RISE-2016-Lysomod-734825, FONDEF D10E1077.