EFFECTIVENESS OF RF22C, A SELECTIVE 5-LO INHIBITOR, IN PULMONARY ARTERIAL HYPERTENSION TREATMENT AND INNOVATIVE OPTIMIZATION OF ITS DELIVERY

Renata Esposito[1], Angela Liparulo[1], Giuseppe Spaziano[1], Nello Giugliano[1], A.C. Munoz Ramirez[2], Annalisa Capuano[1], Rosanna Filosa[1], Carmelo Puglia[3], Bruno D'Agostino[1]

[1]Department of Experimental Medicine, Section of Pharmacology, University of Campania Luigi Vanvitelli, Naples - Italy, [2]Universidad de Santiago de Chile, Facultad de Química y Biología, Santiago de Chile - Chile, [3]Department of Drug Sciences, University of Catania, Catania - Italy

Introduction: Pulmonary Arterial Hypertension (PAH) is a rare but fatal disease characterized by persistent elevated blood pressure in the pulmonary circulation, due to increased resistance to blood flow, through the lungs. The pathobiology of PAH is complex and the exact initiating processes are still unknown. However, vascular resistance in PAH has also been attributed to an inflammatory response, resulting in a higher levels eicosanoid products of leukocytes in particular leukotrienes, with high levels of 5-lipoxygenase (5-LO) expression. Therefore, in monocrotaline (MCT) rat model of PAH, the role of 5-LO in pulmonary arterial hypertension development has been investigated, through a selective 5-LO inhibitor (RF22c). In particular, the formulation of RF22c loaded solid lipid nanoparticles (RF22c-SLN) has been evaluated as a novel therapeutic strategy for PAH treatment.

Material and methods: The rats were randomly grouped as follows: control group, receiving MCT vehicle at day 0; MCT group, receiving a single subcutaneous injection of MCT at day 0; MCT + RF22c group, receiving a single subcutaneous injection of MCT at day 0 and immediately treated with a intraperitoneal administration of SLN loaded with RF22c daily for 5days. After 21days, all the animals were sacrificed to perform functional and histological evaluations. In particular, isolated and perfused lung technique (IPL2) and double occlusion have been performed to measure the mean pulmonary arterial pressure (mPAP), pre-capillary resistance(R-pre) and post-capillary resistance (R-post). Histological evaluations have been performed on lungs and hearts. The wall thickness index (WI), arteriolar area ratio index (AI) and the cross-sectional area (CSA) of cardiomyocytes have been calculated to evaluate the degree of distal pulmonary vessels muscularization and the right ventricular hypertrophy, respectively.

Results: MCT induced pulmonary hypertension, increased pulmonary vascular resistances and vascular remodelling 21days after injection. RF22c-SLN treatment was able to significantly reduce the mPAP and R-pre compared to the MCT group. The MCT-induced rise in medial wall thickness of pulmonary arterioles (WI and AI) and the cardiomyocytes width (CSA) were significantly attenuated by RF22c-SNL formulation upon treatment.

Discussion and conclusions: The results showed that the selective inhibition of 5-LO improved hemodynamic parameters as well as vascular and cardiac remodelling by preventing MCT-induced pulmonary hypertension. The improved sustained release properties and targeting abilities achieved with the innovative nanotechnological approach may be therapeutically beneficial for PAH patients as a consequence of the increase of pharmacological effects and of the possible reduction and/or optimization of the drug frequency of administration. However, further studies will be needed to investigate the unique properties of the new formulation, thus providing the basis for new therapeutic strategies in PAH that exploit the 5-LO objective and a nanotherapeutic delivery system.