Lomitapide treatment highly affects lipoprotein profile and HDL funcionality in patients with familial hypercholesterolemia

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Homozygous familial hypercholesterolemia (HoFH) is a genetic disorder characterized by extensive aortic valve calcification and an unparalleled high risk of ischaemic heart disease. Lomitapide is a recently approved cholesterol lowering agent that has been approved for treatment of HoFH. Cholesterol Efflux Capacity (CEC), index of HDL functionality, was found impaired in FH patients. The aim of this work was to evaluate Lomitapide effect on serum lipoproteins and on HDL functionality in four European FH patients. Lipoprotein particles were separated by density. Serum HDL CEC was measured with cells-based assays. After Lomitapide treatment VLDL-C and LDL-C decreased up to 80% and 60%, respectively. LDL shift to larger buoyant particles (less atherogenic) resulting in a lower capacity to load cholesterol into macrophages. HDL-C levels initially decreased but seemed to return to baseline when treatment was maintained (P2). All patients showed decrease of the HDL3 subpopulation (smaller). SR-BI-CEC decreased (average -30%;$p<0.05$) in parallel to HDL-C levels and in P2 it increased back with treatment continuation. ABCG1-CEC increased after treatment in P2, P3 and P4 (average +40%; $p<0.05$) and was not modified in P1, independently of HDL-C levels. ABCA1-CEC was reduced in all patients (average -40%;$p<0.05$), probably due to the HDL3 subpopulation reduction. Total efflux from macrophages, that takes into account the contributions from all efflux pathways, resulted unchanged in P2, P3 and P4. We may conclude that in severe FH patients Lomitapide treatment, beyond its high cholesterol-lowering efficacy, induces significant HDL structural changes that greatly impact on HDL functionality, independently of total HDL-C plasma levels. Whether Lomitapide is overall beneficial or detrimental with respect to CEC on the basis of this small series of cases remains to be determined, but it appears that the efficient increase of ABCG1-CEC compensates the reduction of ABCA1 process.