LOMITAPIDE REDUCES TRIGLYCERIDE (TG) LEVELS IN FAMILIAL CHYLOMICRONEMIA SYNDROME (FCS)

A.B. Cefalù[1], L. D'Erasmo[2], A. Giammanco[1], A. Montali[2], G. Iannuzzo[3], A. Zambon[4], F. Forte[5], D. Noto[1], P. Suppressa[5], C.M. Barbagallo[1], S. Giannini[6], M. Arca[2], M. Averna[1]
[1]University of Palermo; [2]"Sapienza" University of Rome; [3]"Federico II" University of Naples; [4]University of Padua; [5]University of Bari; [6]Careggi Hospital, Florence
E-mail: abaldassare.cefalu@unipa.it

Background. FCS is a rare autosomal recessive disorder caused by impaired lipoprotein lipase (LPL) function, resulting in elevated TG levels, intense abdominal pain, hepatosplenomegaly and recurrent episodes of acute pancreatitis. Treatment requires a strict, extremely low-fat diet (<10% fat/day) to control TG levels <750-1000 mg/dL, which does not fully control the disease. Lomitapide is a microsomal triglyceride transfer protein (MTP) inhibitor that prevents assembly of triglycerides (TGs) into chylomicrons, in addition to very low-density lipoproteins and thereby reduces circulating levels of TGs.
Methods. This open-label, single arm 'LOCHNES' study of lomitapide in FCS, enrolled adult patients ≥18 years with genetically confirmed FCS, elevated fasting TG≥750 mg/dL and a history of pancreatitis, across 3 Italian centres. Patients were administered escalating-doses of lomitapide to maximum tolerated dose (MTD) for 26 weeks. The primary endpoint was the percent change in TGs from baseline to Week 26, with lomitapide in combination with other lipid lowering therapy
Results. Eighteen patients were enrolled in the study (mean ±SD: age 46.6±16.7y; body mass index 23.7±4.1 kg/m^2). Median baseline TG levels were 1804 mg/dL (range 810-4151 mg/dL). Lomitapide dose increased from standard starting dose 5 mg/day at baseline to mean 32.8±17.8 mg/day at Week 26. Median TGs reduced to 305mg/dL (range 70-1818 mg/dL) at Week 26. This equates to a 70.5% reduction in median fasting triglyceride levels. At Week 26, 14 patients achieved TG levels <1000 mg/dL and 13 of these achieved TGs ≤750 mg/dL. Treatment with lomitapide was generally well tolerated with no patient discontinuations. Adverse events were mild to moderate and were mainly related to gastrointestinal tolerability (n=9) and ALT/AST enzyme elevations ≥3x upper limit of normal (n=4). Where available (n=13), liver MRI imaging revealed increases in hepatic fat in some patients (n=5/13), and three patients with a baseline hepatic fat >20% (range 22-30%), experienced increases to 30-50% hepatic fat at 26 weeks. No patient experienced an episode of acute pancreatitis or severe abdominal pain during lomitapide treatment. One patient who temporarily interrupted lomitapide treatment due to an episode of diarrhoea, experienced acute pancreatitis during the treatment interruption period.
Conclusions. Lomitapide is effective in reducing triglycerides in FCS and preventing the recurrence of acute pancreatitis in this pilot study. The extent of the benefit of lomitapide to patients with FCS should be further evaluated in a larger prospective clinical trial.

EFFECT OF HDL/APOA-I DEFICIENCY ON CORONARY ATHEROSCLEROSIS, EXTRAVASCULAR LIPID DEPOSITION AND IMMUNE-INFLAMMATORY PROFILE

A. Colombo[1], M. Busnelli[1], S. Manzini[1], E. Franchi[1], F. Arnaboldi[2], E. Donetti[2], E. Scanziani[3], G.D. Norata[1], G. Chiesa[1]
[1]Department of Pharmacological and Biomolecular Sciences, Università degli Studi di Milano; [2]Department of Biomedical Sciences for Health, Università degli Studi di Milano; [3]Department of Veterinary Medicine, Università degli Studi di Milano
E-mail: alice.colombo@unimi.it

Aim. HDL and its main protein component, apolipoprotein A-I, exert a pivotal role in regulating cell cholesterol homeostasis and in modulating inflammatory response and immune cell activation. This study was aimed at investigating the impact of genetic manipulation of HDL/apoA-I levels on lipid deposition in heart vessels and extravascular tissues in relation to local and systemic immune-inflammatory activation.
Methods. ApoE deficient (EKO) mice, apoE/apoA-I double deficient (DKO) mice, DKO mice overexpressing human apoA-I (DKO/hA-I) and C57Bl/6 control mice were fed chow diet until 30 weeks of age. Plasma lipids were quantified, atherosclerosis development at the aortic sinus and in coronary arteries was measured, skin ultrastructure was evaluated by electron microscopy. Blood and lymphoid organs were characterized through histological, immunocytofluorimetric and whole transcriptome analyses.
Results. DKO mice were characterized by an almost complete lack of plasma HDL-cholesterol and by total cholesterol levels comparable to those of control mice. Only DKO mice showed severe alterations of skin morphology and skin-draining lymph nodes, whose transcriptome analysis revealed increased activation of the immune system and an unbalanced expression of genes involved in energy metabolism. An increased presence of CD4+ T effector memory cells was detected in blood, spleen and in the skin-draining lymph nodes of DKO mice. A worsening of atherosclerosis at the aortic sinus and coronary arteries was also observed in DKO mice vs EKO mice. Human apoA-I overexpression in the DKO background was able to rescue the skin phenotype and to halt atherosclerosis development.
Conclusions. HDL deficiency, in the absence of hyperlipidemia, is associated with severe alterations of skin morphology, coronary atherosclerosis, local and systemic inflammation.