Apolipoprotein B-100 decreases in association with reduction in PCSK9 concentration in Acid Sphingomyelinase Deficiency following enzyme replacement therapy

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BACKGROUND

Acid sphingomyelinase deficiency (ASMD), commonly known as Niemann-Pick Disease (NPD) is a lysosomal storage disorder, caused by genetic mutations, that affects cellular metabolism. ASMD is a serious and life-threatening disorder caused by insufficient activity of the enzyme ASM resulting in accumulation of sphingomyelin in multiple organs of the body. Common clinical manifestations include enlarged liver and spleen, liver dysfunction, infiltrative lung disease, bleeding complications, cardiovascular and bone disease, and growth delay.

Enzyme replacement therapy (ERT) with olipudase alfa, a recombinant human acid sphingomyelinase (rhASM), is developed for the treatment of patients with ASMD.

OBJECTIVES

The aim of this study was to investigate the effect of ERT in Niemann-Pick disease type B (NPD-B) patients on lipoproteins and to assess common markers of systemic inflammation associated with increased risk of CVD.

METHODS

Serum and plasma samples of 5 NPD-B patients were collected as part of a phase 1b clinical trial (DFI13412 study). We analysed serum and plasma samples collected at multiple pre- and post-ERT time points (day 1, week 8, week 16 and week 26).

3 age and sex matched healthy controls were recruited for each of the 5 NPD-B patients. Eligibility criteria for control subjects included no significant pre-existing medical conditions and no prescribed medications. A single fasting blood sample was obtained from each control subject.

RESULTS

	Controls (n=15)		Niemann-Pick disease type B (n=5)			
			Baseline	P-value*	Week 26	P-value*
Total cholesterol	5.1±1.5		4.5±0.8	0.426	3.6±0.7	0.051
Triglyceride	1.0±0.3		2.2±1.5	0.003	1.0±0.4	0.650
HDL-C	1.29±0.27		0.79±0.28	0.002	0.74±0.24	0.001
LDL-C	3.4±1.3		2.9±0.5	0.469	2.4±0.5	0.130
ApoAI	1.39±0.17		0.84±0.25	<0.001	0.89±0.27	<0.001
ApoB-100	0.72±0.26		0.94±0.21	0.098	0.77±0.15	0.724
ApoB-48	61.0±12.3		89.8±11.9	<0.001	97.1±21.1	<0.001
sdLDL	29.0±18.5		44.7±18.2	0.118	32.5±13.6	0.702
PCSK9 mass	366.8±127.8		599.0±237.6	0.011	378.2±142.1	0.868
TNFα	27.7±8.8		76.0±10.7	<0.001	43.3±22.2	0.033
PON1 activity	158.1±128.8		98.5±79.0	0.347	99.9±89.7	0.365
Cholesterol efflux capacity	13.1±1.5		11.9±1.4	0.150	12.6±1.5	0.518

Table 1. Comparison of lipid profile, markers of lipoprotein quality and functionality, and markers of inflammation between patients with Niemann-Pick disease type B and controls at baseline and week 26
Data are presented as mean±SD
*P-value for comparison with controls using independent samples t-test
**P-value for comparison between baseline and week 26 using paired samples t-test

NPD patients had higher TG [mean±SD; 2.2±1.5 vs 1.0±0.3; $P=0.003$], apoB-48 [89.8±11.96 vs 61.0±12.3; $P=<0.001$], TNFα [76.0±10.7 vs 27.7±8.8; $P=<0.001$], PCSK9 mass [599.0±237.6 vs 366.8±127.8; $P=0.011$], and lower HDL-C [0.79±0.28 vs 1.29±0.27; $P=0.002$] and apoA1 [0.84±0.25 vs 1.39±0.17; $P=<0.001$] compared to controls at baseline. At the end of ERT, there were reductions in total cholesterol, TG, LDL-C (Figure 1), ApoB-100, PCSK9 and TNFα.

Figure 1. Percentage change in lipid profile at different time points

Percentage changes of PCSK9 and ApoB-100 are shown at all time points of ERT (pre- and post-dose) in Figures 2, 3. ApoB-100 decreased in association with PCSK9 (Spearman's $\rho=0.900$, $P=0.037$) (Figure 4).

Figure 2. Percentage change in PCSK9 mass at different time points.

Figure 3. Percentage change in ApoB-100 at different time points.

Figure 4. Correlation between percentage change in PCSK9 and ApoB-100.

CONCLUSION

NPD is associated with an adverse cardiovascular risk profile compared to controls, with higher triglyceride, apoB-100 and TNFα, and lower HDL levels. ERT results in a improvements in lipid profile and marker of inflammation. PCSK9 facilitates LDL receptor degradation and the reduction in PCSK9 levels observed, therefore, provides a potential mechanistic explanation for reductions in apoB-100 and LDL-C following ERT.

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Acknowledgments:

With thanks to the EAS for support in the form of a Travel Grant

Genzyme, a Sanofi company provided support for the design and conduct of the study

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