Treatment of Cholesteryl Ester Storage Disease with Combined Cholestyramine and Lovastatin

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Cholesteryl ester storage disease is a rarely reported lipid storage disorder characterized as genetic deficiency of lysosomal acid lipase, with clinical features of progressive storage of cholesteryl ester and triglyceride predominantly in liver and spleen resulting in hepatosplenomegaly.[1] Hyperlipoproteinemia is also commonly seen, and this may lead to premature atherosclerosis.[2] Choice of the treatment is limited. Decrease of apo B secretion was reported with the use of lovastatin.[3] Efficacy of the use of low-density lipoprotein (LDL) linked acid lipase was studied but only *in vitro*.[4]

We report results of treatment of a homozygous case of the disease with combined cholestyramine and lovastatin. The male patient, currently 13 years old, was found at the age of 3 years with hepatosplenomegaly, cholesteryl ester accumulation in hepatocytes, and hypercholesterolemia. Acid lipase activity, measured by Dr. A. Beaudet, Baylor College of Medicine, was extremely low in the leucocytes of the patient, and half of normal in his parents. He had an ease of bruising but did not show significant change in the parameters for blood coagulation except for slight decrease in platelets. Cholestyramine, 8 g twice a day (bid), reduced total plasma cholesterol from 8.18 ± 1.15 (mM) to 6.56 ± 0.30, triglyceride from 3.01 ± 0.62 to 2.60 ± 0.37, and raised high-density lipoprotein cholesterol from 0.37 to 0.63 ± 0.05 over a period of 7 years (5 to 12 years old). Additional lovastatin, 20 mg bid, attained total cholesterol 4.76 ± 0.44, triglyceride 1.68 ± 0.18, and HDL cholesterol 0.77 ± 0.07 over a period of 1.5 years. Lipoprotein lipid analysis by ultracentrifugation showed specific decrease in LDL and very low density lipoprotein (VLDL) and increase in HDL with lovastatin. There is no adverse effect observed. The sizes of liver and spleen seem to have decreased in terms of palpable size on physical examination since combination treatment but that of spleen measured by ultrasonogram did not show significant change. His bruising tendency was improved.

Although most of the effects of cholestyramine and lovastatin are attained by enhancing LDL receptor activity in hepatocytes,[5] total influx of LDL lipid into the cells should be lower when plasma LDL level reaches steady state. Thus, the treatment led to decrease of lipid influx via LDL and increase via HDL into liver. A recent report suggested that HDL cholesteryl ester is hydrolyzed by extralysosomal enzyme even in the cell with complete acid lipase deficiency *in vitro*,[6] so that the results of this treatment

may mean change of the direction of cholesteryl ester influx from the nonhydrolyzable pool to the hydrolyzable pool in the cells. Direct LDL removal using LDL apheresis[7] may help such an attempt more efficiently.

REFERENCES

1. SCHMITZ, G. & G. ASSMANN. 1989. *In* The Metabolic Basis of Inherited Disease C. R. Scriber, A. L. Beaudet, W. S. Sly & D. Valle, Eds. 6th edit.: 1623-1644. McGraw Hill. New York, N.Y.
2. KELLY, D. R., J. M. HOEG, S. T. DEMOSKY, JR. & H. B. BREWER, JR. 1985. Biochem. Med. **33:** 29-37.
3. GINSBERG, H. N., N-A. LE, M. P. SHORT, R. RAMAKRISHNAN & R. J. DESNICK. 1987. J. Clin. Invest. **80:** 1692-1697.
4. POZNANSKY, M., S. K. HUTCHISON & P. J. DAVIS. 1989. FASEB J. **3:** 152-156.
5. BILHEIMER, D. W., S. M. GRUNDY, M. S. BROWN & J. L. GOLDSTEIN. 1983. Proc. Nat. Acad. Sci. USA **80:** 4124-4128.
6. SPARROW, C. P. & R. C. PITTMAN. 1990. Biochim. Biophys. Acta **1043:** 203-210.
7. YOKOYAMA, S., R. HAYASHI, M. SATANI & A. YAMAMOTO. 1985. Arteriosclerosis **6:** 613-622.