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(54) Title: METHOD FOR TREATING ACID LIPASE DEFICIENCY DISEASES WITH AN MTP INHIBITOR AND CHOLESTEROL LOWERING DRUGS

(57) Abstract

A method is provided for inhibiting or treating diseases associated with acid lipase deficiency by administering to a patient an MTP inhibitor, alone or optionally, in combination with another cholesterol lowering drug, such as pravastatin.

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METHOD FOR TREATING ACID LIPASE DEFICIENCY DISEASES WITH AN MTP INHIBITOR AND CHOLESTEROL LOWERING DRUGS

Field of the Invention

The present invention related to a method for inhibiting or treating diseases associated with acid lipase deficiency, including Wolman disease and/or cholesteryl ester storage disease, by administering an MTP inhibitor alone or in combination with another cholesterol lowering drug, such as pravastatin.

Background of the Invention

Wolman disease and cholesteryl ester storage disease are characterized by a deficiency in activity of lysomal acid lipase which results in massive accumulation of cholesteryl esters and triglycerides in most tissues of the body. Cholesteryl esters and triglycerides are derived from plasma lipoproteins taken up by the cells and are substrates for acid lipase. Acid lipase is responsible for the hydrolysis of cholesteryl esters and triglycerides in the lysosomes.

If plasma cholesterol levels are lowered sufficiently, then cholesteryl ester and triglyceride accumulation in the lysosomes and the consequences of the accumulation could be minimized.

Wolman disease is the more severe of the two diseases and is almost always fatal before the age of 1 year. In contrast, cholesteryl ester storage disease may go undetected until adulthood by which time lipid deposition is widespread. Hyperbetalipoproteinemia is common in cholesteryl ester storage disease, and premature atherosclerosis may be severe.

To date, there has been no specific therapy for acid lipase deficiency other than attempts at suppression of cholesterol synthesis and apolipoprotein B production by

3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in combination with cholestyramine treatment and a diet excluding foods rich in cholesterol and triglycerides. The above apparently provided improvement in only one or two cases of cholesteryl ester storage disease. Thus, for the most part, Wolman disease and cholesteryl ester storage disease have been untreatable.

See Scriver, C.R. et al "The Metabolic and Molecular Bases of Inherited Disease", Vol. II (1995), Chap. 82, "Acid Lipase Deficiency: Wolman Disease and Cholesteryl Ester Storage Disease", pp. 2563-2587.

Until now, there have not been any therapeutic agents available which could lower plasma cholesterol levels sufficiently to minimize cholesteryl ester and triglyceride accumulation in the lysosomes.

The microsomal triglyceride transfer protein (MTP) catalyzes the transport of triglyceride (TG), cholesteryl ester (CE), and phosphatidylcholine (PC) between small unilamellar vesicles (SUV). Wetterau & Zilversmit, Chem. Phys. Lipids 38, 205-22 (1985). When transfer rates are expressed as the percent of the donor lipid transferred per time, MTP expresses a distinct preference for neutral lipid transport (TG and CE), relative to phospholipid transport. The microsomal triglyceride transfer protein from bovine liver has been isolated and extensively characterized (1). This has led to the cloning of cDNA expressing the protein from several species, including humans (2). MTP is composed of two subunits. The small subunit is the previously characterized multifunctional protein, protein disulfide isomerase. This is supported by biochemical analysis of the protein (3) as well as co-expression studies performed in insect Sf9 cells using the baculovirus expression system. Expression of soluble active MTP requires the co-expression of PDI and the unique large subunit of MTP (4).

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In vitro, MTP catalyzes the transport of lipid molecules between phospholipid membranes. Presumably, it plays a similar role in vivo, and thus plays some role in lipid metabolism. The subcellular (lumen of the microsomal fraction) and tissue distribution (liver and intestine) of MTP have led to speculation that it plays a role in the assembly of plasma lipoproteins, as these are the sites of plasma lipoprotein assembly. Wetterau & Zilversmit, Biochem. Biophys. Acta 875, 610-7 (1986). The ability of MTP to catalyze the transport of TG between membranes is consistent with this hypothesis, and suggests that MTP may catalyze the transport of TG from its site of synthesis in

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