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Lipoprotein apheresis and new therapies for severe familial hypercholesterolemia in adults and children

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Familial hypercholesterolemia (FH), the most common and severe monogenic form of hypercholesterolemia, is an autosomal co-dominant disease characterized by an increased plasma low density lipoprotein (LDL)-cholesterol concentration and premature coronary heart disease (CHD). The clinical phenotype depends on the gene involved and severity of mutation (or mutations) present. Patients with homozygous or compound heterozygous FH have severe hypercholesterolemia (LDL-cholesterol >13 mmol/L) due to a gene dosing effect and without treatment have accelerated atherosclerotic CHD from birth, and frequently die of CHD before

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proprotein convertase subtilisin/kexin type 9 inhibitors

age 30. Cholesterol-lowering therapies have been shown to reduce both mortality and major adverse cardiovascular events in individuals with FH. Lipoprotein apheresis concomitant with lipid-lowering therapy is the treatment of choice for homozygous FH. This article describes the rationale and role of lipoprotein apheresis in the treatment of severe FH and outlines the recent advances in new pharmacotherapies for this condition.

Introduction

Familial hypercholesterolemia (FH), the most common and severe monogenic form of hypercholesterolemia, is characterized by an increased plasma low density lipoprotein (LDL)-cholesterol concentration due to a decrease in the clearance of LDL particles by dysfunctional LDL-receptors in the liver [1].

FH is an autosomal co-dominant condition caused primarily by mutations in the LDL-receptor (*LDLR*) gene [2]. Over 1200 mutations causing FH have been reported that span the entire *LDLR* gene [3]. Single amino acid substitutions in apoB-100, a ligand for the LDL-receptor, may result in a form of FH known as familial ligand-defective apoB-100. 'Gain-of-function' mutations in the proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene are associated with a severe form of FH due to their effect on reducing the number of LDL-receptors on the cell surface. *LDLRAP1* mutations lead to LDL-receptor malfunction and cause the very rare autosomal recessive hypercholesterolemia (ARH) [2].

The clinical phenotype depends on the gene involved and severity of mutation (or mutations) present, with severe mutations causing complete absence of LDL-receptor activity, and less severe mutations resulting in reduced LDL-receptor function (to ~25% residual function) [4]. FH demonstrates a gene dosing effect where patients with homozygous or compound heterozygous FH (HoFH) demonstrate a more severe clinical phenotype than those with heterozygous FH (HeFH).

In HeFH, atherosclerotic coronary heart disease (CHD) develops by age 50 years in 50% of males and in 30% of women by age 60 [4]. Unfortunately, most individuals with FH are currently undiagnosed and those whom are diagnosed are frequently under treated [5]. The study of FH has increased our knowledge of lipoprotein physiology and has paved the way for novel therapies to improve the survival of individuals with this severe monogenic condition [1].

This article describes the rationale and role of lipoprotein apheresis in the treatment of HoFH and severe HeFH (symptomatic CHD or advanced subclinical CHD) [6] and outlines the recent advances with respect to new pharmacotherapies for this condition.

Metabolic basis

Metabolic studies in patients with FH using radioisotopes demonstrated reduced plasma LDL clearance and an increase in LDL synthesis, with HoFH more affected than HeFH [7]. Consistent with this finding, stable isotope studies have shown a decreased fractional catabolic rate of LDL-apoB in FH, and in most an increased production of very low density lipoprotein (VLDL)-, intermediate density lipoprotein (IDL)- and LDL-apoB [8,9], with increased VLDL-apoB production rates more evident in HoFH [9]. However, FH is a metabolic disorder that extends beyond the hypocatabolism of LDL particles, and coexisting conditions, such as obesity and insulin resistance, and other genetic variants, for example in lipoprotein (a) [Lp(a)], may also perturb lipoprotein metabolism in FH [10].

Prevalence

HeFH, in which there is a single causative mutation, is estimated to affect 1 in 300–500 individuals globally, but in some populations, founder effects have led to an increased prevalence, with 1 in 67 South African Ashkenazi Jews [11], 1 in 100 Afrikaners [12], 1 in 170 Christian Lebanese [13], and 1 in 270 Québécois [14] affected. HoFH, which refers to true HoFH with two identical mutations and compound HeFH with two different mutations, has an estimated population prevalence of one in a