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Review Article

Familial hypercholesterolemia and estimation of US patients eligible for low-density lipoprotein apheresis after maximally tolerated lipid-lowering therapy

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Abstract: Familial hypercholesterolemia (FH), an autosomal-dominant inherited disorder, can occur in either the heterozygous (HeFH) or homozygous (HoFH) state, and is characterized by high levels of serum low-density lipoprotein cholesterol (LDL-C). Although potent statins and maximally tolerated lipid-lowering therapy (LLT) have greatly reduced the risk of premature coronary heart disease (CHD) and death, all patients with HoFH and many with severe HeFH remain far from treatment goals and are thus at risk of cardiovascular disease. LDL apheresis is the treatment of choice for these patients but remains underutilized. No formal studies or epidemiologic data have estimated the prevalence of HoFH. An HeFH prevalence of 1:500 and a simplified Hardy–Weinberg equilibrium model was used to determine the probability of finding HoFH as 1:1 million in the general population. A US population of approximately 314.8 million was used to determine the number of cases of HoFH and HeFH. The following key parameters were used to estimate the prevalence of severe HeFH: baseline pretreatment LDL-C level and distribution of patients with FH, posttreatment LDL-C level and distribution after maximally tolerated LLT, and baseline percentage of patients with HeFH who have CHD. We assumed an HeFH prevalence of 1:500 and used statistics for a Gaussian distribution after the posttreatment means and standard deviations of LDL-C levels in patients with HeFH receiving maximally tolerated LLT, as has been documented by data from clinical trials and cross-sectional studies. These estimates do not include the statin-intolerant population. The objective of this analysis was to determine the prevalence of the US population with severe HeFH with or without CHD who still will be eligible for LDL apheresis despite maximally tolerated LLT. We estimated that there are 315 US patients with HoFH and 650,000 with HeFH. The estimated prevalence of the severe HeFH population eligible for apheresis is approximately 1:20,000 (range, 1:11,700–1:62,500). This estimate suggests that, based on the efficacy of maximally tolerated LLT and CHD status, approximately 15,000 (approximately 2.4%) of the 625,000 patients with HeFH who are maximally treated will still be eligible for LDL apheresis.

Familial hypercholesterolemia (FH) is an autosomal codominant inherited disorder with a gene–dosage effect.[1] The clinical phenotype of FH is characterized by increased levels of serum low-density lipoprotein cholesterol (LDL-C) and apolipoprotein B (apo B). Consequently, FH confers an

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increased risk of premature coronary heart disease (CHD), with significant rates of morbidity and mortality.[2–4]

FH can occur in either the heterozygous or homozygous state, with 1 or 2 mutant alleles, respectively.[5] Heterozygous carriers of a defective gene are clinically affected and have serum cholesterol levels of approximately2- to 3-fold higher than normal; the extremely rare homozygous persons are much more seriously affected, with cholesterol levels at 3- to 6-fold higher than normal.[6] Persons affected by FH are typically either heterozygotes or homozygotes for the LDL receptor (*LDLR*) gene.[5] Phenotypic FH can also occur because of mutational defects in either the *APOB* gene (familial defective apolipoprotein B-100 [FDB]) or the proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene (FH type III).[1,7] Heterozygotes and homozygotes for the *APOB* and *PCSK9* genes have been described.[8,9] The clinical homozygous FH (HoFH) phenotype may be due to a true genetic homozygote that has the same mutation on both alleles or may be due to a genetically compound heterozygote in which a different mutation is found at each allele.[10,11] Collectively, these monogenic inherited familial disorders result in phenotypic FH and are also referred to as autosomal dominant hypercholesterolemia (ADH).[4,12]

Mutations in the LDL receptor adaptor protein 1 cause autosomal recessive hypercholesterolemia (ARH), which is extremely rare.[7] Patients with ARH are similar to those with HoFH but with greater phenotypic variability.[13,14]

The estimated phenotypic prevalence of clinical heterozygous FH (HeFH; or heterozygous ADH), which is diagnosed on the basis of clinical symptoms and plasma cholesterol values, is approximately 1:500 persons in most Western countries. FH, or ADH, is one of the most frequent monogenic hereditary disorders in the general population.[4,5,10,12,15]

No formal studies or categorical epidemiologic data to estimate the prevalence of HoFH are available. On the basis of the HeFH prevalence of 1:500 and a simplified Hardy–Weinberg equilibrium, the probability of finding the homozygous form of FH is interpreted as 1:1 million in the general population [1/500 (mother) × 1/500 (father) × 1/4(child)].[16] In current literature, the prevalence of HoFH in the United States, the European Union, and globally is approximately 1:1 million.[1,6,17] With the use of this often-cited prevalence and assuming a US population of approximately 314.8 million, there are an estimated 315 cases of HoFH and 650,000 cases of HeFH in the United States.[18] Comprehensive molecular genetic analyses from various countries have found that 20% to 48% of patients with the clinical FH phenotype do not harbor a known causative mutation in the *LDLR*, *APOB*, or *PCSK9* gene, and additional loci may contribute to a familial ADH-like phenotype.[4,17,19–22] On the basis of the relative frequencies of the various genetic defects that cause HeFH, one can assume that the relative frequencies of homozygotes for these genes are also the same.

Efficacy of statins and use of LDL apheresis

Potent statins and maximally tolerated lipid-lowering therapy (LLT) used to treat patients with homozygous FH have greatly reduced the related risks of premature CHD and death, affording survival into the third and fourth decades of life.[23] Because these risks in FH are largely driven by very high LDL-C and apo B levels from birth,[3] treatment strategies focus on early detection, reduction of these levels, and management of other risk factors.[17] Statins alone and in combination with other LLTs can lower LDL-C levels by an average of 25% in HoFH and 45% to 60% in HeFH.[12,24–27] However, almost all patients with HoFH and a small proportion with HeFH continue to have dangerously high LDL-C levels, regardless of maximally tolerated LLT, and are at an excessively high risk of cardiovascular-related death.[23] These patients with severe FH can benefit from LDL apheresis, a procedure that rapidly produces marked reductions in LDL and apo B particles.[5,17]

The use of LDL apheresis in severe FH is approved by the US Food and Drug Administration (FDA).[28] FDA criteria recommend LDL apheresis in patients who have failed prior treatment with dietary therapy and maximally tolerated LLT (defined as a trial of drugs from ≥2 separate classes of hypolipidemic agents) for ≥6 months and who have HoFH with LDL-C levels >500 mg/dL (>12.95 mmol/L), HeFH with LDL-C levels ≥300 mg/dL (≥7.76 mmol/L), or HeFH with LDL-C levels ≥200 mg/dL (≥5.2 mmol/L) plus documented CHD.[29,30] A prevalence estimate of the severe FH pool eligible for apheresis is not available.

Apheresis-eligible population

Current guidelines emphasize the need to aggressively lower LDL-C levels in patients with FH. Among heterozygous patients, the presence of CHD is an important parameter that drives the eligibility for apheresis. In 2011, the National Lipid Association recommended that 4 additional patient segments be considered candidates for LDL apheresis, including functional patients with (1) HoFH and LDL-C levels ≥300 mg/dL (≥7.76 mmol/L; or non–HDL-C ≥ 330 mg/dL [≥8.55 mmol/L]); (2) HeFH and LDL-C levels ≥300 mg/dL (≥7.76 mmol/L; or non-HDL-C ≥330 mg/dL [≥8.55 mmol/L]) and 0 to 1 risk factors; (3) HeFH and LDL-C levels ≥200 mg/dL (≥5.2 mmol/L; or non–HDL-C ≥ 230 mg/dL [≥5.96 mmol/L]) and high-risk characteristics (eg, ≥2 risk factors or high lipoprotein(a) levels ≥50 mg/dL [≥1.30 mmol/L] with the use of an isoform insensitive assay); and (4) HeFH with LDL-C levels ≥160 mg/dL (4.14 mmol/L; or non-HDL-C ≥190 mg/dL [≥4.92 mmol/L]) and very-high-risk characteristics (established CHD, other cardiovascular disease [CVD], or diabetes).[17] National Lipid Association guidelines also state that comprehensive risk assessment for CHD including the measurement of lipoprotein (a) [Lp(a)] levels and management of CHD are critical because the presence of multiple