Journal of Clinical Lipidology (2016) 10, 1303–1310

Journal of Clinical Lipidology

Original Articles

Disease control via intensified lipoprotein apheresis in three siblings with familial hypercholesterolemia

Christina Taylan, MD*, Andrea Schlune, MD, Thomas Meissner, MD, Karolis Ažukaitis, MD, Floris E. A. Udink ten Cate, MD, PhD, Lutz T. Weber, MD

Pediatric Nephrology, Children's and Adolescents' Hospital, University Hospital of Cologne, Cologne, Germany (Drs Taylan and Weber); Department of General Pediatrics, Neonatology and Pediatric Cardiology, University Children's Hospital, Düsseldorf, Germany (Drs Schlune and Meissner); Pediatric Nephrology, Vilnius University–Hospital, Vilnius, Lithuania (Dr Ažukaitis); and Department of Pediatric Cardiology, Heart Center Cologne, University Hospital of Cologne, Cologne, Germany (Dr Udink ten Cate)

KEYWORDS:
Hyperlipidemia;
Children;
Cardiovascular monitoring;
Statins;
Evolocumab

BACKGROUND: Familial hypercholesterolemia (FH), the prevalent monogenic form of hypercholesterolemia, carries the risk of premature coronary heart disease. Lipoprotein-apheresis is established in children with severe dyslipidemia. We present 3 siblings with a negative/negative residual low-density lipoprotein (LDL) receptor mutation (p.Trp577Arg), unresponsive to drug treatment.

OBJECTIVE: Intensified lipoprotein-apheresis is well tolerated and results in permanently low lipid values without harming the health-related quality of life in children.

METHODS: Three homozygous FH siblings, aged 7–13 years, had been treated with statins and ezetimibe for 12 months but still showed highly elevated low-density lipoprotein cholesterol (LDL-C) plasma concentrations. They were started on double-filtration plasmapheresis that was subsequently intensified according to plasma lipid levels.

RESULTS: Each lipoprotein apheresis session reduced LDL-C concentration by 66% to 70%. Treated plasma volume was doubled after 6 months due to a sustained rebound of LDL-C between sessions. However, the rebound remained unchanged. Only an increase in frequency of sessions to every 3 to 4 days resulted in acceptable pre-treatment LDL-C concentrations (Cmax). Neither cessation of statins nor reduction of plasma exchange volume to 1.5 fold in follow-up influenced Cmax. Intensified therapy did not harm health-related quality of life as assessed by PedsQL and was well tolerated.

CONCLUSIONS: In pediatric FH patients unresponsive to drug treatment, intensified lipoprotein apheresis can normalize plasma lipid levels. Apparently, treatment frequency rather than volume has greater influence on its efficacy. The potential burden of intensified therapy to daily life has to be regarded. Serum lipid levels in FH should be normalized to minimize cardiovascular risk.

Background

Homozygous familial hypercholesterolemia (HoFH) is a severe autosomal co-dominant form of hypercholesterolemia. Its heterozygous form (HeFH) has an estimated prevalence in

* Corresponding author. Department of Pediatrics, University Hospital of Cologne, Kerpener Str. 62, Cologne 50937, Germany.
E-mail address: christina.taylan@uk-koeln.de
Submitted February 26, 2016. Accepted for publication August 10, 2016.

1933-2874/
http://dx.doi.org/10.1016/j.jacl.2016.08.006

Germany of at least 1 in 500 persons, but higher prevalence rates of up to 1 in 72 persons[1] are found in some populations. In line with these findings, the margin of prevalence of HoFH is also high ranging from 1 in 30.000[1] to 1 in 860.000.[2] In 85% to 90% of the patients, FH is caused by a mutation in the low-density lipoprotein receptor (LDLR) gene.[3,4] Reduced LDLRs and LDLR dysfunction inhibit the uptake of low-density lipoprotein (LDL) and subsequently increase hepatic cholesterol synthesis. In consequence, patients display findings like increased LDL-cholesterol (LDL-C) plasma concentrations and its extra-plasmatic deposition such as in the tendons (xanthomas) and around the eyes (xanthelasmas). HoFH carries the risk of premature coronary heart disease (CHD) and shows the causal relationship between elevated LDL-C concentrations and vascular disease.[3,4] The atherosclerotic burden depends on the degree and duration of exposure to high LDL-C levels.[5] In severe cases, such as those with HoFH, early detection is therefore critical and aggressive lipid-lowering therapies shall begin in early childhood to reduce the risk of CHD.[6,7] For example, these risks become manifest in extensive calcification of the ascending aorta and aortic stenosis.[8]

Although CHD generally does not manifest before adulthood, two indicators of early atherosclerotic development, namely endothelial dysfunction and thickening of the arterial vessel wall, can already be present in children with HoFH.[9,10]

HMGCoA reductase inhibitors (statins) are currently the mainstay in the management of hypercholesterolemia and are often combined with cholesterol uptake inhibitors and catalysts of cholesterol excretion. Statins ensure the upregulation of LDLR, thereby enabling removal of excess LDL-C. However, they display a high inter-individual efficacy variance. In many patients, statins do not have any effect at all due to genetically determined absence of LDLR or complete receptor dysfunction.[11] The same unpromising situation holds true for the employment of monoclonal antibodies against proprotein convertase subtilisin/kexin type 9 (PCSK-9), the recently approved new medical approach to hypercholesterolemia in individuals with mutations affecting LDL transportation.

Lipoprotein apheresis (LDL apheresis) can serve as an additional treatment to remove LDL-C in patients with severe dyslipidemia that cannot be treated satisfactorily with a combination of statins and other cholesterol lowering agents such as ezetimibe, bile acid resins, and monoclonal antibodies against PSKK-9.

Besides removal of LDL-C, LDL apheresis additionally reduces P-selectin, C-reactive protein, and fibrinogen, thereby having an important impact on the improvement of atherosclerosis.[12] Overall, the benefits of LDL apheresis extend beyond the reduction of LDL cholesterol, to positive effects on membranes of erythrocytes and platelets as well as on rheology and vascular endothelium (i.e., induction of blood vessel dilating factors, cytokines, and anti-inflammatory effects).[13,14]

Lots of efforts have been invested in developing biochemical targets to guide LDL apheresis in HoFH, but little is yet reported about the recommended frequency or the plasma exchange volume needed.[15] The frequency and exchange volume of each apheresis procedure should be orientated on the patient's acceptability of the treatment, the severity of the patient's HoFH phenotype, individual cardiovascular risk factors, and pre-existent cardiovascular disease.[16] Most children fail to attain targeted lipid goals owing to persistent shortcomings in diagnosis, monitoring, and treatment.[15]

This work highlights the efficacy of intensified LDL apheresis in 3 siblings with HoFH, who were unresponsive to drug treatment due to their underlying LDLR mutation.

Patients and methods

Patients

Three consanguine siblings of Turkish origin with LDLR mutation (p.Trp577Arg) causing a class 2a defect with a complete LDL-receptor absence who had already been undergoing a therapy with statins (20 mg/d atorvastatin) and ezetimibe (10 mg/d) were presented to our department for further treatment. The treatment was regarded to be insufficient as median LDL-C blood values even increased from 516 mg/dL (13.2 mmol/L; range, 505–534 [13–13.7 mmol/L]) to 568 mg/dL (14.6 mmol/L; range, 496–628 mg/dL; 12.7–16.1 mmol/L) mg/dL after 12 months of drug treatment and cutaneous cholesterol deposits kept growing.

Figures 1 and 2 representatively show cutaneous cholesterol deposits at the time of first presentation in patient 3 (7.6 years) before the beginning of LDL apheresis.

Owing to unsatisfactory response to drug therapy, the start of LDL apheresis was recommended to the parents and patients and started on their informed consent. At that time the children were 7.6 (patient 3), 10.0 (patient 2), and 12.0 (patient 1) years and showed no atherosclerotic findings in echocardiography. All children had normal office blood pressure values.

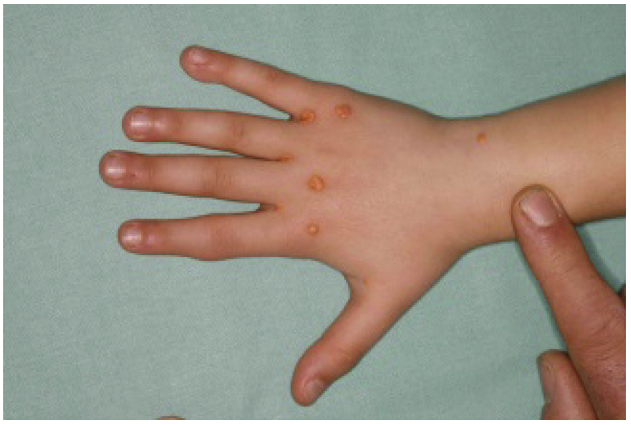

Figure 1 Cutaneous cholesterol deposits (right hand) at the time of first presentation in patient 3 (7.6 years).