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Case Study

Low-density lipoprotein receptor–negative compound heterozygous familial hypercholesterolemia: Two lifetime journeys of lipid-lowering therapy

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Mipomersen;
Lomitapide;
Treatment

Abstract: We present the case history of 2 patients with low-density lipoprotein receptor–negative compound heterozygous familial hypercholesterolemia who did not receive lipoprotein apheresis. We describe the subsequent effect of all lipid-lowering medications during their life course including resins, statins, ezetimibe, nicotinic acid/laropiprant, mipomersen, and lomitapide. These cases tell the story of siblings affected with this rare disease, who are free of symptoms but still are at a very high cardiovascular disease risk, and their treatment from childhood.

Introduction

Patients with homozygous familial hypercholesterolemia (HoFH) have extremely high low-density lipoprotein cholesterol (LDL-C) levels, rendering them susceptible to a very high risk of premature cardiovascular disease (CVD) and extensive aortic valve calcification and stenosis. Therefore, effective treatment is required starting in early childhood. However, until recently available drug therapies for these patients render insufficient lipid-lowering capacity.[1] The combination of lipid-lowering medication and lipoprotein apheresis is considered the optimal treatment for these patients. However, in the Netherlands, lipoprotein apheresis is not reimbursed, and this has generated an extreme challenge in providing optimal treatment for patients with HoFH. Here, we present 2 adult patients with compound heterozygous FH (HeFH) without clinical CVD events, who have been treated with a wide array of lipid-lowering medication but not with lipoprotein apheresis. We describe the effects of these lipid-lowering treatment regimes during their life course in the light of the available medical management of HoFH in past and present. These case histories provide a unique insight in the effects and side effects of these treatment options and can aid clinicians who treat patients with HoFH.

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Case series

Two patients, a 25-year-old man (patient 1) and his 23-year-old sister (patient 2) with compound HeFH, have 2 mutated alleles encoding the LDL receptor (LDLR), from their mother, the Leiden-3 mutation 4.4 kb duplication exon 12, and from their father, the Capetown-2, 2.5 kb deletion exon 7,8; Fig. 1. Both mutations are considered as LDLR-negative mutations, and no LDLR-protein activity is expected. They were treated from the age of 5 and 3 years, respectively, at the outpatient clinic of the Sophia Children's Hospital and subsequently at the Cardiovascular Genetics Clinic of the Erasmus Medical Center, Rotterdam, The Netherlands. In 2010, they were offered to be referred to the only center in the Netherlands performing lipoprotein apheresis, but they declined because of the travel distance and the intensity of this treatment.

Patient 1 is a 25-year-old man with compound HeFH. At the age of 5 years, he was referred to the pediatrician on the suspicion of HoFH with painful tendon xanthomas at his Achilles tendon and hands and eruptive xanthomas on his elbow. Lipid measurements at baseline showed a total cholesterol (TC) of 21.0 mmol/L (812 mg/dL) and LDL-C level of 19.6 mmol/L (758 mg/dL). He started with a cholesterol-lowering diet and lipid-lowering medication: simvastatin (the first available statin in the Netherlands) 20 mg/d in combination with niacin 3 × 100 mg/d up to 3 × 200 mg/d. This therapy resulted in an LDL-C level of 16.4 mmol/L (634 mg/dL; maximum decrease of 16%). Subsequently, at the age of 6 years, he switched to increasing dosages of pravastatin 10 to 40 mg/d (lowest LDL-C 15.6 mmol/L [603 mg/dL], −20%) for a few months. Because LDL-C levels were still very high, pravastatin was switched to increasing dosages of atorvastatin 20 mg to 80 mg/d (lowest LDL-C 11.2 mmol/L [433 mg/dL], −43%). At the age of 13 years, ezetimibe was added to this treatment regimen, resulting in 20% additional reduction of the LDL-C level to 9.0 mmol/L (348 mg/dL). In 2011, at the age of 20 years, twice daily nicotinic acid/laropiprant 1000/20 mg was added to the treatment without side effects, leading to 16% additional reduction of the LDL-C level to 7.6 mmol/L (294 mg/dL). However, in January 2013, he had to stop this medication as it was withdrawn from the market.

He went back on treatment with atorvastatin and ezetimibe, and his LDL-C level was 12.7 mmol/L (491 mg/dL). In February 2013, mipomersen 200 mg once weekly subcutaneously was added to this treatment regimen. Mipomersen was prescribed as usual care in a named patient program and resulted in a maximum additional 29% reduction of the LDL-C level to 9.0 mmol/L (348 mg/dL). He had mild injection-site reactions and no liver test elevations. However, after 14 months of treatment, he was hospitalized with petechiae and epistaxis. Laboratory measurements showed a thrombocyte count <3 × 10E9/L. He was diagnosed with idiopathic thrombocytopenic purpura (ITP). Despite thorough analysis at the hematology department, it was not possible to establish whether the ITP was caused by mipomersen treatment or not. This episode of ITP was reported as a possible side effect of mipomersen to Genzyme as part of pharmacovigilance. Prednisone treatment was initiated and tapered slowly when his thrombocytes normalized and withdrawn 3.5 months later. Mipomersen was not restarted. In September 2014, he began with lomitapide in a named patient program. He started with lomitapide 5 mg/d, slowly uptitrated to 20 mg/d, resulting in a maximum additional 45% reduction of LDL-C level to 7.0 mmol/L (271 mg/dL). Before the start of lomitapide, an ultrasonography of the liver in combination with a fibroscan showed no abnormalities, especially no hepatosteatosis. He adhered to a low-fat diet with supplementation of vitamin E and omega 3 and 6. He occasionally has stomach complaints and diarrhea if he does not adhere to the diet. However, his liver tests did not increase above the upper limit of normal during follow-up. His most recent LDL-C level was 9.4 mmol/L (363 mg/dL). The intention is to increase the lomitapide dose to 30 mg.

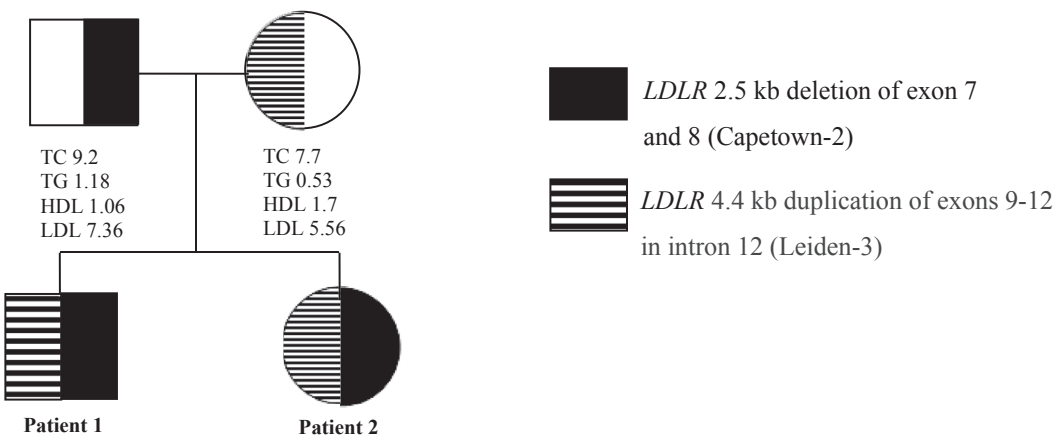

Figure 1 Pedigree of the affected patients, with untreated lipid levels in parents. HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride.