Journal of Clinical Lipidology (2015) 9, 607–617

Journal of Clinical Lipidology

Treating homozygous familial hypercholesterolemia in a real-world setting: Experiences with lomitapide

Jeanine Roeters van Lennep, MD*, Maurizio Averna, MD, Rodrigo Alonso, MD

Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands (Dr Roeters van Lennep); Department of Internal Medicine and Medical Specialties, Università di Palermo, Palermo, Italy (Dr Averna); Lipid Clinic, Fundación Jiménez Díaz, Madrid, Spain (Dr Alonso); and Lipid Unit, Department of Nutrition, Clínica Las Condes, Santiago, Chile (Dr Alonso)

KEYWORDS:
Homozygous familial hypercholesterolemia;
Lomitapide;
Familial hypercholesterolemia;
Treatment;
Case study

Abstract: Homozygous familial hypercholesterolaemia (HoFH) is a rare genetic disease characterised by markedly elevated plasma levels of low-density lipoprotein-cholesterol (LDL-C). Lomitapide is a microsomal triglyceride transfer protein (MTP) inhibitor approved as an adjunct to other lipid-lowering therapies (LLTs), with or without lipoprotein apheresis (LA), for the treatment of adult HoFH. Diet with <20% calories from fat is required. Due to a varying genetic and phenotypic profile of patients with HoFH, individual patients may respond to therapy differently; therefore examining individual cases in a 'real-world' setting provides valuable information on the effective day-to-day management of HoFH cases. Four HoFH cases were selected for analysis and discussion: a 20-year-old female compound heterozygote; a 62-year old female homozygote; a 42-year-old female compound heterozygote; and a 36-year-old male homozygote. Each patient was commenced on lomitapide according to the prescribed protocol and subjected to routine follow-up. All four patients experienced clinically meaningful reductions in LDL-C levels of 35–73%. Three of the patients had evidence of steatosis or mildly elevated liver function tests) before lomitapide was started, but effects of lomitapide on hepatic function were not universal. Three of the patients experienced gastrointestinal adverse events, but were managed with appropriate dietary control. Lomitapide is an effective adjunct LLT in the management of patients with HoFH, with or without LA. Real-world use of lomitapide has a side-effect profile consistent with clinical trials and one that can be managed by adherence to recommendations on dose escalation, dietary modification and dietary supplements.

Introduction

Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disease caused most frequently by loss-of-function mutations in the low-density lipoprotein receptor (LDL-R) gene[1,2] or less frequently in other genes that result in similar phenotypes (such as loss-of-function mutations in *APOB* and/or gain of function in the *PCSK9* gene, or homozygosity for mutations in *LDRAP1*).[1,2] HoFH is characterized by markedly and varying elevated plasma levels of low-density lipoprotein cholesterol (LDL-C).[3] Common (but not universal) signs of HoFH include cutaneous xanthoma and early-onset atherosclerosis.[3–5] In untreated patients, premature atherosclerosis develops, and patients may die prematurely.[1,2]

* Corresponding author. Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands.
E-mail address: j.roetersvanlennep@erasmusmc.nl
Submitted March 5, 2015. Accepted for publication May 7, 2015.

1933-2874/
http://dx.doi.org/10.1016/j.jacl.2015.05.001

A consensus panel of the European Atherosclerosis Society has defined treatment targets in HoFH in adults as <2.5 mmol/L (~100 mg/dL)[6] and in adults with clinical cardiovascular disease (CVD) as <1.8 mmol/L (~70 mg/dL).[6] Conventional treatments for HoFH have included optimizing lifestyle, such as adopting a low-cholesterol diet, and lipid-lowering therapies (LLTs), such as statins.[7] However, because of the lack of or deficiency in LDL-R function that characterize most HoFH patients, conventional lipid-lowering drugs that rely on upregulation of expression of intact LDL-R pathways (such as statins) do not result in adequate responses in many patients.[4,7–9] Therefore, HoFH treatment often includes lipoprotein apheresis (LA).[8,10,11]

LA can acutely reduce LDL-C levels in the blood by ≤50% and delay the onset of atherosclerosis.[8,10,11] However, the kinetics of LDL-C is such that levels rebound to baseline within 2 weeks.[12] Even with LA, patients can endure persistently high levels of LDL-C and remain at risk of developing premature CVD.[13] Given the limitations of therapies for HoFH, recent research has focussed on the development of agents that circumvent the LDL-R or disrupt the synthesis of apolipoprotein B or of the LDL precursor very low–density-lipoprotein.[14,15]

Lomitapide is a microsomal triglyceride transfer protein (MTP) inhibitor. It is approved in the United States, European Union, Canada, and Mexico as an adjunct to other LLTs (including LA) for the treatment of adult patients with HoFH.[16,17] MTP is a key protein in the assembly and secretion of apolipoprotein B–containing lipoproteins in the liver and intestine, and lomitapide, therefore, acts to lower LDL-C in a manner independent of LDL-R expression.[18]

In a pivotal phase 3 study of 29 patients with HoFH (AEGR733-005; NCT00730236), individualized dosing with lomitapide resulted in a mean 40% to 50% (depending on type of analysis used) reduction in LDL-C levels ($P < .001$) at the end of the efficacy phase (week 26) and a mean ≈ 40% reduction at the conclusion of the 78-week study.[19] Adverse events (AEs) were primarily gastrointestinal (GI) disturbances (mild to moderate) and elevations in hepatic transaminase levels. Six patients discontinued the study: 5 due to AEs (4 GI and 1 headache), and 1 patient withdrew consent. No patient discontinued the trial due to liver toxicity.[19] Patients on lomitapide are required to adhere to a low-fat eating plan to minimize GI issues and set forth strict parameters for managing and monitoring hepatic transaminase levels.

In the clinical trial setting, significant efficacy was demonstrated, along with an understanding of the risk profile of lomitapide. However, little information has been presented on the benefit and/or risk profile of lomitapide and patient management in real-world clinical use. The aim of the present case series was to review four individual real-world patients with HoFH who received lomitapide to illustrate how these patients responded to therapy and to demonstrate how side effects were managed in the clinical practice setting.

Case reports

Patient 1

Patient 1 is from the Netherlands and is treated at the Cardiovascular Genetics Outpatient Clinic of the Erasmus Medical Center, Rotterdam. She is a 20-year-old female with loss-of-function compound heterozygous FH caused by 2 different severe mutations in the *LDLR* gene: a 2.5-kbase deletion from exon 7 and 8 of *LDLR* (Cape Town: 2 mutations) and a 4.4-kbase duplication in exon 12 (Leiden-3 mutation; Table 1). As a result, this patient is LDL-R negative.

The patient was initially diagnosed with HoFH at age 3 years and had received treatment with conventional LLT because the age of 4. Despite maintenance therapy with oral atorvastatin (80 mg, daily) and colesevelam (1250 mg, twice daily) for 13 years, total cholesterol levels ranged from 9.9 mmol/L to peak at 18.9 mmol/L, and LDL-C levels ranged from 7.5 to 17.8 mmol/L (290–688 mg/dL). In January 2014 (at the age of 20 years), the patient was started on lomitapide (5 mg, daily). The dose was escalated stepwise to 30 mg, daily. After initiation of lomitapide (5 mg), LDL-C levels decreased from 14.11 mmol/L (566 mg/dL) to 13.8 mmol/L (534 mmol/L) in 2 months. Over the course of 5 months as lomitapide dose escalated up to 20 mg, levels of LDL-C, total cholesterol, and high-density lipoprotein-cholesterol (HDL-C) all declined. With increasing dose (30 mg), LDL-C levels were suppressed to their lowest level of 2.4 mmol/L (93 mg/dL), thereby representing an 83% reduction over 8 months (Fig. 1; Table 2).

Levels of total cholesterol were reduced from 17.3 mmol/L (669 mg/dL) before therapy to 6.1 mmol/L (236 mg/dL) over the same period (Fig. 1; Table 2).

Overall, side effects with lomitapide therapy were tolerable and primarily consisted of GI disturbances. Specifically, at the 5 mg lomitapide dose level, the patient complained of nausea and diarrhea during the initial 2 days of treatment, but not beyond that point, and intervention for GI AEs was not required. With escalation to 10 mg, side effects remained tolerable if dietary advice was adhered (diet with <20% energy from fat) to, and the patient ate regularly. Further escalation to 20 mg saw the return of diarrhoea, some abdominal pain and stomach "rumblings." However, the patient noted that these GI symptoms were lessened if she ate every 2 hours. Initially, she did not have additional side effects after dose escalation to 30 mg. However, after 3 weeks, dose was reduced back to 20 mg because of stomach discomfort, diarrhoea, and fatigue. After returning to the 20 mg dose, the patient felt better and did not have any further problems with side effects as long