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Clinical experience of lomitapide therapy in patients with homozygous familial hypercholesterolaemia

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Abstract

The microsomal triglyceride transfer protein (MTP) inhibitor lomitapide is a licenced adjunct to a low-fat diet and other lipid-lowering medication, with or without low-density lipoprotein apheresis, for the treatment of adults with homozygous familial hypercholesterolaemia (HoFH). In a recently published phase 3 study, patients with HoFH received lomitapide in addition to maximally tolerated lipid-lowering therapy. Treatment with lomitapide resulted in a mean approximate 50% reduction in LDL-C levels after 26 weeks compared with baseline levels ($p < 0.0001$). This decrease in LDL-C was maintained at Weeks 56 and 78 (44% [$p < 0.0001$] and 38% [$p = 0.0001$], respectively). This paper offers clinical perspectives based on selected case histories of patients participating in the phase 3 lomitapide study. These cases provide illustrative examples of the efficacy of lomitapide, with or without apheresis, and show that the effective management of adverse effects can enable patients to remain on effective treatment.

Keywords: Homozygous familial hypercholesterolaemia; Microsomal transfer protein inhibitor; Lomitapide; Liver function tests; Apheresis; Low fat diet; LDL-cholesterol

1. Introduction

Homozygous familial hypercholesterolaemia (HoFH) is characterised by markedly elevated low-density lipoprotein cholesterol (LDL-C) levels and increased cardiovascular disease burden. Although currently available lipid-lowering drugs and apheresis have significantly improved the prognosis for patients with HoFH, most patients with the disease still have LDL-C levels far above the target level of <2.5 mmol/L [1,2], and will experience progressive atherosclerosis and cardiovascular complications [2]. Furthermore, apheresis is not universally available and is not suitable for all patients. Thus despite advances in the treatment of HoFH, management of the condition remains problematic, and novel treatment approaches are urgently required.

Pathophysiologically HoFH is characterised by impaired LDL receptor function, with phenotypic variation driven by wide heterogeneity in mutation profiles [3]. In general, patients carrying mutations in the gene encoding for LDL receptor have been historically characterised as either receptor-defective (<20% of normal LDL-receptor function) or receptor-negative (<2% of normal LDL-receptor function). As standard lipid lowering drugs, such as statins or ezetimibe, act mainly via mechanisms that lead to up-regulation of the LDL receptor, it is not unexpected that the response to these treatments among patients with HoFH

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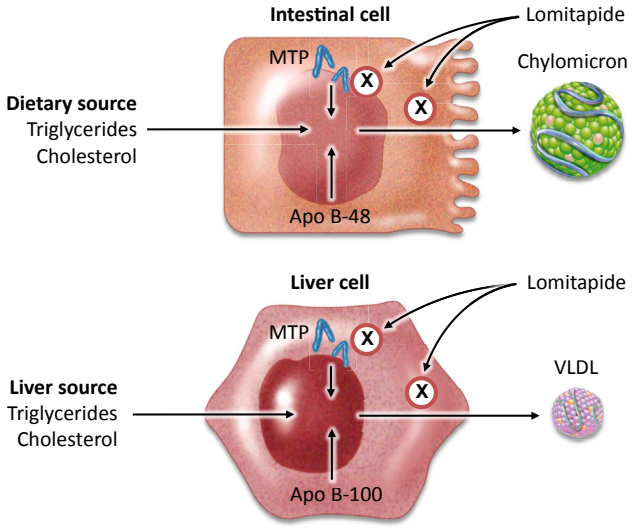

Fig. 1. Lomitapide inhibits the microsomal triglyceride transfer protein (MTP) activity in the liver and in the intestine.

is often poor. Unsurprisingly, HoFH patients who are LDL-receptor negative are less likely to respond to such agents than patients with defective LDL-receptor function [4]. Similar results are also observed with newer lipid-lowering agents that are currently in development, such as monoclonal antibodies to proprotein convertase subtilisin/kexin 9 (PCSK9) that also act by increasing the number of LDL receptors [5].

Recent research has focussed on investigating other mechanisms of lowering LDL-C levels in HoFH patients that do not rely on functioning LDL receptors, including inhibition of lipoprotein synthesis. Two proteins have been targeted in this effort: 1. apolipoprotein B_{100} (apoB_{100}; an essential structural component of LDL-C) and its precursor, very low-density lipoprotein (VLDL); and 2. microsomal triglyceride transfer protein (MTP) – a key protein in the assembly and secretion of apoB-containing lipoproteins in the liver and intestine. Mipomersen, an antisense oligonucleotide, was developed to reduce LDL-C by inhibiting the synthesis of apoB_{100} in the liver. In a phase 3 clinical trial in patients with HoFH the mean change in LDL-C from baseline to the end of the 26-week treatment period was 25% with mipomersen compared with 3.7% with placebo [6]. In this paper we describe recent clinical experience with lomitapide, which reduces plasma levels of LDL-C by inhibiting the activity of MTP in the liver and the intestine, thereby inhibiting the synthesis of VLDL and chylomicrons (Fig. 1). Lomitapide has received regulatory approval in the European Union, the United States of America, Canada and Mexico for use under a restricted program as add-on treatment in patients with HoFH.

The overall findings and aggregate data from a single-arm open-label phase 3 study of lomitapide in HoFH patients are published and will be reviewed only briefly here. More details of the study may be found in the primary publication [7]. This paper offers clinical perspectives based on case studies of individual patients who received lomitapide during the phase 3 study, and illustrates the efficacy of the drug, in patients treated with and without apheresis. The cases also demonstrate how effective management of adverse effects can enable most patients to remain on lomitapide to control their condition.

2. Overview of phase 3 study [7]

2.1. Study design and patient disposition

Male and female patients aged 18 years or older were eligible for inclusion in the study if they had a diagnosis of HoFH according to clinical criteria, fibroblast activity or documented mutations in both alleles of the LDL-receptor or alleles known to affect LDL receptor functionality.

Because the study design did not include a placebo treatment arm (Fig. 2), lipid-lowering therapies, including apheresis, had to be stable before lomitapide was initiated. This was achieved by including a minimum 6-week run-in period during which background lipid-lowering therapies were stabilised and patients were established on a low-fat diet (less than 20% energy from fat per day) to mitigate any gastrointestinal adverse events that might be expected to occur with lomitapide.

The run-in period was followed by an efficacy phase of 6 months duration (Week 26), during which the dose of lomitapide was titrated from 5 mg daily to a maximum of 60 mg daily while concomitant lipid-lowering therapies were kept stable. The aim of the dose titration was to establish an individual 'maximal tolerated dose' for each

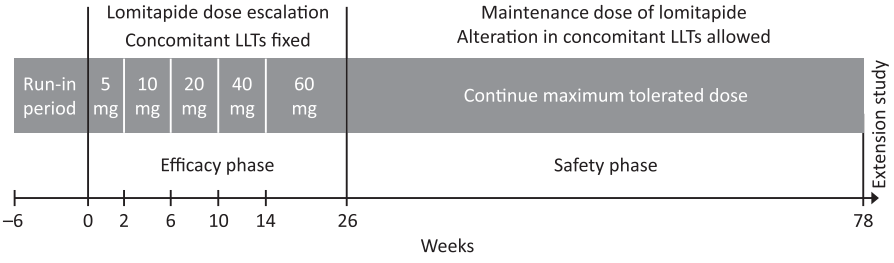

Fig. 2. Design of phase 3 study of lomitapide in patients with homozygous familial hypercholesterolaemia.