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Original Article

Pediatric experience with mipomersen as adjunctive therapy for homozygous familial hypercholesterolemia

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BACKGROUND: Homozygous familial hypercholesterolemia (HoFH) is a rare, inherited condition resulting in severely elevated low-density lipoprotein cholesterol levels (LDL-C) leading to premature cardiovascular disease and, often, death. Mipomersen is an antisense oligonucleotide that inhibits apolipoprotein B (apo B) synthesis, lowering LDL-C levels. Mipomersen has demonstrated efficacy in adult HoFH patients, possibly providing a therapeutic option for pediatric patients. Study objectives were to summarize mipomersen efficacy and safety in the pediatric cohort of a phase 3 randomized controlled trial (RCT) and subsequent open-label extension study (OLE).

METHODS: Seven patients aged 12–18 years were randomized to 200-mg mipomersen or placebo weekly (26 weeks) and received mipomersen in the OLE (52 or 104 weeks). Plasma LDL-C and apo B concentrations and adverse events were assessed.

RESULTS: All pediatric patients completed the RCT and entered OLE. The 3 mipomersen patients in the RCT experienced mean reductions from baseline to RCT end of 42.7% and 46.1% for LDL-C and apo B, respectively. Of the 4 placebo patients, 3 responded well to mipomersen during OLE, with reductions in LDL-C of 26.5%–42.1%. Three patients completed OLE treatment, and 4 patients discontinued therapy due to adverse events. Lipid level fluctuations were observed and were likely due to poor compliance.

CONCLUSIONS: Long-term mipomersen treatment was successful regarding efficacy parameters for pediatric HoFH patients. The safety profile was consistent with other phase 3 clinical trials. Long-term compliance was an issue. Measures supporting adherence should be encouraged.

Introduction

Homozygous familial hypercholesterolemia (HoFH) is a rare condition usually caused by mutations in both copies of the low-density lipoprotein (LDL) receptor gene, resulting in very high plasma levels of LDL cholesterol (LDL-C)

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from birth.[1] Based on a recent Dutch study, the prevalence of HoFH was estimated to be approximately 1 in 300,000 individuals.[2] In untreated patients with HoFH, atherosclerosis develops rapidly with clinically significant atherosclerotic vascular disease and often with sudden death from myocardial infarction or acute coronary insufficiency before the age of 30 years.[1,3] Lowering LDL-C concentrations in adult HoFH patients with modern lipid-lowering therapy (a statin with or without ezetimibe) have been shown to reduce the risk of major adverse cardiovascular events and death.[1]

Pediatric patients with HoFH also urgently require lipid-lowering pharmacotherapy to prevent atherosclerosis and prolong life[4,5]; yet, data are limited on therapeutic options in this patient population. Furthermore, in patients with HoFH, lipid-lowering therapies are often unable to lower LDL-C sufficiently, even when used in the highest doses and in combination.[6] In addition to lipid-lowering drugs, LDL apheresis is the standard of care for pediatric patients with HoFH.[7] However, this therapy has limited availability, is expensive, and is an invasive and time-consuming procedure for young children. Additional therapies for pediatric patients with HoFH are therefore needed.

Mipomersen is an antisense oligonucleotide that inhibits the synthesis of apolipoprotein B (apo B)–100 without reliance on LDL-receptor function (Fig. 1).[8] In the United States, mipomersen (marketed as Kynamro) is indicated for use as an adjunct to lipid-lowering medications and modified diet to reduce LDL-C, apo B–100, total cholesterol, and non–high-density lipoprotein cholesterol concentrations in patients with HoFH.[9] However, safety and efficacy of mipomersen have not been established in pediatric patients.[9]

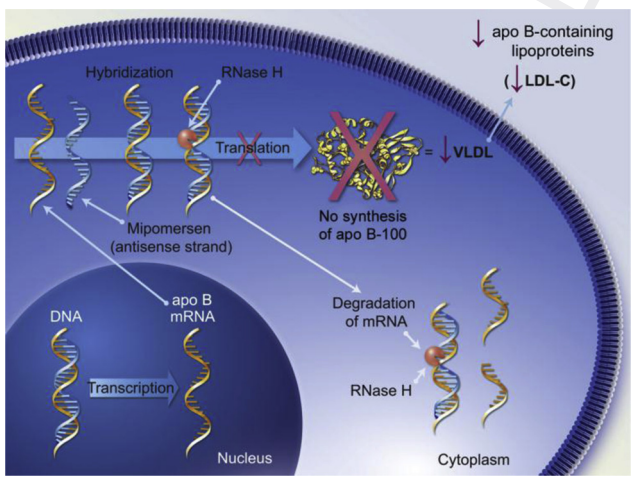

Figure 1 Mipomersen mechanism of action. apo B–100, apolipoprotein B–100; LDL-C, low-density lipoprotein cholesterol; mRNA, messenger ribonucleic acid; RNase H, ribonuclease H; VLDL, very low density lipoprotein. Reprinted from the *Journal of the American College of Cardiology,* Vol. 62/No.23, Thomas GS, Cromwell WC, Ali S, Chin W, Flaim JD, Davidson M, Mipomersen, an apolipoprotein B synthesis inhibitor, reduces atherogenic lipoproteins in patients with severe hypercholesterolemia at high cardiovascular risk: A Randomized, Double-Blind, Placebo-Controlled Trial, pp 2178–2184, Copyright 2013, with permission from the American College of Cardiology Foundation.

We present here a posthoc subanalysis of 7 pediatric patients (aged 12 to 18 years) with HoFH who participated in a 26-week phase 3, randomized double-blind, placebo-controlled trial (RCT, NCT00607373) of mipomersen and its 52-week or 104-week open-label extension study (OLE, NCT00694109). This analysis includes the efficacy and safety of mipomersen in these 7 pediatric patients who were all taking a maximally tolerated statin, a cholesterol-absorption inhibitor, a bile acid sequestrant, and/or nicotinic acid.[10] The design, methods, and results of the RCT and the OLE have been previously published.[10,11]

Methods

Study participants

For entry into the RCT, patients aged had to be ≥12 years with either a genetic confirmation of HoFH or a clinical diagnosis based on an untreated LDL-C concentration of >500 mg/dL (or >13 mmol/L), together with either xanthoma before 10 years of age or evidence of heterozygous familial hypercholesterolemia in both parents.[10] Patients were required to be stable on a low-fat diet and on a preexisting, maximally tolerated lipid-lowering drug (a statin, a cholesterol-absorption inhibitor, a bile acid sequestrant, nicotinic acid, or a combination thereof).[10] Also, patients had a fasting LDL-C concentration of ≥130 mg/dL, triglyceride concentration of <350 mg/dL, and body weight of ≥40 kg.[10] Patients receiving LDL apheresis within 8 weeks of the screening visit were excluded.[10] Additional exclusion criteria included significant cardiovascular events within 12 weeks of screening, unstable or inadequately treated stable angina, congestive heart failure, uncontrolled hypothyroidism, or any other disorder that might predispose to secondary hyperlipidemia, serum creatine phosphokinase levels ≥3 times the upper limit of normal, or a history of significant renal or hepatic disease.[10] For entry into the OLE, patients had to have satisfactorily completed dosing and week 28 assessments in the RCT and had to have an acceptable safety profile.[11] Both the RCT and OLE required that the parents and/or legal guardians give informed consent, and, if appropriate for the patient's age that the patient give consent and/or assent for study participation.[10,11]

Study design

Descriptions of the design of the initial clinical trial and the main study population have been previously published.[10]

After a screening phase of ≤4 weeks, patients were randomly assigned in a 2:1 ratio to 26 weeks of