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Long-term mipomersen treatment is associated with a reduction in cardiovascular events in patients with familial hypercholesterolemia

P. Barton Duell, MD, Raul D. Santos, MD, MSc, PhD, Bridget-Anne Kirwan, PhD, Joseph L. Witztum, MD, Sotirios Tsimikas, MD, John J. P. Kastelein, MD, PhD*

Knight Cardiovascular Institute, Oregon Health and Sciences University, Portland, OR, USA (Dr Duell); Lipid Clinic Heart Institute (InCor), University of São Paulo Medical School Hospital, São Paulo, Brazil (Dr Santos); SOCAR Research SA, Nyon, Switzerland (Dr Kirwan); London School of Hygiene & Tropical Medicine, London, UK (Dr Kirwan); Division of Endocrinology and Metabolism, University of California San Diego, La Jolla, CA, USA (Dr Witztum); Division of Cardiovascular Medicine, Sulpizio Cardiovascular Center, University of California San Diego, La Jolla, CA, USA (Dr Tsimikas); Ionis Pharmaceuticals, Carlsbad, CA, USA (Dr Tsimikas); and Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands (Dr Kastelein)

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BACKGROUND: Familial hypercholesterolemia (FH) is characterized by severely elevated LDL-cholesterol and up to a 20-fold increase in premature cardiovascular disease (CVD).

OBJECTIVE: Mipomersen has been shown to lower the levels of these atherogenic lipoproteins, but whether it lowers major adverse cardiac events (MACEs) has not been addressed.

METHODS: This post hoc analysis of prospectively collected data of three randomized trials and an open-label extension phase included patients that were exposed to ≥12 months of mipomersen. MACE rates that occurred during 24 months before randomization in the mipomersen group were compared to MACE rates after initiation of mipomersen. Data from the trials included in this report are registered in Clinicaltrials.gov (NCT00607373, NCT00706849, NCT00794664, NCT00694109). The occurrence of MACE events, defined as cardiovascular death, nonfatal acute myocardial infarction, hospitalization for unstable angina, coronary revascularization and nonfatal ischemic stroke, was obtained from medical history data pre-treatment and adjudicated by an independent adjudication committee for events occurring post-treatment with mipomersen.

RESULTS: MACEs were identified in 61.5% of patients (64 patients with 146 events [39 myocardial infarctions, 99 coronary revascularizations, 5 unstable angina episodes, 3 ischemic strokes]) during 24 months before mipomersen treatment, and in 9.6% of patients (10 patients with 13 events [1 cardiovascular death, 2 myocardial infarctions, 6 coronary interventions, 4 unstable angina episodes]) during a mean of 24.4 months after initiation of mipomersen (MACE rate 25.7 of 1000 patient-months vs 3.9 of 1000 patient-months, OR = 0.053 [95% CI, 0.016–0.168], $P < .0001$ by the exact McNemar test). The reduction in MACE coincided with a mean absolute reduction in LDL-C of 70 mg/dL (−28%) and of non-HDL cholesterol of 74 mg/dL (−26%) as well as reduction in Lp(a) of 11 mg/dL (−17%).

* Corresponding author. Academic Medical Center, University of Amsterdam, Rm. F4.159-2, Meibergdreef 9, P.O. Box 22660, Amsterdam 1100 DD, The Netherlands.
E-mail address: j.j.kastelein@amc.uva.nl
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CONCLUSION: Long-term mipomersen treatment not only lowers levels of atherogenic lipoproteins but may also lead to a reduction in cardiovascular events in FH patients.

Introduction

Patients with the autosomal co-dominant genetic disorder, familial hypercholesterolemia (FH), have extreme elevations of LDL cholesterol (LDL-C) that are associated with a 10 to 20-fold increase in risk of premature CVD events.[1] If untreated, patients with heterozygous FH (HeFH) have an approximately 50% chance of developing ASCVD by the age of 50 years in men and 60–65 years in women.[2,3] Hence, FH is a highly atherogenic disorder that warrants aggressive lipid-lowering therapy.

Unfortunately, many patients with FH are unable to achieve sufficient LDL-C lowering in response to treatment with standard therapies that now include statins, ezetimibe, and bile acid sequestrants. Such medications act through upregulation of hepatic LDL receptor (LDLR) expression, and thus, the efficacy of these drugs is diminished in patients with severe forms of FH, in which hepatic LDLR expression is diminished or absent.[4] For this reason, FH patients with refractory hypercholesterolemia require the addition of an adjunctive therapy that does not rely on upregulation of LDLR expression, but in contrast, inhibits the synthesis of apolipoprotein B-100 (apoB-100), the major apolipoprotein of atherogenic lipoproteins.

Mipomersen, a second-generation antisense oligonucleotide, inhibits translation of apolipoprotein B-100 mRNA, thereby reducing hepatic synthesis of apolipoprotein B-100 and lowering the concentration of apoB-100 containing atherogenic lipoproteins.[5–10] In fact, levels of plasma total cholesterol, LDL-C, non-HDL cholesterol, apoB, and lipoprotein(a) [Lp(a)] have been consistently and significantly reduced in response to treatment with mipomersen.

As mipomersen produces large absolute reductions in plasma LDL-C in patients with FH, we hypothesized that treatment with this novel therapy would significantly reduce CVD events. This hypothesis was bolstered by our observation that major adverse cardiac events (MACEs) were infrequent among FH patients during experimental treatment with mipomersen, despite the fact that all the patients had a diagnosis of CVD before study entry. We therefore tested the hypothesis that mipomersen therapy would decrease CV events by assessing the prevalence of MACE during 2 years before the initiation of mipomersen compared to the incidence of MACE after at least 12 months and up to 4.5 years of treatment with mipomersen.

Methods

Study design and selection of patients

Individual patient data are derived from 3 phase 3 randomized clinical trials (RCTs) conducted in patients with FH from the mipomersen program.[5,7,8] Briefly, patients who had participated in one of the 3 phase 3 blinded, randomized, placebo-controlled trials of 6-month duration ("index studies"), in addition to the open-label extension study (NCT00694109) and who had a minimum of 12 months of exposure from the combined RCT and open-label extension phases to mipomersen were eligible for inclusion.[9] Subjects with <12 months of exposure to mipomersen were excluded because lipoprotein lowering for at least 12 months is typically required to demonstrate discernible reductions in MACE.[11] The design of the index studies is depicted in. One third of patients (n = 34) were randomly allocated to placebo in the index RCT study followed by an open-label study with treatment with mipomersen for at least 12 months. Two-thirds (n = 70) were randomly allocated to blinded mipomersen for 6 months in the index RCT studies followed by at least 6 months treatment with mipomersen in the open label study. In total, 104 subjects fulfilled the selection criteria for inclusion in this post hoc analysis. The prevalence and incidence of MACE events was then determined in these 104 subjects before and after initiation of mipomersen according to the protocol defined below.

All RCTs included in this post hoc analysis were performed in accordance with the Declaration of Helsinki and Good Clinical Practice. The appropriate national and institutional regulatory authorities and ethics committees approved all study protocols. All subjects provided written informed consent. MACEs included in this report were cardiovascular death, nonfatal acute myocardial infarction (AMI), hospitalization for unstable angina (UA), coronary revascularization percutaneous coronary intervention (PCI) and/or coronary artery bypass graft (CABG), and ischemic stroke.

The protocol for the identification of MACE events before and after initiation of treatment with mipomersen was done as follows: before initiation of mipomersen: For patients randomized to (blinded) mipomersen in the index study, information was obtained from the medical history section of the case report forms, using the investigator-reported terms for events consistent with MACE that had an onset date no earlier than 24 months before inclusion in the index study. For patients randomized to placebo, MACE