Mipomersen (Kynamro)

A Novel Antisense Oligonucleotide Inhibitor for the Management of Homozygous Familial Hypercholesterolemia

Elaine Wong, PharmD, BCPS; and Tamara Goldberg, PharmD, BCPS

INTRODUCTION

Familial hypercholesterolemia (FH) is an autosomal dominant genetic condition resulting from mutations of the low-density lipoprotein-cholesterol (LDL-C) receptor, apolipoprotein B (apo B), or pro-protein converase subtilisin/kexin 9 (PCSK9).[1–3] The diagnosis is dependent on factors such as family history, clinical presentation (e.g., xanthomas, coronary atherosclerosis), genetic testing, and severe elevations in plasma cholesterol levels.[1–4]

Depending on the genetic mutation, patients can be identified as having either heterozygous or homozygous FH. Heterozygous FH (HeFH) is more common, occurring in approximately one in 500 individuals worldwide. Homozygous FH (HoFH), on the other hand, is seemingly rare, occurring in approximately one in every 1 million individuals.[3] Typical lipid abnormalities seen with either condition are as follows:[2,4]

- HeFH: total cholesterol (TC) = 350–550 mg/dL; LDL-C = 200–400 mg/dL
- HoFH: TC = 650–1,000 mg/dL; LDL-C above 600 mg/dL

As a result of longstanding dyslipidemia since childhood, there is a significant concern for premature coronary heart disease (CHD) associated with atherosclerosis in patients with FH.[1,2] Moreover, early and aggressive treatment is of the utmost importance to minimize this lifetime risk of CHD.[1–3]

Dr. Wong and Dr. Goldberg are Assistant Professors of Pharmacy Practice at Arnold & Marie Schwartz College of Pharmacy and Health Sciences, Long Island University, in Brooklyn, New York. Drug Forecast is a regular column coordinated by Alan Caspi, PhD, PharmD, MBA, President of Caspi & Associates in New York, New York.

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Consistent with the National Cholesterol Education Program–Adult Treatment Panel (NCEP–ATP) III guidelines, all patients with FH should be counseled on therapeutic lifestyle changes. Dietary modifications would include reducing saturated fat and cholesterol intake and increasing the consumption of plant stanols or sterol esters and soluble fiber. Patients should limit alcohol consumption, avoid tobacco use, and engage in physical activity to maintain a healthy body weight.[1,5]

According to the National Lipid Association, patients require pharmacotherapy when LDL-C is 190 mg/dL or higher, or non-high-density lipoprotein cholesterol (non-HDL-C) is 220 mg/dL or higher after lifestyle changes. Statins should be prescribed as the initial therapy for adults (20 years of age and older) to achieve a 50% or greater reduction in LDL-C. More aggressive therapy to target an LDL-C level below 100 mg/dL and a non–HDL-C level below 130 mg/dL may be warranted in patients at higher risk. Indicators for the intensification of therapy include characteristics such as clinically evident CHD, diabetes, an early family history of CHD, being a current smoker, or having two or more CHD risk factors. If patients are unable to tolerate statins or require additional pharmacotherapy, ezetimibe (Zetia, Merck/Schering-Plough), bile acid sequestrants, or niacin may be considered. Of note, combination therapies may be needed to achieve therapeutic goals.[1]

For patients who are unable to achieve their target LDL-C goal with these therapies (as is more often the case with HoFH), alternative strategies such as LDL apheresis may need to be pursued.[1–3,6] Several novel therapies are in development, including apo B-antisense oligonucleotide inhibitors, microsomal transfer protein inhibitors, PCSK9 inhibitors, squalene synthase inhibitors, and thyroid hormone analogues.[6,7]

In January 2013, the FDA approved mipomersen (Kynamro, Genzyme), an antisense oligonucleotide inhibitor of apo B, as an orphan drug for the management of HoFH.[8–10] Mipomersen is indicated as an adjunct therapy to lipid-lowering agents and to lifestyle changes for reducing LDL-C, apo B, TC, and non–HDL-C levels.[7,8] Notably, an orphan drug status is granted for therapies that are used to manage rare diseases, such as HoFH, which affects fewer than 200,000 people in the U.S.[9,10]

PHARMACOLOGY

Mipomersen is an antisense oligonucleotide inhibitor of apo B-100 synthesis, an essential component of lipoproteins such as very-low-density lipoprotein (VLDL) and LDL.[8,11] This novel technology utilizes short, single-stranded synthetic DNA molecules to target and complement a specific messenger RNA (mRNA) sequence responsible for coding apo B-100. The hybridized mipomersen and mRNA molecule results in the activation of RNase H, an enzyme that catalyzes RNA cleavage, and inhibition of protein translation to decrease apo B concentrations.[8,11–13] Ultimately, the production of atherogenic lipoproteins is decreased.[13,14]

PHARMACOKINETICS (PHASE 2 TRIALS)

Kastelein et al.[15] and Akdim et al.[16]

The pharmacokinetic properties of mipomersen were evaluated in two phase 2, double-blind, placebo-controlled, dose-escalation studies.[15,16]

In a phase 2 study by Kastelein et al.,[15] patients initially received intravenous (IV) infusions of mipomersen over the course of one week until steady-state levels were achieved in hepatic tissues. This was followed by three once-weekly subcutaneous (SC) doses ranging from 50 to 400 mg. Patients were observed for either a maximum of 12 weeks or until 90% or more of TC levels returned to baseline.[15]

Dose-dependent increases in mipomersen concentrations were observed with both the IV and SC routes. The maximum plasma concentration (C_{max}) ranged between 4.8 and 21.5 mcg/mL and 1 to

2.7 mcg/mL with the IV and SC routes, respectively. Although the C_{max} differed in the IV and SC mipomersen groups, area-under-the-curve (AUC) concentrations were similar in both groups.[15]

The elimination half-life was dose-dependent, ranging from 23 ± 1 days to 31 ± 11 days. The longer half-life of mipomersen allows for a less frequent dosing interval.[15]

In the randomized phase 2 study by Akdim et al.,[16] patients received mipomersen with or without a loading dose for 13 weeks. Patients in the loading-dose arm received SC mipomersen 100 or 200 mg every other week after a two-week loading period (200 mg twice weekly). Patients in the non–loading high-dose cohort received SC mipomersen 200 to 400 mg once weekly. Trough concentrations were obtained every seven days prior to the dose for the duration of the study period. These levels ranged between 8 ng/mL (for those receiving 50 mg/week) and 51 ng/mL (for those receiving 400 mg per week) after one week.

For doses between 100 and 300 mg, the mean C_{max} ranged from 1.2 to 4.3 mcg/mL. The C_{max} was not available for the 400-mg/week arm due to discontinuation of treatment. The mean time to achieve C_{max} ranged between 3.4 and 4 hours, with an observed terminal half-life between 46 and 48 days.[16]

Moreover, mipomersen has a reported distribution half-life of approximately two to five hours and an elimination half-life of one to two months. It is more than 90% protein-bound. Steady-state plasma trough concentrations are typically achieved within six months of therapy. Mipomersen is metabolized by tissue endonucleases to form shorter oligonucleotides that are further metabolized by exonucleases. The cytochrome P450 (CYP) enzyme system is not involved with the metabolism of this drug. The estimated SC bioavailability of mipomersen is between 54% and 78% after a once-weekly dose of 50 to 400 mg.[8]

PIVOTAL PHASE 3 CLINICAL TRIALS[17–19]

Homozygous Familial Hypercholesterolemia

Raal et al.[17]

In a multicenter, randomized, double-blind study, mipomersen was compared with placebo in 51 patients with HoFH. In addition to receiving prior lipid-lowering therapy at stable maximally tolerated doses, patients 12 years of age and older received either SC mipomersen 200 mg once weekly (n = 28) or placebo (n = 17) for 26 weeks. A dose reduction of 160 mg was used in patients weighing less than 50 kg and randomized to the mipomersen group. In accordance with the NCEP–ATP III guidelines, patients were also advised on therapeutic lifestyle changes.

Patients were excluded from the study if they had significant cardiovascular events within 12 weeks of enrollment, unstable angina, uncontrolled stable angina, congestive heart failure, uncontrolled hypothyroidism, a serum creatine phosphokinase level more than three times the upper limit of normal (ULN), or a history of significant hepatic or renal disease. Patients undergoing LDL apheresis within eight weeks of study initiation were also excluded. The primary objective was the percentage of change in LDL-C levels from baseline.[17]

Of 51 patients, 45 completed the study at 26 weeks. The mean patient age was 31.3 years. Ninety-eight percent of patients received additional lipid-lowering therapy. A majority of patients also had a cardiovascular history consisting of revascularization, atherosclerotic disease, aortic valve stenosis, or aortic valve replacement. At baseline, mean LDL-C levels were 11.4 mmol/L and 10.4 mmol/L in the mipomersen and placebo groups, respectively.

The mean percentage changes in LDL-C levels from baseline were –24.7% with mipomersen and –3.3% with placebo ($P = 0.0003$). The percentage changes in apo B, TC, non–HDL-C, HDL-C, triglycerides, lipoprotein a, and VLDL-C levels were also significantly greater in the mipomersen patients than in the placebo patients.[17]

McGowan et al.[18]

A subsequent multicenter, randomized, double-blind study was conducted to compare mipomersen with placebo in 58 patients with severe hypercholesterolemia. For 26 weeks, patients received either SC mipomersen 200 mg weekly or placebo in addition to maximally tolerated lipid-lowering therapy. Eligible patients had to be 18 years of age or older with LDL-C levels of 300 mg/dL (7.8 mmol/L) or higher, or LDL-C levels of 200 mg/dL (5.1 mmol/L) or higher with a history of CHD. Patients also had a stable weight and followed a low-fat diet.

Patients were excluded from the study if they had undergone LDL apheresis or had experienced significant cardiovascular or cerebrovascular events within 24 weeks, congestive heart failure, uncontrolled type-2 diabetes, type-1 diabetes, hypertension, or a history of significant hepatic or renal disease. The primary endpoint was the percentage of change in LDL-C levels from baseline to two weeks after the last dose.

Forty-five of the 58 patients completed the study. The mean age was 50.5 years. Most of the patients had a medical history of CHD or atherosclerosis. Other baseline characteristics, such as sex, body mass index (BMI), and lipid-lowering medications, were similar between the groups, except for alcohol and tobacco use. Mean baseline LDL-C levels were 7.2 mmol/L with mipomersen and 6.5 mmol/L with placebo.

The mean percentage changes in LDL-C levels from baseline were –35.9% with mipomersen and 12.5% with placebo ($P < 0.001$). Beneficial effects of mipomersen were also noted for apo B, TC, non–HDL-C, lipoprotein a, triglycerides, and VLDL-C, but not HDL-C.

Heterozygous Familial Hypercholesterolemia

Stein et al.[19]

A multicenter, randomized, double-blind study was conducted in patients with HeFH and coronary artery disease. Eligible patients had LDL-C levels of 100 mg/dL or higher (2.6 mmol/L) and TC levels below 200 mg/dL (2.26 mmol/L). They were receiving maximally tolerated statin therapy with or without additional lipid-lowering therapy. Unlike the other studies, LDL apheresis was an option in this study. A total of 124 patients received SC mipomersen 200 mg weekly (n = 83) or placebo (n = 41) for 26 weeks. The mean reduction in LDL-C was greater with mipomersen (–28%) than with placebo (5.2%) ($P < 0.001$). Statistically significant changes with other lipid parameters were seen, except for HDL-C.[19]

SAFETY PROFILE

Adverse Events

The most common adverse events reported in the phase 3 trials were

Table 1 Adverse Effects of Mipomersen (Kynamro) in Phase 3 Clinical Trials

	Mipomersen (N = 156)		Placebo (N = 77)	
	*No. of Events**	*No. of Patients (%)*	*No. of Events**	*No. of Patients (%)*
Adverse effects				
Injection-site reaction	2,187	138 (88.5)	79	27 (35)
Influenza-like symptoms	202	73 (49.8)	33	21 (27.3)
Nausea	30	17 (10.9)	11	7 (9)
Laboratory abnormalities				
ALT ≥ ULN and < 2 x ULN	—	55 (35.3)	—	27 (35.1)
ALT ≥ 2 x and < 3 x ULN	—	33 (21.2)	—	5 (6.5)
ALT ≥ 3 x and < 10 x ULN	—	26 (16.7)	—	1 (1.3)
ALT ≥ 10 x ULN	—	2 (1.3)	—	0 (0)

ALT = alanine aminotransferase; ULN = upper limit of normal.
*Events were not reported for laboratory abnormalities.
Data from Raal FJ, et al. *Lancet* 2010;375:998–1006;[17] McGowan MP, et al. *PLoS One* 2012;7(11);[18] and Stein EA, et al. *Circulation* 2012;126:2283–2292.[19]

injection-site reactions such as erythema, pruritus, and pain. There were also reports of influenza-like symptoms such as fatigue, pyrexia, chills, malaise, myalgia, and arthralgia (Table 1).[17–19]

Serious adverse events specific to elevations in alanine aminotransferase (ALT) were more common with mipomersen than with placebo (Table 1).[8,17–19] In the McGowan phase 3 trial, there was a similar incidence of renal adverse events, defined as an increase in serum creatinine of 1.3 times from baseline in the mipomersen patients (21.1%) versus the placebo group (20.5%) (*P* value not provided). Cardiac events, including acute myocardial infarction (MI), angina, cardiac failure, coronary artery disease, and supraventricular extrasystoles were reported with a greater frequency in the mipomersen group (12 events) than in the placebo group (one event).[18]

Warnings and Precautions

The FDA issued a boxed warning for mipomersen concerning the risk for hepatotoxicity. In addition to elevations in transaminase levels, mipomersen may cause an increase in hepatic fat. Clinicians are advised to obtain ALT, aspartate transaminase (AST), alkaline phosphatase, and total bilirubin values at baseline. Periodic ALT and AST monitoring should be performed thereafter. If ALT or AST levels are elevated more than three times the ULN, mipomersen should be temporarily withheld until alternative causes are excluded (Table 2).[8]

Mipomersen should be used with caution when prescribed with other hepatotoxic medications such as methotrexate, acetaminophen (more than 4 g/day for more than three days per week), tamoxifen (Nolvadex, AstraZeneca), isotretinoin (Accutane, Hoffman-LaRoche), and alcohol. Further studies are needed to evaluate the use of mipomersen with other LDL-lowering agents and the risk of hepatotoxicity (see Drug Interactions).[8]

Contraindications

Mipomersen is contraindicated in patients with moderate or severe hepatic impairment (Child–Pugh category B or C), as well as in patients with active liver disease or persistent elevated serum transaminase levels.[8]

Risk Evaluation and Mitigation Strategy (REMS)

Because of its associated risk of hepatotoxicity, mipomersen is available only through a REMS program. Providers and pharmacies need additional certification to prescribe and dispense the medication.[8]

Special Populations

Mipomersen is classified as a Pregnancy Category B medication. Animal studies have not shown any harm to the fetus. It is not known whether this drug is excreted in human breast milk.[8]

DOSAGE AND ADMINISTRATION

Before patients begin mipomersen therapy, baseline laboratory tests for liver transaminases, alkaline phosphatase, and total bilirubin should be performed. The suggested SC dose is 200 mg once weekly. Mipomersen should be administered on the same day every week. If a dose is missed, the medication should be given at least three days before the next scheduled weekly dose.[8]

A lipid panel should be assessed every three months for the first year of mipomersen treatment. Maximal LDL-C reductions should be noted after six months of therapy.[8]

Only the SC route is to be used. Mipomersen may be injected into areas such as the abdomen, thigh, or upper

Table 2 Recommendations for Elevated Liver Transaminase Levels

ALT or AST	Recommendation
≥ 3 x and < 5 x ULN	• Repeat laboratory tests within 1 week. • If results are confirmed, withhold the dose, and identify the likely cause of the elevations. • If reinitiating therapy after transaminases are decreased to less than three times the ULN, consider more frequent monitoring of relevant liver tests (AST, ALT, total bilirubin, and alkaline phosphatase).
≥ 5 x ULN	• Withhold the dose and obtain additional relevant liver tests to identify the likely cause of elevated transaminases. • If reinitiating therapy after transaminase levels decrease to less than three times the ULN, perform more frequent monitoring of relevant liver tests.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit normal.
Adapted from Kynamro (mipomersen sodium) prescribing information.[8]

outer-arm regions. All patients should be properly instructed on how to give the injections to minimize the risk of injection-site reactions.[8]

DRUG INTERACTIONS

There are no significant pharmacokinetic or pharmacodynamic interactions with mipomersen.[8] In a study that was conducted to evaluate the use of mipomersen with simvastatin (Zocor, Merck) or ezetimibe, no clinically relevant pharmacokinetic interactions were found. As such, the AUC concentration from 0 to 24 hours, the C_{max}, and the elimination half-life of mipomersen were similar when it was administered with oral doses of simvastatin or ezetimibe. Mipomersen did not inhibit major CYP450 isoenzymes.[20]

COST AND AVAILABILITY

Mipomersen is available as a single-use 1-mL vial with a concentration of 200 mg/mL.[8] The average wholesale price (AWP) for one week of therapy with mipomersen is $5,759.65; the AWP for 30 days of therapy is $23,038.60.[21]

CONCLUSION

Mipomersen is a novel antisense oligonucleotide inhibitor of apolipoprotein B. It is approved by the FDA only as an orphan drug for use in HoFH, a relatively rare genetic condition. Ongoing clinical trials are being conducted to evaluate the safety and efficacy of mipomersen in varying populations. Additional data are needed to determine its use in patients with hepatic impairment.

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