Review of Mipomersen Sodium (Kynamro®) for Familial Hypercholesterolemia

Lunawati L. Bennett[1,*] and Megan Chalk[2]

[1]*Pharmaceutical Sciences,* [2]*Union University, School of Pharmacy 1050 Union University Drive Jackson, TN 38305,USA*

Abstract: *Objective:* To review the pharmacology and pharmacokinetics, and to evaluate the clinical efficacy, safety, and place in therapy of mipomersen sodium (Kynamro®) for the treatment of familial hypercholesterolemia (FH).

Data Sources: A literature search through Pub Med and clinicaltrials.gov (1984–May 2014; English language) was performed using the key words: homozygous familial hypercholesterolemia (HoFH), heterozygous familial hypercholesterolemia (HeFH), FH, dyslipidemia, apolipoprotein B-100 (apoB-100), low density lipoprotein cholesterol (LDL-C), antisense oligonucleotides (ASOs), and ISIS 301012. Searches were limited to published studies in humans.

Study Selection and Data Extraction: All articles in English identified from reviews, abstracts, presentations, and clinical trials of mipomersen in humans were selected and included.

Data Synthesis: Mipomersen sodium (Kynamro®), an oligonucleotide inhibitor of apoB-100 synthesis, is approved for reducing apoB-100, LDL-C, total cholesterol (TC), and non-high density lipoprotein cholesterol (non-HDL-C) in HoFH patients as an adjunctive treatment with other lipid lowering drugs and low fat diet.

Conclusion: Mipomersen is effective in decreasing LDL-C, apoB-100, TC, and non-HDL-C in patients that are refractory to other lipid lowering drugs. Mipomersen is administered as 200 mg subcutaneous (s.c.) once weekly injection. The drug is contraindicated in patients with moderate to severe hepatic impairment. The most common adverse reactions include injection site reaction (ISRs), influenza-like symptoms and increases in serum hepatic transaminase. Kynamro® is only available through restricted program under Risk Evaluation and Mitigation Strategy (REMS) called Kynamro® REMS

Keywords: HoFH, HeFH, FH, ASO, ISIS 301012, LDL-C**.**

INTRODUCTION

Familial hypercholesterolemia (FH) is an autosomal lipid metabolism disorder that is characterized by lifelong significant elevations in LDL-C and apoB-100 levels resulting in increased risk of atherosclerosis and cardiovascular disease (CVD) [1, 2]. FH can be categorized into HeFH and HoFH. The prevalence of HeFH is approximately 1 in 300 to 500 worldwide and as high as 1 in 100 among African, Lebanon, Finland and Quebec populations. The prevalence of HoFH is estimated to be about 1 in one million people of the same populations [1-4]. HeFH patients under the age of 20 years usually have LDL-C levels of 190 mg/dL or higher, and those older than 30 years may have LDL-C levels above 250 mg/dL [3]. HoFH which is a more severe form of FH, are seen in early childhood. If this disease is left untreated, HoFH patients will die before the age of 30 [5-7].

Several hypotheses exist regarding FH. It can be due to mutation in the LDL-receptors (LDLRs) genes, apoB-100 genes, pro-protein convertase subtilisin/ kexin type 9 genes (PCSK9), or a rare mutation in the LDLR adaptor protein 1 (LDLRAP1) genes [3-5], [8-12]. About 85% of FH cases are due to mutations in LDLRs genes, in which over 1600 mutated genes have been identified. A single nucleotide substitution or large structural rearrangement of LDLRs gene has been identified [3, 9]. Mutations in apoB-100 genes can cause defective clearance of atherogenic lipoproteins from plasma, due to ApoB-100 plays important roles in the packaging and distribution of dietary and endogenous cholesterol and triglyceride (TG). ApoB-100 also plays important role in the lipid metabolism, and in providing structural core for other atherogenic lipoproteins such as LDL-C, very low density lipoprotein cholesterol (VLDL-C), and lipoprotein (a) [Lp (a)].

Mutations in PCSK9 genes can lead to either hypercholesterolemia (HC) or increased risk of premature CVD. This is due to the role of the PCSK9 genes in enhancing intracellular degradation of LDLRs and in preventing the number of LDLRs at the hepatocyte cell surface [10]. When there is an increase in LDLRs expression, there is a parallel increased in the PCSK9 synthesis showing its important role in preventing excessive reuptake of cholesterol into cells [11]. The LDLRAP1 genes play important role in trafficking LDLR into the liver. Mutations in these genes have been found in FH autosomal dominant or recessive patients [2, 12].

*Address correspondence to this author at the Union University, School of Pharmacy 1050 Union University Drive Jackson, TN 38305, USA, Tel: 731-661-5921; Fax: 731-661-5980; E-mail: llbennett@uu.edu

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Current therapies for the treatment of FH includes diet and lifestyle modifications, cholesterol-lowering drugs, lipid apheresis or liver transplantation [1]. Lifestyle modifications are aiming to lower LDL-C and other risk factors of CVD [1]. However, only a minimal reduction in LDL-C is usually achieved even when patients have very restricted diet such as taking less than 200 mg cholesterol per day [1]. Statins are the most common, safe and effective drugs used to lower LDL-C in FH patients. While HeFH response well to statins, HoFH patients response rate to statins is less predictable. Reduction of LDL-C from 6% to 50% have been seen in HeFH patients [13]. Patients who require greater LDL-C reduction usually need to use combination of statins with other lipid lowering drugs such as ezetimibe, niacin, fibrates, or bile acid sequestrants [2]. Options for HoFH patients who are refractory or resistant to statins include lipid apheresis or liver transplantation. Lipid apheresis procedure removes apoB-100 from blood circulation, but this procedure is time consuming, costly and gives unpredictable results [14]. It is difficult to optimizing the frequency of lipid apheresis due to the fluctuation in serum cholesterol after the procedure [14]. Several successful liver transplantation have been performed to HoFH patients, however, limited donor organs and the need for ongoing post-operative immunosuppressant made this procedure is less preferable [1, 14].

Other approaches to decrease LDL-C in HeFH and HoFH patients includes cholesterol ester transfer protein (CETP) inhibitors which reduce transfer of cholesterol esters from HDL-C to LDL-C, microsomal transfer protein (MTP) inhibitors which inhibit the assembly of VLDL, PCSK9 inhibitors which regulate LDLR degradation, and antisense oligonucleotide (ASO) which prevents formation of functional proteins [15-17].

The Food and Drug Administration (FDA) of USA approved mipomersen sodium (Kynamro®) as an orphan drug for the treatment of HoFH as an adjunctive treatment with other lipid lowering drugs and low fat diet. The European Union approved this drug for HoFH and for severe form of HeFH. Mipomersen is administered as a 200 mg s.c. injection once weekly to reduce LDL-C, apoB-100, TC, and non HDL-C levels [18, 19].

PHARMACOLOGY

Mipomersen sodium (ISIS 301012 or ISIS 147764, Genzyme Corporation, Isis Pharmaceuticals) is a synthetic 20-mer 2'-O-(2-methoxy) ethyl- modified oligonucleotide, a second generation single stranded ASO with specific complementary binding to the coding region of human apoB-100 messenger RNA (mRNA) [nucleotide 3249-3269] [20]. This inhibitor has 20 nucleotides with coding sequences as 5'-GCCTCAG-TCTGCTTCGCACC-3", and it is chemically stabilized via a phosphorothioates backbone [21]. The center nucleotide region of mipomersen is incorporated with 2'-deoxyribose sugars: 2'-O-methyl (2'OMe) and 2'-O-methoxyethyl (2'MOE) modified ribose in 3' and 5' flanking regions of mipomersen. These substitutions differentiate the second from the first generation [21]. ASOs are designed to specifically bind to apoB-100 mRNA preventing the translocation of mRNA into forming functional apo-B 100 [22-24]. Endogenous RNAase enzymes such as RNAse H or Arganaute 2 recognize the duplex apo B-100 mRNA and mipomersen, degrade the mRNA strand; therefore, functional apoB-100 protein is not formed [25, 26]. Besides degradation by the enzymes, apoB-100 is not expressed due to improper splicing of pre-mRNA into mature and functional mRNA [21, 23]. Figure **1** showed the structure of mipomersen. Figure **2** showed the mechanism of action of mipomersen sodium [27].

In nature, apoB exists in two isoforms: apoB-48 and apoB-100. ApoB-48 is a truncated form of apoB-100. It is only expressed in the intestine to absorb fat. ApoB-100 is a large amphipathic protein that is mainly produced in the liver. It functions as a carrier of cholesterol in the bloodstream. It is present on all lipoprotein particles such as LDL-C, VLDL-C, and Lp (a) that are responsible for atherosclerosis formations [28]. Inhibiting apoB-100 synthesis is significantly caused decrease in plasma TC, VLDL-C, LDL-C, and Lp (a), while the advantage of inhibiting apoB-48 formation is unknown [8, 21]. As a second generation ASO, mipomersen is better than the first generations ASO due to it has greater potency and affinity, has enhanced stability to the degradation by enzyme nucleases, has longer half-life, and cause less adverse reactions [21,24,27, 29-32]. The first generation ASO is easily degraded by endonucleases and exonucleases and has been demonstrated to be toxic to cell growth and proliferation of healthy tissue [33].

PHARMACOKINETICS AND DRUG-DRUG INTERACTIONS

Mipomersen showed similar plasma under curve either given as an intravenous (i.v.) infusion or s.c. routes in healthy individuals. Plasma concentration of mipomersen after 2-hours i.v. was reported from 4.8 to 21.5 μg/mL when variable i.v. loading doses of 50 to

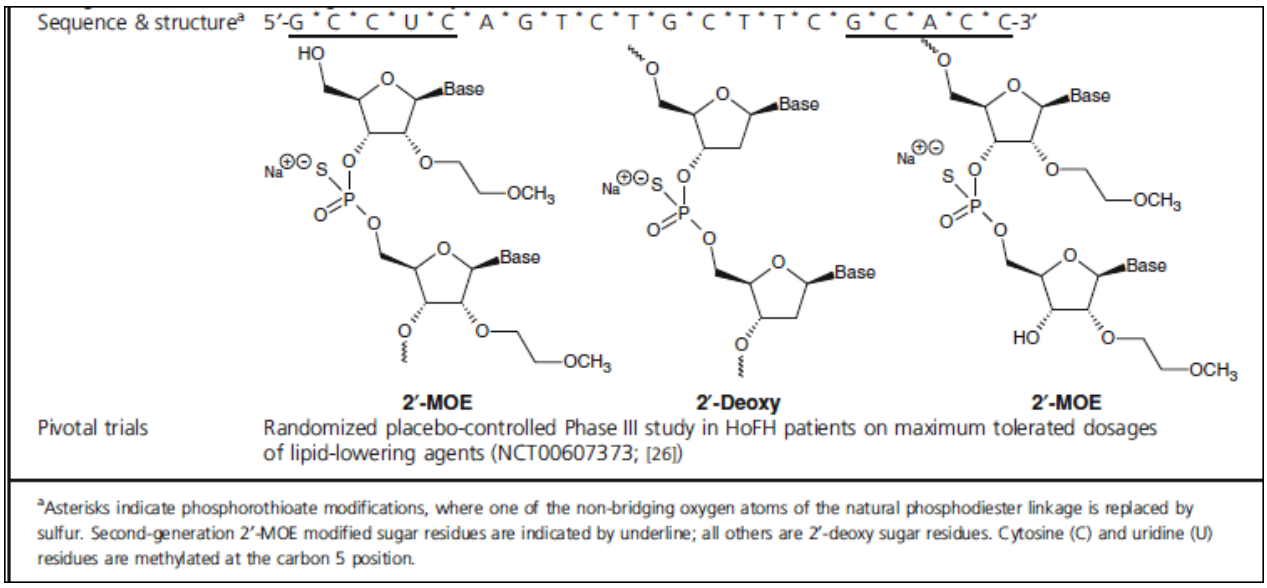

Figure 1: Structure of mipomersen from reference number [27].

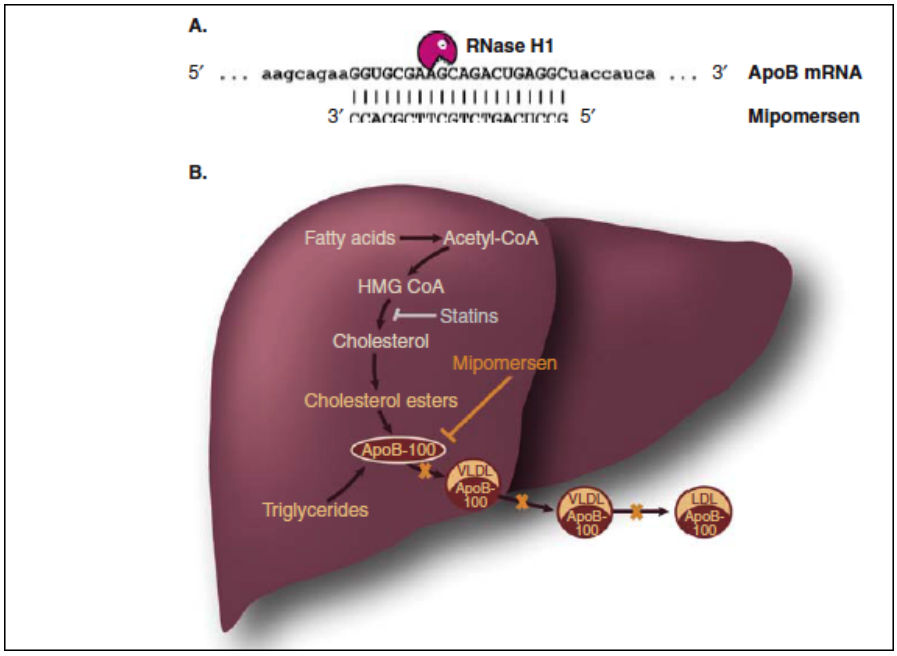

Figure 2: Mechanism of action of mipomersen. **(A):** Mipomersen binds sequence specifically to the apoB mRNA to provide a substrate for RNase H1, which hydrolyzes the apoB mRNA strand to inhibit apoB synthesis. **(B):** Inhibition of apoB synthesis by mipomersen reduces production of atherogenic apoB-containing lipoproteins by the liver [27].

200 mg were administered. Plasma concentration after s.c. injection from loading doses of 50 mg to 200 mg also showed similar result like i.v. route. Absorption was nearly complete following s.c. injection; therefore, for future formulation and most clinical trials, s.c. injection is used. The median time for mipomersen to reach maximum plasma concentration (C_{max}) was from 3.4 to 4 hrs [34]. The elimination half -lives were 23 (±1) days and 31 (±11) days in 50-mg and 200-mg group, respectively [24]. One week after the last dose of 50 mg to 400 mg/week doses, the mean plasma trough concentrations of mipomersen were reported from 8 to 51 ng/mL. Plasma trough concentration reached steady state after 2 weeks [34]. ASO is metabolized into 7-14 nucleotides of the parent compound, and then the parent compound and its metabolites are excreted in the urine [32].

Mipomersen is highly bound to plasma proteins (the fraction of mipomersen bound to protein is 93-96% in

human plasma over a concentration range of 1-20 umol/L). The drug has weak dissociation constant [35]. Mipomersen distributes into most tissues with volume of distribution of 48.3 L/kg. The highest concentrations of drug are detected in the liver and kidney. The drug is poorly distributed into the skeletal muscle, and it does not cross the blood brain barrier [35].

Mipomersen does not inhibit or induce any major cytochrome p450 enzymes such as CYP1A2, CYP2C9, CYP 2C19, CYP2D6 or CYP3A4; therefore, no clinically relevant interactions of mipomersen with other drugs metabolizing by these enzymes have been reported [8, 20]. Moreover, concomitant administration of mipomersen and simvastatin or ezetimibe did not cause significant changes on the pharmacokinetics properties of all drugs. There is no difference in half-life of mipomersen when it is taken by itself or in combination with simvastatin or ezetimibe [35]. There is no literature report the interaction of mipomersen and herbal products.

CLINICAL TRIALS

Data from Phase 1 Clinical Trials

The first phase 1, double-blind, randomized, placebo-controlled, dose-escalation clinical trial was conducted to determine the efficacy and tolerability of mipomersen in 36 patients with mild dyslipidemia age 18 to 65 years [24]. The 36 patients were randomized into five different groups receiving s.c. placebo, or a single s.c. dose of 50, 100, 200 or 400 mg mipomersen for 4 weeks (n=7, 8, 8, 9, and 4 patients, respectively). After 4 week treatment with placebo or mipomersen, there were 4 weeks period of observation in which patients didn't receive any drug. At the end of the 8 weeks, the patients in each group were given multi-dose of mipomersen i.v. given at the same assigned dose. The i.v. doses were intended to stabilize the patients' hepatic tissues to similar value like the baseline. For the next 3 weeks, once weekly s.c. injection were given at the same dose assignment. In total, a maximum of 12 weeks follow up were conducted to observe when the patients' TC levels had returned to greater than 90% of the baseline, whichever occurred first. At baseline, patients fasting TC were reported from 174 to 290 mg/dL [mean 219 (± 27) mg/dL], LDL-C ranged from 91 to 173 mg/dL [mean 128 (± 22) mg/dL], and apoB-100 ranged from 80 to 140 mg/dL [mean 104 (± 23) mg/dL]. Administration of mipomersen resulted in a dose-dependent reduction of apoB-100. In the 200 mg dose group, a 50% apoB-100 reduction from baseline was reported after 72 hrs. which was the highest changed reported among the other groups (p=0.002). Moreover, in the 200 mg-dose group, the TC, LDL-C, TG, and VLDL levels showed maximum reductions of 27% (p=0.002), 35% (p=0.001), 27%, and 30%, respectively. ApoB-100 and LDL-C levels remained significantly below baseline ($p < 0.005$) for up to 3 months after the least dose. The most common adverse reactions reported was an ISR showing as erythema (72% of incidence) which did not worsen upon repeated dosing [22, 24]. Table **2** listed other adverse drug reactions from different clinical trials.

In total, there were eight phase 1 clinical trials recruited a total of 308 healthy or patients having mild to moderate HC as described in Gebhard *et al*. [36]. These trials recruited from 18 to 84 patients with different time lines of treatment, with mipomersen ranged from 24 hrs. 8 days to 13 weeks. Some patients received i.v. or s.c. injections. The aggregate results of these clinical trials showed that mipomersen caused maximum reduction of apoB-100 for up to 50% and LDL-C for up to 35% from the baseline. The levels of apoB-100 and LDL-C remained below baseline for up to 3 months after the last dose [36].

Data from Phase 2 Clinical Trials

Five phases 2 clinical trials were designed to evaluate mipomersen effects in patients having mild to moderated HC, in HC patients taking statin therapy, or in HeFH patients as an add-on therapy [34, 36-38]. A phase 2 randomized, double bind, multi-center, placebo controlled clinical trial recruited 44 HeFH patients age 18 years to 75 years to examine the efficacy and safety of mipomersen as an add-on therapy [38]. While on the study, these patients also continued taking other lipid lowering drugs such as statin, ezetimibe, or bile acid sequestrants. The inclusion criteria were HeFH patients with LDL-C greater than 200 mg/dL (5.2 mmol/L) and at least having one additional criteria: the presence of known mutation in the LDLR gene, the presence of cutaneous xanthomas, history of having adult first-degree relatives with LDL-C greater than 190 mg/dL (4.9 mmol/L) or having a child younger than 18 years with LDL-C greater than 130 mg/dL (3.4 mmol/L), or history of first degree relatives having early CVD at age less than 55 years for male and less than 60 years for female. The exclusion criteria include: having prior CVD surgical intervention, having history of hepatic, renal, or uncontrolled endocrine disorders, having serum creatinine phosphokinase level greater than or equal to three times of

upper limit normal (ULN), or having hepatic alanine aminotransferase (ALT) levels greater than or equal to two times of ULN [38]. The patients were randomly assigned to placebo (n=8) or s.c. mipomersen 50 mg (n=8), 100 mg (n=8), 200 mg (n=11), or 300 mg (n=9) group, respectively. The patients received mipomersen on days 1, 4, 8, and 11, followed by additional once-weekly doses on days 15, 22, 29 and 36. In the 300 mg dose group, patients received additional 7 weeks of s.c. mipomersen on days 43, 50, 57, 64, 71, 78, and 85 [38]. After 6 weeks of treatment, statistically significant reduction of apoB-100 and LDL-C levels were observed in 200 mg and 300 mg group. Mean reduction of apoB-100 was 23% in 200 mg ($p < 0.05$) and 33% in 300 mg ($p < 0.01$) group, respectively, and reduction in LDL-C was 21% in 200 mg ($p < 0.05$) and 34% in 300 mg ($p< 0.01$) group, respectively. Moreover, statistically significant reduction of apoB-100 level by 37% and LDL-C level by 37% were reported in the group given additional of 7 weeks of 300 mg SC mipomersen. Three months after the last dose, continual reduction in apoB-100 and LDL-C levels to below baseline were observed [38]. The most common adverse reaction was 97% of ISR. Other adverse drug reactions are listed on Table **2.** Concomitant administration of mipomersen with simvastatin or ezetimibe did not caused significant effect on the pharmacokinetics properties of all the drugs. The result of this phase 2 clinical trial showed that mipomersen can be given in combination with statins or ezetimibe to further decreasing apoB-100 levels in HeFH patients. Mipomersen is metabolized by nucleases, therefore its level is not effected by combination with other drugs [35, 39].

In total, there were five phase 2 clinical trials recruited 194 patients with HeFH or HC patients as described in Gebhard *et al*. [36]. The aggregate results of these phase 2 trials showed significant reductions in apoB-100 and LDL-C levels ranged from 21% to 47% in patients taking mipomersen as a single agent or as an add-on to statins. Because of the undesirable adverse reactions of mipomersen at 300 mg or 400 mg in phases 1 and 2 clinical trials in different population with variable dyslipidemia conditions, for phase 3 trials and hereafter, the dose of mipomersen is determined as s.c. 200 mg given once weekly.

Data from Phase 3 Clinical Trials

Five randomized, double blind, placebo control phase 3 clinical trials were conducted in patients with HoFH or HeFH. The latest of phase 3 clinical trial is described below, whereas the other four are listed in Table **1.** [7, 40-42]. The most recent planned interim analysis, open label extension trial recruited 141 FH patients (103 HeFH and 38 HoFH) who had successfully completed a phase 3 clinical trial was reported. This report observed the long-term efficacy and safety of mipomersen for 104 weeks or up to 4 years [43]. These patients received s.c. 200 mg mipomersen once weekly and maximal tolerated dosage of other lipid lowering drugs. Inclusion criteria were successfully completed phase 3 trial, did not have abnormalities of liver blood test (AST or ALT), having tolerable ISR or influenza-like syndrome, not having new or worsening condition that interfere with the study, and were willing to limit alcohol consumption to moderate amounts (males 2 drinks (20 g) per day, 8 drinks per week; female 1 drink (10 g) per day, 4 drinks per week). The mean changed in LDL-C levels from baseline on 26, 52, 76, and 104 weeks were -28%, -27%, -27%, and -28%, respectively. The mean changed in apoB-100 levels from baseline on 26, 52, 76, and 104 weeks were -29%, -28%, -30%, and -31%, respectively. Median changes in Lp (a) from baseline on 26, 52, 76, and 104 weeks were -21%, -19%, -18%, and -17%, respectively, while mean increased in HDL-C level from baseline on 26, 52, 76, and 104 weeks were 6%, 6%, 3%, and 10 %, respectively. Mean reduction in TC and non-HDL-C levels were consistent with the mean reduction in LDL-C and apoB-100 levels. The elimination plasma half-lives were from 14.3 to 105 days (median of 35 days). All patients experienced at least one ISR and had at least one episode of influenza-like syndrome. However, the frequency of ISRs decreased by 67% after 24 months. There was an increase in hepatic transaminase during the first 6-12 months, but with continual injection, the level didn't change overtime [43].

ADVERSE REACTIONS, CONTRAINDICATION, AND SAFETY

Common and less common adverse reactions of phase 1, 2 and 3 are listed on Table **2.** ISR happens in at least 98% of the cases, but it is generally self-limiting, and mild to moderate in severity. Every patient experiences at least one ISR during the treatment. Influenza-like symptoms that started within 2 days after the mipomersen injection affects about 65% of the patients. It is the most frequent cause of drug discontinuation.

Mipomersen sodium is contraindicated in patients with moderate to severe hepatic impairment (Child Pugh category of B or C) or active liver disease

Table 1: Summary of 4 other Phase 3 Clinical Trials of Mipomersen Sodium [7, 40-42]

Study	Design	Patients	Outcomes	Results
Raal *et al.* (2010) [7]	R, PC, DB, MC 200 mg/week for 26 weeks Evaluate safety and efficacy of mipomersen	n= 51 HoFH MIP (n=34), PL (n=17) Inclusion: LDL-C > 131 mg/dL and xanthoma before 10 yo, or have HeFH parents, on low fat diet, take statins, ezetimibe, bile acid sequestrants, or combination of the drugs Exclusion: have lipid apheresis the previous 8 weeks, significant CVD events within 12 weeks, CHF, uncontrolled hypothyroidism, unstable angina, hyperlipidemia, or renal or hepatic disease, have liver transaminase ≥ 3 x ULN	Primary: percentage in LDL-C reduction Secondary: percentage change in apoB, TC, HDL-C, Lp(a), TG	MIP: LDL-C* -25 % apoB* -27 % TC -21 % non HDL-C -25 % ratio of LDL/HDL-C -34% HDL-C +15 % PL: ratio of LDL/HDL-C 6%
Stein *et al.* (2012) [40]	R, PC, DB, MC 200 mg/week for 26 weeks Evaluate safety and efficacy of mipomersen as an add-on therapy	n= 124 HeFH with CVD MIP (n=83), PL (n= 41) Inclusion: HC with LDL-C ≥ 100 mg/dL, TG ≥ 200 mg/dL, maximum tolerated statin with or without other lipid lowering drugs Exclusion: have lipid apheresis the previous 8 weeks, DM, unstable angina, CHF, hyperlipidemia, having AST or ALT ≥ 1.5 x ULN, or having renal or hepatic disease.	Primary: percentage LDL-C reduction Secondary: percentage change in apoB, TC, HDL-C, Lp(a), TG	MIP: LDL-C* -28 % apoB* -26 % TC -19 % Non HDL-C* -25 % VLDL-C -14 % TG -14 % HDL-C +3 % Ratio LDL/HDL-C* -29 % PL: LDL-C + 5 % apoB +7 % TC +4 % Non HDL-C +4 % HDL-C +6 % Ratio LDL/HDL-C -3 %
Thomas *et al.* (2013) [41]	R, PC, DB, MC 200 mg/week for 26 weeks Stratified to ≥ 40% patients have T2DM Evaluate safety and efficacy of mipomersen	n= 157 HC with CVD MIP (n=105), PL (n=52) Inclusion: HC with LDL-C > 100 mg/dL and high risk for atherosclerosis on low-fat diet and maximally tolerated statin therapy. Exclusion: significant CVD events with 24 weeks of screening, HF, HTN, T1DM, hyperlipidemia, or having renal or hepatic disease.	Primary: percentage LDL-C reduction Secondary: percentage change in apoB, TC, HDL-C, Lp(a), TG	MIP: LDL-C*-37% apoB*-38% HDL-C+2% TG-26% Lp(a)-24% TC-26% PL: LDL-C-5% apoB-4% HDL-C+2% TG+11% TC-3%
McGowan *et al.* (2012) [42]	R, PC, DB, MC, 200 mg/week for 26 weeks Evaluate safety and efficacy of mipomersen	n= 58 severe HeFH MIP (n=39), PL (n=19) Inclusion: HeFH, have LDL-C ≥ 300 mg/dL without CHD, or ≥ 196 mg/dL with CHD on maximally tolerated lipid lowering therapy and are not on apheresis. Exclusion: active apheresis, significant CVD events with 24 weeks of screening, CHF, HTN, hyperlipidemia, or having renal or hepatic disease.	Primary: LDL-C reduction from baseline to 2 weeks after the last dose Secondary: percentage change in apoB, TC, HDL-C, Lp (a), TG	MIP: LDL-C* -36 % apoB* -36 % non HDL-C -34 % TC-28 % PL: LDL-C +12 % apoB +11 % non HDL-C +14% TC+11 %

Abbreviation: p values v. placebo; *p ≤ 0.001 all populations; R, randomized; OL, open-labeled; DB, double-blind; PC, placebo-controlled; MC, multi center; HC, hypercholesterolemia; CHD, coronary heart disease; CHF, congestive heart failure; HTN, hypertension; MIP, mipomersen; PL, placebo; DM, diabetes mellitus; LDL-C, low density lipoprotein cholesterol; Lp (a), lipoprotein (a); ApoB, apolipoprotein; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; ULN, upper limit of normal; FH, familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia

presenting as unexplained persistent elevation of liver transaminases (ALT or AST) to equal or greater than 3 times ULN [43].

Mipomersen can cause elevations in liver transaminases and hepatic fat (steatohepatitis) which can progress to cirrhosis with or without an increased in the transaminase levels. If symptoms of hepatotoxicity or liver injury are noticed such as nausea, vomiting, abdominal pain, fever, jaundice, lethargy, increased in bilirubin to equal or greater than 2 times ULN, or increased in liver transaminases to equal or greater than 3 times ULN, the mipomersen treatment should be discontinued.

Because this risk of hepatotoxicity, mipomersen is only available through a restricted program called Kynamro® risk evaluating and mitigation strategy (REMS), in which only certified healthcare providers and pharmacies may prescribe and distribute this drug [44]. Patients should have a full liver, total bilirubin and alkaline phosphatase tests before the initiation of the treatment and thereafter tested depending on the levels of the hepatic transaminases. The goals of REMS program are to educate healthcare providers and patients about the risk of hepatoxicity, to ensure patients to have their liver being monitored, and to restrict use of mipomersen to patients with HoFH or severe HeFH only [44].

Table 2: Adverse Drug Reactions from some Phase 1-3 Clinical Trials [24, 37, 40]

Clinical Phase	Adverse Drug Reactions
Phase 1 Study by Kastelein *et al*. [24]	MIP: ISR (erythema, pruritus, irritation, discoloration, pain, swelling, bruising, induration, warmth, rash and hematoma) 72% Influenza- like symptoms (pyrexia, chills, myalgia, arthralgia, malaise) 70% Increase in TG 0.8 % PL: ISR 9 % Influenza-like symptoms 18 % Decrease in TG 0.1 %
Phase 2 Study by Akdim *et al.* [37]	MIP: ISR 90 % Headache 31 % Influenza-like symptoms 25 % Fatigue 19 % Nasopharyngitis 17 % Back pain 17 % Urinary tract infections 10% Pyrexia 10% Increase in ALT to ≥ 3 x ULN 17 % PL: ISR 13 % Headache 40 % Influenza- like symptoms 7 % Nasopharyngitis 7 % Back pain 7 % Increase in ALT to ≥ 3 x ULN 7 %
Phase 3 Study by Stein *et al.* [40]	MIP: ISR 93% Influenza- like symptoms 49 % Nausea 17 % Headache 18 % Diarrhea 11 % Nasopharyngitis 11 % Cough 11 % Increase in ALT to ≥ 2x ULN 41 % ≥ 3x ULN 36% PL : ISR 42 %, Influenza- like symptoms 32 % Nausea 14 % Headache 17 % Diarrhea 12 % Nasopharyngitis 7 % Cough 5 % Increase in ALT to ≥ 2x ULN 34 % ≥ 3x ULN 7 %

Abbreviation: MIP, mipomersen; PL, placebo; ISR, injection site reaction; ULN, upper limit normal; ALT, alanine aminotransferase; TG, triglyceride.

DOSING, ADMINISTRATION AND STORAGE

In the clinical trials, the maximum tolerated dose of mipomersen was defined as 200 mg s.c. injection given once weekly. Mipomersen sodium is available as a single dose of prefilled s.c. syringe or a single vial containing 1 mL of 200 mg mipomersen of colorless to slightly yellow solution. The s.c. injection should be given in abdomen, thigh or upper arm. The drug should be stored in refrigerator at 2°C to 8°C (36°F and 46°F) [19, 45]. It should reach room temperature at least 30 mins before the administration. If refrigerator is not available, it can be stored at or below 30°C (86°F), away from heat sources for up to 14 days [19, 45].

USE IN SPECIFIC POPULATIONS

Although the pregnancy category of mipomersen is B, there were no adequate and well-controlled studies have been done in pregnant women. Studies in pregnant animal showed that there was no harm to the fetus. Although it is not known if mipomersen is excreted into human milk, however, caution should be exercised when mipomersen is administered to nursing mother.

There was no specific guideline from the manufacture regarding use of mipomersen in pediatric population although a clinical trial recruited patients younger than 18 years had been conducted in which 7 out of the 51 were pediatric. There were no differences in adverse reactions in the patients younger than 18 years or in older patients group. The mipomersen prescribing information states, “Safety and effectiveness of mipomersen has not been established in pediatrics [19].” More clinical trials are needed to recruit pediatric patients to determine the safety and effectiveness of mipomersen in this population.

Patients older than 65 years old may experience higher incidence of hypertension and peripheral edema, but the percentage of the incidence is not reported [19]. Hepatosteatosis incidence was greater in patients older than 65 years (13.6%) vs. 10.4% in patient younger than 65 years old [19].

ECONOMIC INFORMATION

Many patients with CVD, severe dyslipidemia, or elevated Lp (a) levels need aggressive treatment to

lower theirs LDL-C, apoB-100, or Lp (a) levels. Patients with HoFH usually respond less effectively to statins than HeFH patients. Additionally, HoFH or HeFH patients usually require lipid apheresis as the treatment option to extra corporeally removing unwanted LDL-C from the blood [46, 47]. Using lipid apheresis procedure, a reduction of about 53% in LDL-C level are seen with weekly or biweekly procedure (from average 19 mmol/L in untreated to 12 mmol/L in treated patients) [46].

Currently in the USA, there are estimated of about 315 HoFH patients and 650,000 HeFH patients [48]. The estimated cost for a lipid apheresis is $4,000 per procedure. Patients who have weekly procedure will pay $208,000 per year, not counting traveling from their homes to one of the 35 lipid apheresis sites available in the USA [49].

The cost of mipomersen per month is $16,269 per 4 injection or $ 176,228 per year [50]. Another drug that is currently approved by FDA for the treatment of HoFH is lomitapide (Juxtapid®). Lomitapide has pregnancy category of X, is an oral drug available at 5, 10 or 20 mg for the cost of $27,156 per 28 capsules. This drug can be taken as 5mg to 60 mg daily for an annual cost ranged from $235,000 to $ 295,000 [51]. Comparing the cost of mipomersen to lipid apheresis or lomitapide, a patient can save from $59,000 to $119,000 annually.

SUMMARY

Mipomersen sodium given as an s.c. injection once weekly at dose of 200 mg/vial is effective in lowering LDL-C, apoB-100, TG, TC and Lp (a) levels in patients with severe HC, HeFH or HoFH as shown in several phase1, 2 and 3 clinical trials. Mipomersen provides significant additional reduction in apoB-100 atherogenic lipoproteins which is difficult to treat in HoFH or HeFH patients, although these patients usually already treated with maximal dose of lipid lowering drugs such as statins or ezetimibe. Mipomersen does not cause drug-drug interactions with other drugs or lipid lowering drugs which provides advantage to the patients who need to take combination of mipomersen and other lipid lowering drugs. Common adverse reactions are ISR, influenza-like symptoms, and increase in ALT or AST levels. Although the clinical significant of the increased in AST, ALT and/or liver fat content that are occurring in some patients remains uncertain, mipomersen was found to not causing increased risk of steatohepatitis or hepatocellular inflammation [45]. The recently open label clinical trial confirmed the safety profile of mipomersen for up to 2 years showing similar profile when it is taken for shorter duration such as 26 weeks. There was also a returned in the liver fat content toward baseline after 1 year treatment. This showed liver has ability to adapt to the drug. Establishing baseline liver function prior to initiation of mipomersen treatment follows by regular monitoring liver test is highly recommended. Mipomersen is available only from certified healthcare providers and pharmacies. The US FDA approved mipomersen with black box warning of causing increased risk of hepatic impairment, as an orphan drug for HoFH patients as an adjunctive treatment to currently available lipid lowering drugs.

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