CLINICAL INVESTIGATION

The role of mipomersen therapy in the treatment of familial hypercholesterolemia

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Familial hypercholesterolemia (FH) is a genetic disorder that results in elevated LDL levels and is associated with an increased risk of cardiovascular disease. HMG-CoA reductase inhibitors are recommended as first-line treatment for FH, but often multiple lipid-lowering agents are required to achieve desired reductions in LDL-C in this patient population. The purpose of our review is to discuss the role of mipomersen in the treatment of FH. A PubMed search revealed three published studies and three abstracts of Phase III extension studies evaluating mipomersen in the treatment of FH, and one study evaluating the safety and efficacy of mipomersen in statin-intolerant patients at high risk for cardiovascular disease, wherein a little more than half of the enrolled patients were diagnosed with FH. Mipomersen, an antisense single-strand synthetic oligonucleotide, may become a potential treatment option for patients with FH that require either additional lipid-lowering or as an alternative to statins in intolerant individuals. Studies have demonstrated that mipomersen significantly reduces LDL-C, ApoB, non-high-density lipoprotein-C, triglycerides and lipoprotein(a) when added to traditional lipid lowering therapy in patients with FH. Safety analysis has shown that mipomersen is well tolerated except for the common finding of injection-site reactions. Further, hepatic steatosis is an ongoing safety concern that warrants future investigation with larger populations and longer study periods. Overall, mipomersen may offer an additional treatment option for patients with FH and has been shown to effectively reduce cholesterol in this population in short-term studies.

Keywords: antisense therapy • efficacy • familial hypercholesterolemia • mipomersen • safety

Familial hypercholesterolemia (FH) is a genetic disorder characterized by mutations in the LDL receptor (LDLR), ApoB, convertase subtilisin/kexin type 9, or *LDLRAP1* gene, all of which result in elevated LDL cholesterol levels. FH can present as heterozygous, defined as having one anomalous copy of the *LDLR* gene, which is the most commonly encountered mutation in this patient population, increasing the risk of cardiovascular disease (CVD) by the age of 50 years, or homozygous FH defined as two anomalous copies of the *LDLR* gene, leading to CVD in early childhood. Patients with identified mutations in the *LDLR* and *PCSK9* genes have demonstrated to have substantially higher total cholesterol levels despite treatment when compared to patients with no identified mutation, in addition to a higher risk of early coronary heart disease [1]. Heterozygous FH has a 1 in 300–500 prevalence, whereby homozygous FH has a 1 in 1 million prevalence [2–4].

The Summary Recommendations from the National Lipid Association Expert

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Panel on Familial Hypercholesterolemia for adult FH patients – defined as patients above 20 years of age – recommend a 50% LDL-C reduction from the baseline lipid levels. HMG-CoA reductase inhibitors, otherwise known as statins, are recommended as first-line treatment [5–6].

Suggested alternative pharmacological agents for intensification of therapy or for patients unable to tolerate statins include ezetimibe, niacin, fibric acids and bile acid sequestrants [3–7].

Overall, FH is difficult to treat and requires aggressive drug treatment with multiple lipid-lowering agents combined with strict lifestyle modification to achieve desired LDL-C levels. This often applies to heterozygotes that usually require combination drug therapy to achieve their respective lipid goals [8]. Homozygotes, however, are often refractory to conventional drug therapy and require interventional procedures, such as LDL plasma apheresis, to control their elevated cholesterol levels [2]. The focus of this review is to explore the potential role of mipomersen in patients with heterozygous and homozygous FH.

Mipomersen is a second-generation antisense single-stranded synthetic oligonucleotide that inhibits ApoB synthesis in the liver. Mipomersen is administered subcutaneously and, when uptaken by the liver, binds to ApoB mRNA, recruiting RNase-H to degrade the duplex, and thereby inhibits ApoB synthesis, resulting in a decrease in the secretion of VLDL particles, the precursor of LDL [9]. Mipomersen has demonstrated promise in prior studies evaluating healthy subjects and patients with hypercholesterolemia, in reducing Apo-B containing lipoproteins in a dose-dependent manner [10–13]. In addition to a long elimination half-life (~30 days) resulting in a prolonged pharmacological response, mipomersen has been demonstrated to be well tolerated [10,11], with the exception of the injection-site reactions which affected almost all patients enrolled in the mipomersen group [12,14,15].

Method

A PubMed search was conducted using the search terms mipomersen and ApoB. Mipomersen has been studied in numerous trials, evaluating medication efficacy, safety and tolerability as monotherapy and given concomitantly with other lipid-lowering medications [101]. To date only three published studies [12,14,15], three abstracts of Phase III extension studies evaluating mipomersen in the treatment of FH [16–18], and one study evaluating the safety and efficacy of mipomersen in statin-intolerant patients at high risk for CVD (wherein a little more than half of the enrolled patients were diagnosed with FH) [19], are available and outlined in Table 1.

Review of Studies

Akdim *et al.* conducted a multicentered, randomized, double-blind, placebo-controlled Phase II trial evaluating the efficacy and safety of mipomersen dose escalation when added to traditional lipid-lowering therapy in patients with heterozygous FH [12]. In total, 44 patients were randomized into four dose cohorts, 50, 100, 200 and 300 mg of subcutaneous mipomersen weekly or placebo for a 6-week treatment period, and subjects enrolled into the 300-mg weekly mipomersen group continued for an extended treatment of 13 weeks. The study included a 5-month follow-up period after the treatment period. Significant reductions in the LDL-C and ApoB levels were noted in the mipomersen 200-mg group, -21 ($p < 0.05$) and -23% ($p < 0.05$), respectively, and the mipomersen 300-mg group, -34 ($p < 0.01$) and -33% ($p < 0.01$), respectively. Similarly, both mipomersen 200- and 300-mg groups demonstrated a nonsignificant triglyceride reduction of -23 and -22%, respectively. Equally notable were the nonsignificant decreases in the (Lp[a]) in mipomersen 200- and 300-mg groups, -17 and -24%, respectively. Likely this is because Lp(a) is a variant of LDL with apo(a) covalently attached to the ApoB, so that with less ApoB synthesis, it would be expected to lower Lp(a) generation. No difference was noted in the HDL-C levels across the treatment groups. Extended treatment to 13 weeks with mipomersen 300 mg weekly resulted in further reductions in the LDL-C of -37% ($p < 0.001$), achieving an LDL-C level of 109 mg/dl, ApoB of -37% ($p < 0.01$), achieving an ApoB level close to goal of 95 mg/dl, and a decrease in Lp(a) of -29% ($p < 0.05$).

Mipomersen treatment was well tolerated except for injection-site reactions, which occurred in almost all patients (vs placebo) in similar frequency within all doses (97 vs 25%), followed by headache (22 vs 0%), nasopharyngitis (19 vs 25%), myalgia (17 vs 13%), and nausea (17 vs 13%). The authors indicate that four patients out of the mipomersen group (one patient of the 50-mg and three patients of the 300-mg group) and one patient in the placebo group, experienced elevations in serum alanine aminotransferase levels (>3 × upper normal limit [ULN]). Alanine aminotransferase (ALT) levels remained elevated for 2–19 weeks post study period in three of the five patients. Computed tomographic scans revealed hepatosteatosis in two patients and hepatomegaly without steatosis in one patient. Due to lack of baseline tomographic scans, a casual relationship between mipomersen treatment and hepatic fat was unable to be established.

The authors conclude that mipomersen 200-mg weekly should be further studied in Phase III trials, and safety studies be focused on the potential of mipomersen to induce hepatosteatosis.

Table 1. Clinical trials evaluating the efficacy of mipomersen therapy.

Author (year)	Patient (n)	Population	Mipomersen dose (mg/week)	Results (%)						Ref.
				LDL-C	ApoB	TG	non-HDL-C	Lp(a)	IHTG	
Akdim *et al.* (2010)	44	Heterozygous FH	50 100 200 300	-13 -11 -21* -34**	-10 -8 -23* -33*	6 6 -23 -22	-12 -8 -21* -31*	-3 -15 -17 -24	NA NA NA NA	[12]
Visser *et al.* (2010)	21	Heterozygous FH	200	-22**	-19.9***	-16.3	-21.3*	-19.6***	+0.8	[14]
Raal *et al.* (2010)	34	Homozygous FH	200	-24.7***	-26.8***	-17.4*			NA	[15]
Stein *et al.* (2010)	124	Heterozygous FH	200	-28*	-26.3*	-14.2	NA	-21.1*	NA	[16]
Tardif *et al.* (2011)	58	Heterozygous FH	200	-36*						[17]
Duell *et al.* (2012)	141	FH	200	-26 to 28	-28 to -31			-14 to -21		[18]

Statistically significant at *p < 0.05; **p < 0.01; ***p < 0.001.

FH: Familial hypercholeterolemia; IHTG: Intrahepatic triglyceride; TG: Triglycerides.

The authors briefly mention that the patients enrolled in this study were on high doses of statins with or without other lipid-lowering agents, but did not provide the readers with the specific statin and doses used.

Visser *et al.* [14] conducted a randomized, double-blind, placebo-controlled study, evaluating the effects of mipomersen 200 mg administered subcutaneously on a weekly basis for a 13-week treatment duration on the intrahepatic triglyceride (IHTG) content measured using 1H MRS imaging and percent reduction in the LDL-C and ApoB from baseline, in 21 subjects with heterozygous FH already receiving traditional lipid-lowering therapy. The authors demonstrated a significant reduction in LDL-C and ApoB, -22 ($p < 0.01$) and -20% ($p < 0.001$), respectively, in the group receiving mipomersen. The group of subjects receiving mipomersen achieved a mean LDL-C level of 118.1 mg/dl and a mean ApoB level of 104.7 mg/dl at week 15. Similar to the findings by Akdim *et al.*, the most common adverse event noted was injection-site reactions, which occurred in all ten patients receiving mipomersen therapy and eight out of 11 (73%) of the patients in the placebo group [11]. The subjects receiving mipomersen demonstrated a +0.8% change versus a -0.1% change in the placebo receiving group in the IHTG content from baseline to week 15 ($p = 0.0513$). The patients with familial hypobetalipoproteinemia not treated with mipomersen demonstrated a mean baseline IHTG content of 21.9%, ranging from 13.2 to 30.1%. No significant increases in the ALT defined as exceeding three-times ULN was noted. One patient receiving mipomersen had an increase in IHTG content from 0.6 to 5.7% at week 15 of treatment, which resolved after the treatment period during follow-up. To note the upper limit of normal is 5.6% for IHTG content. Although not statistically significant, there was a trend toward increased IHTG content in patients treated for 13 weeks with mipomersen. The results from this study suggested the need for a longer treatment period to better evaluate the risk of hepatic steatosis with mipomersen administration.

Raal *et al.* conducted a multicenter, randomized, double-blind, placebo-controlled Phase III trial evaluating the efficacy and safety of mipomersen 200-mg per week versus placebo, when added to existing lipid-lowering treatment in patients with homozygous FH [15]. In total, 51 patients (34 mipomersen, 17 placebo) were treated for 26 weeks with primary outcome of percent change in LDL-C from baseline. Patients were required to maintain stable doses of their background lipid-lowering drug therapy during the trial and subjects receiving LDL apheresis within 8 weeks of the screening visit were excluded. The absence of homozygote FH patients on LDL apheresis could represent a weakness of this study as LDL apheresis is frequently used in this patient population; therefore, future investigation is needed to establish the efficacy of mipomersen in patients undergoing LDL apheresis. The authors demonstrated a significant reduction in LDL-C of -24.7% ($p = 0.0003$) from baseline in patients receiving mipomersen. Of note, there was considerable variability in LDL-C response to treatment ranging from -2 to -82%. Secondary end points in ApoB (26.8% reduction, $p < 0.0001$),

Lp(a) (31.1% reduction, p = 0.0013), VLDL (17.4% reduction, p = 0.0081) and non-HDL (24.5% reduction, p = 0.0002) also illustrated the effectiveness of weekly mipomersen injections in addition to ongoing lipid-lowering therapy (88% were on maximum dose statin therapy). This study also demonstrated a statistically significant increase in HDL-C levels from baseline in mipomersen-treated patients (15%) versus placebo (4%, p = 0.03). The most common adverse events were injection-site reactions consisting of transient erythema, local pain, tenderness and swelling, which were three-times more common in the mipomersen group compared to placebo. Four patients (12%) in the mipomersen group, compared to none in the placebo group, had ALT increases of three-times or more than in the ULN. One patient with hepatic steatosis at baseline developed an increase in hepatic fat content from 9.6 to 24.8% as measured through MRI. Of note, this patient had a substantial reduction from baseline in LDL-C of 75% by week 13 to a concentration of approximately 70 mg/dl. Comprehensive measurements of hepatic steatosis through MRI were not routinely measured in all patients.

Future Perspective

Individuals with FH often do not achieve desired cholesterol goals with available lipid-lowering agents. In a retrospective analysis based on 1249 subjects with a diagnosis of heterozygous FH, it was noted that only 21% of these patients, 96% of whom were receiving statin based therapy, achieved their LDL-C goal of <100 mg/dl [20].

Homozygous FH are refractory to combination lipid-lowering agents and may warrant LDL apheresis, liver transplantation [2], porto-systemic shunting, and partial ileal bypass [21–23]. If approved, mipomersen would become another pharmacologic option for the treatment of FH, either as an add-on therapy for those not achieving desired LDL-C levels while on traditional lipid lowering therapy, or as an alternative in statin intolerant individuals, and potentially reduce the need for interventional procedures [22–23]. Visser *et al.* conducted a randomized, double-blind, placebo-controlled study evaluating the effects of mipomersen 200 mg in statin-intolerant subjects with a high risk for CVD events. Out of the 33 subjects enrolled into the study, 52% had FH. Mipomersen 200-mg weekly administered for a 26-week study period demonstrated a LDL-C reduction of 47% (p < 0.001) with a similar discontinuation rate due to adverse events when compared to the placebo group [19].

Unlike traditional lipid-lowering agents, antisense therapy has a unique mechanism of action, independent of the LDL receptor activity. Studies have demonstrated mipomersen's significant LDL-C and ApoB lowering potential and clinically significant lowering of triglycerides and Lp(a). Equally notable is the lack of drug–drug interaction of mipomersen when coadministered with other lipid-lowering agents [11,14,24].

To date, studies have evaluated the efficacy and safety of mipomersen therapy in short study durations in the FH population. The injection-site reaction poses a major problem to most patients and, being the leading reason for mipomersen discontinuation, needs to be resolved by the manufacturer. A continued safety concern is hepatic steatosis, warranting longer study periods with larger sample sizes, powered to evaluate drug safety.

The addition of mipomersen therapy to the pharmacological armamentarium for the treatment of FH would provide additional options for the management of this difficult-to-treat disease provided forthcoming safety studies are conducted and do not disclose serious adverse events. There are at least three factors that should be kept in mind while going forward in the clinical trials of mipomersen, namely:

- This is the first such drug in the antisense class, so a comprehensive survey of safety issues will be required;
- The injection-site reaction will have to be low or of minor consequence to maintain compliance;
- The risk or exacerbation of hepatic steatosis will have to be determined, especially in the insulin-resistant settings, in which patients are prone to accumulate

Executive summary

- Mipomersen is a second-generation antisense single-stranded synthetic oligonucleotide that inhibits ApoB synthesis in the liver.
- Mipomersen has been demonstrated to significantly reduce LDL-C, ApoB, non-HDL-C, triglycerides and lipoprotein(a) when added to traditional lipid-lowering therapy in patients with familial hypercholesterolemia.
- Mipomersen may offer another pharmacotherapeutic option for patients with familial hypercholesterolemia who require either additional lipid-lowering or as an alternative to statin in intolerant individuals.
- The most common adverse event noted with mipomersen administration was injection-site reactions.
- Hepatic steatosis is an ongoing safety concern in mipomersen treatment warranting additional investigation with larger sample sizes and extended study periods.

hepatic fat.

Financial & competing interests disclosure

R Plakogiannis and L Cioce have nothing to disclose; EA Fisher is on an advisory board and in the speaker's bureau for Merck; JA Underberg has done consulting for Genzyme. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

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