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NOVEL THERAPEUTIC OPTIONS FOR FAMILIAL HYPERCHOLESTEROLEMIA

Muthukumar Rajaram, Melvin George and Elangovan Shanmugam

Department of Cardiology, SRM Medical College Hospital & Research Centre, Chennai – 603203, Tamil Nadu, India

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Correspondence to Author:

Melvin George
Department of Cardiology, SRM Medical College Hospital & Research Centre, Chennai – 603203, Tamil Nadu, India

E-mail: melvingeorge2003@gmail.com

ABSTRACT:

Background: Familial Hypercholesterolemia (FH) is an autosomal dominant disorder caused by mutation in the LDL receptor gene and characterized by raised LDL-C, tendon xanthomata and premature atherosclerosis. Existing therapies for FH such as statins and LDL apheresis do not offer adequate lipid control in most patients, which has led to the search for more definite alternatives. Two new drugs have been approved by the US FDA in the recent past for FH, namely mipomersen, an anti-sense oligo-nucleotide and lomitapide, a microsomal triglyceride transfer protein.

Methods: We did a literature search across PubMed to retrieve articles related to efficacy and safety of mipomersen and lomitapide.

Results: Mipomersen has been found to have reasonable efficacy in clinical trials over and above that seen with concomitant statin therapy in FH. Lomitapide has also shown evidence of adequate LDL-C reduction in clinical trials though the number of studies performed with lomitapide is relatively fewer. The subcutaneous route of administration for mipomersen may affect compliance especially with long term treatment. The most common adverse reactions seen with mipomersen include injection site reactions and flu-like symptoms. Lomitapide has a boxed warning for hepatic steatosis, though there is no evidence so far to indicate that it could progress to hepatic cirrhosis.

Conclusion: Although mipomersen and lomitapide show promise as novel therapeutic options for FH, the long term safety data is definitely warranted before it becomes a front line therapy in FH.

INTRODUCTION: Familial hypercholesterolemia (FH) is an autosomal-dominant condition that is characterized by elevated levels of plasma LDL cholesterol and apo-lipoprotein B resulting in an increased risk for atherosclerosis[1]. If untreated, patients may develop premature coronary artery disease (CAD).

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FH is considered to be the first genetic disease of lipid metabolism to be characterized at the molecular level [2].

Studies have consistently shown a positive correlation between plasma levels of LDL-C and the prevalence of CAD [3]. It is not surprising that, several cases of FH go undiagnosed or only diagnosed after their first coronary event.

The major underlying defect in FH is mutations of the low-density lipoprotein (LDL) receptor gene i.e., mutations in the pro-protein convert as subtilisin/ kexin type 9 gene and mutations in the apolipoprotein B100 gene [4].

The molecular mechanisms by which these sequence variations in PCSK9 reduce the LDL-C level are not known. PCSK9 is a glycoprotein that is expressed at its highest levels in the liver, intestine, and kidney [5]. Over expression of PCSK9 or the mouse orthologue in the livers of mice results in a marked reduction in LDL receptors in this organ [6-9], which is the main pathway for the removal of LDL from the plasma, and a corresponding increase in circulating LDL-C levels.

Thus, high levels of PCSK9 lead to high plasma levels of LDL-C, whereas low levels of PCSK9 lead to low LDL-C levels. It was the seminal work of Goldstein and Brown et al that led to the elucidation of LDL-receptor pathway [10]. The concept that defects in the LDL-receptor lead to FH came to light through their work, for which they were awarded the Nobel Prize in Physiology or Medicine in 1985 [11, 12].

The treatment of FH continues to be a challenging prospect since many patients do not achieve adequate lipid control even with maximal statin therapy. This is because patients with homozygous familial hypercholesterolemia (HoFH) lack functional LDL receptor activity and most of the current drugs work mainly through upregulation of LDL receptor in the liver. Over the last decade intensive research has been undertaken to discover novel drug targets that could be modulated favorably for the treatment of FH. This article is an overview on two molecules that have been recently approved for HoFH, namely mipomersen and lomitapide by the US FDA [13].

Mipomersen: Mipomersen, an antisense oligonucleotide, is a novel approach in the management of familial hypercholesterolemia (FH) [14]. Mipomersen consists of a 20-mer 2′-O-methoxyethyl modified nucleotide complementary and specific to human ApoB-100 mRNA [15]. It specifically targets ApoB-100 mRNA, blocking the translation of the gene product [16-18]. Following the binding of the oligonucleotide to the mRNA, degradation by endogenous RNase H is induced. As a result, the synthesis of apolipoprotein B is reduced, resulting in decreased production and secretion of apolipoprotein B-containing lipoproteins.

Pharmacokinetics of Mipomersen: The pharmacokinetic studies have shown that mipomersen has complete systemic absorption and is rapidly and extensively distributed to tissues (volume of distribution in humans 48.3 L/kg). Greater than 85% of mipomersen in plasma is bound to plasma proteins. Animal studies have also showed that the highest levels of the oligonucleotide are found in liver and kidney. Mipomersen is catabolized by endonucleases and exonucleases, which are abundantly expressed in all cells and tissues. The metabolites are largely excreted in the urine [18, 19]. The drug does not have any dependency on Cytochrome P450 metabolism. The half-life of mipomersen in humans has been calculated to be approximately 30 days [15]. Urinary excretion of mipomersen was found to be minimal in the first 24 hours. Oligonucleotide metabolites can also be detected in urine along with mipomersen. Mipomersen does not have any pharmacokinetic interactions when, co-administered with either simvastatin or ezetimibe [19]. The proposed mipomersen dose is 200 mg once weekly as a subcutaneous injection.

Efficacy of Mipomersen: A Phase I trial by Kastelein et al demonstrated that, in healthy individuals with mild dyslipidemia, once weekly dose of mipomersen (50-400 mg/week) therapy for 4 weeks brought a dose-dependent reduction of LDL-C, total cholesterol, lipoprotein(a), apolipoprotein B100, and triglycerides [17]. The observed reduction in LDL-C, lipoprotein(a), and apolipoprotein B was found to be independent of the underlying cause and independent of concomitant drug therapy. There was a sustained decrease in plasma apolipoprotein B and LDL-C for 3 months.

Phase II and III trials have demonstrated that mipomersen is an effective lipid-lowering therapy in FH. In a Phase II randomized double blind dose escalation study, 44 patients with heterozygous FH were administered 8 doses of mipomersen or placebo at weekly intervals. The dose of mipomersen varied between 50 to 300 mg/week [20]. The results showed significant reductions in apolipoproteinB (23% and 33%) and LDL-C (21% and 34%) in the 200 mg and 300 mg dose groups respectively.

But there was a trend towards reductions in lipoprotein (a) [Lp(a)], an important risk factor for coronary artery disease in FH [21-23], though the changes were not significant. Mipomersen did not have any effect on triglycerides and HDL-C. In a randomized double blind placebo controlled phase 3 clinical trial by Raal *et al*, 51 patients with HoFH were randomized to receive mipomersen (200mg/week) or placebo for 26 weeks in addition to standard therapy. The study showed that the mean percentage change in LDL-C concentration was significantly greater with mipomersen (-24.7%, 95% CI -31.6 to -17.7) than with placebo (-3.3%, -12.1 to 5.5; p=0.0003). Yet a high degree of variability was observed in changes to LDL-C, which ranged between 2% to −82% which could not be explained by baseline LDL-C, age, race, or sex.

Mipomersen also caused a significant reductions in Lp(a) (−31%) and triglyceride levels (−17%), and an increase in HDL-C (15%) [24]. Visser *et al* showed the effect of mipomersen in 33 statin-intolerant patients at high risk for cardiovascular disease [25]. More than half the patients in this study were found to be FH heterozygotes. The result showed that the patients who are on treatment with 200 mg/week mipomersen for 26 weeks had a 47% decrease in LDL-C, ranging from −19% to −77%. This was predominantly the result of a reduction in small LDL particles (−56%; P = 0.001 vs placebo) rather than large LDL particles (−4%; P, 0.017 vs placebo). While triglycerides and Lp(a) levels were significantly reduced by mipomersen treatment, HDL-C and ApoA-I concentrations did not change. A summary of studies done with mipomersen is depicted in **Table 1.**

TABLE 1.CLINICAL STUDIES PERFORMED WITH MIPOMERSEN AS ON DATE

Author, year	Patient population	Sample size	Outcome of the Study
Gowan *et al* (2012)[48]	Severe hypercholesterolemia with CHD	58	Reduction in LDL-C by 36% was observed in the mipomersen group versus an increase of 13% in the placebo group at 200mg/week subcutaneous dose with no change in HDL-C
Visser *et al* (2012)[25]	High-risk patients intolerant to statins	33	LDL-C decreased by 47.3%, with a similar decrease in apolipoprotein B (46.2%) and a decrease of lipoprotein(a) by 27.1% at 200mg/week
Tardif *et al* (2011)[49]	Severe FH.	58	Mipomersen 200 mg/week for 26 weeks reduced LDL-C by 36% from a mean baseline level of 276 mg/dL and also significantly decreased apolipoprotein B and lipoprotein(a), with no change in HDL-C.
Akdim *et al* (2011)[50]	Heterozygous familial hypercholesterolemia	50	In the 200 mg/week and 300 mg/week groups, mean reductions from baseline in LDL-C were 45% and 61%, corresponding to a decrease in apolipoprotein B concentration of 46% and 61%, respectively. Triglyceride levels were also lowered with median reductions up to 53%.
Cromwell *et al* (2011)[51]	Hypercholesterolemia and high cardiovascular risk	158	Mipomersen 200 mg/week for 26 weeks reduced LDL-C by 37%, with similar changes in apolipoprotein B and lipoprotein(a).
Raal *et al* (2010)	Homozygous FH	51	LDL-C decreased by 24.7%. Similarly, apolipoprotein B decreased by 26.8% and lipoprotein(a) by 31.1% at 200mg dosage.
Stein *et al* (2010)[52]	Heterozygous FH and cardiovascular Disease	124	200 mg/week of mipomersen resulted in an LDL-C reduction of 34%, an apolipoprotein B reduction of 26.3%, and a lipoprotein(a) reduction of 20% for 26 week
Akdim *et al* (2010)[20]	Heterozygous familial hypercholesterolemia	44	LDL-C was reduced by 21% in the200 mg/week group and 34% in the 300 mg/week group, with a reduction in apolipoprotein B by 23% and 33%, respectively
Akdim *et al* (2010)[53]	Hypercholesterolemia	74	The apo B and LDL-C were reduced by 19% to 54% and 21% to 52%, respectively, at doses of 100 mg/week mipomersen and higher in the 5-week treatment cohorts.
Kastelein *et al* (2006)[17]	Mild dyslipidemia	36	Apolipoprotein B and LDL-C were reduced by up to 50% and 35%, respectively.

Safety of Mipomersen: Initially the potential of mipomersen in causing tumors was assessed in carcinogenicity studies in mice and rats. There was a statistically significant increase in the incidence (over control) of benign hepatocellular adenoma in female mice treated with 60 mg/kg/week mipomersen. There was also an increased incidence of malignant fibrous histiocytoma in both males and females species at 10 and 20 mg/kg/ wkmipomersen respectively and an increase in malignantfibrosarcoma in females alone at the same dose as mentioned.But no malignant neoplasms have been reported at the injection site in mipomersen-treated individuals [26].

Mipomersen demonstrated a fair degree of safety in Phase II and Phase III studies. The most common adverse events experienced were injection site reactions (75%–100%). These reactions were dose-dependent and characterized by transient, mild to moderate erythema, occurring within 24 hours of drug injection. The two types of delayed responses observed were reappearance of erythema and hyperpigmentation. Whereas hyperpigmentation may be a common response to skin injury [27], the pathophysiological mechanism for reappearance of the erythema is unknown. Injection site reactions are considered an antisense class-related phenomenon as they are common with other antisense drugs. Though injection site reactions may not be classified as serious safety concerns, it could interefere with patient compliance.

Flu-like symptoms were also more often reported in the mipomersen group than in the placebo group in most studies. The flu-like symptoms usually appear shortly after mipomersen administration, but resolve within 1–2 days, and are generally limited to the first few weeks of treatment. Elevated transaminases (alanine aminotransferase level more than three times the upper limit of normal) was observed in 6%–15% of mipomersen-treated patients (0% in the placebo groups). After discontinuation of treatment, transaminases returned to normal in all patients. The exact reason for elevation of transaminase during mipomersen treatment is unclear, and it was not seen in preclinical studies. Hepatic steatosis was also been detected in some mipomersen-treated patients [28]. But hepatic steatosis and alanine aminotransferase resolved soon after discontinuation of treatment. Although the drug has been approved by the FDA, the high discontinuation rate among patients in clinical trials, hepatic steatosis and unproven cardiovascular benefit have made the regulators of EMA to with-hold approval of the drug [29]. The use of mipomersen in conjunction with LDL apheresis is currently being investigated in a phase 3 clinical trial in Germany to determine whether mipomersen will result in reduced apheresis time or frequency[30].Future trials with larger patient numbers will help establish the utility of mipomersen as a potential therapeutic option for the treatment of patients with severe hypercholesterolemia.

Lomitapide: Lomitapide (AEGR-733, previously known as BMS-201038) is a microsomal triglyceride transfer protein (MTTP) inhibitor and is the only drug that has been approved by both FDA and EMA [31] for homozygous familial hypercholesterolemia. MTTP is mainly responsible for transferring the triglycerides onto apolipoprotein B within the liver in the assembly of very-low-density lipoprotein (VLDL), the precursor to LDL [32]. Inhibition of MTP by lomitapide leads to a reduction in the circulating levels of apoB-containing lipoproteins, including LDL-C [33]. The development of MTP inhibitors was facilitated by the identification of patients with abetalipoproteinemia, a rare genetic disorder resulting from inhibition of the assembly of apolipoproteinB containing lipoproteins due to the absence of functional MTP [33, 34]. The action of MTP inhibitor provide potentially a powerful therapeutic method to reduce the production of apolipoproteinB-containing lipoproteins, especially VLDL, the precursors of LDL.

Pharmacokinetics of lomitapide: The proposed dose range of MTP inhibitor that is administered orally is based upon a well characterized dose–response relationship [35-37]. The results of phase I study indicated a mean absolute bioavailability of approximately 7% and a terminal half-life of ~29 h. Lomitapide is a CYP3A4 substrate Co-administration with strong CYP3A4 inhibitors or inducers may alter the exposure to lomitapide. But when it is administered with other lipid-lowering agents such as statins or fibrates there is no significant interaction. The recommended dose of lomitapide is 5- 60 mg orally once daily [38].

Efficacy of lomitapide: In animal studies lomitapide had shown to have dose-dependent decreases in LDL-C and triglyceride levels by 29% and 87% respectively with subsequent decrease in HDL levels [39]. It was initially tested ina dose-escalation study of 6 patients with HoFH byCuchel et al in 2007 [**Table 2**]. The patients had been instructed to follow a low fat diet and after cessation of all other lipid-lowering therapies they received lomitapide orally for 4 weeks. The results showed that lomitapide caused an approximately 50% reduction of plasma LDL-C levels in the highest dosage (0.1 mg/kg/day) [40]. A subsequent trial was conducted in 10 homozygous patients, at a maximum dose of 60 mg/day and this resulted in a 44% reduction in LDL-C levels, over and above the effect achieved already by concomitant lipid lowering therapy [41].

TABLE 2: CLINICAL STUDIES PERFORMED WITH LOMITAPIDE AS ON DATE

Author, year	Patient population	Sample size	Outcome of the Study
Cuchel *et al* (2012)[34]	Homozygous familial hypercholesterolemia	29	LDL-C reduced by 50% at week 26, 44% at week 56 and 38% at week 78at 60 mg dosage daily
Cuchel *et al* (2009)[47]	Homozygous familial hypercholesterolemia	10	LDL-C reduced by 44% at 60 mg/day dosage
Samaha *et al* (2008)[42]	Hypercholesterolemia	84	LDL-C reduced by 19% at 5 mg, 26% at 7.5mg, and 30% at 10 mg and with combination of ezetimibe resulted in 35%, 38%,and 46%, respectively at the above three lomitapide doses
Cuchel *et al* (2007)[40]	Homozygous familial hypercholesterolemia	6	LDL-C levels decreased by50.9% and apolipoproteinB levels by 55.6% from baseline in the highest dosage (0.1mg/kg/day).

A multi-centric randomized double blind study by Samaha *et al* used a low dose regimen of lomitapide in 84 patients with hyper-cholesterolemia for 12 weeks. Patients were randomized to ezetimibe, 10 mg, daily (n=29); or lomitapide in increasing dosages (5.0, 7.5, and 10 mg daily, each dose for 4 consecutive weeks [n=28]); or ezetimibe, 10 mg daily, and lomitapide administered with the similar dosetitration described as in the second group (n=28). Ezetimibe therapy resulted in an expected LDL-C reduction of 20%.

Lomitapide was shown to induce a lowering of LDL-C levels in a dose dependent manner: 19%, 26%, and 30% in the 5, 7.5, and 10mg dosing regimens, respectively.Combined therapy produced similarbut larger dose-dependent decreases in LDL-C (35%, 38% and 46%, respectively).Out of 56 patients, nine had increase in hepatic transaminases, and other side effects included such as nausea, diarrhea, gassiness, and gastrointestinal cramping. But the mainreason for discontinuation from study was elevated transaminases [42]. In a phase III study lomitapide demonstrated the LDL reduction in a single arm, open label trial in patients with HoFH. The study was performed in 29 patients who had HoFH and it was observed that lomitapide reduced LDL between 24% and 62% (mean 38%) after 78 weeks of treatment. Patients were also on maximally tolerated background therapy, including other lipid-lowering medications and LDL-apheresis. Due to a significant number of patients discontinuing treatment early (21%) and lack of a control group, the precision of these results is uncertain. However, there is no evidence currently that it improves clinically meaningful outcomes, such as cardiovascular morbidity and mortality. A summary of the evidence for lomitapide is mentioned in Table 2.

Safety of Lomitapide: The most common adverse reactions reported with an incidence of at least 20% include: diarrhea, nausea, vomiting, dyspepsia, and elevations in liver transaminases [38]. Lomitapide has a boxed warning for risk of elevated transaminases and hepatic steatosis. Hepatic steatosis estimated by magnetic resonance imaging ranged from less than 10% to 40% (normal b1%) and was consistent with changes seen in animal studies [43]. Another adverse effect that hinders the beneficial effects of MTP inhibitors was increased stool frequency [38]. Because of potential serious side effects, the FDA has initiation a Risk Evaluation and Mitigation (REMS) program to ensure lomitapide is only used in HoFH [44].

Limitations: Lomitapide received approval from FDA for use only in patients with HoFH, with the requirement of use by a restricted program called the JUXTAPID Risk Evaluation and Mitigation Strategy by the manufacturer [45]. In addition to that the dose of lomitapide is not fixed and must be titrated in individual patients according tothe gastrointestinal side-effects, liver enzyme elevation, and the amount of hepatic fat accumulation. So the drug usage will probably be restricted to patients at specialized lipid clinics. Since HoFH is a rare disease; all studies performed so far with lomitapide are limited by a small sample size [46]. So it is important to continue evaluating the drug in post marketing studies to study the safety of the drug especially with respect to its long term consequences and to detect rare adverse effects that could be gauged in a larger population.

CONCLUSION: Familial hypercholesterolemia is a disorder of LDL-C metabolism. FH patients are at a sharply increased lifetime risk for cardiovascular disease (CVD) and, if left untreated, clinical symptoms of CVD typically manifest in men, in the fourth decade and in women, in the fifth decade of life. Mipomersen, an anti-sense oligonucleotide and lomitapide, an MTP inhibitor are two new drugs approved by US FDA for FH, which may offer benefit in these patients beyond that seen with existing drug therapy. Clinical trials have shown mipomersen and lomitapide to be highly effective and safe as lipid-lowering agents when used as monotherapy or in conjunction with statin therapy.

Nevertheless, the long-term safety of these drugs needs to be explored before they become front-line therapy in the management of FH.

Conflict of Interest: The authors declare that they do not have any conflict of interest.

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