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REVIEW

Mipomersen: evidence-based review of its potential in the treatment of homozygous and severe heterozygous familial hypercholesterolemia

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Klaus G Parhofer

Medical Department II, Grosshadern, University Munich, Munich, Germany

Abstract: Familial hypercholesterolemia (FH) is an autosomal-dominant inherited disease with a prevalence of one in 500 (heterozygous) to one in 1,000,000 (homozygous). Mutations of the low-density lipoprotein (LDL) receptor gene, the apolipoprotein B100 gene, or the PCSK9 gene may be responsible for the disease. The resulting LDL hypercholesterolemia results in premature atherosclerosis as early as childhood (homozygous FH) or in adulthood (heterozygous FH). Current treatment modalities include lifestyle modification, combination drug therapy (statin-based), and apheresis. Mipomersen is an antisense oligonucleotide which inhibits apolipoprotein B production independent of LDL receptor function and thus works in homozygous FH, heterozygous FH, and other forms of hypercholesterolemia. Mipomersen is given 200 mg/week subcutaneously. Phase III studies indicate that the LDL cholesterol concentration can be reduced by 25%–47%, lipoprotein(a) levels by 20%–40%, and triglyceride concentrations by approximately 10%. In general, mipomersen has no effect on high-density lipoprotein cholesterol concentrations. Although there is considerable interindividual variability, the observed lipid effects are largely independent of age, gender, concomitant statin therapy, and underlying dyslipoproteinemia. The most common side effects are injection site reactions (70%–100%), flu-like symptoms (29%–46%), and elevated transaminases associated with an increased liver fat content (6%–15%). Mipomersen may be an interesting addon drug in patients with heterozygous or homozygous FH not reaching treatment goals, either because baseline values are very high or because high-dose statins are not tolerated.

Keywords: antisense oligonucleotide, statin intolerance, apolipoprotein B

Core evidence clinical impact summary for mipomersen for familial hypercholesterolemia (FH)

Outcome measure	Evidence	Implications
Disease-oriented evidence		
LDL-cholesterol reduction	Substantial	In patients with homozygous or heterozygous FH LDL-cholesterol reduction of 25%–47% on top of maximally tolerated drug therapy
Lipoprotein(a) reduction	Substantial	Approximately 30% lipoprotein(a) reduction; Significant reduction of lipoprotein(a), not achievable with currently available drugs
Patient-oriented evidence		
Injection site reactions	Substantial	Most patients (70–100%) describe injection site reaction

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Correspondence: Klaus G Parhofer
Medical Department II, Grosshadern, University Munich, Marchioninistraße 15, 81377 Munich, Germany
Tel +49 89 7095 3010
Fax +49 89 7095 8879
Email klaus.parhofer@med.uni-muenchen.de

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Outcome measure	Evidence	Implications
Flu-like symptoms	Moderate	Approximately 30% of patients describe flu-like symptoms (not significantly different from placebo)
Elevated LFTs	Moderate	6%–15% of patients have elevated LFTs
Economic evidence	Unknown	The drug has not yet been approved by US FDA or European agencies

Abbreviations: LDL, low-density lipoprotein; LFT, liver function test; FDA, Food and Drug Administration.

Familial hypercholesterolemia

Familial hypercholesterolemia (FH) is an inherited disease, characterized by an autosomal-dominant mode of inheritance. Heterozygous FH has a prevalence of approximately one in 500 while the prevalence of homozygous FH is approximately one in 1,000,000 in Western Europe. The frequency may be considerably higher in selected populations with high consanguinity.

Mutations of the low-density lipoprotein (LDL) receptor gene are the underlying defect in the majority of FH patients, but mutations in two other genes can also cause FH, ie, mutations in the apolipoprotein B100 gene and mutations in the pro-protein convertase subtilisin/kexin type 9 gene. The LDL receptor gene is located on chromosome 19, and more than 1000 mutations affecting the function of the receptor are described.[1] The resulting defects refer to different functions, ie, ligand binding, transport, internalization, recycling, or total lack or receptors.[1] Several types of LDL receptor mutation have been described, including premature stop codons, single amino acid substitutions, large rearrangements, mutations affecting the promoter region, and mutations affecting splicing of premessenger RNA. Clinically, the most severe forms of FH are related to total lack of receptors, while receptor-defective mutations usually lead to lesser symptoms.

Although it was initially thought that FH is characterized by an overproduction of lipoproteins, kinetic studies, and particularly the work of Brown and Goldstein, demonstrated that the underlying metabolic defect in FH is the absence of a high affinity receptor for uptake of LDL.[2,3]

Clinical FH can also be the result of ligand-defective apolipoprotein B. In contrast with the many mutations described for the LDL receptor, there are only two mutations described for defective apolipoprotein B (both affecting ARG 3500).[4,5] Finally, gain of function mutations of PCSK9 may also lead to clinical FH, because PCSK9 reduces hepatic LDL receptor activity.[6] Interestingly, loss of function mutations are associated with lower LDL cholesterol concentrations and less atherosclerosis.[7]

FH is characterized by elevated plasma LDL cholesterol and apolipoprotein B levels, resulting in a severely increased risk for atherosclerosis. In untreated patients, clinical symptoms of atherosclerosis typically develop in the fourth or fifth decade of life. Other risk factors, such as smoking, hypertension, diabetes, and elevated lipoprotein(a) may change the clinical course.

Current treatment options

Current guidelines recommend lowering the LDL cholesterol concentration by at least 50% of baseline.[8] Ideally, a LDL cholesterol level <100 mg/dL should be achieved. Lifestyle modification, statins, ezetimibe, bile acid sequestrants, nicotinic acid, and fibrates are used to achieve this goal. Lifestyle modification aims at lowering LDL cholesterol and reducing other risk factors for cardiovascular disease.[9] However, in patients with FH, only a modest reduction of LDL cholesterol can be induced, even if the diet contains less than 7% saturated fat and less than 200 mg cholesterol per day. Although helpful and generally recommended, these means are rarely sufficient to achieve treatment goals. Therefore, drug therapy is required in almost all patients.

Statins can safely lower LDL cholesterol levels by up to 50%, and there is overwhelming evidence that statins reduce cardiovascular morbidity and mortality as well as overall mortality.[10,11] It has also been shown that the prognosis of patients with heterozygous and homozygous FH has been dramatically improved since the introduction of statins.[12,13] While patients with heterozygous FH usually respond very well to statin treatment, the response rate in homozygous FH is usually less predictable. Depending on the underlying defect, LDL cholesterol reductions between 0% and 50% are observed in such patients. Observational data from large cohorts suggest that long-term statin treatment reduces the risk of cardiovascular disease considerably.[14]

However, treatment goals cannot be achieved by statin therapy in many patients, or statin therapy is contraindicated or poorly tolerated. Ezetimibe, bile acid sequestrants, nicotinic acid, and fibrates may be used in this situation, either

as addon therapy to statins or as monotherapy. The most potent combination is probably high-dose statins combined with ezetimibe and bile acid sequestrants.[15] However, even if combination therapy is performed at maximal doses, LDL cholesterol reduction rarely exceeds 60%.

Another option to decrease LDL cholesterol is regular apheresis or plasmapheresis. This treatment modality has been in use for more than 30 years.[16,17] A single apheresis usually decreases LDL cholesterol by approximately 70%, resulting in a mean LDL cholesterol reduction of approximately 30%. However, if regular apheresis is performed at weekly intervals, LDL cholesterol does not rebound to the original baseline value, resulting in an average LDL cholesterol concentration of approximately 50% of the original baseline value. Several studies indicate that FH patients treated with regular apheresis benefit from such treatment.[16] Recommendations concerning when to initiate such treatment differ considerably between countries. In Japan and Germany, where regular apheresis is relatively widely used, patients with established coronary heart disease and LDL cholesterol above goal may qualify for such treatment. In the US, apheresis is only recommended in patients with FH and LDL cholesterol $>$ 300 mg/dL (without coronary heart disease) or $>$200 mg/dL (with coronary heart disease).[18] Although regular apheresis is a time-consuming and cost-intensive form of therapy, it is generally well tolerated with very few side effects. Finally, liver transplantation can be used in selected cases of homozygous FH. This treatment option has been primarily used in pediatric patients sometimes as a combined heart-liver transplant.[19]

New therapeutic strategies

A number of new therapeutic strategies (Table 1) to lower LDL cholesterol have been developed over recent years.[20] These include inhibition of apolipoprotein B production, inhibition of PCSK9 production, monoclonal antibodies binding to PCSK9, thyroid mimetics, cholesterylester transfer protein (CETP) inhibitors, and microsomal triglyceride transfer protein (MTP) inhibitors. All of these approaches have been shown to reduce LDL cholesterol to varying degrees. Although this review primarily focuses on mipomersen, an antisense oligonucleotide for inhibition of production of apoprotein B, the other new approaches will also be briefly discussed.

Strategies to lower PCSK9

PCSK9 is an important regulator of LDL receptor degradation, because binding of PCSK9 to the LDL receptor results

Table 1 Currently developed treatment modalities for FH

Substance	Mechanism	Main lipid effect	Adverse effects	Comments
Mipomersen	Antisense oligonucleotide inhibiting apolipoprotein B synthesis	Decrease of LDL-C by 20%–50%, variable TG reduction; no HDL change; lipoprotein(a) reduction 30%	Injection site reactions Flu-like symptoms Increase of liver function test	May work in homozygous and heterozygous FH and in other forms of hypercholesterolemia
PCSK9 inhibitors	Increased LDL-C function by lower PCSK9 activity either by antisense oligonucleotide (decreased production) or small interfering RNA or monoclonal antibodies	LDL-C reduction	?	
Thyroid mimetics	Selective agonists for hepatic thyroid receptor; induction of hepatic LDL receptors	LDL-C reduction by 25%–30%	Eprotirome was recently discontinued due to effects of cartilage in long-term animal studies	
MTP inhibitors	Reduced secretion of lipoproteins from liver	Decrease in triglycerides and LDL-C	Hepatic fat accumulation; gastrointestinal side effects increased in liver function tests	
CETP inhibitors (dalcetrapib, anacetrapib, evacetrapib)	Inhibition of CETP, thereby reduced transfer of cholesterol esters from HDL to LDL	HDL-C increase by 45%–70%; LDL-C decrease by 0% (dalcetrapib) to 30% (anacetrapib) lipoprotein(a) reduction		First CETP inhibitor (torcetrapib) was terminated because of increased mortality and morbidity (probably due to off-target effect on blood pressure)

Abbreviations: CETP, cholesterylester transfer protein; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; MTP, microsomal triglyceride transfer protein; TG, triglycerides.

in degradation of the receptor, thereby preventing recycling of the receptor. Loss of function mutations of PCSK9 are associated with increased LDL receptor function, low LDL cholesterol, and reduced cardiovascular risk.[7] PCSK9 activity can be reduced by antisense oligonucleotides inhibiting PCSK9 production, by small interfering RNAs also inhibiting production, or by monoclonal antibodies.[21–23] Interestingly, statins and fibrates increase PCSK9 expression, probably as part of a feedback mechanism following increased LDL receptor-mediated uptake of cholesterol during therapy with these drugs; therefore, combination therapy may be of particular potential to reduce LDL cholesterol levels.[24] However, it should be noted that this approach will only work if functional LDL receptors are present, thus only in heterozygous FH and not in the homozygous form of the disease.

Thyroid mimetics

It is well known that hyperthyroidism is associated with low LDL cholesterol concentration, and hypothyroidism with hypercholesterolemia. A number of selective agonists to the thyroid receptor expressed in the liver have been developed. One of them, eprotirome, has been shown to decrease LDL cholesterol by approximately 30% if added to a statin.[25] However, the development of eprotirome was recently stopped because of side effects in cartilage seen in animal studies. Whether this holds true for the other thyroid mimetics remains unclear.

CETP inhibitors

CETP is a key enzyme of lipid metabolism, and facilitates the transfer of cholesterol esters from high-density lipoprotein (HDL) particles to other lipoproteins.[26] The inhibition of CETP results in an increase of HDL cholesterol and LDL cholesterol is decreased if torcetrapib, anacetrapib or evacetrapib are used, while dalcetrapib has no effect on LDL cholesterol levels. The development of torcetrapib has been stopped because of off-target effects (blood pressure increase) resulting in an unexpected increased mortality and morbidity, while the development of Dalcetrapib was stopped because of lack of efficacy. Anacetrapib is evaluated in a large outcome trial. If these outcome trials show benefit, then CETP inhibition may also be useful in patients with FH.

MTP inhibition

MTP is an enzyme necessary for the assembly of very-low-density lipoprotein. Mutations of MTP result in hypobetalipoproteinemia, so MTP inhibition was developed as a strategy to lower LDL cholesterol concentrations.[27] MTP inhibition by lomitapide results in an LDL cholesterol reduction of approximately 30%. MTP inhibition also induces an increase in hepatic steatosis, the importance of which is unclear. However, it should be noted that patients with hypobetalipoproteinemia also have hepatic steatosis and are still characterized by longevity.

Mipomersen: antisense-oligonucleotide inhibiting apolipoprotein B

Apolipoprotein B is the central protein of very-low-density lipoprotein, intermediate density lipoprotein, and LDL. Although epidemiological and interventional studies have focused on LDL-cholesterol, newer data indicate that apolipoprotein B concentrations may be a better predictor and target for atherosclerosis prevention.[28] This also relates to the fact that apolipoprotein B containing lipoproteins only contain one molecule of apolipoprotein B, while the amount of cholesterol and cholesterol ester is to a certain point variable (leading to LDL size heterogeneity). Apolipoprotein B is essential for the production and catabolism of very-low-density lipoprotein and LDL. Without apolipoprotein B, these lipoproteins cannot be produced. Furthermore, apolipoprotein B100 is the main ligand for the LDL receptor.

Based on these observations, apolipoprotein B is an interesting target for atherosclerosis prevention. While most currently available approaches (statins, ezetimibe, bile acid sequestrants) primarily induce increased catabolism of apolipoprotein B-containing lipoproteins, another promising strategy would be to reduce the production of these lipoproteins. While MTP inhibition also interferes with the assembly and secretion of apolipoprotein B-containing lipoproteins, a much more direct approach is to reduce the production of apolipoprotein B100.

Mipomersen (previously ISIS-301012) is a 20-nucleotide second-generation antisense oligonucleotide targeting human apolipoprotein B100 that is complementary to a sequence within the coding region of human apolipoprotein B mRNA (exon 22, position 3249–3269 base pairs).[29] Following the binding of the oligonucleotide to the mRNA, degradation by endogenous RNase H is induced. As a consequence, the synthesis of apolipoprotein B is reduced, resulting in decreased production and secretion of apolipoprotein B-containing lipoproteins. Production and secretion of apolipoprotein B48 from enterocytes, which is required to form chylomicrons, is not inhibited.

Phase I studies

The initial Phase I study was conducted as a double-blind, randomized, placebo-controlled, dose-escalation study in

36 volunteers with mild dyslipidemia.[30] Subjects were treated with weekly doses of mipomersen 50–400 mg subcutaneously. Apolipoprotein B and LDL cholesterol were reduced by up to 50% and 35%, respectively. No significant changes in HDL cholesterol were observed. Apolipoprotein B and LDL cholesterol remained below baseline for up to 3 months after the last dose. The most common adverse event was erythema at the injection site in more than 70% of subjects.

In a second Phase I study, the interaction of mipomersen with simvastatin and ezetimibe was evaluated.[31] This study confirmed that there are no clinically relevant interactions between these drugs in 10 healthy volunteers. In addition, it was shown that mipomersen does not inhibit the major cytochrome P450 isoform enzymes, which is consistent with the fact that antisense drugs are not metabolized through the cytochrome system.

Phase II studies

In a number of Phase II trials, mipomersen has been shown to result in prolonged, dose-dependent reduction of LDL cholesterol, apolipoprotein B, triglycerides, and lipoprotein(a), as shown in Table 2. In one study, 44 patients with heterozygous FH were enrolled and received doses ranging from 50 mg to 300 mg of mipomersen for up to 13 weeks.[32] LDL cholesterol was reduced by 21% in the 200 mg/week group and 34% in the 300 mg/week group, with a reduction in apolipoprotein B of 23% and 33%, respectively. Given that all patients were on conventional lipid-lowering therapy (statins), this study shows that mipomersen has an incremental LDL cholesterol-lowering effect when added to conventional lipid-lowering therapy in FH patients.

Similarly, it was shown in a group of 74 patients with hypercholesterolemia receiving stable statin therapy that mipomersen induced significant changes from baseline in apolipoprotein B and LDL cholesterol at doses between 100 mg and 400 mg per week over 13 weeks, while 30 mg per week had no significant effect.[33] After 13 weeks of dosing at 200 mg/week, mipomersen reduced apolipoprotein B and LDL cholesterol by 36% and triglycerides by 15%. HDL cholesterol did not change. Injection site reactions (erythema in 90%) and hepatic transaminase increases (17%) were the most common side effects, leading to discontinuation in three subjects.

The same authors also reported the effect of mipomersen in 50 subjects with mild to moderate hyperlipidemia, and showed that doses ranging from 50 mg/week to 400 mg/week resulted in a dose-dependent reduction in all apolipoprotein B-containing lipoproteins over a period of 13 weeks.[34] In the 200 mg/week and 300 mg/week groups, mean reductions from baseline in LDL cholesterol were 45% and 61%, corresponding to a decrease in apolipoprotein B concentration of 46% and 61%, respectively. All subjects treated with mipomersen experienced injection site reactions and 18% showed transaminase elevations more than three times the upper limit of normal. To evaluate further the increase in liver function tests, intrahepatic triglyceride content was studied by model reference technology in a randomized, double-blind, placebo-controlled study in 21 patients with FH receiving weekly mipomersen doses of 200 mg or placebo for 13 weeks while continuing statin therapy. Mipomersen reduced LDL cholesterol and apolipoprotein B by approximately 20%. For the whole group, there was a trend towards an increase in intrahepatic triglyceride content, and one patient developed mild hepatic steatosis, which was reversible following discontinuation of mipomersen.

Phase III studies

Five randomized, double-blind, placebo-controlled Phase III studies using 200 mg of mipomersen have been

Table 2 Dose-dependent effect of mipomersen on LDL-C, apolipoprotein B, and lipoprotein(a) in Phase II studies of 5–13 weeks' duration (% change compared with baseline)

Subjects	Statins	n	Duration	30 mg/w	50 mg/w	100 mg/w	200 mg/w	300 mg/w	400 mg/w
Heterozygous FH	Yes	44	6 w						
			LDL-C		−13 ± 15	−11 ± 10	−21 ± 23	−34 ± 18	
			ApoB		−10 ± 12	−8 ± 11	−23 ± 19	−33 ± 22	
			Lp(a)		−3 ± 10	−15 ± 10	−17 ± 19	−24 ± 26	
Hypercholesterolemia	Yes	74	5–13 w						
			LDL-C	2 ± 12		−21 ± 10	−27 ± 21	−52 ± 14	−38 ± 31
			ApoB	0 ± 12		−19 ± 11	−24 ± 20	−54 ± 19	−44 ± 22
Mild to moderate	No	50	13 w						
hyperlipidemia			LDL-C		−8	−16	−44	−61	−70
			ApoB		−17	−22	−45	−61	−71

Abbreviations: ApoB, apolipoprotein B; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); w, week.

completed.[35–39] Only one study is been published in full so far, and the others are only available in abstract form. In all Phase III studies, mipomersen 200 mg/week was evaluated in patients with homozygous FH or heterozygous FH and with severe hypercholesterolemia, and in patients with statin intolerance. Except for the latter group, mipomersen was always coadministered with other lipid-lowering agents, including statins. The duration of all the Phase III studies was 26 weeks, and the primary and secondary efficacy endpoints were met in all cases (Table 3).

Mipomersen 200 mg/week was tested in a multicenter study of 51 patients with homozygous FH on a low-fat diet and maximum tolerated lipid-lowering drugs. Thirty-four patients were assigned to mipomersen and 17 to placebo. LDL cholesterol (mean at baseline 11.4 ± 3.6 mmol/L) decreased by 24.7%. Similarly, apolipoprotein B decreased by 26.8% and lipoprotein(a) by 31.1%. In line with the Phase II studies, the most common adverse events were injection site reactions (76% in the mipomersen group and 24% in the placebo group) and increases in liver function tests (12% in the mipomersen group).[36]

In 124 adult patients with heterozygous FH and cardiovascular disease, 26 weeks of mipomersen 200 mg/week resulted in an LDL cholesterol reduction of 34%, an apolipoprotein B reduction of 26.3%, and a lipoprotein(a) reduction of 20%. Again, injection site reactions and flu-like symptoms were the most common adverse events. Liver function tests increased to more than three times the upper limit of normal in 6% of patients treated with mipomersen.[37]

Another study evaluated mipomersen in 58 patients with severe FH. Mipomersen 200 mg/week for 26 weeks reduced LDL cholesterol 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 cholesterol. Side effects were similar as in other mipomersen studies, with injection site reactions (90% in mipomersen group, 32% in placebo group) and flu-like symptoms (46% in mipomersen group, 21% in placebo group) being the most common adverse events. In 15% of mipomersen-treated patients (but in none of the placebo patients) alanine aminotransferase was elevated to above three times the upper limit of normal.[38]

In a larger study in 158 adults with hypercholesterolemia and high cardiovascular risk, mipomersen 200 mg/week for 26 weeks reduced LDL cholesterol by 37%, with similar changes in apolipoprotein B and lipoprotein(a). In 50% of mipomersen-treated patients, LDL cholesterol was decreased to <70 mg/dL. Injection site reactions and flu-like symptoms were again the most common side effect. Fourteen percent of mipomersen-treated patients had alanine aminotransferase elevations above three times the upper limit of normal.[35]

Finally, mipomersen 200 mg/week for 26 weeks was evaluated in high-risk patients intolerant to statins.[39] LDL cholesterol decreased by 47.3%, with a similar decrease in apolipoprotein B (46.2%) and a decrease of lipoprotein(a) by 27.1%. Eighteen percent of the mipomersen-treated patients and 17% of the placebo-treated patients discontinued due to adverse events. As in statin-tolerant patients, injection site reactions and flu-like symptoms were the most common side effects. Liver function tests were above three times the upper limit of normal in 33% of mipomersen-treated patients.

Efficacy of mipomersen

Mipomersen results in a dose-dependent reduction of LDL cholesterol, lipoprotein(a), apolipoprotein B100, and triglycerides. At the dose chosen for further development (200 mg/week), LDL cholesterol reduction varies between 30% and 47% compared with placebo. Apolipoprotein B and lipoprotein(a) reduction is slightly less at 20%–35%. Triglyceride reduction is more variable and usually between 10% and 20%. Within each study, there is considerable variability in the reduction of LDL cholesterol, for example, in homozygous FH, LDL reduction varied between 2% and 82%. If reported, the treatment effect was independent of baseline LDL cholesterol values, age, race, or gender. The observed reduction in LDL cholesterol, lipoprotein(a), and apolipoprotein B seems to be independent of the underlying cause and independent of concomitant drug therapy.

Safety and tolerability

Mipomersen has been generally well tolerated and had an acceptable safety profile in the Phase II and Phase III studies. The most common adverse events were injection site reactions, flu-like symptoms, and increases in liver function tests, especially alanine aminotransferase.

Injection site reactions occur in most patients (75%–100%). These are dose-dependent and characterized by transient, mild to moderate erythema, occurring within 24 hours of drug injection. On subsequent injection, a flare-up of the previous injection site may occur. Injection site reactions are considered an antisense class-related phenomenon also observed with other antisense drugs. However, the exact

Table 3 Phase III studies evaluating mipomersen

Study	Patients	Design	Outcome	Key results	Adverse events
Raal et al[36]	Homozygous FH on stable low-fat diet and maximum lipid-lowering drugs n = 51	Randomized, placebo-controlled; mipomersen 200 mg/week for 26 weeks	**Primary outcome** LDL-C reduction **Secondary outcome** Change in apoB, total cholesterol, HDL-C, lipoprotein(a), triglycerides	**Placebo** LDL-C −3.3% Lp(a) −7.9% ApoB100 −2.5% **Mipomersen** LDL-C −24.7%; $P = 0.0003$ Lp(a) −31.1%; $P = 0.0013$ ApoB100 −26.8%; $P = 0.0001$	**Injection site reactions** Placebo 24% Mipomersen 70% **Flu-like symptoms** Placebo 24% Mipomersen 29% **Elevated transaminases (≥3 × ULN)** Placebo 0% Mipomersen 12%
Stein et al[37] (abstract)	Heterozygous FH and cardiovascular disease on low-fat diet and stable lipid-lowering drugs n = 124	Randomized, placebo-controlled; mipomersen 200 mg/week for 26 weeks	**Primary outcome** LDL-C reduction **Secondary outcome** Change in apoB, total cholesterol, HDL-C, lipoprotein(a), triglycerides	**Placebo** LDL-C −5.2% Lp(a) 2.4% ApoB100 7.0% **Mipomersen** LDL-C −34.0%; $P = 0.001$ Lp(a) −20.4% $P = 0.001$ ApoB100 −26.3%; $P = 0.001$	**Injection site reactions** Placebo 42% Mipomersen 93% **Flu-like symptoms** Placebo 39% Mipomersen 42% **Elevated transaminases (≥3 × ULN)** Placebo 0% Mipomersen 6%
Tardif et al[38] (abstract)	Severe heterozygous FH and high risk for atherosclerosis on maximally tolerated statin therapy n = 58	Randomized, placebo-controlled; mipomersen 200 mg/week for 26 weeks	**Primary outcome** LDL-C reduction **Secondary outcome** Change in apoB, total cholesterol, HDL-C, lipoprotein(a), triglycerides	**Placebo** LDL-C 12.5% **Mipomersen** LDL-C −35.9%; $P = 0.001$	**Injection site reactions** Placebo 32% Mipomersen 90% **Flu-like symptoms** Placebo 21% Mipomersen 46% **Elevated transaminases (≥3 × ULN)** Placebo 0% Mipomersen 15%
Cromwell et al[35] (abstract)	Hypercholesterolemia and high risk for atherosclerosis on low-fat diet and maximally tolerated statin therapy n = 158	Randomized, placebo-controlled; mipomersen 200 mg/week for 26 weeks	**Primary outcome** LDL-C reduction **Secondary outcome** Change in apoB, total cholesterol, HDL-C, lipoprotein(a), triglycerides	**Placebo** LDL-C −4.5% **Mipomersen** LDL-C −42.2%; $P = 0.001$	**Injection site reaction** Placebo 31% Mipomersen 78% **Flu-like symptoms** Placebo 21% Mipomersen 34% **Elevated transaminases (≥3 × ULN)** Placebo 0% Mipomersen 14%
Visser et al[39]	High-risk patients in tolerant to statins n = 33	Randomized, placebo-controlled; mipomersen 200 mg/week for 26 weeks	**Primary outcome** LDL-C reduction **Secondary outcome** Change in apoB, total cholesterol, HDL-C, lipoprotein(a), triglycerides	**Mipomersen** LDL-C −47.3%; $P = 0.01$ Lp(a) −27.1%; $P < 0.001$ ApoB −46.2%; $P < 0.001$	**Discontinuation** Placebo 17% Mipomersen 18%

Abbreviations: ApoB, apolipoprotein B; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Lp(a), lipoprotein(a); TG, triglycerides; ULN, upper limit of normal.

underlying mechanism is unknown. Injection site reactions are not considered to be serious safety concerns but may affect patient compliance.

Flu-like symptoms were reported somewhat more often in the mipomersen groups than in the placebo groups. 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). These elevations were not accompanied by other clinical or laboratory findings suggestive of hepatic dysfunction nor were there any cases of Hy's law. Elevated alanine aminotransferase most likely reflects accumulation of hepatic fat secondary to inhibition of apolipoprotein B synthesis and therefore very-low-density lipoprotein secretion. Hepatic steatosis has been observed in some mipomersen-treated patients.[40] Hepatic steatosis resolves and alanine aminotransferase elevations return to normal after discontinuation of treatment.

Therapeutic potential of mipomersen

The currently available studies indicate that mipomersen may decrease LDL cholesterol in homozygous and heterozygous FH patients by approximately 30%, independent of concomitant drug therapy. The effect of mipomersen in patients treated with apheresis is currently unknown, but there is little doubt about similar efficacy in such patients.

Thus, mipomersen could theoretically be used in all patients not at goal with respect to LDL cholesterol and at sufficient absolute risk to justify treatment with a drug for which no long-term data are currently available. Mipomersen may be of particular benefit to patients with homozygous FH or severe heterozygous FH, given that treatment options are very limited in such patients. It should also be noted that mipomersen, in contrast with other established approaches, such as statins, bile acid-binding resins, and ezetimibe, and in contrast with other newly developed approaches, such as PCSK9 inhibitors, does not rely on the LDL receptor to achieve LDL cholesterol reduction.

The following patient groups may be primary candidates for treatment with mipomersen:

- Patients with homozygous FH, many of whom do not respond to statin therapy and even if they do, usually do not reach treatment goals. In this patient group, a Phase III study has shown efficacy with respect to LDL, apolipoprotein B, and lipoprotein(a) reduction.
- Patients with severe heterozygous FH, who usually respond to statin therapy, with an LDL cholesterol reduction of up to 50%, but may not reach treatment goals either because baseline values are too high or because they do not tolerate high-dose statins. Mipomersen as an addon therapy to a statin (and potentially ezetimibe and bile-acid binding resins) may further reduce LDL cholesterol and result in a considerably larger fraction of patients reaching treatment goals. Such patients have been studied in a Phase III trial, but the results have only been published in abstract form so far.
- Patients with severe hypercholesterolemia and coronary heart disease not reaching treatment goals. Similar to patients with heterozygous FH, these patients usually respond to conventional drug therapy, but efficacy may be inadequate. Addon therapy with mipomersen may allow more patients to reach treatment goals.
- Patients at high risk for atherosclerosis intolerant to statin therapy, in whom mipomersen may be a treatment alternative allowing attainment of treatment goals.

Theoretically, all patients qualifying for regular apheresis should be candidates for mipomersen treatment. In fact, according to German guidelines, a hypothetical evaluation shows that approximately 50% of aphereses could be avoided if mipomersen was available on the German market and tolerated as well as apheresis.[41] Obviously, mipomersen may also be an interesting addon therapy to apheresis, which may lead to lower pre-apheresis and post-apheresis values, and thus to better average values. In some patients, this may have the benefit of apheresis being required less frequently. However, before mipomersen can be used as concomitant therapy in apheresis-treated patients, a proper study must be performed in this patient group.

Although mipomersen has a significant ability to lower LDL, apolipoprotein B, and lipoprotein(a), and may thus allow more people to reach therapeutic goals, it also has significant side effects (injection site reactions, elevation of transaminases) which may affect compliance and must be taken into account in cost-benefit analysis. Until more long-term data are available, especially with respect to elevated liver enzymes, this form of therapy will be used primarily in patients with severe forms of hypercholesterolemia and at very high cardiovascular risk.

In summary, inhibition of apolipoprotein B production using mipomersen may be an interesting approach for patients with heterozygous and homozygous FH not at target with current forms of drug therapy. Mipomersen reduces LDL cholesterol by up to 45%, but leads to injection site reactions in almost all patients, and flu-like symptoms and elevated transaminases in some.

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