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REVIEW

Familial hypercholesterolaemia: new treatment options

M. Ezzahti*, E.J.G. Sijbrands, M.T. Mulder, J.E. Roeters van Lennep

Department of Vascular Medicine, Erasmus MC, Rotterdam, the Netherlands, *corresponding author: e-mail: m.ezzahti@erasmusmc.nl

ABSTRACT

Familial hypercholesterolaemia is a relatively frequently occurring disease that is strongly associated with vascular disease. Current treatment with cholesterol-lowering agents is partly effective but shows variable responses between patients with familial hypercholesterolaemia. Recently, new cholesterol-lowering drugs have been developed. Here we describe the most promising of these new agents for which results from phase 2 or phase 3 trials are available. We will discuss the data regarding lipid-lowering potential and safety issues and speculate about the potential reductions of the residual risk of statin-treated FH patients.

KEYWORDS

Familial hypercholesterolemia, treatment, PCSK9, apolipoprotein B, synthesis inhibitor, CETP, MTP

INTRODUCTION

Familial hypercholesterolaemia (FH) is an autosomal dominant disorder. More than 85% of FH cases are due to mutations in the low-density lipoprotein-receptor (LDL-R) encoding gene.[1] More than 1000 different mutations in the LDL-R encoding gene have been described. The LDL-R is responsible for clearing LDL cholesterol (LDL-C) from the blood by endocytosis and intracellular degradation. If the receptor is defective or lacking, this will lead to reduced clearance of cholesterol. As a result the endogenous cholesterol synthesis in the liver is increased, enhancing very low-density lipoprotein (VLDL) production. FH is a co-dominant disease. Heterozygous FH is relatively common in Caucasian populations (1:450-500) whereas homozygous FH is rare (1:1.000,000).[2] Occasionally, FH may also be caused by mutations in the genes encoding for apolipoprotein B-100 (Apo B-100) and the proprotein convertase subtilisin/kexin type 9 (PCSK9).[1,3] The diagnosis of FH is based on clinical criteria or by detection of a pathogenic mutation in the *LDL-R, Apo B* or *PCSK9* gene.[4] FH patients are at increased risk for premature cardiovascular disease (CVD): clinical manifestations of CVD occur in 50% of untreated male heterozygous FH patients before the age of 50 years and in women before the age of 60 years.[5]

According to the current guidelines, the treatment goal for FH patients is lowering LDL-C <2.5 mmol/l for primary cardiovascular prevention and <1.8 mmol/l in the secondary prevention setting.[6] The mainstay of treatment is lifestyle modifications and statin therapy. And classical cardiovascular risk factors should be treated aggressively in FH patients.

Statins inhibit hepatic cholesterol synthesis and indirectly raise expression of LDL-Rs.[7] Statins effectively reduce CVD mortality and morbidity in FH patients.[8-12] In primary prevention, statin therapy in FH patients reduced total coronary heart disease (CHD) by 48%.[13] The reduction of CHD mortality by statins in patients with a history of symptomatic CHD was much smaller, namely 25%.[13] Only 21% of patients with FH in the Netherlands achieved the treatment goal of LDL-C <2.5 mmol/l.[14] This treatment goal remains difficult to reach despite the use of high-dose statins, even in combination with other cholesterol-lowering drugs. The LDL-lowering capacity of statins in combination with other lipid-lowering drugs is maximally around 50-60%.[15] FH patients have such a strongly elevated LDL-C that in most cases maximal current treatment is not sufficient to reach the mentioned LDL targets. Moreover, side effects, especially myalgia without CK elevation, occur frequently: in 5-10% of all statin-treated patients.[15] This is a growing problem in routine clinical practice. Therefore,

FH patients still have a large residual CVD risk despite the use of statins and there is a medical need for new additional drugs to further lower LCL-C in patients with FH to improve the prognosis of these patients.

Recently, new cholesterol-lowering drugs have been developed.[16] In the current review we describe the most promising of these new therapies of which results from phase 2 or phase 3 trials are available. We will discuss the data regarding lipid-lowering potential and safety issues and speculate about the potential reductions of the residual risk of statin-treated FH patients.

NEW THERAPEUTIC OPTIONS

PSCK9 targeted therapy

Proprotein convertase subtilisin/kexin type 9 (PSCK9), a serine protease, stimulates the lysosomal degradation of the LDL-R within hepatocytes.[17] PCSK9 is synthesised primarily in the liver. PCSK9 binding to the LDL-R causes degradation of the LDLR-LDL complex in the lysosomes which leads to a decreased number of available LDL-Rs (*figure 1*).[18] Therefore, gain-of-function mutations in the *PCSK9* gene cause hypercholesterolaemia.[19] And loss-of-function mutations result in low levels of LDL-C and lead to an 80% CVD risk reduction.[20-22] These findings made PCSK9 extremely interesting as a new target for lipid-lowering therapy. Different therapeutic strategies to lower PCSK9 concentration are in development, such as monoclonal antibodies to PCSK9, small interfering RNAs and antisense oligonucleotide-based therapy. Most human studies have been performed with the monoclonal antibody variants so far.

REGN727 is a fully human monoclonal antibody highly specific for human PCSK9 which blocks its interaction with the LDL-R. Recently, Stein *et al.* reported a multicentre, randomised, placebo-controlled phase 2 trial conducted in 77 high-risk patients with heterozygous FH.[23] In this dose-finding study, the cholesterol-lowering effect and safety of REGN727 was evaluated. All patients were treated with high doses of statins and 71% of the patients were also using ezetimibe. The mean reductions in LDL-C after 12 weeks of subcutaneous REGN727 ranged dose-dependently from 29% to 68% compared with 11% in the placebo group. The most effective dose was 150 mg subcutaneously every two weeks. With this dose 94% of patients reached an LDL-C ≤2.5 mmol/l and 81% an LDL-C ≤1.8 mmol/l. The most common adverse events were mild reactions at injection sites but serious adverse events were not reported. Another study in patients with primary hypercholesterolaemia who had an LDL-C ≥2.5 mmol/l showed that the reduction of LDL-C from baseline was significantly larger in patients receiving either atorvastatin 10 mg + REGN727 150 mg subcutaneously every two weeks or atorvastatin 80 mg + REGN727 150 mg subcutaneously every two weeks compared with atorvastatin 80 mg + placebo (66.2% and 73.2% *vs* 17.3%, p<0.001).[24] Of the patients receiving REGN727, 100% and more than 90% of patients attained an LDL-C of ≤2.5 mmol/l and ≤1.8 mmol/l, respectively, compared with 52% and 17% of those patients receiving atorvastatin 80 mg alone.

REGN727 is the first of the PSCK9 inhibitors to show significant LDL-C reduction, is well tolerated and showed a favourable safety profile during short-term administration in FH patients (*table 1*).

AMG145, another monoclonocal antibody to PCSK9, was recently evaluated in a phase 2 study and showed promising results in statin-intolerant patients. The mean reductions in LDL-C after 12 weeks of subcutaneous AMG145 ranged dose-dependently from 41% to 63% compared with 15% in the ezetimibe/placebo group.[25] The RUTHERFORD study evaluated AMG145 in patients with heterozygous FH with statin therapy with or without ezetimibe. After 12 weeks of therapy, the mean LDL-C reduction was 43% and 53% with AMG 145 350 mg and 420 mg respectively, compared with 3% increase with placebo.[26] And in this trial, 70% and 89% of the FH patients reached the target LDL levels with 350 mg and 420 mg respectively. AMG145 was administered subcutaneously every four weeks in both studies, with minimal adverse events. In the coming years, studies addressing the effect of different strategies for injections (frequency, dose) will be performed.

Future studies on mortality and morbidity are required to determine the role of this promising approach in the treatment of FH. If these studies show that this new treatment option is indeed as effective and safe as the results indicate so far, then this class of medication will have a major impact on the number of FH patients who can reach

Figure 1.

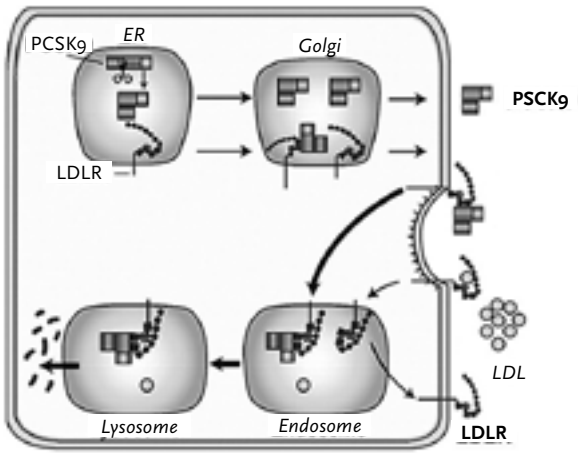


Table 1.

Therapy	Study	Patients	Design	Outcome	Results	Adverse events
REGN727	Stein et al.[23]	Hetero-zygous FH n=77	Phase 2 study: randomised, placebo-con-trolled trial	LDL-C reduction after 12 weeks	**Dose 150 mg every 2 weeks:** **LDL-C** Placebo: -10.65% REGN727: -67.9% (p<0.0001) **ApoB100:** Placebo: -6.39% REGN727: -50.19% (p<0.0001) **Lp(a):** Placebo: -3.91% REGN727: -23.38% (p=0.2559)	**Dose 150 mg every 2 weeks:** **Injection site reactions:** Placebo: 13% REGN727: 44%
REGN727	Roth et al.[24]	Primary hyper-cholesterol-aemia n=92	Phase 2 study: randomised, placebo-con-trolled trial	LDL-C reduction after 8 weeks	**Atorvastatin 80 mg + placebo:** -17.3% **Atorvastatin 10 mg + REGN727:** -66.2% **Atorvastatin 80 mg + REGN727:** -73.2%	**Injection site reactions**: Atorvastatin 80 mg + placebo: -6.5% Atorvastatin 10 mg + REGN727: -0% Atorvastatin 80 mg + REGN727: -3.3%
AMG145	Raal et al.[26]	Hetero-zygous FH n=77	Phase 2 study: randomised, placebo-con-trolled trial	LDL-C reduction after 12 weeks	**Placebo:** +3% **AMG145 350mg:** -43% **AMG145 420 mg:** -55%	**No difference between groups**

their treatment goals. The hope is that this will lead to a reduction in residual risk of CVD, especially in secondary prevention. Whether PCSK9 targeted therapy leads to LDL-C reduction in homozygous FH patients with no LDL-receptor function is doubtful because of its mode of action.

Inhibitors of apolipoprotein B synthesis

Apo B-100 is an essential component of LDL-C and all other atherogenic lipoproteins. Apo B-100 is the main ligand for the LDL-R.[27] Inhibition of apo B production is therefore an interesting concept to lower the production of atherogenic lipoproteins with the objective of reducing risk of CVD in FH patients.

Mipomersen is the first apo B synthesis inhibitor for human use. Mipomersen is a second-generation antisense oligonucleotide and inhibits the synthesis of apo B-100.[28] This antisense oligonucleotide binds to the mRNA of apo B-100, thereby stimulating the degradation of apo B by endogenous RNase H. This results in reduced synthesis of apo B and a decrease in very-low-density lipoprotein (VLDL) and LDL levels. As the mode of action of mipomersen is independent of the presence of LDL-Rs, this therapy is also suitable for homozygous FH patients.

Five randomised double-blind, placebo-controlled trials using mipomersen have been conducted.[29-33] These studies evaluated mipomersen 200 mg once weekly (subcutaneously) in patients with heterozygous FH,[30,31] homozygous FH[29] and severe hypercholesterolaemia with a high risk of CVD.[32,33] The duration of all these studies was 26 weeks and the primary outcome was LDL-C reduction. Mipomersen was administered in combination with other lipid-lowering drugs, including statins. Mipomersen 200 mg/week resulted in a significant reduction in LDL-C between 21% and 47% compared with placebo.[29-33] Mean apo B and lipoprotein (a) were also reduced by 20% to 35%. The reduction in LDL-C, apo B and lipoprotein (a) seemed to be independent of the underlying type of hypercholesterolaemia and independent of concomitant drug therapy.

Mipomersen was reasonably well tolerated in the five studies, despite the fact that the majority of the patients had mild to moderate injection site reactions (*table 2*). This side effect is dose-dependent, occurs within 24 hours of the drug injection and is in general transient.

Because of the mode of action of mipomersen, accumulation of hepatic fat is a serious concern. Elevated

Table 2.

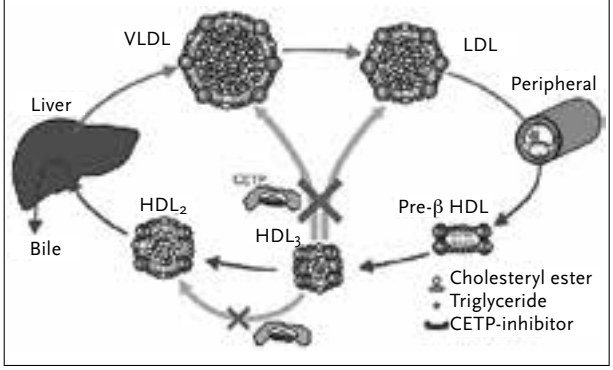
Therapy	Study	Patients	Design	Outcome	Results	Adverse events
Mipomersen	Raal et al.[29]	Homozygous FH n=51	Phase 3 study: randomised, placebo-controlled: mipomersen 200 mg/week for 26 weeks	LDL-C reduction, reduction of apo B, HDL-C, triglycerides and lipoprotein (a)	**LDL-C:** Placebo: -3.3% Mipomersen: -24.7% (p=0,0003) **ApoB100:** Placebo: -2.5% Mipomersen: -26.8% (p=0.0001) **Lp(a):** Placebo: -7,9% Mipomersen: -31.1% (p=0.0013)	**Injection site reactions:** Placebo: 24% Mipomersen: 70% **Flu-like symptoms:** Placebo: 24% Mipomersen: 29% **Elevated transaminases** (>3 ULN): Placebo: 0% Mipomersen: 12%
Mipomersen	Stein et al.[30]	Heterozygous FH n=124	Phase 3 study: randomised, placebo-controlled: mipomersen 200 mg/week for 26 weeks	LDL-C reduction, reduction of apo B, HDL-C, triglycerides and lipoprotein (a)	**LDL-C:** Placebo: -5.2% Mipomersen: -34% (p=0.001) **ApoB100:** Placebo: +7% Mipomersen: -26.3 (p=0.001) **Lp(a):** Placebo:+2.4% Mipomersen: -20.4% (p=0.00)	**Injection site reactions:** Placebo: 42% Mipomersen: 93% **Flu-like symptoms:** Placebo: 39% Mipomersen: 42% **Elevated transaminases** (>3 ULN): Placebo: 0% Mipomersen:6%
Mipomersen	McGowan et al.[31]	Severe heterozygous FH and high risk for atherosclerosis n=58	Phase 3 study: randomised, placebo-controlled: mipomersen 200 mg/week for 26 weeks	LDL-C reduction, reduction of apo B, HDL-C, triglycerides and lipoprotein (a)	**LDL-C:** Placebo: +6% Mipomersen: -36% (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%

alanine aminotransferase (ALAT >3 x upper limit of normal) occurred in 6% to 15% of patients treated with mipomersen.[29-33] The elevated liver transaminases were not accompanied by other findings of hepatic dysfunction. Elevated ALAT most likely reflects accumulation of hepatic fat secondary to inhibition of apo B and therefore VLDL. Hepatic steatosis has indeed been observed in a number of mipomersen-treated patients.[34] After discontinuation of treatment with mipomersen, the elevated ALAT returned to normal and hepatic steatosis resolved in all patients within ten weeks.[34]

Recently the Federal Drug Agency (FDA) approved mipomersen for the treatment of homozygous FH patients. However, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) gave a negative opinion on approving mipomersen because of safety concerns, specifically accumulation of hepatic fat. Currently, a phase 3 trial in severe heterozygous FH patients and an early access program for homozygous FH patients are still going on in Europe.

In summary, mipomersen seems an effective additional therapy on top of statins in patients with severe hypercholesterolaemia. However, because of the side effects and the lack of morbidity and mortality data, it is unlikely that mipomersen will be available in Europe within the near future.

Figure 2.



Cholesterol ester transfer protein inhibitors

Cholesterol ester transfer protein (CETP) is a plasma glycoprotein that is bound to HDL particles and promotes the exchange of cholesteryl esters between HDL and triglyceride-rich lipoproteins.[35-37] Inhibition of CETP raises HDL-C and decreases LDL-C (*figure 2*), leading to a more favourable lipid profile which could reduce the risk of CVD in FH patients.[38] Torcetrapib, the first CETP inhibitor, was tested in FH patients. However, all torcetrapib trials were terminated because torcetrapib was associated with an excess mortality in patients at high risk for CVD in the large Illuminate study.[38,39] Torcetrapib was also associated with increased blood pressure and aldosterone levels.[40] These adverse effects were unrelated to the inhibition of CETP and were considered to be molecule-specific.[41,42] New CETP inhibitors, such as dalcetrapib and anacetrapib, did not show an effect on blood pressure. After promising safety data,[43,44] the dal-OUTCOMES trial was unexpectedly stopped in May 2012 after an interim analysis showed that dalcetrapib was not significantly reducing CVD events in patients with hypercholesterolaemia.[45,46] Recently, the DEFINE study showed in a secondary prevention setting that in addition to statin therapy, anacetrapib 100 mg daily compared with placebo significantly decreased LDL-C by 36% and significantly increased HDL-C by 138% after 24 weeks.[47] The REVEAL study is currently testing whether anacetrapib reduces the number of CVD events in atorvastatin-treated patients with a history of CVD.[48] The new CETP inhibitors were not specifically tested in FH patients. However, if anacetrapib is effective and safe in patients with hypercholesterolaemia, anacetrapib is also likely to benefit FH patients.

Microsomal triglyceride transfer protein inhibitors

Microsomal triglyceride transfer protein (MTP) is primarily an enzyme responsible for transfer of triglycerides from their site of synthesis into the lumen during the assembly of VLDL and chylomicrons. VLDL is the major source of LDL in plasma.[49] Blocking MTP reduces LDL-C, VLDL and triglycerides by affecting the packaging and secretion of VLDL and chylomicrons.[50] Because the mechanism of action does not involve LDL-Rs, this treatment is also suitable for homozygous FH patients.

Phase 2 studies showed that lomitapide treatment in homozygous FH patients results in a reduction in LDL-C of 50% to 60%. In these patients liver-fat content increased during the use of lomitapide, which at the highest dose ranged from less than 10% to more than 40%.[51,52] A phase 3 study was conducted by Cuchel *et al*. in 29 patients with homozygous FH to assess LDL-C reduction and safety of lomitapide.[53] These patients used different combinations of lipid-lowering therapies, including LDL apheresis in 62% of the patients. The median dose of lomitapide in this study was 40 mg. LDL-C was reduced by 50% after 26 weeks of therapy with lomitapide. This effect was sustained and remained stable after 78 weeks of therapy. Similar reductions were observed for apo B. Gastrointestinal symptoms were the most common adverse event and occurred in 93% of patients, but the symptoms were usually mild. About 14% of patients had elevations in liver aminotransferases, but they could all continue lomitapide after dose reduction or temporary suspension of the therapy. Hepatic fat content increased by approximately 7% after 78 weeks of therapy. Since the clinical significance and long-term implications of the increase in hepatic fat as a result of lomitapide therapy is not clearly understood, rigorous and standardised long-term monitoring will be necessary.

In analogy of mipomersen, lomitapide is currently approved by the FDA for the treatment of homozygous FH patients. The approval procedure by the EMA CHMP is currently ongoing. Lomitapide is a promising drug for patients with homozygous FH: the benefit-risk ratio of lomitapide in patients with homozygous FH, who are at a high risk of cardiovascular events and death at a young age, could possibly be favourable. Future studies are needed to evaluate the long-term safety of lomitapide.

Other therapies in development

A novel lipid-lowering therapy in the development is CER-001, which is a recombinant HDL mimetic and is based on human apolipoprotein A-I, the major structural protein of HDL.[54] CER-001 is designed to mimic HDL, which removes cholesterol from tissues and blood vessels and carries it to the liver. Preclinical and clinical data showed efficacy of CER-001 in mobilising cholesterol and promoting reverse lipid transport.[55] The available drugs to treat FH are targeted at reducing LDL-C. These measures can retard the progression of cardiovascular disease; however, they are unlikely to lead to regression of existing disease due to years of cholesterol accumulation in the vessel walls. HDL has multiple actions that could lead to plaque stabilisation and regression. Currently, the effect on plaques is being evaluated in a study in which CER-001 infusion is being tested in homozygous FH patients. Even if this new therapy is shown to be efficacious and safe, the route of administration will certainly limit widespread use.

Recently, significant progress in gene transfer technology has encouraged investigators to further develop LDL-R gene transfer approaches for the treatment of FH. The advantage of gene therapy over other therapeutic regimes is the potential for lifetime correction with a single vector administration. In experimental animal models of FH, LDL-R overexpression following viral vector-based gene transfer resulted in long-term stable correction

of hyperlipidaemia, with attenuation of atherosclerosis progression, and in certain cases even with lesion regression.[5,6] Despite the considerable progress, no viral vector so far is ideal for *in vivo* gene transfer. Future research will focus on making gene transfer vectors safer and more efficient.

CONCLUSIONS

There are many new lipid-lowering drugs for FH patients in development. The drugs we have described in this review are currently the furthest developed, although data on cardiovascular endpoints are not available for most of these agents. These new drugs have an impressive lipid-lowering ability. So far, PCSK9 inhibitors have shown very few side effects, which makes them attractive for a large group of FH patients. Other drugs will be probably reserved for the most severely affected FH patients, such as homozygous FH patients, because of the severity of the side effects and the expectation that PCSK9 inhibitors will have no effect in patients without LDL-R function. With the development of new drugs, the possibilities of treating FH patients to target will improve enormously. This will bring us closer to the ultimate goal: to abolish the residual risk of FH patients, thereby reducing the risk of CVD in FH patients.

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