Familial hypercholesterolemia: the Dutch approach

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Chapter 16

Treatment of familial hypercholesterolemia

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Chapter 16
INTRODUCTION

Familial hypercholesterolemia (FH) is the most common monogenetic disorder of lipid metabolism. The average prevalence of the heterozygous form of FH is 1 in 500 individuals, resulting in nearly ten million patients worldwide. Homozygous FH is rare, affecting 1 per million individuals. LDL-C is elevated about tenfold in homozygous- and threefold in heterozygous patients. The high LDL-C levels lead to deposition of cholesterol in various tissues, presenting as tendon xanthomas, xanthelasmata and arcus cornealis. Accumulation of cholesterol in the arterial walls finally leads to premature atherosclerotic cardiovascular disease (CVD). In untreated heterozygous patients, about 50% of males and 30% of females develop CVD before the age of 60, whereas homozygous patients suffer from CVD events in the second decade of life already.

Therefore, patients with FH should be treated with lipid lowering medication, preferably from childhood onwards. Although no controlled clinical trials have evaluated the effect of lipid lowering treatment on cardiovascular endpoints in FH specifically, the relationship between hypercholesterolemia and the risk of CVD is indisputable. Furthermore, treatment with most LDL-C lowering agents has been proven to reduce the risk. In the present chapter current and possible future treatment modalities for patients with FH are discussed.

TREATMENT OF FH

Treatment goals

High levels of LDL-C have consistently been shown to be associated with coronary heart disease (CHD) risk. Furthermore, the link between LDL-C lowering and the reduction of CVD risk has been clearly established, and “the lower, the better” has become a paradigm in the management of hypercholesterolemia.

Although no clear goals have been defined specifically for treatment of the FH population in most countries, LDL-C targets can be deduced from the recently adapted National Cholesterol Education Program (NCEP) and European guidelines. Those guidelines recommend a stringent LDL-C target of below 1.8 mmol/L for very high-risk patients, i.e. persons with multiple CHD risk factors who have an absolute 10-year risk for major coronary events of >20%. These targets can also apply to FH patients with manifest CVD or to those with a severe family history of premature CVD. For most FH patients the LDL-C goal for “normal” high risk patients, i.e. below 2.6 mmol/L, is acceptable as minimum treatment target. In the Dutch
guideline, internists, cardiologists and general practitioners are recommended to start medical treatment in patients with heFH when LDL-C levels are >2.5 mmol/l, in line with the European Guidelines with treatment targets for (other) patients at high cardiovascular risk. In the United Kingdom, a target of > 50% LDL-C reduction is recommended.

As the first step, FH patients are advised to adhere to a healthy lifestyle including diet, frequent physical activity, and no smoking. However, these lifestyle modifications almost never do result in targeted LDL-C levels and therefore the vast majority of patients with FH depend on pharmacological interventions to lower LDL-C. In untreated FH subjects LDL-C levels are typically in the range of 5-10 mmol/L. Consequently, reductions of 50-75% are required to reach an LDL-C target level of 2.6 mmol/L or lower.

**Current treatment options**

Since the second half of the 20th century efficacious pharmacological interventions for FH patients have only gradually become available. Without effective treatment of patients with a severe FH phenotype at first relied on radical measures such as portocaval shunting, ileal bypass and liver transplantation. Because of major advancements in pharmacological treatment of FH, these surgical modalities are only sporadically used in treatment resistant FH patients today.

In this section, the commonly used registered pharmacological interventions will be discussed with the focus on the treatment of adult heterozygous FH patients.

**Statins**

Statins -or hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors- play a central role in the primary and secondary prevention of CVD and are currently considered the most effective drugs lowering plasma LDL-C levels. By inhibiting the rate limiting step of cholesterol synthesis, where HMG CoA is converted to mevalonate (figure 1), statins decrease the hepatic cholesterol pool, which in turn stimulates the production of mRNA for the LDLR gene.
Figure 1 Cholesterol and VLDL-C synthesis and inhibitory agents in these pathways.

Panel A shows the cholesterol, bile acid, and VLDL cholesterol synthesis with the enzymes catalyzing these processes.

Panel B demonstrates the site of action of agents which can impair the cholesterol or VLDL synthesis. Under conditions of low hepatic cholesterol LDLR synthesis is increased, which results in LDL-C clearance from plasma via the LDLR pathway. Cholesterol can be esterified and stored as cholesterol esters in the hepatocytes, packaged into VLDL particles and secreted into the plasma, secreted directly into the bile, or converted to bile acids by cholesterol 7alpha-hydroxylase and subsequently secreted into the bile.
Enhanced LDL-C liver uptake via the LDLR results in increased LDL-C clearance and lower plasma LDL-C levels. Results of a meta-analysis, which included the data from 164 randomized placebo-controlled trials on LDL-C reduction, demonstrated that the six commonly used statins in their most potent doses yielded LDL-C reductions between 33 and 58%. In a series of primary as well as secondary prevention trials using various statins it was consistently shown that reductions in LDL-C were associated with a clear decrease in cardiovascular event rate. In fact, the relationship between LDL-C reduction and event rate was strikingly predictable, every 1 mmol/L (39 mg/dL) reduction in LDL-C being associated with a 23% reduction in CHD risk. As a consequence, statin induced LDL-C reduction has become the cornerstone of current treatment guidelines for cardiovascular prevention.

Although there were no randomized placebo-controlled clinical trials specifically investigating in patients with FH, the clinical efficacy of statins in reducing CHD events was highlighted in the large Simon Broome cohort with clinically diagnosed FH subjects. The timeframe of this study, which overlaps the introduction of statins, allowed observations and comparison between treated and non-treated FH patients in 1999. Treatment was found to effectively lower the risk of CHD in patients with clinical FH as shown by the declined relative risk for coronary mortality from 1992 onwards. In line with this finding is the robust reduction in CHD risk induced by statin treatment, which was observed in a large FH cohort in the Netherlands.

One of the trials with statins that showed beneficial effects in FH subjects is the ASAP trial, in which the intima-media thickness of the carotid artery (cIMT) was used as an endpoint. cIMT as measured by ultrasonography is a surrogate marker for atherosclerosis and a validated predictor for cardiovascular events. Two-year treatment with atorvastatin 80 mg/day reduced LDL-C by 51%, accompanied by a decrease in cIMT of 0.031 mm. Treatment with simvastatin 40 mg/day reduced LDL-C by 41%, but in contrast to the findings in the atorvastatin arm, IMT increased by 0.036 mm. These results suggest the benefit of more aggressive lipid lowering in FH patients.

Ezetimibe

Ezetimibe is the first of a new class of drugs that selectively inhibits cholesterol absorption. This agent inhibits cholesterol uptake and transport through the enterocyte most likely by blocking the Niemann-Pick C1-like 1 (NPC1L1) transporter in enterocytes (figure 2). This reduces the fractional cholesterol absorption by 54% and results in a reduced cholesterol transport from the intestine to the liver via
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chylomicrons. By way of compensation, LDLR expression is up regulated and clearance of LDL-C from plasma increased.\textsuperscript{21} In patients with primary hypercholesterolemia, ezetimibe monotherapy reduced LDL-C levels by 17-20%\textsuperscript{21, 22}

Combination therapy of ezetimibe with several statins resulted in 12-23% incremental decrease in LDL-C when compared to statin treatment alone.\textsuperscript{23, 24} The safety profile does not differ between combination and statin monotherapy, but combination therapy allows significantly more patients to achieve their LDL-C goals than statin monotherapy (71.5% vs 18.9%).\textsuperscript{25} Moreover, the combination of ezetimibe with a low dose statin has a similar effect on LDL-C than high dose statins, which is of considerable benefit for patients who do not tolerate high doses of statins.\textsuperscript{25} However, the long-term effects of the addition of ezetimibe to statin treatment remain to be elucidated. A randomized controlled trial in 720 FH patients, i.e. the ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) trial, compared the 2-year efficacy of daily therapy with 80 mg simvastatin in combination with 10 mg/day of ezetimibe or with placebo. The addition of ezetimibe to 80 mg/day simvastatin did not reduce cIMT, the primary outcome measure, in this cohort of FH patients, despite a 16% incremental reduction in LDL-C (table 1). The reason why this incremental LDL-C reduction did not beneficially affect cIMT remains unclear.\textsuperscript{26} Thus, the outcomes of the ongoing clinical endpoint trial which evaluates the effect of addition of ezetimibe are eagerly awaited.\textsuperscript{27}

Bile acid sequestrants

Bile acid sequestrants lower cholesterol levels by binding bile acids in the intestine and thereby interrupting the enterohepatic cycle (figure 2). As a consequence of the diminished return of bile acids to the liver, hepatic bile acid synthesis from cholesterol by cholesterol 7alpha-hydroxylase (CYP7A1) is increased in order to maintain constant bile acid levels.\textsuperscript{28} The decrease in hepatic intracellular cholesterol levels due to the conversion to bile acids leads to lower hepatic cholesterol concentrations and increased hepatic LDLR expression, which subsequently decreases plasma LDL-C levels (figure 1).\textsuperscript{29}

Colestyramine, colestipol and colesevelam are the most widely used agents in this class of cholesterol lowering drugs and they reduce LDL-C on average by 15%.\textsuperscript{30} Colestyramine was the first lipid lowering drug to show a survival benefit in hypercholesterolemic patients in a large placebo-controlled trial.\textsuperscript{31} However, colestyramine and colestipol are associated with gastrointestinal side effects,
in particular constipation and flatulence, making long-term compliance poor. Colesevelam – a newly engineered bile acid sequestrant – has a greater affinity to bind bile acids per gram of product, thereby providing a much better tolerability profile than the other sequestrants. Colesevelam in doses of 3.75 gram per day has been shown to reduce LDL-C up to 13-19% when taken as monotherapy and up to an additional 16% when taken in combination with atorvastatin. If combined with ezetimibe, it reduced LDL-C by an additional 11%.

Colesevelam was recently tested in 86 FH patients in a phase IV trial – the TRIPLE study. In this study colesevelam is combined with a statin and ezetimibe to provide additional LDL-C lowering in FH patients who have not reached the LDL-C target despite maximal tolerated dose of statin and ezetimibe (table 1). Differences in LDL-C (95%CI) between colesevelam and placebo were -12.0% (-17.8 to -6.3) after 12 weeks.

LDL-apheresis
Although the use of LDL-apheresis is primarily reserved for homozygous FH patients, it is sometimes used in heterozygous FH patients as well. For instance in patients with a severe phenotype who do not respond to conventional drug treatment or in pregnant women with heterozygous FH and CVD, in whom the use of conventional drugs is contraindicated. LDL-apheresis is a safe procedure that can transiently reduce LDL-C levels. A small number of trials have demonstrated that apheresis could lower LDL-C by about 55%, but large trials showing an effect on cardiovascular endpoints are lacking. Furthermore, LDL-apheresis is expensive and must be performed every one or two weeks.

Plant sterols and stanols
Foods enriched with plant sterol or stanols can also inhibit the uptake of dietary and biliary cholesterol from the small intestine. Plant sterols and stanols presumably displace cholesterol from mixed micelles and thereby reduce intestinal absorption, but the exact mechanism is unknown. Abundant evidence shows that consuming 2 g/day of plant sterols and stanols reduces LDL-C by about 10%. Consumption of foods rich in plant sterols or stanols is generally recognized as safe. However, any adverse effects of the absorption of plant sterols into the circulation are currently unknown and no trials have directly tested the effects of sterols and stanols on cardiovascular risk. Nevertheless, based on current evidence, the NCEP-ATPIII reports recommend a diet designed for maximal LDL-C lowering including foods enriched with plant sterols/stanol (2g/day).
Figure 2 Intestinal cholesterol and bile acid uptake and inhibitory agents in these pathways.

ACAT=acyl coenzyme A:cholesterol acyltransferase; ASBT=ileal apical sodium-dependent bile acid transporter; BAS=bile acid sequestrants; CE=cholesterol esters; FC=free cholesterol; MTP=microsomal triglyceride transfer protein; NPC1L=Niemann-Pick C-1-like protein; TG=triglycerides. Dietary cholesterol and bile acids can be absorbed in the small intestine. NPC1L1 is critical for intestinal cholesterol absorption and ASBT for bile acids. Cholesterol and bile acid (re-)uptake as well as the formation of chylomicrons can be inhibited by several (future) treatment modalities as shown in this cartoon.

Treatment in development

Nicotinic acid
Recent meta-analyses have shown that even the most aggressive treatment with statins reduce the cardiovascular risk by only 30%, which leaves a considerable residual CVD risk. High-density lipoprotein cholesterol (HDL-C) levels were inversely associated with subsequent recurrent CVD in patients who had reached LDL-C levels below 1.8 mmol/L (70 mg/dl) with intensive statin treatment. Also in FH patients, a low HDL-C was strongly associated with the progression of atherosclerosis as measured by IMT and with the risk for clinically documented coronary artery disease. Those data suggest that HDL-C raising strategies could have an important therapeutic role in FH patients, especially in those with low HDL-C levels.

Among the currently registered drugs with the capacity to increase HDL-C, nicotinic acid derivative compounds are the most accepted ones, and the HDL-C increase is accompanied by a decrease in LDL-C and very low density lipoprotein cholesterol (VLDL-C). Niacin is such an nicotinic acid derivate and treatment with
niacin has been demonstrated to result in a rise in HDL-C of about 21% and to a decrease in the IMT.\textsuperscript{45} Despite these favourable outcomes, niacin has several side effects, of which the most important is flushing. These flushes limit wider clinical use of niacin. Flushes can be suppressed by MK0524 (also known as laropiprant) which antagonizes the prostaglandin D2 receptor 1.\textsuperscript{46} In 2006, a phase III clinical trial was launched to evaluate the efficacy and tolerability of niacin in combination with laropiprant in FH subjects who had not reached target LDL-C (<2.6 mmol/L) with other medicinal options (the Assessment of Coronary Health Using an Intima-Media Endpoint for Vascular Effects, i.e. the ACHIEVE trial (table 1).\textsuperscript{47} However, the trial was terminated during enrolment due to based on the ENHANCE trial results,\textsuperscript{48} which indicated that the ACHIEVE trial would lack sufficient statistical power. A lack of power was expected due to a much lower than anticipated cIMT progression in statin treated patients in the ENHANCE trial.\textsuperscript{49}

\textit{CETP-inhibitors}

Cholesteryl ester transfer protein (CETP) plays an important role in cholesterol metabolism because it is responsible for the transfer of cholesteryl esters from high-density lipoprotein (HDL) to very-low-density lipoproteins (VLDL) and low-density lipoproteins (LDL). As a consequence, CETP inhibition is expected to raise HDL-C and lower LDL-C, thereby providing a therapeutic option to reduce the risk of CVD. FH patients with high CETP levels were demonstrated not only to have a more atherogenic lipid profile that was less amendable to statin treatment, but also to show an increased progression of IMT.\textsuperscript{50} The CETP-inhibiting agent torcetrapib has been tested in a phase III study, i.e. RADIANCE 1. In this 2-year parallel study, 850 FH subjects were randomized to receive either atorvastatin plus torcetrapib or atorvastatin alone. Despite a significant and robust increase of 52% in HDL-C and a significant decrease of 21% in LDL-C, the addition of torcetrapib to atorvastatin did not inhibit the progression of atherosclerosis. In fact, the secondary end point, i.e. the annual change in mean IMT for the common carotid, showed an increase of 0.0038 mm per year in the torcetrapib-atorvastatin group compared to a decrease of 0.0014 mm per year in the atorvastatin monotherapy group.\textsuperscript{51} Furthermore, the addition of torcetrapib increased the average systolic blood pressure by 2.8 mm Hg. In a simultaneously initiated study on 15,000 (non-FH) patients, the addition of torcetrapib to atorvastatin treatment was demonstrated to lead to excess mortality at interim analysis.\textsuperscript{52} This led to early termination of the study and withdrawal of torcetrapib in the end of 2006.
Treatment of FH

At this moment, the key question is whether the adverse effect on cardiovascular outcome caused by the addition of torcetrapib was due to CETP inhibition itself or to agent specific toxicity. Very recently, the DAL-Outcomes I study, with CETP inhibitor dalcetrapib,53, 54 was terminated for futility. Currently, several other CETP inhibitors are in a final stages of development, such as evacetrapib55 and anacetrapib.56 One large phase III trial is ongoing specifically in heterozygous FH patients, i.e. the REALIZE trial with anacetrapib (clinical.trials.gov identifier: NCT01524289). This is a 1-year, worldwide, randomized placebo-controlled study to assess the efficacy and tolerability of anacetrapib (100mg/daily) when added to ongoing statin therapy with or without other lipid modifying treatment in 300 patients with heterozygous familial hypercholesterolemia. The primary outcome is percent change in LDL-C and the study is due to complete in 2014.

Squalene synthase inhibitors
A step further than the conversion of HMG-CoA to mevalonate in the cholesterol biosynthetic pathway is the conversion of farnesyl pyrophosphate into squalene by squalene synthase (figure 1). Squalene synthase inhibitors impede this conversion. Unlike HMG-CoA reductase inhibitors, squalene synthase inhibitors do not lower the levels of mevalonate, which is not only the precursor of cholesterol, but also of e.g. coenzyme Q10, a key component of the mitochondrial respiratory chain. Therefore, it was postulated that selective inhibition of squalene synthase might result in better tolerability when compared to statins because of fewer liver abnormalities and myopathy related to depletion of non-squalene-metabolites of mevalonate.57 Animal studies have shown promising results 58, 59 and the squalene synthase inhibitor lapaquistat (TAK-475) is now in phase III development (table 1). Several studies with lapaquistat in combination with statins and ezetimibe were initiated in both homozygous FH patients as in patients with primary hypercholesterolemia.60, 61 However, the entire lapaquistat development was discontinued because of the observation of increased frequency of transaminase elevations in 2007.62
Table 1 Phase III or IV randomized controlled trials in (primarily) adult FH patients completed or terminated from 2002 to 2012

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Phase</th>
<th>Inclusion criteria</th>
<th>Treatment</th>
<th>Duration (wks)</th>
<th>Primary endpoint</th>
<th>Start date</th>
<th>Results</th>
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<tr>
<td>ENHANCE 48</td>
<td>III</td>
<td>HeFH 30-75 y unLDL-C ≥5.43 mmol/L</td>
<td>N=357 simvastatin 80 mg + ezetimibe N=363 simvastatin 80 mg + placebo</td>
<td>104</td>
<td>ΔcIMT</td>
<td>June 2002</td>
<td>No benefit of ezetimibe addition to simvastatin 80 mg on cIMT, see text 48</td>
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<td>RADIANCE 51</td>
<td>III</td>
<td>HeFH 18-70 y</td>
<td>N=450 atorvastatin + torcetrapib N=454 atorvastatin + placebo</td>
<td>104</td>
<td>ΔcIMT</td>
<td>December 2003</td>
<td>No benefit of torcetrapib addition on IMT, see text 51</td>
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<td>CAPTIVATE 66</td>
<td>III</td>
<td>HeFH 40-75 y LDL-C ≥2.5 mmol/L</td>
<td>N=443 current therapy + CS-505 (pactimibe) N=438 current therapy + placebo</td>
<td>65*</td>
<td>ΔcIMT</td>
<td>February 2004</td>
<td>More cIMT progression in treatment group. *Premature discontinuation after 15 mo, see text 66</td>
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<td>ACHIEVE 47</td>
<td>III</td>
<td>HeFH 18-70 y LDL-C ≥2.6 mmol/L</td>
<td>N=450 intensive lipid lowering treatment + MK0524A N=450 intensive lipid lowering treatment + placebo</td>
<td>96</td>
<td>ΔcIMT</td>
<td>October 2006</td>
<td>Terminated in 2008 due to anticipated lack of power, see text 47</td>
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<td>TRIPLE 35</td>
<td>IV</td>
<td>HeFH 18-75 y LDL-C &gt;2.5 mmol/L</td>
<td>N=40 current therapy (including ezetimibe) + colesevelam N=40 current therapy (including ezetimibe) + placebo 3 mo double blind, 9 mo open label</td>
<td>ΔLDL-C</td>
<td>August 2007</td>
<td>ΔLDL-C (95%CI) between colesevelam and placebo: -12.0% (-17.8 to -6.3) after 12 wks 35</td>
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<td>TAK-475-016 68</td>
<td>III</td>
<td>HomoFH &gt; 8 y</td>
<td>N=20 current therapy + lapaquistat 100mg (50mg) N=20 current therapy + placebo</td>
<td>24 + ext</td>
<td>ΔLDL-C</td>
<td>November 2005</td>
<td>Due to liver enzyme increase 100 mg dose lowered to 50 mg November 2007, see text 68</td>
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<td>Hipomersen in HomoFH 73</td>
<td>III</td>
<td>HomoFH &gt; 12 y LDL-C ≥3.4 mmol/L</td>
<td>N=36 current therapy + mipomersen N=8 current therapy + placebo</td>
<td>26</td>
<td>ΔLDL-C</td>
<td>September 2007</td>
<td>Reduction LDL-C in mipomersen treated patients significantly greater than placebo. (-24.7% vs. 3.3%, p=0.0003) 73</td>
</tr>
</tbody>
</table>

Δ=change from baseline; *=premature discontinuation; cIMT=carotid intima-media thickness; ext.=extension period; HeFH=heterozygous FH; HomoFH=homozygous FH; LDL-C=low-density lipoprotein cholesterol; mg=milligram; mo=months; wks=weeks; y=year. Only trials which intended to only include patients with FH are described in this table. These trials were found in the online databases www.clinicaltrials.gov, www.controlled-trials.com and EudraCD, using the search terms "Familial Hypercholesterolemia" and "Primary hypercholesterolemia" and limits "Phase III and/or Phase IV-trials".
ACAT inhibitors

Acyl coenzyme A: cholesterol acyltransferase (ACAT) is responsible for cholesterol esterification (figures 1 and 2). There are two isoforms of this enzyme, ACAT1 and ACAT2. ACAT1 is expressed ubiquitously and regulates cholesterol homeostasis in the brain, macrophages and adrenal glands. ACAT2 is expressed in the liver and small intestine, where it esterifies cholesterol, thereby regulating hepatic lipoprotein and cholesterol absorption. ACAT inhibitors have been shown to decrease plasma cholesterol levels and to have beneficial effects on the arterial wall in experimental animal models. Avasimibe and pactimibe are non-selective ACAT inhibitors that both have reached phase III clinical trials. However, both pactimibe and avasimibe failed to show beneficial effects and treatment with these compounds even resulted in increased coronary plaque volume as assessed by intravascular ultrasound (IVUS). Furthermore, pactimibe increased IMT progression in FH subjects. The conclusion of these negative findings was that non-selective ACAT inhibition is unable to inhibit the progression of atherosclerosis and may even promote atherogenesis. As a consequence, further development with avasimibe and pactimibe for cardiovascular prevention in humans was discontinued in 2003 and 2005, respectively.

Currently, selective inhibition of isoform hepatic ACAT2 by antisense oligonucleotides remains under development. ACAT2 specific inhibition has been shown to effectively reduce atherosclerosis in animal models, but the consequences in humans are still unknown.

MTP inhibitors

In the absence of functional microsomal triglyceride transfer protein (MTP), as in the rare recessive genetic disorder abetalipoproteinemia, the liver cannot synthesize VLDL, leading to absence of all lipoproteins containing APOB in the plasma. Due to the decreased levels of the atherogenic APOB particles such as VLDL and LDL, inhibition of MTP was hypothesized to slow the progression of atherosclerosis. Clinical trials with MTP-inhibitors such as BMS-201038 have shown promise, since the highest doses reduced plasma LDL-C by more than 50%. However, BMS-201038 treatment was accompanied with significant hepatic fat accumulation at even moderately effective doses. Such accumulation of liver fat may be intrinsically linked to the mechanism of action of MTP-inhibitors (figure 1), which is in accordance with increased incidence of steatosis demonstrated in subjects with familial hypobetalipoproteinemia. Although this finding could present a serious barrier to the clinical use of this class of agents, these compounds are developed further and are currently tested in clinical trials. Lomitapide from Aegerion Pharmaceuticals (AEGR-733) is currently the MTP
inhibitor in the most advanced stage of clinical development. During a long term, phase III open label clinical trial its long-term efficacy and safety is evaluated at the maximum tolerated dose (clinical trials gov identifier: NCT00943306). This study will be performed in patients with homozygous FH on current lipid-lowering therapy.

**APOB antisense**

Selective inhibition of mRNA by antisense oligonucleotides is an entirely new approach to modify cholesterol levels (figure 1). Administration of antisense oligonucleotides (ASOs) to human APOB that interferes with the synthesis of APOB 100 messenger RNA is in advanced development and has shown striking results in phase II studies both as monotherapy as well as in combination with statins. Mipomersen (ISIS 301012) is currently the APOB antisense drug that is in the most advanced stage of development. Data generated over the last year with the mipomersen phase II trials in all types of patients with elevated LDL-C have shown good efficacy. The antisense inhibitor mipomersen is a 20-mer oligonucleotide, complementary to part of the coding region of human APOB-100 mRNA. The drug is administered subcutaneously once a week or less, and appears to have a substantial LDL-C lowering efficacy when added to conventional lipid lowering therapy in FH patients.\(^{70, 71}\) Thus far, the use of APOB antisense has proven safe.\(^{70, 72}\)

Recently, the findings of a phase III trial in homozygous FH patients were published (see Table 1).\(^{73}\) Patients aged > 12 years were randomized to be treated with mipomersen 200 mg subcutaneously every week or placebo on top of their conventional lipid-lowering treatment for 26 weeks. Forty five patients completed the 26 week period and it was observed that mean percentage change of LDL-C 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). The most common adverse events were injection site reactions and modest alanine aminotransferase increase.

Currently, a large phase 3 randomized-controlled study is ongoing with patients with severe heterozygous FH to assess the safety and efficacy of two different regimens of mipomersen (clinical trials gov identifier: NCT01475825), i.e. FocusFH. Patients with inadequately controlled LDL-C will be randomized to subcutaneous mipomersen 200 mg once weekly, mipomersen 70 mg thrice weekly, or placebo. The primary objective of this study is to determine whether mipomersen significantly reduces atherogenic lipid levels and to assess long term safety and tolerability.
**PCSK9 inhibition**

Statins increase the expression of both the **LDLR** and **PCSK9** genes. The increased expression of PCSK9 may attenuate the LDL-C-lowering effect of statins. Inhibition of PCSK9 activity could therefore enhance the effects of statins. Several pharmaceutical companies are currently testing their PCSK9 inhibiting compound in clinical settings. Currently registered trials (clinical trials gov) can be found from **AMGEN** (Identifiers: NCT01624142, NCT01588496, NCT01516879, NCT01380730, NCT01375777, NCT01135522, NCT01439880), Regeneron/Sanofi-Aventis (NCT01576484, NCT01623115, NCT01604824), Alnylam Pharmaceuticals (NCT01437059), Santaris Pharma A/S (NCT01350960), Pizzer-Rinat (NCT01350141) and Bristol-Myers Squibb (NCT01082562). Particularly, the compounds of Regeron/Sanofi-Aventis (REGN727) and **AMGEN** (AMG 145) are in advanced stages of development. In addition, Merck, Novartis and Serometrix are currently testing PCSK9 inhibiting compounds. Favourable results have been made public with some PCSK9 inhibitors already. Recently, the results of a phase II trial were published with the specific monoclonal antibody to PCSK9 (REGN727) tested among 77 patients with heterozygous FH. The patients with LDL-C levels ≥ 2.6 mmol/l despite treatment with a statin, and some also with ezetimibe, were randomized to different doses of REGN727 or placebo and treated for 12 weeks. LDL-C was reduced with least-square means from baseline from 29% to 68% with the lowest or highest dose of REGN727, and was well tolerated. Preliminary publication of data from a study with the AMGEN compound (AMG 145) showed promising results on cholesterol parameters in heterozygous FH patients receiving cholesterol lowering medication.

As can be appreciated from the interest of several pharmaceutical companies in PCSK9 inhibition, more results of trials with PCSK9 inhibition in FH patients will be expected in the near future.

**Gene therapy**

Liver-directed gene transfer of the LDL-C receptor theoretically is attractive but awaits the development of better and safer vectors. Initially the use of gene therapy was hindered by the lack of a physiological control mechanism that protects the hepatocytes from pathological accumulation of lipids and cholesterol. Recently, progress has been made with constructing vectors based on adeno-associated virus 8 for gene therapy in FH and results from clinical studies are eagerly awaited.
Chapter 16

SUMMARY

FH is a prevalent inherited disorder that gives rise to premature CVD. Early diagnosis gives the opportunity to initiate with preventive measures and pharmacological interventions early in life.

Lowering LDL-C is the mainstay of treatment for FH. First choice agents are HMG-CoA-reductase inhibitors (statins), most often atorvastatin, rosuvastatin or simvastatin at maximally tolerated doses in order to reach the LDL-C target of below 2.6 mmol/L or a 50% reduction in LDL-C.

In several FH patients, statins or the higher doses of statins cannot be used due to side effects, less efficacy or contraindications such as pregnancy. Monotherapy or combination therapy with agents targeting cholesterol absorption or interrupting the enterohepatic cycle of bile acids can further lower LDL-C.

In order to raise HDL-C, several novel compounds such as CETP-inhibitors are in advanced stages of clinical trials in FH patients.

Novel cholesterol synthesis inhibitors that target squalene synthase and inhibitors of VLDL-C synthesis such as MTP inhibition and in particular APOB antisense therapy are currently in advanced stages of clinical trials, particularly in homozygous FH patients.

During recent years PCSK9 inhibitors have been developed by several pharmaceutical companies and the first studies in FH patients show promising results.

The combination of statin therapy with ezetimibe, APOB mRNA inhibition and maybe also PCSK9 inhibition has the potential to finally enable the vast majority of FH patients to reach their target LDL-C goals.
REFERENCES


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