Curr Cardiol Rep (2011) 13:527–536
DOI 10.1007/s11886-011-0219-9

Familial Hypercholesterolemia: Present and Future Management

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Published online: 21 September 2011

Abstract Patients suffering from familial hypercholesterolemia (FH) are characterized by increased plasma levels of low-density lipoprotein cholesterol (LDL-C) levels and are at increased risk for premature cardiovascular disease (CVD). Current guidelines emphasize the need to aggressively lower LDL-C in FH patients, and statins are the cornerstone in the current regimen. However, additional therapies are eagerly awaited, especially for those patients not tolerating statin therapy or not reaching the goals for therapy. Our understanding of LDL metabolism has improved over the last years and an increasing number of potential novel targets for therapy have been recently identified. Apart from novel targets, we have also been confronted with novel modalities of treatment, such as mRNA antisense therapy. Some of these emerging therapies have proven to be effective in lowering plasma LDL-C levels and are as such expected to have beneficial effects on CVD. Hopefully, they will enrich our armamentarium against the severe dyslipidemia observed in FH patients in the not too distant future.

Keywords Familial hypercholesterolemia · Treatment · HMG-CoA reductase · Bile sequestrants · Fibrates · Nicotinic acid · Apolipoprotein B antisense inhibitor · MTP · CETP · PCSK9 · Thyroid mimetics

Clinical Trial Acronyms

AIM-HIGH	Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/ High Triglycerides and Impact on Global Health Outcomes
ASAP	Atorvastatin Versus Simvastatin on Atherosclerosis Progression
HPS-2-Thrive	Treatment of High-Density Lipoprotein to Reduce the Incidence of Vascular Events
HPS3/REVEAL	Randomized Evaluation of the Effects of Anacetrapib Through Lipid Modification
ILLUMINATE	Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events
RADIANCE I	Carotid B-Mode Ultrasound Study to Compare Anti-Atherosclerotic Effect of Torcetrapib/Atorvastatin to Atorvastatin Alone
SHARP	Study of Heart and Renal Protection.

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Introduction

Familial hypercholesterolemia (FH) is an autosomal-dominant disorder characterized by elevated plasma low-density lipoprotein cholesterol (LDL-C) levels. Mutations in the gene encoding for the LDL receptor are the underlying molecular defect in the vast majority of FH patients [1], but mutations in *APOB* [2] and *PCSK9* have also been shown to result in Mendelian forms of increased LDL-C levels [3]. FH patients are at sharply increased lifetime risk for cardiovascular disease (CVD) and, if left untreated, clinical symptoms of CVD typically manifest in men in their fourth decade and in women in their fifth decade of life [4]. Apart from the elevated LDL-C levels, other traditional CVD risk factors (ie, smoking, hypertension, diabetes) do add to the total risk in FH patients, and all modifiable risk factors should therefore be aggressively addressed. Current guidelines recommend lowering the LDL-C concentration to at least 50% from baseline. Statins are shown to safely lower LDL-C levels and

are therefore the treatment of choice [5, 6]. Moreover, large clinical trials have provided us with overwhelming evidence that statins reduce cardiovascular mortality and morbidity [7••].

However, treatment goals are not achieved in a significant number of FH patients [8–10]. In such patients, and in case statin therapy is contraindicated or poorly tolerated, alternative lipid-lowering medications should be initiated. Ezetimibe, bile acid sequestrants, nicotinic acid, and fibrates are frequently prescribed as add-on therapy to initial treatment with statins [6].

In recent years, several novel promising therapeutic strategies for LDL-C lowering have been developed. In this review, we discuss the present and future treatment options for lipid lowering in FH patients, especially those medications that have been shown, or are anticipated, to result in LDL-C reduction.

Currently Approved Lipid-Lowering Therapy

Lifestyle Modification

In FH patients, lifestyle modification to lower LDL-C and reduce other CVD risk factors should be introduced, despite the modest and variable degree of LDL-C reduction (10%). A diet containing less than 7% saturated fat and less than 200 mg of cholesterol is to be advised. Additional use of plant sterol esters or plant stanol esters will reduce LDL-C levels, although trials showing a beneficial effect of these substances on CVD outcome are lacking [11, 12]. Patients should be encouraged to achieve and maintain a healthy body weight through physical activity and appropriate caloric intake. Alcohol consumption should be restricted and smoking should be discouraged, as it is strongly associated with CVD in patients with hypercholesterolemia [13, 14]. It should be kept in mind that lifestyle modification is rarely, if ever, sufficient to achieve the LDL-C treatment goal in patients with FH and drug therapy is therefore required in almost all patients.

Statins

Statins are 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (Table 1). They inhibit the rate-limiting step in cholesterol synthesis by reducing the conversion of HMG-CoA reductase to mevalonate. The consequently decreased intracellular cholesterol levels induce an upregulation of the LDL receptor, which leads to increased clearance of LDL-C and decreased plasma LDL-C concentrations [15]. Apart from the reduction in LDL-C, statins have been shown to improve endothelial function, stabilize atherosclerotic plaques, decrease oxidative stress and inflammation, and inhibit the thrombogenic response [16].

Statins have convincingly been shown to be safe and well-tolerated agents that reduce CVD morbidity and mortality in a wide range of patients [17]. Therefore, guidelines recommend these drugs as the first-line therapy in patients with FH.

Statins are the most commonly prescribed drugs in FH patients [18] and their impact on the natural cause of vascular disease in FH is large. Observational data from large FH cohorts suggest that long-term statin treatment removes the excess lifetime risk of CVD due to FH and reduced it to a level similar to that of the general population [19, 20].

Statins reduce LDL-C levels in a dose-dependent manner [7••], and the rationale to treat FH patients with high dosages of these therapeutics is based on clinical trials showing benefit in terms of reductions of cardiovascular events and death [21]. Although trials with events as primary outcome are lacking in FH patients, the ASAP trial showed a beneficial effect of intensified therapy on carotid intima-media thickness (cIMT), a surrogate marker of atherosclerosis [22]. FH patients should initially be treated with more potent statins, which have been shown to reduce LDL-C levels by 50% to 60% at their maximum approved doses [23]. Initial concerns about the safety profile of statins, especially in children, have been refuted by a number of clinical trials [24–26].

Other Currently Available Treatment Options

In many FH patients, LDL-C treatment goals cannot be reached with the maximum available or tolerated dose of a statin. In such cases, adding ezetimibe, a bile acid binding resin, fibric acid derivates, or nicotinic acid should be considered. In homozygous FH individuals or in heterozygous FH patients at extreme risk (which is not uniformly specified), LDL apheresis has been shown to be an effective means to reduce LDL-C as well.

Ezetimibe selectively inhibits the intestinal absorption of both dietary and biliary cholesterol by blocking the Niemann-Pick C1-like 1 (NPC1L1) protein transporter, which reduces the delivery of intestinal cholesterol to the liver (Table 1). As a result, the LDL receptor expression is upregulated and clearance of LDL-C from plasma is increased. In patients with FH, ezetimibe can be safely coadministrated with statins [27]. Ezetimibe reduces LDL-C by approximately 15% to 20% [28, 29•]. The clinical benefit of adding ezetimibe to statin therapy has not been proven. In fact, in a large clinical trial in which adult FH patients were randomized to statin or a combination of statin and ezetimibe, no effect was found on the extent of atherosclerosis assessed by cIMT, despite a significant

Table 1 Currently approved therapeutics for lipid lowering

Agent	Mechanism of action	Effects on lipid profile	Adverse effects
HMG-CoA reductase inhibitors (statins)	Inhibition of HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis	LDL↓ up to ~50%	Myopathy, rhabdomyolysis (extremely rare), hepatoxicity
Atorvastatin		HDL ↑ up to~10%	
Fluvastatin		TG ↓ up to~20% [76]	
Lovastatin			
Pravastatin			
Rosuvastatin			
Simvastatin			
Ezetimibe	Inhibition of cholesterol absorption by interfering Niemann-Pick C1-like 1 protein, responsible for transluminal cholesterol transport	LDL ↓~15%	Gastrointestinal symptoms
		HDL variable, but not clinically relevant [77, 78]	
		TG no significant change [78]	
Bile acid sequestrants	Decrease of the hepatocyte cholesterol content, resulting in an upregulation of the LDLR expression and increased LDL cholesterol clearance	LDL ↓ 18%[a]	Gastrointestinal symptoms including constipation and dyspepsia
Colesevelam		HDL no significant change	
Colestipol		TG variable [79, 80]	
Cholestyramine			
Nicotinic acids	Unclear	LDL ↓ 12%	Flushing
Niacin		HDL ↑ 16%	Gastrointestinal symptoms
		TG ↓ 20% [81]	Hepatotoxicity
			Hyperglycemia
Fibrates	Probably mediated by agonizing PPAR-α	LDL ↓ 8%	Rhabdomyolysis
Bezafibrate		HDL ↑ 9% to 10%	Liver failure[b]
Ciprofibrate		TG ↓ 30% to 36% [81, 82]	especially in combination with statins (extremely rare)
Gemfibrozil			
Fenofibrate			

↑ = Increase; ↓ = Decrease

[a] Data from pooled analysis of statin-colesevelam trials showed LDL lowering of 9%. Depending on statin use, LDL lowering up to 18% was shown

[b] Other side effects mentioned in the meta-analysis from Birjmohun et al. [81] included skin reactions, musculoskeletal symptoms, and hepatotoxicity. However, the occurrence of these side effects did not significantly differ from the side effects reported in the control groups

HDL high-density lipoprotein; *HMG-CoA* 3-hydroxy-3-methylglutaryl coenzyme A; *LDL* low-density lipoprotein; *LDLR* low-density lipoprotein receptor; *PPAR-α* peroxisome proliferator-activated receptor-α; *TG* triglycerides

reduction in LDL-C in the combination therapy arm [29•]. A possible explanation for this rather counterintuitive finding is the fact that the baseline cIMT measured in the enrolled patients was not as severely affected as anticipated. The potential beneficial effect of ezetimibe is demonstrated in a recent analysis, in which ezetimibe was shown in FH patients to not only result in significant reductions in LDL-C but also in other CVD-associated plasma markers in FH patients [30]. The SHARP trial showed a beneficial effect on CVD risk (risk reduction, 17%; P=0.002) of simvastatin

combined with ezetimibe compared with placebo in a large cohort (> 9000) patients suffering from chronic kidney disease. In this study, the combination therapy was not associated with altered risk of myopathy or cancer during the 4.9 years of follow-up [31]. Although there is no direct clinical evidence that ezetimibe would result in a beneficial vascular outcome, it is reasonable to consider it as add-on therapy to statins in FH patients given its tolerability and safety.

Bile acid binding resins act by binding to bile acids in the intestinal lumen. This interrupts the enterohepatic circulation of bile acids, leading to increased conversion of cholesterol into bile in the liver. The resulting decreased cholesterol levels in the hepatocytes induce a hepatic upregulation of LDL receptor activity, causing an increased clearance of LDL-C from the circulation by up to 20% [32]. Because bile acid binding sequestrants act in the intestinal lumen and are not systemically absorbed, they are considered to be safer than other lipid-lowering drugs. However, cholestyramine and colestipol are associated with significant adverse gastrointestinal side effects, drug-drug interactions, and poor patient compliance. The second-generation bile acid sequestrant colesevelam can be used at a lower dose and is associated with less gastrointestinal side effects, and is therefore currently the recommended bile acid sequestrant for use in patients with FH in combination with statins [33].

The mechanism of action of fibric acid derivates is complex and largely unknown, but is commonly thought to be mediated via a peroxisome proliferator-activated receptor-α regulated mechanism. Treatment with fibrates results in decreased production of very low density lipoprotein cholesterol (VLDL-C) and an increased clearance of triglycerides. Fibrates have also shown to lower total cholesterol and LDL-C and elevate HDL-C to some extent (Table 1). Adverse reactions are to some extent similar to statins (Table 1); however, the combination of fibrates, most notably gemfibrozil, with statins will increase the risk of myopathy or rhabdomyolysis [34], and therefore fibrates are not recommended in FH patients without elevated triglyceride levels.

The mechanism of action of nicotinic acid or niacin is not fully understood. Niacin is a water-soluble B vitamin and favorably affects VLDL, LDL-C, and increases HDL-C. The adverse effects of niacin (Table 1), mainly flushing due to vasodilatation, are considered a major drawback, but by combining niacin with a prostaglandin D2 inhibitor (laropiprant), this side effect was significantly decreased [35–37]. A meta-analysis has shown cardiovascular risk benefit of niacin in terms of reduction of cardiovascular events and atherosclerosis [38], but a more definitive answer regarding CVD reduction of niacin will be provided by the HPS-2-Thrive study. As for all other agents, however, no conclusions can be drawn regarding the benefit of niacin added to statin therapy in FH patients. The AIM-HIGH trial investigated whether adding extended-release niacin to statin treatment in high-risk patients would be beneficial in risk reduction. This trial has recently been stopped prematurely by the National Heart, Lung, and Blood Institute after 18 months, because no effect was shown in the interim analysis (http://public.nhlbi.nih.gov/newsroom/home/GetPressRelease.aspx?id=2792).

LDL apheresis may be considered for homozygous FH patients or heterozygous FH patients who require intensification of therapy because of high LDL-C levels despite a maximal dose of statins and/or multiple other risk factors for CVD. LDL apheresis selectively removes apo B–containing lipoprotein particles from the circulation with extracorporeal precipitation through different techniques, resulting in an LDL-C reduction of approximately 60% [39]. Furthermore, it reduces lipoprotein (a) levels by more than 50%. The procedure is time consuming, must be repeated every 1 to 2 weeks, and is costly. However, several clinical trials have shown that LDL apheresis delays the progression of CVD [40].

Future Lipid-Lowering Therapy

Antisense Oligonucleotides to Inhibit Apolipoprotein B Production

Apolipoprotein B (apo B) is mainly expressed in the liver and is regarded as an essential protein at core and on the surface of atherogenic lipoproteins. It is crucial for the production of VLDL (the precursor of LDL) and following secretion by the liver, apo B is bound to its lipoprotein particle. Apo B is also pivotal for the subsequent clearance of cholesterol transported by lipoproteins; upon binding to the LDL receptor, cholesterol is withdrawn from the plasma pool [41]. In FH patients apo B levels are invariably increased, and large prospective studies have shown that apo B levels are directly associated with CVD risk [42]. In line with this, patients with extremely low levels of apo B (< 5th percentile) due to familial hypobetalipoproteinemia seem to be protected against CVD [43, 44]. Based on these observations apo B is conceptually an attractive target to reduce CVD risk. Mipomersen (formerly known as ISIS-301012), a second-generation apo B synthesis inhibitor, is the first agent available for human use to directly target apo B100 production. This subcutaneously administered short single-stranded synthetic oligonucleotide is complementary to apo B100 mRNA, and upon binding to the mRNA, degradation by endogenous RNase-H takes place. This subsequently results in inhibition of synthesis of the apo B protein, and a decrease in VLDL and LDL levels [45].

The initial phase 1 study [46] showed a dose-dependent effect on apo B and LDL as well as on all other atherogenic particles. The highly significant dose reductions in LDL-C (Table 2) were confirmed in a number of studies, including trials in FH patients [47–50]. The effect on plasma lipids was shown not to be influenced by coadministration of other lipid-lowering medication [47, 50]. In addition to its beneficial effect on LDL-C, mipomersen also lowered serum levels of apo B, triglycerides, and lipoprotein (a). A dose of 200 mg of mipomersen once weekly administered subcutaneously was selected for further evaluation in phase 3 clinical trials. Reductions in LDL-C lasted up to 4 weeks after the last dose and pharmacokinetic studies showed no clinically relevant interactions of mipomersen with the disposition and clearance of simvastatin or ezetimibe [51], which is pivotal for the role of mipomersen as additive medication.

In a recently published double-blind trial, 51 homozygous FH patients, treated with maximum tolerated dosages of lipid-lowering medications, were randomly assigned to mipomersen, 200 mg, subcutaneously every week or placebo. After 26 weeks of treatment, a mean reduction in LDL-C of 25% was observed in the mipomersen-treated group versus 3% in placebo-treated patients ($P<0.001$). In addition, patients treated with mipomersen experienced a 27% reduction in apo B and a 21% reduction in total cholesterol. No correlation was found between the LDL receptor mutation and response to therapy [50].

Similar reductions in LDL-C levels (28%) were shown in a study conducted in 124 patients with heterozygous FH, who were on maximally tolerated statin therapy and had a history of coronary heart disease. It is of note that 45% of these high-risk patients treated with mipomersen reached the treatment goal of LDL-C below 100 mg/dL [52].

Mipomersen is well tolerated and commonly described adverse events include injection site reactions, flu-like symptoms, and increases in alanine aminotransferase. The latter were shown not to be directly related to increased steatosis, as being measured in a study using magnetic resonance spectroscopy [53].

Mipomersen should be considered a potential novel treatment modality in FH, given its lipid-lowering effect, relatively easy mode of administration, and lack of interactions with other lipid-modifying drugs.

PCSK9 Targeted Therapy

After the initial report that gain-of-function mutations in the gene encoding for proprotein convertase subtilisin/kexin type 9 (PCSK9) cause Mendelian hypercholesterolemia [3], PCSK9 has gained large interest as a target for lipid lowering. PCSK9 has been shown to be a pivotal regulator of LDL-C metabolism by virtue of its role in lysosomal degradation of the LDL receptor within hepatocytes. The notion that loss-of-function PCSK9 mutations confer an 80% CVD risk reduction [54] has further substantiated the role of PCSK9 as a potential target. Although PCSK9 could be anticipated to act as a protease on other substrates as well, it is of importance to note that subjects with lifelong half normal activity of PCSK9 due to loss-of-function mutations were not characterized by other untoward clinical features.

A number of strategies to specifically lower PCSK9 activity are currently in different stages of development and testing: antisense nucleotide-based therapy (similar to mipomersen described above) [55], monoclonal antibodies binding to the catalytic site of PCSK9 (eg, AMG 145, 1D05-IgG2, and REGN727), and small interfering RNAs.

Although animal studies have shown beneficial effects of use of these novel compounds (with LDL lowering up to 80%) [56, 57], no human studies on the effect of either of these different strategies have been published thus far. The finding, however, that statins and fibrates induce increased PCSK9 expression [58] further underlines that PCSK9 inhibition could induce robust LDL-C reductions as add-on therapy and a number of phase 2 and phase 3 trials will likely be initiated soon.

Microsomal Triglyceride Transfer Protein Inhibitors

Microsomal triglyceride transfer protein (MTP) plays an important role in the hepatic assembly of plasma lipoproteins, by mediating the transfer of triglycerides to VLDL [59, 60]. MTP mutation carriers are characterized by hypobetalipoproteinemia [61] and one could therefore anticipate an MTP-lowering therapy to result in a decrease of VLDL and LDL-C levels (Table 2). Cuchel et al. [62] showed that MTP inhibition by means of BMS-201038 gave rise to approximately 50% reductions of plasma LDL-C levels in the highest dosage (0.1 mg/kg/day). However, this trial, performed in six homozygous FH patients [62], also showed that MTP inhibition induced an increase in hepatic steatosis. This finding raised serious concerns, and the drug is therefore only studied at its higher dosages in homozygous FH patients where LDL-C reduction is considered to outweigh potential steatosis. The maximum studied dose in a subsequent trial in 10 homozygous patients was 60 mg/day, and this regimen resulted in a 44% reduction in LDL-C levels, over and above the effect already achieved by coadministered other lipid-modifying medication [63]. The extent of steatosis in this trial was reduced compared with the initial trial.

A low-dose regimen of MTP inhibition was studied by Samaha et al. [64]. The 84 patients with hypercholesterolemia were randomized to ezetimibe, 10 mg, daily ($n=29$); MTP inhibition by lomitapide (also known as AEGR-733 and BMS −201038) in increasing dosages (5.0, 7.5, and 10 mg

Table 2 Overview of future therapeutics for lipid lowering

Agent	Phase of investigation	Mechanism of action	Effect on lipid profile	Adverse effects
Apolipoprotein B synthesis inhibitors Mipomersen	Phase 2 and 3	Inhibition of apolipoprotein B production	LDL ↓ 21% to 52% (dose dependent) HDL variable (range: no significant change to ↑ 15.1%) TG: variable (range: no significant change to ↓ 17% to 41% [47, 48, 50][a]	Injection side reactions Increase of alanine aminotransferase levels
Thyroid mimetics: Eprotirome	Phase 2	Selective affinity for thyroid receptor β, which is expressed in the liver. Induction of metabolic beneficial pathways	LDL ↓ 22% to 32% HDL ↓ 5% to 6% TG ↓ 16% to 33% [65, 83][b]	Abdominal pain and gastrointestinal side effects; mild increase of transaminase levels
PCSK9 inhibitors	Phase 1	Inhibition of PCSK9; protease which inhibits the expression of LDL receptors	PCSK9 inhibitors are currently being investigated in phase 1 clinical trials	PCSK9 inhibitors are currently being investigated in phase 1 clinical trials
MTP inhibitors	Phase 2 and 3	Inhibition of MTP, thereby interfering in the assembly of plasma lipoproteins in the liver by mediating the transfer of triglycerides and onto VLDL (liver) and chylomicron (intestine)	LDL ↓ 25% to 51% HDL variable (range: no significant change to ↓ 10.4%) TG ↓ 34% to 65% [62]	Gastrointestinal side effects Increase of transaminase levels and hepatic fat accumulation
CETP inhibitors	Phase 3	Inhibition of CETP, which mediates the exchange of cholesteryl esters from HDL to LDL particles	Torcetrapib [84][c]	Increase of transaminase levels
Torcetrapib			LDL ↓ 8% to 29% HDL ↑45% to 72%	Flu like symptoms The ILLUMINATE trial was terminated early because of increased mortality and morbidity in patients treated with torcetrapib on top of a statin [72]
Dalcetrapib			TG ↓18% to ↑ 14% Dalcetrapib [84][d] LDL ↓ 6% HDL ↑ 27% to 28% TG ↓ 0% to 8%	
Anacetrapib			Anacetrapib [74, 84][e] LDL ↓ 27% to 62% HDL ↑ 80% to 139% TG ↓ 30% to ↑ 18%	

↑ = Increase, ↓ = Decrease

[a] Changes mentioned are in subjects on conventional lipid-lowering therapy at baseline

[b] Effects shown are in addition to statin therapy after 12 weeks of treatment with eprotirome dosages ranging from 25 to 100 μg

[c] Data shown include treatment in subjects with HDL less than 40 mg/dL, healthy subjects, subjects with mixed dyslipidemia, heterozygous FH patients, patients with type IIB hyperlipidemia, high-risk patients, patients with CAD, patients with HDL levels below average, and patients with HDL levels below average and eligible for statin treatment

[d] Data shown include treatment in subjects with HDL less than 60 mg/dL and subjects with type II dyslipidemia

[e] Data shown include treatment in subjects with LDL 100 to 190 mg/dL or 100 to 160 mg/dL and moderate risk of CAD, treatment in subjects with primary hypercholesterolemia or mixed hyperlipidemia, and treatment in healthy subjects

CAD coronary artery disease; *CETP* cholesterol ester transfer protein; *FH* familial hypercholesterolemia; *HDL* high-density lipoprotein; *ILLUMINATE* Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events; *LDL* low-density lipoprotein; *MTP* microsomal triglyceride transfer protein; *PCSK9* proprotein convertase subtilisin/kexin type 9; *TG* triglycerides; *VLDL* very low density lipoprotein

daily for each consecutive 4 weeks [n=28]); or ezetimibe, 10 mg daily, and lomitapide administered with the dose titration described above (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 10-mg dosing regimens, respectively. Combined therapy produced similar but larger dose-dependent decreases (35%, 38% and 46%, respectively). Mild transaminase elevations (n=9) and diarrhea were the primary cause for discontinuations from lomitapide (Table 2). Despite the fact that MTP inhibition induced steatosis in high dosages, one might consider MTP an attractive candidate for lipid lowering in FH patients if administered in lower dosages.

Thyroid Mimetics

The notion that hyperthyroidism results in sharply decreased LDL-C levels reduced has driven the attempts to mimic this by administration of thyroid hormone analogues. As seen in hyperthyroidism, however, these therapies (D-thyroxine and tiratricol) failed, due to the associated cardiac and bone-related side effects.

Recently, the differential molecular mechanisms underlying the "beneficial" (mainly via the thyroid receptor-β [TRβ] route; this receptor is mainly expressed in the liver) and "deleterious" aspects (mediated by TRα [expressed in brain and heart]–induced processes) of hyperthyroidism have been elucidated. Eprotirome (KB2115; Karo Bio AB, Stockholm, Sweden), sobetirome (QRX-431/GC-1; formerly owned by QuatRx Pharmaceuticals, Ann Arbor, MI), and MB07811 (Ligand Pharmaceuticals, La Jolla, CA) are selective TRβ agonists and they are currently in different stages of investigation.

A recent study showed the effects of adding eprotirome to standard statin therapy [65]. In this 12-week trial, Ladenson et al. [65] enrolled 184 patients, who were treated with placebo or eprotirome on top of a statin (simvastatin≤ 40 mg and atorvastatin≤20 mg daily). Randomization to placebo or eprotirome in three dosages (25, 50 and 100 ug daily) resulted in a decrease of LDL-C level by 7%, 22%, 28%, and 32%, respectively (Table 2). Eprotirome was not associated with adverse events on heart (arrhythmia) or bone (serum markers of bone turnover) [65]. A large phase 3 trial will start in FH patients in the near future.

Sobetirome and MB07811 have not been tested for their effect on dyslipidemia in humans, but the beneficial effect of eprotirome on LDL-C levels in non-FH patients holds promise for FH patients.

Cholesterol Ester Transfer Protein Inhibitors

The HDL-bound enzyme cholesterol ester transfer protein (CETP) mediates the process of transfer of cholesteryl esters from HDL particles to apolipoprotein B–containing particles [66]. Elevated CETP levels were shown to be associated with an increased risk for coronary artery disease in apparently healthy subjects [67], and inhibition of CETP in rabbit models of atherosclerosis dramatically reduced the extent of the disease [68]. Two approaches to inhibit CETP activity have been described; a vaccine-based strategy and a small molecule inhibitor-mediated method.

CETi-1 (Avant Immunotherapeutics, Needham, MA) is a synthetic peptide that includes residues of the human CETP protein. Upon administration, this vaccine raises an immune response and production of autoantibodies against CETP. Initial animal studies showed the efficacy of this vaccine to increase HDL-C levels and reduce aortic atherosclerosis [69]. However, the phase 1 trial in humans showed a relatively poor response in terms of the presence of autoantibodies (in 1 out of 23 patients) and the effect on plasma lipid levels was negligible [70].

Torcetrapib (Pfizer, New York, NY), anacetrapib (MK-0895; Merck, White House Station, NJ), dalcetrapib (formerly known as JTT-705; Roche, Basel, Switzerland), and evacetrapib (LY2484595; Eli Lilly; Indianapolis, IN) are molecules that antagonize CETP activity by binding to the protein. The reason why these primarily HDL-C–increasing medications are mentioned in this review is the fact that torcetrapib is tested in FH patients and that all CETP inhibitors have been shown to beneficially affect LDL-C levels.

The RADIANCE I trial, in which over 800 patients with FH were enrolled, showed that addition of torcetrapib to atorvastatin did not result in reduction of atherosclerosis, as assessed by intima-media thickness [71], despite a significant reduction in LDL-C (21%) and increase in HDL-C (52%). These findings are in line with the ILLUMINATE trial, which was prematurely terminated because of unexpected increased mortality and morbidity in patients treated with atorvastatin combined with torcetrapib [72]. The exact mechanism underlying this counterintuitive finding is not fully elucidated, but a recent chemical systems biology analysis shed light on this topic. The study suggested the presence of off-target effects of torcetrapib, and these might partially explained by the blood pressure increase induced by torcetrapib [73]. The fact that the other CETP inhibitors do not show an effect on blood pressure further confirms a molecule-specific off-target effect.

The two remaining CETP inhibitors in phase 3 development, anacetrapib and dalcetrapib, have been shown to be effective lipid modifiers [74, 75], but the cardiovascular outcome trials (DAL-outcomes I and II and HPS3/REVEAL) are eagerly awaited. Once shown to benefit mild hypercholesterolemic patients and other patients at CVD risk, CETP inhibition is likely to benefit patients with FH.

Conclusions

During the last decade we have been confronted with an increase in our understanding of human lipid biology. This knowledge has given great impetus to the identification of novel strategies to inhibit specific pathways in dyslipidemia. Upon approval of efficacy in CVD reduction, these agents will be beneficial for all patients at risk, such as FH patients.

Disclosure Conflicts of interest: B. Sjouke: none; D.M. Kusters: none; J.J.P. Kastelein: has been a consultant for AstraZeneca, MSD, Novartis, Roche, Eli Lilly, Isis, Cerenis, Genzyme, Boehringer Ingelheim, Sanofi-Aventis, Regeneron, and Anthera; G.K. Hovingh: none.

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