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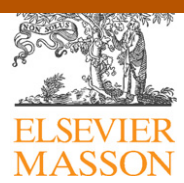

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REVIEW

Severe familial hypercholesterolaemia: Current and future management

Hypercholestérolémie familiale sévère : prise en charge actuelle et future

Michel Farnier[a,*], **Eric Bruckert**[b]

[a] *Point médical, rond point de la Nation, 21000 Dijon, France*
[b] *Service endocrinologie-prévention cardiovasculaire, hôpital Pitié-Salpêtrière, AP—HP, 75651 Paris cedex 13, France*

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Summary Familial hypercholesterolaemia is an inherited disorder, leading to accumulation of low-density lipoprotein (LDL) particles in plasma and premature cardiovascular disease. Although the phenotype of the rare homozygous form is always severe, the phenotypic expression of the common heterozygous familial hypercholesterolaemia can vary considerably. Beyond the magnitude of the LDL-cholesterol elevation and the type of mutation, additional genetic, metabolic and environmental cardiovascular risk factors lead to the substantial variations in the clinical manifestations and severity of atherosclerotic disease. Heterozygous familial hypercholesterolaemia is often under-diagnosed and under-treated, and there is an unmet need in terms of management of severe heterozygous forms. Homozygous and severe heterozygous familial hypercholesterolaemia should receive more intensive treatment and alternative therapeutic approaches are needed for these high-risk patients. In this article, we review the recommendations for diagnosis and treatment of severe familial hypercholesterolaemia and the agents currently available or under development.

Abbreviations: ApoB, apolipoprotein B; ALT, alanine aminotransferase; ASO, antisense oligonucleotide; CETP, cholesterol ester transfer protein; CHD, coronary heart disease; CVD, cardiovascular disease; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; FH, familial hypercholesterolaemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LDL-R, low-density lipoprotein receptor; LLT, lipid-lowering treatment; Lp(a), lipoprotein(a); mRNA, messenger ribonucleic acid; MTP, microsomal triglyceride transfer protein; NLA, National Lipid Association; PCSK9, proprotein convertase subtilisin/kexin type 9; TG, triglyceride; VLDL, very-low-density lipoprotein.

* Corresponding author. Fax: +33 3 80 70 38 14.
E-mail address: michelfarnier@nerim.net (M. Farnier).

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MOTS CLÉS
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Traitement ;
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Nouveaux traitements

Résumé L'hypercholestérolémie familiale est une maladie héréditaire qui induit une accumulation de particules LDL dans le plasma et un risque accru de maladies cardiovasculaires précoces. Alors que le phénotype de la rare forme homozygote est toujours sévère, l'expression phénotypique de la forme hétérozygote fréquente peut varier considérablement. En dehors de l'importance de l'élévation du LDL-cholestérol et du type de mutation, de nombreux facteurs de risque cardiovasculaire additionnels génétiques, métaboliques et environnementaux ont un rôle important dans la variabilité des manifestations cliniques et dans la sévérité de la maladie athéromateuse. Les hypercholestérolémies familiales hétérozygotes restent mal diagnostiquées et insuffisamment traitées et il existe un besoin médical non satisfait en termes de prise en charge des formes hétérozygotes sévères. Les hypercholestérolémies familiales homozygotes et hétérozygotes sévères doivent recevoir un traitement plus intensif et de nouvelles alternatives thérapeutiques sont nécessaires pour ces patients à très haut risque. Cet article est une revue des recommandations vis-à-vis du diagnostic et du traitement des hypercholestérolémies familiales sévères, avec présentation des médicaments actuellement disponibles et en développement.

Background

Autosomal dominant familial hypercholesterolaemia (FH) is among the most common inherited disorders [1]. FH is characterized by an elevation of low-density lipoprotein cholesterol (LDL-C) due to reduced uptake of plasma LDL particles by the liver. Affected subjects are at increased risk of all atherosclerotic diseases secondary to lifelong elevations in LDL-C. The pattern of inheritance is autosomal codominant and the main gene involved in FH is the *LDL receptor* (*LDL-R*) gene. However, mutations leading to FH have been also described in two other genes: *apolipoprotein B* (*ApoB*) and *proprotein convertase subtilisin/kexin type 9* (*PCSK9*). The vast majority of families show only heterozygous carriage of the causal gene. Homozygotes or compound heterozygotes are rare but are characterized by very high concentrations of LDL-C and severe atherosclerosis during childhood. As a result, all patients with homozygous FH must be classified in the category of severe hypercholesterolaemia.

Although the cause of FH is monogenic, heterozygous FH can have widely different concentrations of LDL-C. Moreover, various additional environmental and metabolic factors are assumed to affect the clinical phenotype of heterozygous FH. Major cardiovascular risk factors in individuals with heterozygous FH have been identified and several categories of risk have been proposed according to the presence of these major risk factors and/or clinical atherosclerosis [2,3].

Despite the use of currently available lipid-lowering treatments (LLTs), a high proportion of patients with severe forms of FH, including homozygous FH and severe heterozygous FH, do not reach treatment goals and remain at increased risk of atherosclerotic cardiovascular diseases (CVDs). New therapeutic approaches are crucial for these patients. There is a need to better define the categories of severe FH eligible for these new treatment options.

Diagnosis and cardiovascular risk of FH

FH is caused by mutations mainly in *LDL-R* gene but also in other genes (*ApoB*, *PCSK9*, etc.) [4]. Individuals with two mutations (homozygous FH) are easy to diagnose due to the severity of the disease. By comparison, many people with the heterozygous form are undiagnosed or are only diagnosed after their first coronary event.

Homozygous FH

Homozygous FH is a very rare (1 per 1 million people) autosomal dominant disease, usually caused by mutations in the *LDL-R* gene or other genes, leading to very high plasma concentrations of LDL-C and earlier onset of coronary heart disease (CHD) than in subjects with heterozygous FH. Homozygous FH patients are classified into two major groups based on the amount of LDL-R activity: patients with less than 2% of normal LDL-R activity are classified as receptor-negative and patients with 2 to 25% of normal LDL-R activity as receptor-defective. In practice, children with two heterozygous FH carrier parents have a 25% chance of inheriting both defective genes, leading to homozygous FH with either the same genetic mutation from both parents or two different mutations from each parent (also named compound heterozygous).

Homozygous FH is characterized by extremely high concentrations of total cholesterol (usually in the range 6.0—10.0 g/L) and LDL-C. In a large homozygous FH cohort, the mean LDL-C concentration for untreated subjects was 6.15 g/L [5]. High-density lipoprotein cholesterol (HDL-C) concentrations are often decreased and triglyceride (TG) concentrations are usually normal [5].

In childhood, patients with homozygous FH develop multiple types of xanthomas, including tendinous and tuberous xanthomas, xanthelasmas and particularly cutaneous planar xanthomas, being considered as pathognomonic of the disease [1]. Accelerated atherosclerosis appears in childhood and develops initially in the aortic root, causing valvular and supravalvular aortic stenosis, then extension into the coronary ostia. Untreated patients with homozygous FH who are receptor-negative rarely survive beyond the second decade; receptor-defective patients have a slightly better prognosis but, with few exceptions, develop clinically significant atherosclerotic vascular disease by the age of 30 years (and often sooner) [1,6].

Heterozygous FH

The prevalence of heterozygous FH is 1 in 300—500 in Western populations, making heterozygous FH one of the most common inherited disorders. Known causes of heterozygous FH include mutations in three major genes: the *LDL-R*, *ApoB* and *PCSK9* genes [4,7]. However, heterozygous FH is most commonly attributable to mutations in the *LDL-R* gene. In a recent French cohort, the respective contributions of each known gene were 73.9% for *LDL-R*, 6.6% for *ApoB* and only 0.7% for *PCSK9* [7]. No mutation was found in 19% of the probands, underscoring the existence of mutations located in still unknown genes.

The clinical criteria used to identify patients with heterozygous FH include high plasma concentrations of total cholesterol and LDL-C, the presence of tendon xanthomas in the patient or first-degree relative, a family history of hypercholesterolaemia (especially in children) and a personal or family history of premature CHD [8]. Usually, heterozygous FH patients have LDL-C concentrations ranging from 1.9 to 4.0 g/L. However, the range of total cholesterol and LDL-C concentrations in heterozygous FH overlaps with concentrations observed in polygenic hypercholesterolaemia. Moreover, heterozygous FH patients can have LDL-C concentrations less than 1.90 g/L. Thus, additional criteria are needed to confirm the diagnosis of FH. TGs are usually in the normal range but some patients with FH have elevated TG concentrations explained either by environmental factors or by interactions with other genes. Plasma concentrations of lipoprotein(a) (Lp[a]) are also often elevated in FH patients. Tendon xanthomas are essentially pathognomonic of FH. However, tendon xanthomas are rare until the fourth decade of life. Additional sites of cholesterol deposits are the cornea (cornea arcus) and the eyelids (xanthelasmas) but these sites are not specific for heterozygous FH.

In practice, clinical diagnosis can still be difficult due to the variability of clinical expression, even among individuals who share the same genetic defect. By consequence, several sets of criteria have been developed for diagnosing FH. Among the best validated criteria, the Simon Broome Register criteria (Table 1) [2] and the Dutch Lipid Clinic Network criteria (Table 2) [8] for FH are the most widely used. Using these scores, a clinical diagnosis of FH can be made on the basis of clinical characteristics and laboratory findings. When the diagnosis is uncertain (possible or probable), the detection of a mutation in the causal gene provides the only unequivocal diagnosis. Diagnosis of heterozygous FH using DNA-based mutation screening methods should be proposed to decrease the rate of under-diagnosis. The NICE guidelines state that all patients with a clinical diagnosis of FH should be offered a DNA diagnostic test and referral for family cascade testing in order to identify relatives affected [2]. Indeed, the most effective strategy for diagnosing patients with FH is to screen close relatives of patients already diagnosed with FH [9,10]. Cascade screening involves testing lipid concentrations in all first-degree relatives of diagnosed FH patients. In families where the mutation has been identified, genetic testing should also be included in cascade screening.

Untreated patients with FH are at very high risk of premature CHD and death. Before statin treatment, around 50% of men experienced cardiovascular disease by the age of 50 years and around 30% of women by the age of 60 years [2,11]. However, among people with FH, the phenotypic expression in terms of onset and severity of atherosclerotic disease varies considerably. The type of genetic mutation, as well as other genetic factors, may contribute to this variability [12]. However, the risk differs even among individuals who share the same defect [12] and LDL-C concentrations are a more important risk factor than the type of *LDL-R*

Table 1 Diagnosis of FH: Simon Broome Register criteria [2].

A definite diagnosis of FH requires
Cholesterol concentrations as defined in this table and tendon xanthomas in the patient or in a first- or second-degree relative
OR
DNA-based evidence of an LDL-R mutation, an ApoB mutation or a PCSK9 mutation

A possible diagnosis of FH requires cholesterol concentrations as defined in this table and at least one of the following
Family history of myocardial infarction before age 50 years in a second-degree relative or before age 60 years in a first-degree relative
OR
Family history of raised cholesterol > 2.9 g/L (7.5 mmol/L) in an adult first- or second-degree relative or > 2.6 g/L (6.7 mmol/L) in children aged < 16 years

Cholesterol concentrations to be used as diagnostic criteria for the index individual

	Total cholesterol	LDL-C
Child/young person	> 2.60 g/L (> 6.7 mmol/L)	> 1.55 g/L (> 4.0 mmol/L)
Adult	> 2.90 g/L (> 7.5 mmol/L)	> 1.90 g/L (> 4.9 mmol/L)

ApoB: apolipoprotein B; FH: familial hypercholesterolaemia; LDL-C: low-density lipoprotein cholesterol; LDL-R: low-density receptor; PCSK9: proprotein convertase subtilisin/kexin type 9.

Table 2 Diagnosis of FH: Dutch Lipid Clinic Network criteria [8].

Characteristics			Number
Family history			
First-degree relative known to have premature[a] CVD			1
First-degree relative known to have LDL-C > 95th percentile OR			
First-degree relative with tendon xanthoma or arcus cornealis			2
Children aged < 18 years with LDL-C > 95th percentile			
Clinical history			
Patient has premature[a] CAD			2
Patient has premature[a] cerebral or peripheral vascular disease			1
Physical examination			
Tendon xanthomas			6
Arcus cornealis below age 45 years			4
Laboratory analysis			
LDL-C	> 3.30 g/L	> 8.5 mmol/L	8
LDL-C	2.50—3.29 g/L	6.5—8.4 mmol/L	5
LDL-C	1.90—2.49 g/L	5.0—6.4 mmol/L	3
LDL-C	1.55—1.89 g/L	4.0—4.9 mmol/L	1
DNA analysis			
Functional mutation gene present			8
Diagnosis of FH			
Certain when			> 8 points
Probable when			6—7 points
Possible when			3—5 points

CVD: cardiovascular disease; CAD: coronary artery disease; FH: familial hypercholesterolaemia; LDL-C: low-density lipoprotein cholesterol.
[a] Men aged < 55 years or women aged < 60 years.

mutation [13]. Additional atherogenic risk factors play a crucial role in the clinical expression of FH [14]. Risk factors for cardiovascular disease are similar in individuals with or without FH. However, in the setting of high cholesterol concentrations, the effect of each risk factor is amplified [3].

In summary, the clinical prognosis of heterozygous FH is related not only to the magnitude of the LDL-C elevation and to the longer duration of high LDL-C exposure but also to the presence of other genetic or environmental cardiovascular risk factors. Individuals with FH who are at highest risk, especially those with the more severe forms of FH, must be identified and should receive more intensive treatment.

Identification of severe FH

An important step in improving the management of patients with severe FH is better definition of this patient subpopulation that needs specific therapeutic options. Indeed, despite the use of currently available LLTs, a significant proportion of patients with severe forms of FH, including homozygous FH and severe heterozygous FH, do not reach treatment goals and therefore remain at elevated risk for atherosclerotic CVD.

Until now, no clear definition of severe heterozygous FH has been proposed [15]. Recommendations from the National Lipid Association (NLA) Expert Panel on FH have defined characteristics of FH patients at the highest cardiovascular risk [3]: established CHD or other atherosclerotic CVD, or the presence of additional major risk factors, including diabetes, smoking and family history of very premature CVD (Table 3), places patients with heterozygous FH in the very-high-risk category [3].

Several other risk factors contribute to amplifying the risk in FH patients. The NLA recommendations propose that the presence of two or more associated risk factors should place these patients in the very-high-risk category (Table 3). Particularly, recent evidence supports a specific role for high Lp(a) in the global cardiovascular risk of FH patients [16]. In clinical practice, all the categories of patients listed in Table 3 should be considered at very high risk, need more aggressive modification of lifestyle and other modifiable cardiovascular risk factors and should receive more intensive treatment of their hypercholesterolaemia. Among these very-high-risk FH patients, some could be classified as having 'severe FH', including homozygous FH and severe heterozygous FH, with severe heterozygous FH clinically defined as: patients on maximal LTT with LDL-C greater or equal to 3.0 g/L and 0—1 risk factor; or LDL-C greater or equal 2.0 g/L and greater or equal 2 risk factors or Lp(a) greater or equal

Table 3 Higher-risk FH patients (adapted from [3]).

Homozygous FH patients
Heterozygous FH patients with any of these very-high-risk characteristics
Established CHD or other CVD
Smoker
Diabetes mellitus
Family history of very-premature-onset CHD
First- or second-degree male relative with onset before age 45 years
First- or second-degree female relative with onset before age 55 years
Two or more cardiovascular risk factors among this list:
Increasing age (men > 30 years; women > 40 years)
LDL-C > 2.50 g/L
Male sex
Family history of premature-onset CHD
First-degree male relative with onset before age 55 years
First-degree female relative with onset before age 65 years
Metabolic syndrome
HDL-C < 0.40 g/L
Hypertension (BP > 140/90 mmHg or drug treatment)
Lp(a) ≥ 0.50 g/L
Tendon xanthoma

BP: blood pressure; CHD: coronary heart disease; CVD: cardiovascular disease; FH: familial hypercholesterolaemia; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Lp(a): lipoprotein(a).

0.50 g/L; or LDL-C greater or equal 1.6 g/L and established CHD or other CVD or diabetes.

The recent European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines [17] and NLA recommendations [3] proposed an LDL-C goal less than 1.0 g/L (2.5 mmol/L) [or less than 0.7 g/L (1.8 mmol/L) in ESC/EAS guidelines for very-high-risk subjects]. However, these targets cannot be reached in patients with high LDL-C concentrations. An alternative target is to reduce LDL-C concentrations by greater or equal 50% for severe FH. In practice, the maximal reduction of LDL-C should be considered using appropriate drug combinations in tolerated doses.

Current treatment options

The aim of treatment of FH patients is the reduction of plasma LDL-C concentrations to decrease the risk of CVD. Even if lifestyle modifications alone are insufficient to obtain desirable LDL-C concentrations, healthy lifestyle remains an important aspect of FH treatment, with many benefits beyond LDL-C lowering. Lifestyle intervention comprises a healthy diet, reduction of excessive body weight, no smoking and moderate physical activity [17]. The recommended diet for all FH patients includes reduced intake of saturated fats and cholesterol (total fat 25—35% of total calories; saturated fat less than 7% of total calories; cholesterol less than 200 mg per day), use of plant stanols or sterols (1.5—2 g per day) and use of soluble fibres (10—20 g per day) [18].

All adults with heterozygous FH and children with LDL-C greater or equal 1.9 g/L after lifestyle changes will require drug therapy. The current treatment options are reviewed for heterozygous and homozygous FH, with a focus on the unmet medical needs.

Heterozygous FH

Placebo-controlled cardiovascular endpoint trials are unethical in adults with a diagnosis of FH as these individuals are at very high risk of premature onset CHD. Clinical management is therefore largely based on extrapolation from the results of cholesterol-lowering trials done in hypercholesterolaemic patients [19]. The current treatment steps for the management of adults with heterozygous FH are listed in Table 4: FH patients should receive a potent statin (mainly atorvastatin and rosuvastatin). In a meta-analysis of 14 randomized placebo-controlled trials of statin treatment, patients with baseline LDL-C greater than 1.75 g/L had the same relative risk reduction as those with lower LDL-C concentrations [19]. In a subsequent meta-analysis, high doses of statin reduced the risk of CVD more than moderate doses, regardless of baseline LDL-C concentration [20]. Moreover, observational data from two large cohorts of FH patients in Europe confirmed the efficacy of statins in heterozygous FH [21,22]: in the Dutch cohort study, the risk of myocardial infarction in statin-treated FH patients was not significantly greater than that in an age-matched sample from the general population [22]. Similarly, in the UK Simon Broome register, asymptomatic FH patients treated with statins had reductions in all-cause, cancer and coronary mortality [21]. All-cause mortality was 33% lower than in the general population, mainly due to a 37% lower risk of fatal cancer.

Statins are generally safe and well tolerated [23]. The potential adverse effects of statins in FH patients are similar to those observed for other patients receiving statin treatment, particularly increased liver enzymes and myopathy. Patients who do not tolerate potent statin therapy might be offered another statin or very-low-dose statin therapy in

Table 4 Current treatment steps for the management of heterozygous FH.

First step	Lifestyle changes (including dietary adjuncts) and moderate-to-high doses of high-potency statins to achieve LDL-C goal < 1.0 g/L (or < 0.7 g/L for very-high-risk subjects) or LDL reduction ≥ 50% from baseline
Second step	Combination therapy Statin + ezetimibe (addition of ezetimibe for patients not at goal or intolerant)
Third step	Triple therapy Statin + ezetimibe + bile acid sequestrant OR Statin + ezetimibe + nicotinic acid
Last step	LDL aphaeresis (for severe patients with LDL-C > 2.0 g/L in secondary prevention or > 3.0 g/L in primary prevention on maximally tolerated LLT)

FH: familial hypercholesterolaemia; LDL-C: low-density lipoprotein cholesterol; LLT: lipid-lowering therapy.

combination with other LLT. Low potency statins may be less likely to induce myopathy but do not enable achievement of the greater than 50% reduction in LDL-C recommended for FH patients [3]. Alternative LLT includes ezetimibe, bile acid sequestrants (cholestyramine or colesevelam) or niacin. Even among patients who tolerate the maximum doses of the most potent statins, a combination of one or more non-statin drugs is often necessary to achieve the recommended LDL-C goals, particularly for the severe forms previously described. Given the tolerability and safety profile of ezetimibe, it is reasonable to consider, as a second treatment step, the addition of ezetimibe to a maximal dose of statin in FH patients who require intensification of therapy. A 20 to 30% complementary reduction in LDL-C concentration is obtained with ezetimibe but few patients with severe heterozygous FH reach the LDL-C goal less than 1.0 g/L [24]. The third step is triple therapy, such as a statin with ezetimibe and bile acid sequestrant or a statin with ezetimibe and niacin; the addition of colesevelam to a statin and ezetimibe decreased LDL-C concentrations by 12% [25].

In the real word, a large proportion of patients with FH do not reach treatment goals and, by consequence, remain at increased risk of CVD [26,27]. For example, in a recent large cross-sectional study conducted in the Netherlands, nearly all heterozygous FH patients (96%) were on statin treatment. Only 21% of patients achieved the LDL-C goal less than 1.0 g/L (less than 2.5 mmol/L) and about 5% of patients still had an LDL-C concentration greater than 2.0 g/L. Among those not at goal, 27% were on combination therapy of maximum statin dose and ezetimibe [27]. These data emphasize the need for new LDL-lowering therapies. Until now, for patients with severe heterozygous FH and inadequate LDL-C reduction, only LDL-aphaeresis—an extracorporeal system to remove atherogenic lipoproteins—can be proposed in addition to LLT.

Homozygous FH

To retard the progression of premature coronary and/or aortic valvular disease [28], aggressive LLT must begin in early childhood. LDL-aphaeresis is the standard treatment for patients with homozygous FH—it can lower LDL-C and Lp(a) concentrations safely and effectively [29,30]. However, the drawbacks of aphaeresis include limited availability in some countries, high cost, procedure duration and the need to maintain adequate vascular access [30].

Statins can lower LDL-C concentrations substantially in homozygous FH patients [31,32] by decreasing secretion of ApoB-containing lipoproteins in receptor-negative FH and by increasing residual LDL-R activity in receptor-defective FH. In addition, ezetimibe induces a complementary reduction in LDL-C concentrations [33]. By consequence, statins and ezetimibe are classically used in patients treated with LDL-aphaeresis to obtain better achievement of LDL-C goals [33].

Even if the LDL-lowering effect of treatment with a statin or a statin plus ezetimibe is less than the effect usually observed in heterozygous FH patients, these LLTs can be associated with a significant reduction in cardiovascular morbidity and mortality, as shown in a recent retrospective study [5]. This important study was done in a country where few patients are treated with LDL-aphaeresis and the prevalence of homozygous FH is higher: the hazard ratio for benefit from lipid therapy was 0.34 for the endpoint of death ($P = 0.02$) and 0.49 for the endpoint of major cardiovascular events. This benefit occurred despite a mean reduction in LDL-C of only 26.4% with a maximal dose of rosuvastatin or atorvastatin associated with ezetimibe for half of the patients [5]. This study highlights the importance of early diagnosis and initiation of LLT in young children with homozygous FH and the need for new therapeutic options for these very-high-risk subjects.

Future treatment options

Several agents under development target key steps in LDL metabolism. Some other agents targeting HDL metabolism may also induce a decrease in LDL-C concentrations. Among the emerging therapeutic options, the most advanced is the use of antisense oligonucleotides (ASOs) to ApoB100.

Mipomersen

Targeting the ApoB100 protein seems an effective approach to reducing the concentrations of circulating atherogenic lipoproteins, as ApoB100 is required for the synthesis of very-low-density lipoproteins (VLDL) in the liver and so the production of LDL particles. Inhibition of the synthesis of

ApoB100 can be achieved by blocking the translation of messenger ribonucleic acid (mRNA) with an ASO complementary to the mRNA. Mipomersen is a second-generation 20-mer phosphorothioate ASO, complementary in sequence specifically to a segment of the human ApoB100 mRNA. Mipomersen is administered via subcutaneous injection and is predominantly distributed to the kidney and the liver, thus minimizing potential inhibition of ApoB48 in the intestine [34]. Mipomersen is not metabolized via cytochrome P450 enzymes involved in the metabolism of statins and other drugs. Lack of interaction supports its use in combination with oral LLTs. As the mean terminal half-life of mipomersen is around 30 days in humans [34], it has been estimated that steady state will not be achieved before 6 months of treatment.

The clinical efficacy of mipomersen has been evaluated in several studies conducted in various patient populations, including FH [35—40]. The dose of 200 mg mipomersen once weekly was selected for phase 3 trials and the efficacy results observed with this dose are summarized in Table 5. Two phase 3 trials have evaluated the efficacy of mipomersen in homozygous FH and severe heterozygous FH patients on maximal tolerated LTT. Fifty-one patients with homozygous FH not treated by LDL-aphaeresis were randomized 2:1 to 200 mg mipomersen or placebo [39]. After 26 weeks of treatment, the mean reductions in LDL-C and ApoB were, respectively, 25% and 27% in the mipomersen group compared with 3% and 3% in the placebo group ($P < 0.001$). In the second phase 3 study [40], 58 high-risk patients with severe heterozygous FH (LDL-C greater or equal 3.0 g/L or LDL-C greater or equal 2.0 g/L with CHD or another form of clinical atherosclerotic disease, despite maximally tolerated LLT) were randomized 2:1 to 200 mg mipomersen or placebo. After 26 weeks of treatment, a mean reduction in LDL-C of 36% was observed in the mipomersen group versus an increase of 13% in the placebo group ($P < 0.001$). Similarly, mipomersen produced significant ($P < 0.001$) reductions in other atherogenic lipoproteins (ApoB:—36%; Lp(a):—33%).

Common adverse events observed during mipomersen treatment include injection site reactions, flu-like symptoms and increases in alanine aminotransferase (ALT). More than 90% of patients experienced local injection site reactions, generally characterized by a painless transient erythema occurring within 24 hours after the injection. Patients complained sometimes of pain, tenderness, local swelling, pruritus and discoloration at the injection site. The most important long-term safety concern is directly related to the mechanism of action of mipomersen: the inhibition of ApoB synthesis may induce an accumulation of TGs in the liver by inhibition of VLDL production, leading to an increase in concentrations of transaminases and hepatic steatosis. With the recommended dose of 200 mg per week, in patients with severe heterozygous FH [40], 15% of patients had persistent ALT elevations greater than three times the upper limit of normal. In homozygous patients [39], four patients among the 34 randomized to mipomersen had a significant increase in ALT (greater than three times the upper limit of normal) and only one patient had a significant increase in hepatic fat from an abnormal baseline of 9.6% up to 24.9%, which returned to 6% after stopping treatment. ALT elevations have not been associated with clinically significant increases in bilirubin.

A specific study was conducted to evaluate the effect of mipomersen on intrahepatic TG content using proton magnetic resonance spectroscopy [41]. Twenty-one patients with heterozygous FH on stable LLT, TG less than 2.0 g/L and no diabetes mellitus or liver disease, received a weekly subcutaneous injection of 200 mg mipomersen or placebo for 13 weeks: 1/10 subjects in the mipomersen group developed mild hepatic steatosis (intrahepatic TG content of 5.7%), which resolved in the follow-up. For the whole group, there was a non-significant trend towards an increase in intrahepatic TG content. Even if this study was reassuring, limitations included the small sample size, the exclusion of patients at increased risk of hepatic steatosis and the short treatment period. There is still a need for long-term safety data regarding the effect of mipomersen on intrahepatic TG content, including patients with an increased risk of hepatic steatosis, prior to broadening the use of this new strategy. To date, the indication of mipomersen is limited to patients with homozygous FH and patients with severe heterozygous FH, as an adjunct to maximally tolerated LLT.

MTP inhibitors

In the liver, the assembly of lipids with the ApoB100 molecule is mediated by the microsomal triglyceride transfer protein (MTP). Consequently, MTP inhibition could lead to reductions in the secretion of atherogenic lipoproteins from the liver and also reduce the assembly and secretion of chylomicrons in the intestine. However, pharmacological inhibition of MTP has resulted in significant increases in hepatic steatosis in animals and humans. Few clinical data are available for the MTP inhibitor lomitapide [42,43]: in a 16-week open-label ascending-dose study conducted in six patients with homozygous FH receiving a low fat diet (less than 10% energy from fat) to avoid potential steatorrhoea, lomitapide was given at increasing doses of 0.03, 0.10, 0.30 and 1.0 mg/kg per day for 4 weeks [42]. Only the doses of 0.30 and 1.0 mg/kg reduced LDL-C significantly (by 25% and 51%, respectively) with concomitant reductions in TG and ApoB. Four patients had elevated ALT and all patients had some degree of hepatic steatosis. A second study [43] was conducted with lower doses of lomitapide (5.0, 7.5 and 10.0 mg per day) in patients with hypercholesterolaemia and randomized to lomitapide or ezetimibe or lomitapide plus ezetimibe combination therapy. Significant reductions in ApoB (24% with monotherapy, 37% with combination therapy) and non-HDL-C were reported; however 16% of the patients receiving lomitapide discontinued the drug due to increased transaminase concentrations. Gastrointestinal adverse effects were frequent and hepatic steatosis was not evaluated in this short-term study. Increased intrahepatic fat content remains a serious concern with this class of drugs and long-term safety data are required.

PCSK9 inhibitors

PCSK9 is a key regulator of LDL receptor activity. Indeed, secreted PCSK9 binds LDL-R and enhances degradation of LDL-R in the liver, thereby modulating LDL-C plasma concentrations [44]. Loss-of-function mutations of PCSK9 in humans are associated with low concentrations of LDL-C and

Table 5 Efficacy[a] of mipomersen 200 mg per week on plasma lipid and lipoprotein concentrations.

Study description [reference]	LDL-C (%)	ApoB (%)	VLDL-C (%)	Non-HDL-C (%)	TG (%)	Lp(a) (%)
4-week multiple-dosing phase 1 study in volunteers with mild dyslipidaemia [38]	−35.2	−38.5	NA	NA	NA	NA
13-week double-blind placebo-controlled phase 2 study in hypercholesterolaemic patients (monotherapy) [36]	−45	−46	−53	−44	−46	−42
6-week double-blind placebo-controlled phase 2 study in patients with heFH (add-on therapy) [37]	−21	−23	−14	−21	−23	−17
13-week double-blind placebo-controlled phase 2 study in hypercholesterolaemic patients on stable statin therapy [35]	−35.8	−35.7	−11.0	−28.5	−14.6	NA
26-week double-blind placebo-controlled phase 3 study in patients with hoFH on stable LLT [39]	−24.7	−26.8	−17.4	−24.5	−17.4	−31.1
26-week double-blind placebo-controlled phase 3 study in patients with severe hypercholesterolaemia [40]	−36	−36	NA	−34	−15	−33

ApoB: apolipoprotein B; HDL-C: high-density lipoprotein cholesterol; heFH: heterozygous familial hypercholesterolaemia; hoFH: homozygous familial hypercholesterolaemia; LDL-C: low-density lipoprotein cholesterol; LLT: lipid-lowering treatment; Lp(a): lipoprotein(a); NA: not available; TG: triglyceride; VLDL-C: very-low-density lipoprotein cholesterol.
[a] Efficacy evaluated 14 days post-dosing.

protection against CHD [45]. Inhibition of PCSK9 is emerging as a very attractive new alternative for lowering LDL-C concentrations, particularly in combination with statins, as statin therapy can induce an increase in PCSK9 expression [44]. Several approaches have been described for targeting PCSK9 [46]. The most advanced strategy is the use of monoclonal antibodies against PCSK9: a monoclonal antibody can inhibit PCSK9 binding to LDL-R and attenuates PCSK9-mediated reduction in LDL-R protein concentration. In monkeys, a single injection of anti-PCSK9 antibody reduced LDL-C by 80% and a significant decrease was maintained for 10 days [47]. In humans, only data from phase 1 trials and one phase 2 trial are available. In a multidose phase 1 study [48], subjects were treated with subcutaneous injections of 50 mg, 100 mg and 150 mg of REGN727/SAR236553 antibodies or placebo. A decrease in LDL-C reaching around 60% with the 100 or 150 mg doses was observed and maintained for 2 weeks. In a recent phase 2 study [49], when added to atorvastatin, REGN727/SAR236553 further reduced LDL-C by 40% to 72%, additional reductions being dependent on both the dose and dosing frequency. Among the candidate populations for PCSK9 inhibition, patients with severe heterozygous FH are undoubtedly a priority target.

CETP inhibitors

The main objective with this pharmacological strategy is not to lower LDL-C but to inhibit the cholesterol ester transfer protein (CETP); avoiding the transfer of cholesterol ester from HDL to atherogenic particles (VLDL and LDL) can also induce an effect on the atherogenic lipoproteins. This effect has been observed with anacetrapib: at a dose of 100 mg per day, significant reductions in LDL-C (−36%) and ApoB (−18%) were obtained in the DEFINE study, concomitantly with a large increase in HDL-C (+138%) [50]. However, it remains to be determined if CETP inhibition is a valid strategy for reducing the incidence of cardiovascular events.

Conclusion

Patients with severe FH, including homozygous FH and severe heterozygous FH, are at very high risk of atherosclerotic diseases. These patients must be identified early and more intensive treatments are required, as the drugs currently available are insufficient to reduce LDL-C concentrations to recommended targets. Several investigational

agents under development will provide new approaches to lowering LDL-C concentrations for these high-risk patients.

Disclosure of interest

M. Farnier has received grant/research support and speaker's honoraria from and has served as a consultant and advisor for Abbott, Astra Zeneca, Boehringer-Ingelheim, Genzyme, Kowa, Lilly, Merck and Co., Merck-Schering-Plough, Novartis, Pfizer, Recordati, Roche, Sanofi-aventis, and SMB. E. Bruckert has received grant/research support and speaker's honoraria from or has served as a consultant and advisor for Abbott, AMT, Astra Zeneca, Boehringer-Ingelheim, Genfit, Genzyme, Lilly, Merck and Co., Merck-Schering-Plough, Pfizer, Roche and Sanofi-aventis.

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