REVIEW

The genetics of familial hypercholesterolemia and emerging therapies

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Abstract: Familial hypercholesterolemia (FH) results in very high levels of atherogenic low-density lipoprotein (LDL) cholesterol from the time of birth. Mutations of the genes encoding for the LDL receptor, apolipoprotein B and proprotein convertase subtilisin/kexin type 9, are causes for this autosomal dominant inherited condition. Heterozygous FH is very common, while homozygous FH is rare. Affected individuals can experience premature cardiovascular disease; most homozygous patients experience this before the age of 20 years. Since effective LDL cholesterol lowering therapies are available, morbidity and mortality are decreased. The use of statins is the first choice in therapy; combining other lipid-lowering medications is recommended to lower LDL cholesterol sufficiently. In some cases, lipoprotein apheresis is necessary. In heterozygous FH, these measures are effective to lower LDL cholesterol, but in severe cases and in homozygous FH there remains an unmet need. Emerging therapies, such as the recently approved microsomal triglyceride transfer protein inhibitor and the apolipoprotein B antisense oligonucleotide, might offer further options for these patients with very high cardiovascular risk. Early diagnosis and early treatment are important to reduce cardiovascular events and premature death.

Keywords: familial hypercholesterolemia, LDL cholesterol, atherosclerosis, genetics, new therapies, mipomersen

Introduction

Familial hypercholesterolemia (FH) is associated with very high levels of low-density lipoprotein (LDL) cholesterol (LDL-C) from the time of birth. This can lead to myocardial infarctions or death early in life, both of which can be prevented or at least delayed.[1–4] FH has been known for a long time; the therapeutical measures to treat it are improving, and there are many recommendations and guidelines for detecting and managing affected persons.[3,5–7] Despite these factors, FH is underdiagnosed and undertreated worldwide.[1,3] It is challenging to convey the importance of this condition to the general population, because high levels of LDL-C do not cause any symptoms and because affected persons generally feel healthy. The severity of this condition has to be explained repeatedly. Because of the exposure to high levels of LDL-C from birth, the lifetime exposure is very different than for persons acquiring hypercholesterolemia later in life.

FH is inherited in an autosomal dominant way and can be present in a homozygous or a heterozygous form. FH is one of the most frequent monogenetic disorders. Heterozygous FH (heFH) is very common; in a study from 2001, one out of every 500 people was affected.[8] In a more recent study, heFH was suspected to be

even more frequent: one out of 250 people was affected.[4] Homozygous FH (hoFH) is thought to be very rare (one out of 1,000,000 people are thought to be affected), but increased and improved diagnostics using a molecular approach indicate that hoFH might be much more common; they indicate that one out of 300,000 people are affected.[9] In founder regions, monogenetic hypercholesterolemia is even more frequent. The European Society of Cardiology/European Atherosclerosis Society guideline for the management of dyslipidemia states very clearly that FH per se is a high risk constellation and has to be treated immediately without any cardiovascular risk estimation.[6] The American Heart Association/American College of Cardiology (AHA/ACC) guidelines are not specific about FH, but patients with FH who are in the category of individuals with LDL-C levels >4.9 mmol/L (>190 mg/dL) qualify for intensive therapy.[10]

Background
Genetics
FH is inherited in an autosomal dominant way; FH is a type of autosomal dominant hypercholesterolemia (ADH). The long known classical FH (ADH1) is defined by mutations of the gene *LDLR*, which encodes for the LDL receptor (LDL-R). Because of the defective receptors that result, the uptake of LDL-C into the cells is either decreased or inhibited.[11] This was first described by Brown and Goldstein.[12] Now, more than 1,700 different variants of mutations in the *LDLR*, which include exonic substitutions, exonic small rearrangements, large rearrangements, promoter variants, and intronic variants, are known worldwide; mutations in the LDLR are the most common causes for FH.[13] LDL-C uptake is decreased also if there is a mutation in the gene *APOB*, which encodes for apolipoprotein B (ApoB), the protein that recognizes LDL-C and enables the binding of LDL-C to the LDL-R. This condition is known as ADH2, or familial defective ApoB100 (FDB).[14] One common mutation (R3500Q) and three rare mutations are known.[15] The effects of mutations in proprotein convertase subtilisin/kexin type 9 (PCSK9) were deciphered comparatively recently. PCSK9 binds to the LDL-R/LDL-C complex and promotes the degradation of the LDL-R in lysosomes, resulting in lower numbers of LDL-R. Gain of function mutations of *PCSK9* (ADH3 and for which >20 mutations are known) result in lower expression of LDL-R on the cell surface and higher levels of LDL-C; conversely, loss of function mutations result in higher expressions of LDL-R on the cell surface and lower levels of LDL-C.[1,16] In individuals with loss of function mutations and lower levels of LDL-C, the incidence of cardiovascular disease (CVD) is

significantly reduced. This supports the suggestion that low levels of LDL-C from the time of birth are associated with lower cardiovascular risk.[16]

Autosomal recessive hypercholesterolemia is very rare and can resemble autosomal dominant hoFH clinically. It is caused by mutations in the LDL-R adaptor protein 1 gene (*LDLRAP1*), which encodes for the putative adaptor protein that binds to the LDL-R and thereby promotes the internalization of the LDL-R/LDL-C complex into the liver cells.[17]

Homozygous FH can be due to simple homozygosity (same mutation in the same gene on both alleles) or due to compound heterozygosity (two different mutations in the same gene). Double heterozygosity, a rare form of hoFH, is a condition in which there are mutations on two different alleles encoding for FH; one mutation is usually on *LDLR*, and the second is on one of the other three loci. The levels of LDL-C in patients with hoFH depend on the receptor activity independent of the causative defect. Patients who are receptor negative (those who have <2% activity) are more severely affected than patients who are receptor defective (those who have 2%–25% activity).[18] Patients with ADH1 seem to be affected by CVD more frequently than patients with ADH2.[19]

LDLR mutations are the most common reasons for FH; they account for over >95% of the cases. Mutations in other genes are rare; *APOB* mutations make up 2%–5% of cases, and mutations in *PCSK9* and *LDLRAP1* each make up <1% of all FH cases.[18]

In sitosterolemia, the intestinal uptake of plant sterols is increased due to mutations in two ATP binding cassette transporter genes, *ABCG5* and *ABCG8,* both of which are autosomal recessive. Homozygosity is rare, but the clinical appearance is similar to hoFH with very high levels of LDL-C, xanthomata of the tendons, and early CVD. Unlike in the plasma of patients with hoFH, plant sterols levels are very high in plasma of patients with sitosterolemia.[18,20]

Clinical manifestations
LDL-C and cardiovascular disease
In FH, LDL-C is markedly elevated from the time of birth. In heFH, levels range from 8–15 mmol/L (310–580 mg/dL) and in hoFH, from 12–30 mmol/L (460–1,160 mg/dL). These high levels increase the risk for premature CVD drastically in men and women of both groups. In heFH, CVD typically develops before the age of 55 years in men and 60 years in women. In hoFH, CVD occurs very early in life. If untreated, CVD causes death usually before the age of 20 years, but sometimes as early as in the first year

of life.[1] The Simon–Broom Registry showed an increased cardiovascular mortality (relative risk) in women (125-fold) and in men (50-fold) aged 20–39 years.[2] Stenoses of the aortic valve and of the aortic root are typical in hoFH.[21]

External signs of hypercholesterolemia

If a child is presenting with xanthomata, these obvious signs should lead to a prompt and complete workup. Xanthomata occur in hoFH and are typically planar (eg, buttocks) or at the tendons (eg, Achilles tendons). If a child is treated for FH, xanthomata might not develop; this has to be kept in mind when diagnosing FH on the basis of clinical features. An arcus lipoides before the age of 45 years, and especially in childhood, is also a sign of FH.

Diagnostics

The diagnosis of FH can be made clinically or genetically. However, in most countries, there are no screening projects or prevention programs, and it is still a coincidence if a person is diagnosed properly.

Clinical diagnosis

The measuring of LDL-C is pathbreaking in most cases. To further elucidate the risk with regard to lipid disorders, high-density lipoprotein (HDL) cholesterol (HDL-C), triglycerides, and lipoprotein a (Lp[a]) should be measured because in FH, HDL-C as a protective factor is often reduced, and Lp(a) as an additional and independent risk factor is often elevated.[22] To define the global cardiovascular risk, all cardiovascular risk factors that aggravate the risk of FH should be recorded. Secondary causes for hypercholesterolemia, such as hypothyroidism, liver dysfunction, renal dysfunction, and diabetes mellitus (DM), have to be excluded.[23] If a person is on a lipid-lowering medication, high levels of LDL-C might be overlooked.

Drawing a detailed pedigree is the cornerstone for diagnosing FH. Data about levels of cholesterol, cardiovascular events in first-degree relatives, and the age at the first event are recorded. It has to be noticed that parents of affected children or young adults are still young themselves. A negative history of cardiovascular events, therefore, does not exclude the diagnosis of FH; but, the family history has to be taken repeatedly over the course of time, and second-degree relatives have to be included in the family history.

There are different criteria to define FH clinically. The Dutch Lipid Clinic Criteria (Table 1) and the Simon–Broome Criteria include lipid values, family history, cardiovascular events of the person to be diagnosed and of that person's relatives, and the existence of tendon xanthomata. Depending

Table 1 Dutch Lipid Clinic Network criteria for diagnosis of heterozygous FH in adults

Criterion[1]	Points
Family history	
First-degree relative with known premature (<55 years, men; <60 years, women) CHD **or**	1
First-degree relative with known LDL cholesterol >95th percentile by age and sex for country	
First-degree relative with tendon xanthoma and/or corneal arcus **or**	2
Child(ren) <18 years with LDL cholesterol >95th percentile by age and sex for country	
Clinical history	
Subject has premature (<55 years, men; <60 years, women) CHD	2
Subject has premature (<55 years, men; <60 years, women) cerebral or peripheral vascular disease	1
Physical examination	
Tendon xanthoma	6
Corneal arcus in a person <45 years	4
Biochemical results (LDL-cholesterol)	
>8.5 mmol/L (>325 mg/dL)	8
6.5–8.4 mmol/L (251–325 mg/dL)	5
5.0–6.4 mmol/L (191–250 mg/dL)	3
4.0–4.9 mmol/L (155–190 mg/dL)	1
Molecular genetic testing (DNA analysis)	
Causative mutation shown in the *LDLR*, *APOB*, or *PCSK9* genes	8

Notes: >8 points: definite FH; 6–8 points: probable FH; 3–5 points: possible FH. The *APOB* and *PCSK9* genes were added to the genetic testing.
Abbreviations: FH, familial hypercholesterolemia; CHD, coronary heart disease; LDL, low-density lipoprotein; DNA, deoxyribonucleic acid; LDLR, LDL receptor; APOB, apolipoprotein B; PCSK9, proprotein convertase subtilisin/kexin type 9.

on the results, the diagnosis of FH is "definite", "probable", or "possible". The Make Early Diagnosis to Prevent Early Death criteria are based on either total cholesterol or LDL-C in the patient and on histories of the first-, second-, and third-degree relatives.[24]

Genetic diagnosis

Genetic testing allows a definite diagnosis in most cases and is recommended by most of the guidelines regarding FH.[1,5–7] Especially if LDL-C is not markedly elevated, the detection of a causative mutation is important for treatment decisions. An effective and cost-effective way is cascade screening. The first diagnosed patient is called the index patient. His or her first-degree relatives are screened only for the detected mutation. This is repeated for the first-degree relatives (older and younger) of every newly detected person who is affected. Because of autosomal dominant inheritance, the chance of finding the mutation in a first-degree relative is 50%. It is noteworthy that although a mutation is detected, LDL-C might not be elevated; conversely, although LDL-C is elevated markedly and FH is diagnosed on the basis of the clinical criteria, a mutation might

not be detected. Since an unknown mutation does not rule out FH, the clinical diagnosis determines the approach. In the first case, it was recommended that the patient should not be started on lipid-lowering therapy, but that he or she be monitored and has follow-up measurements taken. In the second case, the initiation of lipid-lowering therapy was recommended.[1]

The knowledge of the underlying genetic mutation might increase the willingness to start treatment early and the compliance with regular and effective therapy. This has to be evaluated individually, and local laws regarding genetic testing have to be followed. Involving a specialized lipid center might be helpful.

Technical assessments

Findings of technical examinations may help affected persons to understand their risks which, otherwise, are difficult to realize. The guidelines mention different methods. Echocardiography is important because in FH, supravalvular stenosis of the aorta and stenosis of the aortic valve are typical.[6,21,25,26] Exercise electrocardiograms and other stress tests are valuable for early detection of CVD. More elaborate and expensive methods, such as cardiac computed tomography or cardiac magnetic resonance imaging, are not recommended and should be considered on an individual basis. Duplex sonography of the carotid arteries is a well-documented, validated, and noninvasive method. A trial on children showed that the intima-media thickness increases significantly from age 12 years for those with heHF, unlike for children with normal LDL-levels.[27] Ultrasounds of the abdomen would detect calcifications of the abdominal aorta, and measurement of the ankle–brachial index would indicate peripheral arterial disease.

Clinical experiences show that any result of a technical measure facilitates the understanding of the disease. Negative results may motivate patients to preserve their health, and presentation of early alterations may motivate patients to reduce the levels of the alterations or to keep them stable. Regular follow ups to detect changes over time are reasonable, and intervals should be chosen on the basis of the first findings. In cases of positive findings, a cardiologist or angiologist should be involved for further diagnostics or treatment.

Treatment targets

According to the AHA/ACC guidelines, individuals with LDL-C >4.9 mmol/L (>190 mg/dL) qualify for intensive therapy.[10] Most patients with FH would be in this category. The Consensus Statement of the European Atherosclerosis Society recommends an LDL-C level of <3.5 mmol/L (<135 mg/dL) for children, of <2.5 mmol/L

(<100 mg/dL) for adults, and of <1.8 mmol/L (<70 mg/dL) for adults with established CVD or DM in heFH and hoFH.[1] These targets are based solely on the diagnosis of FH as a high risk constellation without any risk calculation.[6] If it is not possible to reach the target value, a LDL-C reduction of at least 50% should be obtained. This is also recommended in the guidelines of the United States National Lipid Association and the National Institute for Health and Care and Excellence in the United Kingdom.[3,5,6] Treatment should start early in life and should be rigorous enough to reduce and postpone cardiovascular sequelae. Reducing cardiovascular morbidity and mortality are the ultimate targets. It should be mentioned again that other potential cardiovascular risk factors have to be addressed, too.

Treatment

Treatment options comprise lifestyle factors, statin-based drug therapy, and lipoprotein apheresis (Table 2).

Lifestyle

Establishing a healthy lifestyle is crucial, even if LDL-C cannot be lowered drastically.[5–7] Lifestyle comprises diet and drinking, physical behavior, and not smoking. The last is the most important; passive smoking also has to be avoided by affected persons. Counseling should be offered repeatedly as patients get older, and smoking parents of affected children have to be included in the treatment. Physical exercise should become a routine early in life. Regarding LDL-C, in the diet, saturated fat should be reduced and unsaturated fatty acids and fiber, especially soluble fiber, should be increased. Additionally, nuts can lower LDL-C. Functional food (eg, margarine,

Table 2 Clinical approach of the diagnosis of and therapy for FH

Measurement of lipid values	As early as possible
Genetic testing, cascade screening	Whenever possible
Lifestyle advice	As early as possible and repeated
Medical therapy	At diagnosis of FH
Goal for LDL-C	<100 mg/dL (<2.5 mmol/L), minimal lowering 50%
Goal for LDL-C if DM or CVD established	<70 mg/dL (<1.8 mmol/L)
Medication	High potency statins, consider combination therapy to lower LDL-C sufficiently

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Abbreviations: FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; DM, diabetes mellitus; CVD, cardiovascular disease.

milk) enriched with phytosterols is mentioned by some guidelines and is recommended by some authors, but this is still debated, since endpoint trials are lacking.[5,6,28] Rare cases of sitosterolemia that can present phenotypically like FH would have to be ruled out before phytosterols are used.

Other healthy diet patterns, such as reducing soft drinks, alcoholic drinks, and short chain carbohydrates, are important to maintain weight or to reduce a high body weight, and to address metabolic syndrome and DM. The global benefits of establishing and maintaining a healthy lifestyle are beyond lipid values and, therefore, should be the focus of counseling.

Lipid-lowering medications

Statins are widely accepted and are recommended as the first-line therapy for lowering LDL-C.[1,5,6] Although the data of prospective and randomized trials in FH are not available, retrospective analyses show substantial benefit. An immediate start with the highest dose of one of the most potent statins was recommended recently.[1] LDL-C should be lowered as fast and as far as possible. After initiation with a statin, ezetimibe, nicotinic acid, or bile acid sequestrants should be added to reduce LDL-C as effectively as possible.[5]

Functional LDL-Rs are crucial for deploying the effect of statins. Their LDL-C lowering capacity in heFH is significant, but in hoFH is limited; this capacity differs widely and depends on the person's underlying genetic makeup. Since the time that statins were first available, the incidence of cardiovascular events has decreased in primary and secondary prevention in non-FH patients.[29] The recommendations for FH patients are based on these data and on studies showing that statins lower LDL-C and CVD events in FH patients as well. The Simon–Broome Register Group showed a declining cardiovascular mortality in heFH after the launch of statins.[2] These observations were made repeatedly. Treatment with statins (mostly simvastatin and atorvastatin) was effective at reducing the risk of myocardial infarction to that of nonaffected individuals.[30]

Ezetimibe reduces intestinal cholesterol absorption, and its LDL-C lowering effect depends on upregulated LDL-R. The drug is proven to be safe and effective in heFH, and the combination of a statin with ezetimibe lowers LDL-C significantly more than statin monotherapy.[31] Long-term treatment either with a statin alone or with a statin and ezetimibe was administered to 89 FH children and adolescents whose data were evaluated retrospectively. Among these patients, cardiovascular risk decreased significantly and no cases of CVD developed.[32]

Bile acid sequestrants lower LDL-C when given as a monotherapy and when given in combination with statin and ezetimibe therapy.[33,34] Nicotinic acid lowers not only LDL-C, but Lp(a) and triglycerides as well. In addition, nicotinic acid increases HDL-C. Thus, if locally available, nicotinic acid can be used to further reduce LDL-C and to improve the levels of other unfavorable lipoproteins.[35]

Although FH and the therapies for it have been known for many years now, and although multiple treatment modalities are available, Pijlman et al[36] showed in a cross-sectional study in 2010 that the majority of FH patients were not receiving optimal treatment. In this study, LDL-C was not reduced <2.5 mmol/L (<100 mg/dL) in 79% of patients, and only 21% of patients were on combined therapy.[36] Firstly, this shows that the available therapies are not used sufficiently, perhaps because of the lack of awareness by patients or doctors and perhaps because of adverse effects, such as statin-induced myopathy. Secondly, this suggests that new measures might be necessary in cases of statin intolerance or in cases in which statins are unable to sufficiently lower LDL-C. Repeated information and support is necessary, and affected persons should be cared for in specialized lipid clinics. Currently, there are some new LDL-C lowering agents under investigation; these will potentially increase the armamentarium of LDL-C lowering drugs. Two of these agents were launched recently (see the following sections).

Apheresis

In hoFH and severe cases of heFH, LDL-C levels cannot be lowered sufficiently by lipid-lowering medications, even if they are used in the highest doses and maximum combinations.[36] In these cases, LDL-C can be reduced significantly by lipoprotein apheresis. This extracorporeal technic decreases ApoB100-containing particles (LDL-C and Lp[a]); apheresis is applied either in addition to the maximally tolerated lipid-lowering medication or alone if lipid-lowering medications are not tolerated. Several technics are available, all reducing LDL-C acutely by about 60%–70%. LDL-C increases again rapidly in the first days following a kinetic of first order.[37] Therefore, apheresis has to be repeated regularly, and the time-averaged lipoprotein levels have to be calculated.[38] Usually, apheresis has to be repeated every week; in some patients who respond very well to the concomitant lipid-lowering medications, a biweekly treatment might be sufficient.[37,39] The recommendations for starting lipoprotein apheresis in FH differ worldwide. In the United States, apheresis is recommended for heFH in patients without CVD whose LDL-C levels are at least 7.76 mmol/L (300 mg/dL) and in patients with established CVD whose LDL-C levels are at least 5.17 mmol/L (200 mg/dL).[5] In Germany,

apheresis is indicated in hoFH without a threshold or further requirements. Apheresis is also indicated in patients with severe hypercholesterolemia whose LDL-C levels cannot be decreased to goal despite the maximal lipid-lowering medication. These, usually, are patients with severe heFH or with established CVD.[40] Lipoprotein apheresis has been in use for over 30 years and is generally well tolerated and safe.[41,42] The use of angiotensin-converting enzyme inhibitors is the only contraindication, because of a bradykinin reaction. Patients who use these inhibitors must change their antihypertensive therapy before they start apheresis. Examples of mild and usually easy-to-handle side effects are venous access problems or hypotension.[39] FH patients undergoing lipoprotein apheresis have significantly reduced LDL-C levels and profit from this treatment option.[37,43] Cardiovascular events can be reduced in hoFH patients.[44] Cardiovascular morbidity and mortality can be significantly reduced in heFH, but they cannot be eliminated.[45] This leads to the postulation that in hoFH, apheresis should be initiated as early in childhood as technically possible (as early as venous access is possible). Since lipoprotein apheresis is time consuming, expensive, and not available ubiquitously, new treatment options are awaited to reduce the necessity for lipoprotein apheresis.

Emerging therapies

Several new lipid-modifying drugs are currently in development. Agents to lower LDL-C target cholesteryl ester transfer protein (primarily developed to increase levels of HDL-C), PCSK-9, microsomal triglyceride transfer protein (MTP), or ApoB.[46,47] All of these are tested in addition to baseline statin therapy and, to varying degrees, they are shown to lower LDL-C more than statin therapy alone. The effect of PCSK-9-inhibitors in FH and especially in hoFH is dependent on functional LDL-R; ongoing trials are addressing these high-risk patients. Agents acting independently of LDL-R might be more effective in FH. Recently, two agents were approved as orphan drugs for hoFH: the MTP-inhibitor lomitapide and the ApoB synthesis inhibitor mipomersen. The US Food and Drug Administration approved both agents; the European Medicines Agency approved lomitapide, but not mipomersen.

ApoB antisense oligonucleotide

Mipomersen is an ApoB antisense oligonucleotide that targets the encoding messenger (m)RNA. This leads to the inhibition of protein translation and the reduced production of ApoB100, the backbone protein of very LDL (VLDL). Less VLDL is assembled in the liver and released into the circulation; this results in lower levels of LDL-C. Another effect is that triglycerides, normally transported via VLDL into the

circulation, accumulate in the cells. This can lead to fat accumulation in the liver and to elevated transaminases.[48,49]

The LDL-C- and Lp(a)-lowering effects were seen in all of the Phase II and Phase III trials, in which different populations were examined. In Phase III trials, 200 mg of mipomersen was injected subcutaneously once per week.[50–53]

A multicenter, randomized (2:1), double-blind study in hoFH compared the effects of 200 mg mipomersen, delivered subcutaneously, with those of the placebo; both treatments were given for 26 weeks and in addition to lipid-lowering therapy.[54] All of the patients were older than 12 years of age and had been diagnosed either clinically or genetically. In the 51 patients, LDL-C was lowered significantly more in the mipomersen group (24.7%, baseline 11.4 mmol/L) than in the placebo group (3.3%, baseline 10.4 mmol/L). As expected, the most common side effects were injection side reactions (76% with mipomersen, 24% with placebo). Alanine aminotransferase rose only in the mipomersen group (12%).

In a 26-week, randomized (2:1) trial, patients with heFH and coronary heart disease were given 200 mg of mipomersen, injected subcutaneously, in addition to ongoing lipid-lowering therapy.[55] LDL-C decreased significantly by 28.0% in the mipomersen group, but increased by 5.2% in the placebo group. As side effects, injection site reactions, flu-like symptoms, and alanine aminotransferase elevations were reported.

The FOCUS FH trial,[56] ongoing as of this writing, compares two different regiments of mipomersen in patients with FH. Mipomersen might reduce the necessity for lipoprotein apheresis,[57] and this question is addressed in trial NCT01598948, which is ongoing as of this writing.[58]

Mipomersen is now indicated in addition to lipid-lowering medications to reduce LDL-C, ApoB100, and non-HDL-C in patients with hoFH. It is contraindicated in moderate or severe hepatic impairment (Child–Pugh B or C), active liver disease, and cases of unexplained persistent elevations of serum transaminases. The most common adverse reactions in trials were injection site reactions (84%), flu-like symptoms (30%), nausea (14%), headaches (12%), and elevations in serum transaminases, specifically alanine transaminase (10%). To monitor these side effects, mipomersen is available only through a restricted prescribing and distribution program called the KYNAMRO Risk Evaluation and Mitigation Strategy.[59] These side effects might reduce patients' compliance, and since endpoint data are not available yet, the clinical benefit has to be evaluated individually.

MTP-inhibitor

The enzyme MTP is essential for the assembly of VLDL in the liver and chylomicrons in the intestine. By inhibiting

MTP, the lower levels of VLDL result in lower levels of LDL-C. Triglycerides are held back in the liver; this leads to increased liver fat content. The dietary fat content has to be reduced to avoid gastrointestinal side effects. In FH, this approach to lower LDL-C is effective because it is independent of LDL-R.

In a single-arm, open-label, Phase III study, 29 patients with hoFH received the MTP-inhibitor lomitapide in addition to lipid-lowering therapy (apheresis was allowed) to assess efficacy and safety; this trial lasted 78 weeks. The dose was escalated up to 60 mg per day, and the median dose was 40 mg per day. Six patients discontinued the treatment. LDL-C was reduced by 50% from baseline to week 26, by 44% to week 56, and by 38% to week 78. Gastrointestinal symptoms were the most common side effects. In addition, the liver fat content increased, and four patients had elevated amino transaminase levels.[60] This trial was extended to show persistent efficacy, and this long-term study is ongoing. Lomitapide is only available through the JUXTAPID Risk Evaluation and Mitigation Strategy Program.[61]

Special considerations
Women
Female patients have to be informed that all medications have to be stopped before a pregnancy is planned, and that medications can be started only after family planning is completed. Because it may not be possible for women to receive effective therapy for many years, it is of utmost importance that the therapy is very strict before and after that time period. In very severe cases, lipid apheresis can be offered during the time that no medical therapy is possible.

Children
LDL-C levels are very high from the time of birth, and children are in danger of experiencing cardiovascular events very early in life. If FH is detected very early, these sequelae can be avoided or delayed by the early onset of therapy (medication, apheresis, or both). It is important to care for FH families. It is important for them to understand that although the knowledge of the genetic condition can be frightening, that knowledge also puts them in a position to act actively for the health of their children. Elevated levels of LDL-C do not hurt and the deleterious effects are very difficult to imagine. Although genetic diagnosis is helpful, potential local laws regarding genetic testing of children have to be followed. If genetic testing is done, it is mandatory that very careful genetic education and explanations about the meaning of the results and about potential implications (eg, insurance policies) are provided before and after testing.

Guidelines of different countries give different advice as when to start statin therapy. Mostly, the ages between 8 years and 14 years are suggested, but the decision has to be made individually in every case and has to be based on lipid values, family history, and clinical appearance. One trial showed that a 2-year treatment with pravastatin in 8–18-year-old children with FH induced a significant regression of carotid intima-media thickness without any adverse events; this finding suggests "the younger, the better" when treating children.[62] However, a Cochrane Review stated that only short-term trials in FH children were done.[63] These trials raised no safety concerns, but long-term safety data are needed. While routine monitoring in adults is not always recommended, in children this monitoring of development and potential side effects is imperative until long-term data are available.[6] Registries could improve our knowledge.

The psychosocial function of children with FH (number [n]=152) and healthy peers (n=62) was determined by a semi-structured interview. Of the FH group, 25% had experienced the loss of or a CVD event in a parent, and this resulted in lower scores. Otherwise, FH children had no greater psychological dysfunction than their peers.[64] The positive view that knowledge enables early treatment and consequently allows children to grow up healthy should be explained repeatedly. A transition clinic of pediatricians and internists could improve the treatment of those on the border between childhood and adulthood.

Quality of life
Some evidence is available about the quality of life of patients with FH. One study evaluated the psychosocial concerns of families with FH. For this study, 145 parents completed a questionnaire. None thought that not having their child diagnosed with FH would be better, but 11% believed that their quality of life would be better without the diagnosis, and 20% attributed familial conflicts to the FH diagnosis. Of the children, 22% (more boys than girls) worried about CVD.[65] In a cohort of elderly FH patients, of which all were ≥65 years of age (n=37, 73% coronary heart disease) all showed the same quality of life as controls.[66] The quality of life of seven hoFH patients on LDL apheresis was not significantly different from that of healthy subjects, except for that of two patients with severe coronary heart disease.[43]

Patients' organizations
Worldwide patients' organizations are established by FH patients and relatives who have the experience of not being addressed and treated optimally. Their aims are to raise the awareness for and to increase the knowledge of FH, to offer a platform for affected individuals and their families for sharing experiences, and to help establish and improve the

care of persons with FH (http://www.cholco.org, http://www.
fhjourneys.com, http://www.fh-foundation.org, http://www.
learnyourlipids.com).

Conclusion

FH is a prime example of a highly effective preventive medicine. The genetic background and the pathophysiology are known, and diagnostic tools are available. The approach is defined in various national and international guidelines and recommendations. Therapy is safe and cost effective, and it reduces morbidity and mortality significantly. Nevertheless, FH is still underdiagnosed and undertreated. Nationally organized screening programs to detect FH early in life could improve the medical care and the morbidity-free life span. Wherever such a program is not established, everyone who cares for individuals with elevated LDL-C or for patients with early cardiovascular events is responsible to initiate and follow up the diagnostic and therapeutical steps. Based on a healthy lifestyle, which should be connoted positively, medical therapy should be started early and continued effectively. The use of statins is the first choice, and combination therapy should be considered to lower LDL-C significantly. Long-term strategies for the medical care are warranted to keep affected individuals on therapy.

The emerging medications might allow more effective treatment. They also offer the possibility to increase the awareness for FH.

In general, it should be emphasized repeatedly that although FH is a serious condition, it is very well known, and the therapy is available and normally very effective in reducing FH-related diseases. Thus, affected individuals and their families can handle the situation positively and actively.

Disclosure

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