Review article

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A narrative review of treatment modalities for familial hypercholesterolemia

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ABSTRACT

Familial Hypercholesterolemia (FH), a commonly missed disorder in a patient with abnormalities in lipid metabolism is described as a heritable disorder presenting elevated LDL cholesterol and lipid deposition in various tissues. This contributes to the early development of manifestations of atherosclerotic disease with the preterm occurrence of severe cardiovascular events. Apparently, decision-making is a strenuous effort and many individuals are underdiagnosed. FH affects LDL receptor and its function plays a critical role in the mechanism of many therapeutic modalities, thus alternative pathways must also be considered. This review addresses the main options of care in individuals with familial hypercholesterolemia along with unconventional drugs like mipomersen, inclisiran, lomitapide, gamcabene, and ANGLT3 inhibitors which have yielded important results for disease management.

KEY WORDS: *Familial hypercholesterolemia, LDLR dependent, LDLR independent*

INTRODUCTION

Familial Hypercholesterolemia (FH) is a well-known but rather underdiagnosed primary disorder of lipoprotein metabolism that is inherited in an autosomal co-dominant pattern and it is the result of gene-mutations that encode the LDL receptor (often termed as autosomal dominant hypercholesterolemia type 1 or ADH1), apolipoprotein B (often termed as autosomal dominant hypercholesterolemia type 2 or ADH2) or proprotein convertase subtilisin/kexin type 9 or PCSK9 (often termed as autosomal dominant hypercholesterolemia type 3 or ADH3). Those affected can have defects in one or both alleles of a gene referred to as heterozygotes or homozygotes respectively. The latter is further classified as receptor-negative with no detectable functional LDL receptors and receptor defective with a very low but present amount of functional LDL receptor. There is also a rare form of the disease that is inherited in an autosomal recessive manner if a mutation occurs in the LDRL adaptor protein[1]. Among the main types of defects described, mutations in the LDL receptor gene are the most common resulting in 80-85% of cases, while those in the apolipoprotein B100 binding site contribute to about 5-10%, while in the PCSK9 gene generally rarely occur in about 2% of cases[2].

FH is a disorder estimated to affect between 14 and 34 million people worldwide with a prevalence of 1 in 311 for heterozygotes (HeFH) and 1 in 200.000-300.000 for homozygotes (HoFH) with the highest rates being

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among Christian Lebanese, South Afrikaners, Ashkenazi Jews and French Canadians in Quebec[3-6]. It is estimated that patients who receive no treatment for HeFH, appear to have an increased probability of experiencing their first coronary event 20 or more years earlier than the general population while in HoFH coronary events can occur even in childhood or adolescence[7].

Clinical suspicion of FH should be considered upon encountering a patient presenting with tendon xanthomas, xanthelasmas, and arcus cornealis and/or a lipid profile of high LDL-C >190mg/dl and total cholesterol with or without hypertriglyceridemia[8]. As of today, there are no universally agreed-upon criteria for the diagnosis of the disease and thus it is carried out on clinical grounds along with the utilization of certain diagnostic tools such as the Dutch Lipid Clinic Network criteria, the Simon Broome system, the US Make Early Diagnosis to Prevent Early Death or MEDPED, the National Lipid Association expert panel recommendations and lately the American Heart Association criteria. Every approach varies from each other but all agree that LDL-C levels are mandatory to establish a diagnosis[9]. To accompany this a solid screening strategy is fundamental to establish early detection of the illness because if one of the parents is heterozygous for FH then 50% of the siblings are anticipated to be affected as well, while if both are heterozygous then there is a 25% and 50% chance of contracting HoFH and HeFH, respectively[10,11]. Once a possibly affected individual is encountered, genetic testing and subsequent cascade screening of any corresponding relative is advised, starting with first-degree relatives[12,13].

THERAPEUTIC MANAGEMENT

According to current EAS/ESC guidelines individuals with FH are stated as high or very high risk depending on the existence of atherosclerotic cardiovascular disease or any other major risk factor. Therefore, an LDL reduction of ≥50% from baseline and a target LDL of <70mg/dl for high risk and <55mg/dl for very high risk individuals with FH, respectively, is advised[14,15]. For every mmol/l of LDL reduction an additional reduction of 22% can be achieved[16]. Patient management begins with lifestyle modifications and the implementation of an appropriate diet as early as possible under proper guidance by an experienced nutritionist, accompanied by weight maintenance with frequent physical exercise of more than one hour for children[17].

Statins

The cornerstone of treatment in both HoFH and HeFH remain the well-known statins or 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors which inhibit sterol synthesis in the liver and enhance LDL receptor affinity, whereas upregulating LDL degradation[18]. Simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin and pitavastatin are approved for use among many countries[19,20]. It is advised that therapy initiation at an earlier stage is of extreme benefit since the risk of experiencing a major cardiovascular event is about ten times lower in those individuals over an approximately 10-year period of treatment[21,22]. In children affected by FH, treatment with statins from 8-10 years of age is advised starting at low doses which could be increased to reach target values[23]. In the pediatric population, pravastatin, simvastatin, fluvastatin, atorvastatin and rosuvastatin have been studied, at a maximum dose of 40mg for pravastatin and simvastatin, 20mg for rosuvastatin and atorvastatin and at 80mg for fluvastatin. Pitavastatin has also been studied in children with FH and has gained approval by the FDA for children ≥8 years of age with HeFH[24-26]. Rosuvastatin lowers the development of increased intima-media thickness (IMT) over a 2-year period and a similar effect in adults can be achieved with atorvastatin within the same time frame. Moreover, statin monotherapy in heterozygous adults might not reach the advised LDL levels by the guidelines and adherence to therapy can be poor (about 50% of appropriate patients)[27]. An important highlight over the usage of statins in pregnancy is the withdrawal of their contraindication in pregnancy by the FDA for pregnant women or for those considering pregnancy. As it became evident from a number of studies investigating the safety of statins, the rate of miscarriages, congenital disturbances, median gestational age at birth or weight at birth did not show significant increases with no reports on teratogenic effects in the first trimester, though preterm birth was noted more frequently[28]. It is of interest to be mentioned that adverse events in pregnancy were noted more commonly with lipophilic statins than with hydrophilic probably due to their potential passage through the placenta[29]. A concerning aspect of statin treatment in an individual with HoFH is the amount of LDL receptors that can be recruited to perform their respective actions, which in receptor-negative patients can possibly render statins as well as PCSK9 inhibitors an effortless choice in reducing LDL-C[30]. Despite that, statins remain the first choice of treatment and they are generally well tolerated, with reports of elevated aminotransferase levels, liver dysfunction and rhabdomyolysis as the most common adverse effects, though they are extremely rare with a rise of aminotransferase values by a factor of 3 in less than 1% of adults on statin treatment and a risk of 0,08% to 0,09% of rhabdomyolysis in children with FH. A particular consideration is made upon the possible effects of statins

in growth and maturation, both of which are still under investigation[31].

Ezetimibe

Ezetimibe is a selective inhibitor of intestinal cholesterol absorption that binds to Niemann-Pick C1 Like protein or NPC1L1 and prevents absorption of biliary and dietary cholesterol by the intestine. It has been evaluated as monotherapy in HeFH with a reductive potential of 25,7% in LDL-C or in combination with statins like simvastatin with up to 49,1% reduction in LDL-C. Ezetimibe is generally well tolerated with reported adverse effects displaying elevated aminotransferase levels or myalgias with no reported alterations in growth, maturation or steroid hormones[32-34]. Furthermore, it is common for increased-risk individuals who are candidates for PCSK9 inhibitor therapy to combine all three medications in order to accomplish a favorable outcome. In actual fact, it is of value to mention that if ezetimibe is withdrawn from this triple regimen it could have a significant effect on LDL-C in certain patients[35].

PCSK9 Inhibitors

Proprotein convertase subtilisin/kexin type 9 or PCSK9 is an enzyme critically involved in the processing of the LDL receptor by binding with the epidermal growth factor-like repeat A (EGF-A) part of the LDL receptor and the resulting complex is redirected to the lysosomes in the hepatocytes for degradation, thus interfering with recycling of the receptor on the surface of the cell. Alternatively, when the receptor binds with LDL it is released from the surface of the hepatocyte and enters the endosome, which in turn dissociates and breaks down LDL under acidic conditions and the receptor returns to repeat this process (about 150 times) further removing LDL off of the circulation. The above-mentioned process is the basis of the mode of action of PCSK9 inhibitors with their main approved representatives being evolocumab at a dose of 140mg every 2 weeks or 420mg monthly and alirocumab at a dose of 75mg every 2 weeks or 300mg every 4 weeks[36,37]. These agents are human monoclonal antibodies, a fact which is essential since, bococizumab a humanized inhibitor of PCSK9 has been pulled over from clinical trials (SPIRE-1 and SPIRE-2) for its non-sustainable reduction of LDL due to neutralizing antibodies. The administration is carried out subcutaneously and at its maximum dose can decrease LDL-C by 60% in the plasma[37,38]. Evolocumab is an immunoglobulin G2(IgG2) and it has been studied in heterozygous familial hypercholesterolemia by the RUTHERFORD study with a mean decrease in LDL-C of 60,2% at weeks 10 and 12 of treatment and in homozygous familial hypercholesterolemia by the TESLA study with no decrease in LDL-C from double receptor negative defects and about 19,3% and 26,3% in four and two weeks, respectively suggesting the necessity of LDL receptor function for PCSK9 inhibitors to work[39,40]. Over and above that in the HAUSER-RCT study of a pediatric population from 10 to 17 years with HeFH evolocumab has shown a level of 38,3% decrease of LDL at 24 weeks, observed intensively at 22 weeks, in the TAUS-SIG study, which involved HoFH and severe HeFH patients with a some of them on lipoprotein apheresis, there was no remarkable difference in LDL reduction between on and off apheresis patients but a portion could lower the frequency of the treatment or discontinue it. Lastly in the FOURIER study cardiovascular outcomes were addressed in high-risk individuals with known stable cardiovascular disease with a reduction of 15% in its primary endpoint[41-43]. Alirocumab has been investigated during the ODYSSEY study which utilized a wide spectrum of subjects namely in HeFH individuals with a reduction of 57,9% (ODYSSEY FH I) in one group and 51,4% in the other(ODYSSEY FH II) at week 24 and dosed 75mg every two weeks, in HeFH with LDL-C ≥ 160mg/dl with 39,1% reduction in a dose of 150mg every 2 weeks (ODYSSEY HIGH FH) and in the pediatric population aged 8-17 years with values of even 46% lower LDL (ODYSSEY KIDS)[44-47]. HoFH cases were assessed in the ODYSSEY HoFH trial, dosed at 150mg every 2 weeks with a mean 26,9% reduction in LDL at week 12 and high variability in among double receptor-negative variants. At this point, it is important to add that alirocumab exhibited an important reduction in ApoB, non-HDL, total cholesterol, and Lp(a) values[48-50]. Interestingly, these medications were not associated with myopathy or elevated liver enzymes, which is a common concern with statins. It can be stated also that the adverse effect profile includes injection-site reactions (3,8% with alirocumab and 2,1% with evolocumab) and a concern of anti-drug antibodies (0,5% for alirocumab in the ODYSSEY OUTCOMES trial and 0,3% for evolocumab in the FOURIER trial). Reports and concerns for neurocognitive impairments or fat-soluble vitamin loss have not been confirmed[51,52].

Bempedoic Acid

Bempedoic acid is an orally administered compound that blocks adenosine triphosphate-citrate lyase (ACL) a key enzyme in cholesterol biosynthesis and as is the case with statins LDL receptors increase in number, resulting in a notable decline in LDL-C in the circulation. This medication is approved for use in HeFH, usually at a dose of 180mg daily with a half-life of 15-24 hours and it can be used in combination with ezetimibe for an additional LDL-lowering effect[53]. During the CLEAR HARMONY study, which evaluated safety and efficacy data during a 1-year

interval, observed adverse effects were mainly nasopharyngitis, myalgia, upper respiratory tract infection, urinary tract infection, arthralgia, dizziness, muscle spasms, diarrhea and increase in the levels of uric acid but were also regarded as mild to moderate[54-56]. A rather interesting aspect of the medication is its specificity for the liver for its activation, avoiding skeletal muscle and related side effects. Therefore, it could be considered a good alternative to statins, especially in cases of intolerance[57].

RNA targeting agents

The introduction of drugs that aim at the mRNA of genes that can cause disease and prevent them from translating into a protein is a rather novel concept but has shown significant results and there are mainly two categories of drugs that have been used, namely antisense oligonucleotides (ASOs) and small interfering RNA (siRNA). ASOs are altered molecules of single-stranded DNA that bind with sense mRNAs in the nucleus or cytoplasm of the cell, are administered subcutaneously, and have a short time of distribution (less than an hour) with a prolonged lifespan intracellularly (about 2-4 weeks), while siRNAs are double-stranded RNA molecules that bind to the RNA-induced silencing complex (RISC) and incorporate their antisense strand into the complex to promote mRNA degradation[58]. Inclisiran is the approved main representative of siRNAs that targets synthesis of PCSK9 in the liver and is usually dosed twice annually. This method has, actually, shown promise through the ORION trial, in which heterozygous patients were administered 300mg of inclisiran sodium a 1,5ml subcutaneous injection on days 1, 90, 270 and 450 and resulted in 39,7% lowering of LDL, a mean absolute reduction of 59mg/dl in LDL cholesterol and a reduction of total cholesterol, non-HDL, triglycerides and Lp(a) along with a rise in HDL values, while side effects were mild to moderate, mostly attributed to injection site reactions[59-61]. Mipomersen is the main representative of ASOs, it targets apolipoprotein B100 mRNA for degradation, it is administered subcutaneously as a sodium formulation and its half-life is approximately 30 days[62]. In about 3-4 hours peak plasma concentrations are achieved and drug metabolism is carried out by endonucleases and exonucleases in a successive fashion without affecting cytochrome P450 metabolized drugs[62]. Regarding its effectiveness in FH, Phase II, and III trials have highlighted that in heterozygous individuals receiving doses of 200mg and 300mg with once-per-week dosing for 6 weeks there is a reduction of 23% and 33% in LDL-C, respectively. Assessment of HoFH individuals under mipomersen treatment showed that, of those who completed the assigned 26-week therapeutic period, a 25% reduction in LDL-C, 31% in Lp(a), and 17% in triglycerides was reached, though there was a substantial variability[63]. The safety profile of this medication contained mostly injection site reactions, due to the mode of administration and hepatic steatosis with an increase in transaminase levels but with no evidence of liver toxicity[64]. Unfortunately, mipomersen had its approval withdraw and is still not approved by the European Medicines Agency[65].

Lomitapide

Lomitapide, a recently approved orphan drug for HoFH, inhibits microsomal triglyceride transfer protein or MTP. This, consecutively prevents the assembly of VLDL in the liver, chylomicrons in the intestine along with LDL-C in an LDR-independent pattern. It is administered orally in addition to diet or other treatment modalities, beginning with a dose of 5mg and is up-titrated to a maximum dose of 60mg with a half-life of about 40 hours[66]. According to many studies, lomitapide can reduce LDL-C up to 40-50% independently of lipoprotein apheresis treatment with mainly gastrointestinal side effects such as diarrhea, increase in liver transaminases in some patients, and the possible appearance of liver steatosis as it was evident from cohorts that utilized ultrasound or MRI. Unfortunately, these studies represented a small number of patients due to the rarity of the disease but have since shown that for each millimole per liter of reduction in LDL-C the relative risk of mortality declined by 23%, the risk of a major cardiovascular event by 15% and mean life expectancy can rise to 5,7 more years if the drug was initiated at an age of 18 years or 6,7 years if it was started at birth[67-69].

Gamcabene

Gamcabene is an orally delivered orphan drug used for HoFH that blocks TG and cholesterol production in the liver as well as apoC-III synthesis, reducing LDL-C levels in an LDLR-independent manner[70]. It is used adjunctively with other lipid-reducing modalities as demonstrated by the COBALT study during which patients for 12-weeks were administered doses of 300mg, 600mg, and 900mg daily for 4 weeks each, achieving reductions in LDL-C of 26% at 300mg, 30% at 600mg and 29% at 900mg, while the only side effects shown were diarrhea, headache and a slight rise in serum creatinine. Most of these side effects were regarded as mild to moderate with good tolerance to the medication[71]. Currently, Gamcabene is not approved for in practice and further evaluation is needed[72].

Angiopoietin-like protein 3 inhibitors

A meaningful addition is angiopoietin-like protein 3

(ANGPTL3) inhibitors a novel line of drugs that surfaced after the realization of several reduced lipid parameters in subjects carrying loss-of-function mutations in the ANGPTL3 gene[73]. ANGPTL3 is produced in the liver and inhibits endothelial and lipoprotein lipases, thus decreasing VLDL and HDL clearance, respectively[74]. This is the case with evinacumab, an approved human monoclonal antibody that targets this protein, decreasing LDL-C values by 47,1% as an intravenous infusion at a dose of 15mg/kg of body weight with good tolerance of the drug as was depicted by the ELIPSE HoFH trial[75]. Currently, an ASO targeting hepatic ANGPTL3 mRNA was being evaluated in the IONIS ANGPTL3-LRx phase 2 clinical trial but was discontinued due to a lack of a sufficient number of participants[70,76].

Invasive Modalities

Many cases of FH fail to accomplish their expected target values of LDL-C pharmaceutically and as is the case with HoFH need to be referred for lipoprotein apheresis (LA) and, though controversial, liver transplantation[86,87]. LA is the extracorporeal selective elimination of apolipoprotein B-containing lipoproteins and the most efficacious way of care if conjointly with standard anti-lipidemic drugs for HoFH, achieving 45-76% reduction in LDL-C in a 2-4h lasting procedure which is performed every one or two weeks according to the severity of the disease. Nowadays, side effects occur in less than 5% and include severe hypotension, hypocalcemia, anemia, bleeding disorder, infections, allergies, and fistulas from the frequent usage of an access route[86]. Liver transplantation relies on the fact that about 75% of LDL receptors are located in the liver and replacement with fully an operational part can normalize cholesterol metabolism with about an 80% decrease in LDL-C. However, it is questionable under what indications the procedure should be considered and it is an issue whether the benefit is higher than the risk both from the aspect of side effects from immunosuppression, possible rejection, or in some instances severe aortic stenosis and

TABLE 1. Approximate % LDL reduction per approved drug by the European Medicines Agency.

Drug Class	Compound		LDL Reduction
Statins	Low Intensity	Simvastatin 10mg	<30%
		Lovastatin 20mg,	
		Pravastatin 10-20mg	
		Fluvastatin 20-40mg	
	Moderate Intensity	Simvastatin 20-40mg	30% - <50%
		Fluvastatin 80mg	
		Lovastatin 40-80mg	
		Pitavastatin 1-4mg	
		Pravastatin 40-80mg	
		Rosuvastatin 5-10mg	
		Atorvastatin 10-20mg	
	High Intensity	Atorvastatin 40-80mg	≥50
		Rosuvastatin 20-40mg	
Intestinal Cholesterol Absorption Inhibitor	Ezetimibe		19-25% If added on statin treatment: +15%
PCSK9 Inhibitors	Evolocumab		55-75%
	Alirocumab		45,7-62,8%
ACL blocker	Bempedoic Acid		22,1%
MTP Inhibitor	Lomitapide		40%
siRNAs	Inclisiran		40-51%
ANGPTL3 inhibitors	Evinacumab		47,1%

LDL-Low Density Lipoprotein, PCSK9-Proprotein Convertase Subtilisin/Kexin type 9, MTP-microsomal triglyceride transfer protein, siRNA-small interfering RNA, ACL-Adenosine triphosphate-Citrate Lyase, ASO-antisense oligonucleotides, ANGPTL3-Angiopoietin like Protein 3[77-85].

from how FH is viewed by its severity among other lethal diseases that do not have other alternatives given the low number of donors[87,88].

Gene therapies

A rather novel concept in the therapeutic armament for FH are gene therapies, which currently utilize adeno-associated viruses(AAV), most commonly AAV-8, to deliver genes or amplify hepatocyte DNA in order to achieve LDLR expression[89]. These methods have been studied in clinical trials and it is important to address the clustered regularly interspaced short palindromic repeats(CRISPR)/ Cas9 system, which involves a gene editing system with Cas9 nuclease and a modified single guide RNA(sgRNA)[90]. DNA-break repair is carried out by either non-homologous end joining, which acts randomly or homology directed repair, which acts more precisely. Regarding FH, it has been utilized in mutant mice to increase LDLR expression by gene addition or inactivate PCSK9 or ANGPTL3. Nonetheless, satisfactory results have yet to be acquired. Potential barriers of these methods are the gene delivery system itself, immune response, persistence of genes and the possibility of these systems to reach their respective targets[90,91] (Table 1).

CONCLUSION

To sum up, various treatment options can be adopted to improve the clinical picture of individuals with FH but none can prevent manifestations of the disease. There are emerging modalities like gene therapy either with a viral vector, stem cells, or exosome-based ones, but they are still under development and careful supervision for potential side effects[76,92]. Decision-making on the best route of treatment is a debated concept since there are no unified consensus and diagnostic criteria among countries perplexing even further this situation. As such, statins are the first choice of treatment along with diet modifications which might be combined with ezetimibe, but in many cases, further measures must also be considered like PCSK9 inhibitors[93]. Novel treatments like mipomersen, inclisiran, lomitapide, gamcabene, and ANGLT3 inhibitors have shown substantial efficacy but their low cost effectiveness and lack of studies with a sufficient number of participants to support their use complicates medical decisions further. Accordingly, there is still room for innovation and development in this field with more studies over a stable diagnostic background.

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Conflict of interest

There is no conflict of interest

ΠΕΡΙΛΗΨΗ

Αφηγηματική Ανασκόπηση των θεραπευτικών μεθόδων στην Οικογενή Υπερχοληστερολαιμία

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Η Οικογενής Υπερχοληστερολαιμία, μια νόσος συχνά διαγνωστικά χαμένη, είναι μια κληρονομική διαταραχή του μεταβολισμού των λιπιδίων με υψηλά επίπεδά LDL χοληστερόλης και εναπόθεσης λιπιδίων στους διάφορους ιστούς με αποτέλεσμα την εκδήλωση αθηροσκληρωτικής νόσου και πρώιμων καρδιαγγειακών συμβαμάτων. Η λήψη αποφάσεων για την διαχείριση της νόσου είναι ιδιαίτερα κοπιώδης με υποδιάγνωση των πασχόντων ατόμων. Η Οικογενής Υπερχοληστερολεμία επηρεάζει τον LDL υποδοχέα οποίος αποτελεί κεντρικό ρόλο στους μηχανισμούς πολλών θεραπευτικών σχημάτων, καθιστώντας αναγκαία την εύρεση εναλλακτικών οδών. Στην παρούσα ανασκόπηση θα γίνει αναφορά στις κύριες επιλογές θεραπείας σε ασθενείς με οικογενή υπερχοληστερολαιμία εστιάζοντας κυρίως στα μη συμβατικά φάρμακα τα οποία έδειξαν σημαντικά αποτελέσματα στην διαχείριση της νόσου.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: *Οικογενής υπερχοληστερολαιμία, LDLR εξαρτώμενα, LDLR μη εξαρτώμενα*

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