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Review Article

Molecular aspects of hypercholesterolemia treatment: current perspectives and hopes

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Abstract

Hypercholesterolemia is a pathological condition which has been reported in 39% of the worlds' adult population. We aimed to review molecular aspects of current and novel therapeutic approaches based on low-density lipoprotein cholesterol lowering strategies. Pathogenic mutations in the *LDLR*, *ApoB*, *PCSK9* and *LDLRAP* genes cause deficient clearance of circulating low-density lipoprotein cholesterol particles via

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statins, Ezetimibe, Bile acid sequestrants and *PCSK9* inhibitors are the main therapeutic agents for the treatment of hypercholesterolemia. Moreover, novel RNA-based therapy had a strong impact on therapeutic strategies in recent decades. Additional development in understanding of the molecular basis of hypercholesterolemia will provide opportunities for the development of targeted therapy in the near future.

• Key Messages

- The most common genes involved in hypercholesterolemia are *LDLR*, *PCSK9* and *ApoB*.
- Pharmacogenetic effects are typically constrained to pathways closely related to the pharmacodynamics and pharmacokinetics.
- Change in lifestyle and diet along with treatment of the underlying disease and drug therapy are the current therapeutic strategies.

Q Keywords: Hypercholesterolemia therapy lipid-lowering drugs low-density lipoprotein cholesterol

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Introduction

Hypercholesterolemia is a pathological condition which has been reported in 38% of the worlds' adult population. Raised cholesterol is defined as total cholesterol value ≥ 5.0 mmol/L (190 mg/dL) [1]. Hypercholesterolemia is characterized by elevated low-density lipoprotein-cholesterol (LDL-C) levels and is closely associated with the development of coronary artery disease (CAD) [2]. Hypercholesterolemia is usually caused by a combination of environmental and genetic factors [3]. In developed

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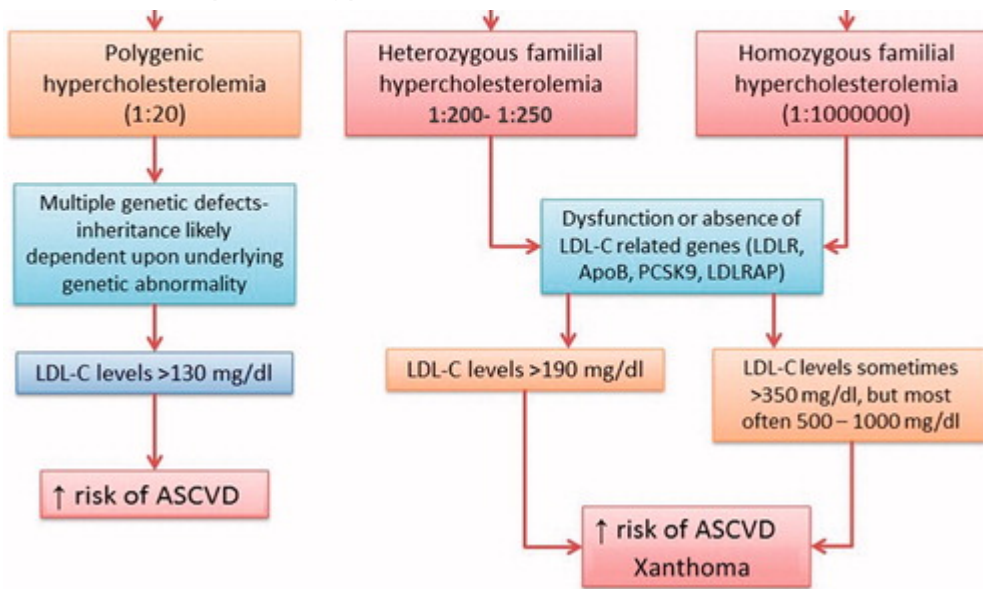
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[4]. Familial hypercholesterolemia (FH) is mostly caused by mutations in genes coding for the *LDLR*, *ApoB*, *PCSK9* and *LDLRAP*. Recently, it has been predicted that heterozygous familial hypercholesterolemia (HeFH) is quite a common disease with a prevalence between 1:200 and 1:250 [5,6]. Identification of novel genes through Next Generation Sequencing (NGS) techniques such as whole exome sequencing (WES) might explain the FH phenotypes. This in turn, may expand the basic knowledge about the molecular basis of the disease, that is essential for diagnosis and paves the path to better therapeutic strategies. In a recent study in the UK, among patients with FH in whom a monogenic cause was found, almost 93% have a mutation in *LDLR*, 5% in *ApoB* and 2% in *PCSK9* (Table 1). Although mutations in other genes have been found, none have been independently confirmed [7]. These pathogenic mutations cause deficient clearance of circulating LDL particles *via* hepatic *LDLR* leading to increased plasma LDL-C levels from birth and deposition in the arterial wall, thus accelerating atherosclerosis and the risk of premature coronary artery disease or PCAD [8]. While hypercholesterolemia may be caused by specific genetic alterations, most cases of hypercholesterolemia are influenced by other factors, such as endocrine or metabolic diseases, lifestyle (exercise and diet) and drugs [9]. As shown in Table 2, statins, ezetimibe, bile acid sequestrants and recent *PCSK9* inhibitors are the main therapeutic drugs for the treatment of hypercholesterolemia which act through increased *LDLR* activity and LDL-C clearance [10]. Furthermore, with the remarkable development of molecular techniques, novel RNA-based therapeutic approaches for therapeutic intervention had a strong impact on therapeutic strategies in recent decades [11]. We aimed to review molecular aspects of current and novel therapeutic approaches based on LDL-C lowering strategies (Figure 2).

Figure 1. Genetic aspects of different hypercholesterolemia forms and outcomes.

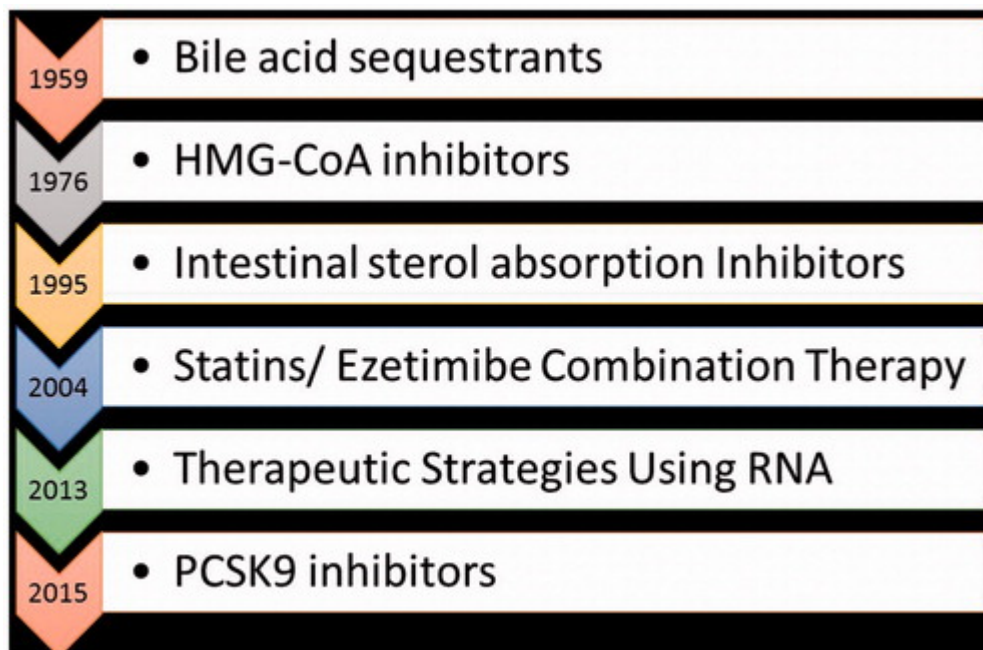
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Figure 2. Therapeutic strategies using ASO approach.



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Table 2. Summary of current LDL-C lowering therapies (based on FDA and EMA reports).



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Bile acid sequestrants (BAS)

Bile acids are the amphipathic agents which are produced as the final products of cholesterol metabolism in the liver. These products have significant roles in the formation of micelles and intestinal lipid absorption. In addition to their classical functions, bile acids act as modulators of a number of intracellular signalling cascades involved in immune response, apoptosis and carcinogenesis [12]. Data suggest that bile acids in the small and large intestine regulate gut microbiota, incretin secretion and production of fibroblast growth factor 15/19 (FGF15/19), which modulate total body lipid, glucose and energy homeostasis [13]. Bile acids are regulators of metabolism acting in an integrated inter-organ manner *via* farnesoid X receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR5). It has been demonstrated that FXR has bile salts as ligands that represses bile acid synthesis [14]. Furthermore, besides their role as physiological detergents for intestinal fat, sterol and vitamin absorption, bile acids also activate FXR, inducing multiple signalling pathways to ensure optimal liver metabolism [15]. Modulation of the bile acid pool size and composition, and selective interference with their receptors could therefore be a therapeutic approach to correct hypercholesterolemia. Even though clinical cardiovascular outcome studies

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agents before statins were introduced [17]. Molecular evidence has revealed the importance of the enterohepatic bile salt cycle. Undeniably, bile salts activate transcription factors in the nucleus, promoting feed-forward cholesterol catabolic pathways that produce bile salts, as well as the feedback regulation of bile acid synthesis [18].

HMG-CoA inhibitors

HMG-CoA reductase inhibitors or statins are lipid-lowering agents which were established to decrease CAD morbidity and mortality [19]. Statins are analogues of 3-hydroxy-3-methylglutarylCoA (HMG-CoA) reductase substrate. They act not only as a competent with the normal substrate in the enzymes active site but also modify the conformation of the enzyme when they bind to its active site. This process prevents HMG-CoA reductase from reaching a functional structure. Conformation change at the active site makes these drugs very effective and specific. The resultant reduction in hepatocyte cholesterol concentration triggers increased expression of hepatic LDL receptors, which clear LDL and LDL precursors from the circulation [20,21]. Currently available statins include Atorvastatin, Simvastatin, Fluvastatin, Lovastatin, Pitvastatin, Rosuvastatin and Pravastatin. Competitive inhibition of HMG-CoA conversion to mevalonate, as a rate limiting step in *de novo* cholesterol biosynthesis, is done *via* binding of statins to HMG-CoA reductase. This causes a temporary and modest reduction in cellular cholesterol concentration [22]. Statins reduce LDL-C by up to 55% and are used as the first-line drugs for the prevention of primary and secondary atherosclerotic cardiovascular disease (ACVD) [23]. Additional to the cholesterol-lowering effect, statins: reduce inflammation *via* attenuating the expression of several proteins that are involved in the formation of atherosclerotic plaque, induce apoptosis

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Despite statins benefits, some side-effects such as myopathy have been reported [25].

According previous studies the risk for myopathies is different in various ethnicities and between genders. There is a threefold increased risk of myopathy in women, whereas the risk for men is around six folds [26]. It has been demonstrated that the individual's genetic architecture has an important role in drug response to statin therapy [27–29]. Variation in several genes, including those encoding cholesterol-7-alpha-hydroxylase (*CYP7A1*) and ATP-binding cassette transporters G5 (*ABCG5*) involved in lipid metabolism (pharmacodynamics factors), and ATP-binding cassette protein B1/multidrug resistance protein 1 (*ABCB1/MDR1*), Cytochrome P450 3A4 (*CYP3A4*) and solute carrier organic anion transporter family member 1B1 (*SLCO1B1*) involved in statin metabolism (pharmacokinetic factors), have revealed an association with variability in statin efficacy [29–31].

Intestinal sterol absorption inhibitors

Ezetimibe is an intestinal cholesterol absorption inhibitor which was approved for clinical application (year 2002). It has been available as a single agent or in combination with a statin such as simvastatin and, more recently approved, a fixed-dose of atorvastatin [32]. Ezetimibe prevents intestinal absorption of both biliary and dietary cholesterol *via* interacting with the Niemann-Pick C1-like 1 (NPC1L1) sterol transporter located on the brush border membrane of proximal jejunum enterocytes [33]. Ezetimibe can reduce plasma LDL-C by 20% and is approved for both primary and secondary prevention of ACVD as a monotherapy in patients intolerant of statins or in combination with statins in high-risk or refractory patients with unsatisfactory statin therapy consequences [34]. However, when the patients were stratified by response, it became clear that some familial hypercholesterolaemic patients were at the extremes of response. Exceptional responders, those in the top 10%, had large $\geq 35\%$ reductions

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excretion (TICE) is an important alternative route to the hepatobiliary pathway [36]. A recent study showed that TICE is essential to macrophage reverse cholesterol transport in mice suggesting a potential antiatherogenic role for TICE [37]. Niemann-Pick C 1-like 1 (*NPC1L1*) gene was identified as related to the Niemann-Pick C1 (*NPC1*) gene [38]. Both proteins are involved in cholesterol transport and show homology to the patched family of proteins. NPC1L1 was later shown to be responsible for intestinal absorption of dietary cholesterol [39]. Additional research identified NPC1L1 as the protein target for Ezetimibe [40–42] and the extracellular loop C of NPC1L1 as the site of Ezetimibe binding [43]. Sequencing and description of genes in exceptional responders have confirmed valuable to detect genetic variations that change protein function [44]. Whereas understanding and refining the effectiveness of these potential pharmacological agents has yet to be considered for cardiovascular disease, it is evidently likely to become an essential weapon in cardiovascular disease treatment. It has been demonstrated that there is a large inconsistency in individual response to several different statins and doses. This rather unpredictable response is supposedly due to a complex interaction between genetic and environmental factors [45]. Combination of Ezetimibe–statins provides statistically significant improvements in triglycerides (TG), HDL-C, non-HDL-C, apolipoprotein B (*ApoB*) and high-sensitivity C-reactive protein (hs-CRP) [46]. Data on cardiovascular risk reduction with statin–Ezetimibe combination therapy have been demonstrated in randomized clinical trials (RCTs) in several clinical settings. Though they were all performed using simvastatin, their results serve as a “proof-of-concept” for the clinical benefits of other statin–Ezetimibe combinations [32,47,48].

Proprotein convertase subtilisin/kexin type 9 (*PCSK9*) inhibitors

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[50]. Several studies have shown that mutations in *PCSK9* gene decreased its binding to *LDLR* by greater than 90% [51]. *PCSK9* overexpression in the liver results in hypercholesterolemia by reducing *LDLR* number [52,53]. Gain-of-function mutations of *PCSK9* gene leads to increase in LDL receptor degradation causing a reduction in the LDL receptor expression on the cell surface which leads to accumulation of LDL-C in plasma [2]. In contrast, it has been shown that mutations that inactivate *PCSK9* (i.e. loss-of-function mutations) lead to lower LDL-C levels and reduced risk of CVD [54,55]. Since the discovery of *PCSK9* in 2003, its role in *LDLR* regulation and plasma LDL-C has produced the most exciting and promising therapeutic strategy in the last three decades [56]. A number of methods which target *PCSK9* have been developed. The most successful approach has been the anti-*PCSK9* monoclonal antibodies. Three human monoclonal antibodies (Alirocumab, Evolocumab and Bococizumab) have been approved for clinical use before cardiovascular outcomes trials were completed [57] based on their powerful LDL-C lowering properties (60–80%) when used alone or on top of statins [58–60]. Despite the powerful effects of these inhibitors, there was a concern that low levels of LDL-C that result from their use were associated with cognitive deficits. However, in a randomized trial including patients who received either evolocumab or placebo in addition to statin therapy, no significant difference between study groups in cognitive function was observed over a median of 19 months [61].

Inhibition of ANGPTL3 in homozygous familial hypercholesterolemia

Responses to statins and *PCSK9* antibodies have limited function due to the dependency on LDL receptor interaction for their activity. Recent drugs such as lomitapide and mipomersen with independent action from LDL receptors for treating

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to ANGPTL4. It has been shown that rare loss of function variants in ANGPTL3 gene was associated with decreased triglyceride levels as well as decreased LDL-C and HDL-C levels in family and general population studies [63]. Previous preclinical studies showed that suppression of hepatic Angptl3 protein production in mice resulted in significant reductions in serum levels of TG, LDL-C and non-HDL-C and an increase in insulin sensitivity, which can in turn lead to a reduction in atherosclerosis progression [64]. Genetic and therapeutic antagonists of ANGPTL3 in human and of Angptl3 in mice were associated with decreased levels of all three major lipid fractions and a decreased risk of ACVD [65]. Importantly, recent data demonstrate that ANGPTL3 targeting seems to reduce LDL-C levels independently of the LDL receptor expression and thereby in a recent study where homozygous FH patients were receiving ANGPTL3 inhibitor (Evinacumab) a significant reduction of LDL-C was obtained on top of reductions already achieved with other used lipid-lowering therapy [66]. This data strongly suggests that inhibition of ANGPTL3 function may be a valid approach to reduce residual risk in homozygous FH patients.

Therapeutic strategies using RNA

Small interfering RNAs (siRNAs) and miRNAs have been recently known as important regulators of genes involved in cholesterol homeostasis and potential novel therapeutic targets for hypercholesterolemia [67,68]. MicroRNAs are about 22 nucleotide RNAs that mediate post-transcriptional gene processing. They bind with an argonaute protein to form a silencing complex and act as specific sequence guides which are directing the silencing complex to transcripts within the 3' untranslated regions (3' UTRs) of target RNAs [69]. Several recent studies and clinical trials focused on using these small RNAs to target the most causative genes including *LDLR* [70], *ApoB*

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using locked nucleic acids increased *LDLR* levels by up to 70% [74].

MiR-27 inhibits the expression of two master regulators of adipogenesis PPAR- γ and C/EBP- α [76,77]. A recent study showed the relationship between GLP-1 and miR-27a in lipid metabolism which suggested that treatment with GLP-1 may reduce the expression of miR-27a, with or without cholesterol. Thus, GLP-1 may have a significant role through inhibiting miR-27a [78].

It has been shown that downregulation of sterol regulatory element-binding proteins (*SREBPs*), as transcription factors of *PCSK9*, could decrease the amount of *PCSK9* transcripts indirectly [79–81]. Interestingly, RNA interference (RNAi) provides alternative treatment options when current drug technology fails. Downregulation of *PCSK9* via antisense oligonucleotides (ASO) or small interfering RNA (siRNA) has been developed in the recent years with variable outcomes [82–84]. Advances such as improved lipid nanoparticles (LNPs) and N-acetylgalactosamine (GalNAc) chemistry have targeted liver for clinically approved RNAi therapeutics. Inclisiran (formerly known as ALN-PCS) is a siRNA designed to inhibit the intracellular synthesis of the *PCSK9* transcript and consequently decrease plasma *PCSK9*, and has been reported to be well tolerated and significantly lower *PCSK9* and LDL-C after a single intravenous dose in patients at high risk of cardiovascular risk [85–87].

Conclusion

The main reason for dyslipidemia treatment is to decrease the related CVD risk through the therapeutic options such as change in lifestyle and diet, treatment of the underlying disease and drug therapy [88]. Since it has been shown that atherosclerotic process initiates in childhood in which it is mediated by several known risk factors.

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years or older. However, in special cases, such as those with homozygous FH, treatment might need to be started at earlier ages [91,92]. Considering the fact that cholesterol is an essential substance for many biological pathways (e.g. steroid hormones, cell membrane, etc.), treatment at earlier ages should be monitored carefully. Several studies focused on the safety of lipid lowering therapy in FH children ≤ 10 years old and reported no significant concerns about recent drugs [93–95]. Regardless of the reduction in cardiovascular outcomes and mortality through statin therapy, remarkable residual risk remains, especially in severe familial hypercholesterolemia. Recent therapeutic strategies to achieve even lower LDL levels are available at this time (Table 2), such as the addition of ezetimibe to inhibit cholesterol absorption, and the recently PCSK9 monoclonal antibodies (Alirolumab and Evolocumab and Bococizumab). Moreover, new LDL-C lowering agents may be effectively administered in those patients who cannot tolerate statins [96]. More than 20 RNAi-based therapeutics (Figure 3) are now in clinical trials, and a number of these are Phase III trials. Sustained positive results from these trials may support further attempts to develop clinically relevant RNAi therapies. To improve treatment efficacy and safety, pharmacogenetic effects are typically constrained to pathways closely related to the primary effects on the drug target (pharmacodynamics) and aspects of drug absorption, distribution, metabolism and elimination (pharmacokinetics) [97]. Additional development in understanding the molecular basis of hypercholesterolemia will provide opportunities for the development of targeted therapy in the near future.

Figure 3. Summary of current therapeutic targets aimed to reduce serum LDL cholesterol. (1) Bile acid sequestrants, (2) HMG-CoA inhibition, (3) intestinal sterol absorption inhibition, (4) PCSK9 inhibition, (5) miRNA therapy: inhibition of translation of related mRNA.

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Disclosure statement

The authors declare that they have no competing interests.

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