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Treatment Advances in Heterozygous Familial Hypercholesterolemia

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Abstract: *Heterozygous Familial Hypercholesterolemia (HeFH) is a prevalent genetic disorder, which is typically characterized by markedly elevated levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C), the presence of tendon xanthomas and corneal arcus, as well as an increased susceptibility to premature atherosclerotic cardiovascular diseases (ASCVD).Extensive research conducted both domestically and internationally has demonstrated that HeFH has a relatively high prevalence. Nevertheless, the awareness and implementation rates of its treatment modalities remain rather low. Currently, commonly adopted treatment strategies encompass lifestyle modifications, the use of statin medications, and PCSK9 inhibitors, among others. As the development of novel lipid-lowering drugs and innovative treatment approaches continues to progress, the range of available treatment options is becoming progressively more diverse. Extensive research conducted both domestically and internationally has demonstrated that HeFH has a relatively high prevalence. Nevertheless, the awareness and implementation rates of its treatment modalities are relatively low. Among the existing treatment regimens, lifestyle interventions, statin drugs, and PCSK9 inhibitors are commonly utilized. As the development of novel lipid-lowering drugs and innovative treatment approaches continues to progress, the range of available treatment options is becoming progressively more diverse. This review aims to explore the existing treatment modalities for heterozygous familial hypercholesterolemia as well as those that can be achieved in the future, with the intention of providing a comprehensive understanding and reference for relevant medical research and clinical practice.*

Keywords: *Familial hypercholesterolemia, Treatment, Statins*

1. Introduction

Heterozygous Familial Hypercholesterolemia (HeFH) is a hereditary disease primarily manifested by receptor-mediated disorders in the metabolism of low-density lipoprotein cholesterol (LDL-C). It is usually diagnosed based on cholesterol levels, premature coronary artery disease, and family history [1]. In the past, its true prevalence was often underestimated. A study involving over 7.3 million people demonstrated that the overall prevalence of Familial Hypercholesterolemia (FH) was 1:311 (0.32%), with the prevalence among children (1:364 [0.28%]) being lower than that among adults (1:303 [0.33%]) [2]. A cohort study in China indicated that the crude prevalence rate of Familial Hypercholesterolemia was 0.19% [3].

HeFH not only has a high prevalence but also significantly increases the occurrence of cardiovascular risk events. Studies have shown that patients with HeFH present elevated levels of low-density lipoprotein cholesterol (LDL-C) since birth. The continuous increase in the exposure to LDL-C throughout life can lead to a higher risk of atherosclerotic cardiovascular diseases (ASCVD) and premature cardiovascular events [4]. Moreover, there is a dose-response relationship between cholesterol and the cardiovascular risk in patients with Familial Hypercholesterolemia. The cholesterol annual score, which is an index for evaluating the cumulative exposure of LDL-C, has been shown to be associated with the occurrence of major cardiovascular events in patients with Familial Hypercholesterolemia [5]. Over time, untreated male and female Familial Hypercholesterolemia patients have a 30% to 50% risk of fatal or non-fatal cardiac events at the ages of 50 and 60, respectively [1, 6]. Therefore, it is of crucial importance to adopt effective lipid-lowering treatments at an early stage.

The 2019 ESC/EAS Guidelines for the Management of Dyslipidemia [7] proposed that in FH patients with ASCVD or other major risk factors, the LDL-C target is to reduce LDL-C by ≥50% compared to

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the baseline, with LDL-C <1.4 mmol/L (<55mg/dL); in FH patients without ASCVD or other major risk factors, the LDL-C target is to reduce LDL-C by ≥50% from the baseline and have LDL-C <1.8 mmol/L (<70 mg/dL). However, the lipid levels of most patients after treatment are far higher than this standard. Hence, the treatment of HeFH still awaits further popularization and attention.

2. Treatment modalities

2.1 Lifestyle interventions

A healthy lifestyle plays an indispensable role as an adjunctive treatment for heterozygous familial hypercholesterolemia. Research has shown that among patients with familial hypercholesterolemia, a higher level of adherence to the Mediterranean diet is correlated with better control of dyslipidemia and a lower degree of inflammation [8]. Regarding diet, it is advisable to increase the intake of foods rich in dietary fiber and high-quality protein while reducing the consumption of foods containing polyunsaturated fats and high cholesterol. Moreover, supplementing with omega-3 fatty acids can contribute to lowering cholesterol and triglyceride levels [9]. In addition, maintaining at least 150 minutes of exercise per week is essential. Smoking is an independent predictor for the occurrence of atherosclerotic cardiovascular diseases within 10 years among patients with FH [10]. Therefore, quitting smoking can effectively decrease the incidence of premature coronary heart disease.

2.2 Pharmacological Treatments

2.2.1 Oral drug treatment

2.2.1.1 Statins

They are the most fundamental treatment approach for heterozygous familial hypercholesterolemia. Their mechanism of action lies in competitively inhibiting hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, thereby reducing cholesterol synthesis and effectively lowering the incidence of cardiovascular events. Treatment is usually divided into three intensities. High-intensity statins (such as atorvastatin 40 - 80 mg or rosuvastatin 20 - 40 mg) can reduce LDL-C by at least 50%; moderate-intensity statins (such as atorvastatin 10 - 20 mg or rosuvastatin 5 - 10 mg) can reduce LDL-C by 30% to 49%; low-intensity statins (such as pravastatin 10 - 20 mg, simvastatin 10 mg or rosuvastatin 2.5 mg) can reduce LDL-C by less than 30% [11]. The 2019 ESC/EAS Guidelines recommend that treatment should start with high-intensity statin therapy [7]. In a large cohort study of patients with heterozygous FH, it was pointed out that moderate-to-high-intensity statin therapy was associated with a approximately 44% reduction in the relative risk of primary prevention for coronary artery disease (CAD) and all-cause mortality [12]. Among children and adolescents, statins are also an effective and safe way to lower lipids. One study indicated that statins can also effectively delay the progression of carotid artery plaques [13, 14]. Another meta-analysis that included nine randomized placebo-controlled studies showed that statins are an effective method for treating FH in children, and the incidence of adverse events was the same in the statin group and the placebo group [15]. All statins have a lipid-lowering effect on patients with heterozygous FH. However, the efficacy of statins partly depends on the increase in LDL receptor activity. Therefore, statins alone are not sufficient to reach the target lipid levels recommended by the guidelines, which is also the reason why many patients with heterozygous FH choose combination drug therapy. The common side effects of statins include abnormal liver function, muscle damage, and effects on glucose homeostasis. As a result, most patients cannot adhere to the use of statins or use statin doses with insufficient intensity. However, some studies have pointed out that long-term statin therapy is very safe and the established cardiovascular benefits of statin therapy far outweigh the risks of adverse reactions [16].For other diseases, such as dementia, hepatic encephalopathy, venous thromboembolism, atrial fibrillation, polycystic ovary syndrome, and cancer, studies have also been conducted, but the impact of statins on these diseases has not been reliably demonstrated [7].Therefore, in the choice of treatment options for heterozygous familial hypercholesterolemia, both in adults and children, statins have an unshakable position at present and in the future.

2.2.1.2 Other oral drugs

Ezetimibe, a cholesterol absorption inhibitor, is capable of selectively inhibiting the cholesterol transport proteins on the brush border of the small intestinal mucosa, thereby reducing the absorption of cholesterol in the intestine. Ezetimibe is usually used in combination with statins. A randomized, double-blind, multicenter, Phase III study indicated that the fixed-dose combination therapy of low-intensity

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rosuvastatin (2.5 mg) and Ezetimibe (10 mg) showed greater reductions in low-density lipoprotein-C (LDL-C), non-high-density lipoprotein, and apolipoprotein B (apoB) compared with monotherapy using moderate-intensity rosuvastatin (5 mg) in patients with different characteristics [11].Probucol, an antioxidant drug, can inhibit the occurrence and development of atherosclerosis and is especially suitable for FH patients with obvious tendon xanthomas. Studies have pointed out that it enhances reverse cholesterol transport by activating plasma cholesterol ester transfer protein and liver scavenger receptor class B type I (SR-BI) [17, 18]. It has a synergistic effect with the lipid-lowering mechanism of statins, enabling more effective reduction of blood lipids. Other drugs such as bile acid sequestrants (e.g., cholestyramine), niacin, and fibrates can all be used as supplementary treatments when the basic lipid-lowering regimens do not achieve satisfactory results.

2.2.2 Injectable Medications

2.2.2.1 PCSK9 Inhibitors

In the realm of managing heterozygous familial hypercholesterolemia (HeFH), PCSK9 inhibitors, with Alirocumab and Evolocumab being the commonly utilized representatives, have emerged as significant therapeutic agents. Their mechanism of action primarily hinges on inhibiting the binding of proprotein convertase subtilisin/kexin type 9 (PCSK9) to the low-density lipoprotein receptor (LDLR). Through this inhibitory action, the quantity of receptors capable of clearing low-density lipoprotein in the bloodstream is increased, consequently leading to a reduction in the levels of low-density lipoprotein cholesterol within the body. The injection frequency of these drugs is typically once every two weeks. Compared with drugs that need to be taken orally on daily basis, this regimen can enhance patient compliance to a greater extent. Two studies have demonstrated that the application of PCSK9 inhibitors can result in a continuous and significant decline in the levels of low-density lipoprotein cholesterol in 55 - 60% of patients with HeFH, and the overall reported rate of adverse reactions is low [19, 20]. Another meta-analysis has indicated that when PCSK9 inhibitors are added to the maximum tolerated statin therapy, the low-density lipoprotein-C (LDL-C) in FH patients is decreased by approximately half [21].Apart from their potent lipid-lowering effect, studies have also shown that PCSK9 inhibitors can significantly alleviate the coronary plaque burden and stabilize plaques as observed through coronary computed tomography angiography [22].Currently, PCSK9 inhibitors are a common treatment option for adult heterozygous FH. Studies have also pointed out that they possess significant efficacy and safety in children [23]. Therefore, despite the continuous emergence of new treatment drugs and approaches for HeFH, PCSK9 inhibitors remain the option chosen by most patients.

2.2.2.2 Small Interfering RNA

A novel lipid-lowering drug with high-precision targeting ability can specifically inhibit the translation of proprotein convertase subtilisin/kexin type 9 (PCSK9) in the liver, thereby increasing the number of low-density lipoprotein receptor (LDLR) in the body and reducing the level of low-density lipoprotein in vivo. Similar to other PCSK9 inhibitors, inclisiran not only reduces the level of low-density lipoprotein cholesterol but also decreases the levels of total cholesterol, apolipoprotein B (Apo-B), lipoprotein (a), and triglycerides, which consequently significantly reduces the risk of cardiovascular events. Inclisiran has a long injection interval. After the initial injections on day 1 and day 90, it only requires an injection once every six months, which can enhance patient compliance. Inclisiran demonstrates excellent lipid-lowering efficacy with few adverse reactions. ORION-9, ORION-10, and ORION-11 are double-blind, randomized, placebo-controlled trials focusing on inclisiran. The results showed that subcutaneous injections of inclisiran once every six months could reduce the level of low-density lipoprotein cholesterol by approximately 50%, and the overall adverse events were generally similar between the inclisiran group and the placebo group [24, 25].Moreover, in another study with a long-term follow-up of 3,274 patients, it was pointed out that inclisiran could continuously and effectively reduce low-density lipoprotein-C, exhibiting long-term safety and tolerability [26].

2.3 Lipoprotein Apheresis

Lipoprotein apheresis is a method that selectively removes apolipoprotein B (ApoB)-containing lipoproteins (including low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and lipoprotein (a)) from plasma through physical techniques. It can not only rapidly reduce blood lipid levels to those that are difficult to achieve with drug treatment but also effectively influence the body's inflammatory response. Literature indicates that among all types of familial hypercholesterolemia (FH), the targeted acute low-density lipoprotein-C reduction rates range from 55% to 70% [27].A study has demonstrated that lipoprotein apheresis treatment is closely associated with significant decreases in total

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cholesterol and LDL-C, as well as reductions in biomarkers related to endothelial dysfunction and inflammation (high-sensitivity C-reactive protein (hsCRP), monocyte chemoattractant protein-1 (MCP-1), and soluble endothelin), not only after each procedure but also during a long-term follow-up of up to 15 years [28].However, the application of lipoprotein apheresis is rather limited in clinical practice. The primary reason is its high treatment cost, which makes it unaffordable for most patients. Secondly, as an invasive treatment measure, each treatment session lasts as long as 2 to 3 hours, thereby affecting patients' quality of life in daily life. With the emergence of new lipid-lowering drugs, the number of patients choosing lipoprotein apheresis to reduce blood lipid levels has decreased significantly. Nevertheless, for patients with homozygous FH, severe heterozygous FH, and those who have not shown significant improvement after using multiple lipid-lowering drugs, lipoprotein apheresis remains an effective treatment option currently available.

2.4 Gene Therapy

Gene therapy represents a novel and effective strategy for permanently correcting the defective low-density lipoprotein (LDL) gene [29]. There are two approaches in gene therapy, namely ex vivo and in vivo methods. Ex vivo gene therapy mainly involves liver resection, hepatocyte isolation, exposing the isolated hepatocytes to retroviruses carrying the functional low-density lipoprotein receptor (LDLR) in vitro, and finally transferring the recombinant hepatocytes back to the liver. In vivo gene therapy, on the other hand, utilizes viral vectors or non-viral vectors to directly deliver the normal LDLR gene into the patient's body. A study has demonstrated that in vivo adeno-associated virus (AAV)-CRISPR/Cas9-mediated correction of the LDLR gene can partially restore LDLR expression and effectively improve the atherosclerotic phenotype in LDLR mutants [30]. Additionally, two other studies have pointed out that the extracellular vesicles (EV)- or exosome-mediated low-density lipoprotein receptor (LDLR) mRNA can effectively restore LDLR expression, which holds great potential for gene therapy [31, 32]. Gene therapy offers the possibility of curing familial hypercholesterolemia (FH). Currently, it has also shown favorable results in animal experiments. However, gene therapy may induce alterations in non-target genes. Therefore, the safety and efficacy for clinical application still need to be further verified. At present, it has not yet become a standard treatment method for FH. With the continuous optimization and improvement of gene therapy, it is expected to become one of the preferred treatment options for FH patients in the future.

3. Conclusions

Heterozygous familial hypercholesterolemia (HeFH) represents a prevalent disorder characterized by the impairment of low-density lipoprotein cholesterol metabolism. In severe scenarios, it may give rise to disability or even pose a life-threatening situation. In recent years, the continuous advent of novel drugs and therapeutic approaches has led to a remarkable enhancement in both the lipid-lowering efficacy and patient compliance. Consequently, it becomes of utmost significance to heighten the level of standardization and the prevalence rate of the diagnosis and treatment of HeFH. Early and standardized interventional treatments have been demonstrated to effectively lower the levels of low-density lipoprotein cholesterol among patients, retard the formation of atherosclerotic plaques, and mitigate the occurrence of premature cardiovascular events. Such outcomes not only contribute to the amelioration of patients' quality of life but also play a crucial role in alleviating the burden on society and families. This highlights the necessity for healthcare professionals to focus on the timely diagnosis and appropriate management of HeFH, ensuring that patients can benefit from the most effective and evidence-based treatments available, thereby optimizing their long-term health outcomes and reducing the overall impact on public health and social welfare.

References

[1] ONORATO A, STURM A C. Heterozygous Familial Hypercholesterolemia [J]. Circulation, 2016, 133(14): e587-9.
[2] HU P, DHARMAYAT K I, STEVENS C A T, et al. Prevalence of Familial Hypercholesterolemia Among the General Population and Patients With Atherosclerotic Cardiovascular Disease: A Systematic Review and Meta-Analysis [J]. Circulation, 2020, 141(22): 1742-59.
[3] AIHAITI X, CHEN S, LI J, et al. Prevalence of familial hypercholesterolemia and its association with coronary artery disease: A Chinese cohort study [J]. Chronic Dis Transl Med, 2023, 9(2): 134-42.
[4] BRANDTS J, RAY K K. Familial Hypercholesterolemia: JACC Focus Seminar 4/4 [J]. J Am Coll

ISSN 2706-6819 Vol. 7, Issue 1: 80-85, DOI: 10.25236/IJFM.2025.070113

Cardiol, 2021, 78(18): 1831-43.
[5] TADA H, OKADA H, NOHARA A, et al. Effect of Cumulative Exposure to Low-Density Lipoprotein-Cholesterol on Cardiovascular Events in Patients With Familial Hypercholesterolemia [J]. Circ J, 2021, 85(11): 2073-8.
[6] MCGOWAN M P, HOSSEINI DEHKORDI S H, MORIARTY P M, et al. Diagnosis and Treatment of Heterozygous Familial Hypercholesterolemia [J]. J Am Heart Assoc, 2019, 8(24): e013225.
[7] MACH F, BAIGENT C, CATAPANO A L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk [J]. Eur Heart J, 2020, 41(1): 111-88.
[8] ANTONIAZZI L, ARROYO-OLIVARES R, BITTENCOURT M S, et al. Adherence to a Mediterranean diet, dyslipidemia and inflammation in familial hypercholesterolemia [J]. Nutr Metab Cardiovasc Dis, 2021, 31(7): 2014-22.
[9] BARKAS F, NOMIKOS T, LIBEROPOULOS E, et al. Diet and Cardiovascular Disease Risk Among Individuals with Familial Hypercholesterolemia: Systematic Review and Meta-Analysis [J]. Nutrients, 2020, 12(8).
[10] PAQUETTE M, BERNARD S, CARIOU B, et al. Familial Hypercholesterolemia-Risk-Score: A New Score Predicting Cardiovascular Events and Cardiovascular Mortality in Familial Hypercholesterolemia [J]. Arterioscler Thromb Vasc Biol, 2021, 41(10): 2632-40.
[11] LEE S A, KIM W, HONG T J, et al. Effects of Fixed-dose Combination of Low-intensity Rosuvastatin and Ezetimibe Versus Moderate-intensity Rosuvastatin Monotherapy on Lipid Profiles in Patients With Hypercholesterolemia: A Randomized, Double-blind, Multicenter, Phase III Study [J]. Clin Ther, 2021, 43(9): 1573-89.
[12] BESSELING J, HOVINGH G K, HUIJGEN R, et al. Statins in Familial Hypercholesterolemia: Consequences for Coronary Artery Disease and All-Cause Mortality [J]. J Am Coll Cardiol, 2016, 68(3): 252-60.
[13] PANG J, CHAN D C, WATTS G F. The Knowns and Unknowns of Contemporary Statin Therapy for Familial Hypercholesterolemia [J]. Curr Atheroscler Rep, 2020, 22(11): 64.
[14] BOS S, DUVEKOT M H, TEN KATE G R, et al. Carotid artery plaques and intima medial thickness in familial hypercholesteraemic patients on long-term statin therapy: A case control study [J]. Atherosclerosis, 2017, 256: 62-6.
[15] VUORIO A, KUOPPALA J, KOVANEN P T, et al. Statins for children with familial hypercholesterolemia [J]. Cochrane Database Syst Rev, 2019, 2019(11).
[16] MACH F, RAY K K, WIKLUND O, et al. Adverse effects of statin therapy: perception vs. the evidence - focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract [J]. Eur Heart J, 2018, 39(27): 2526-39.
[17] YAMASHITA S, MASUDA D, HARADA-SHIBA M, et al. Effectiveness and Safety of Lipid-Lowering Drug Treatments in Japanese Patients with Familial Hypercholesterolemia: Familial Hypercholesterolemia Expert Forum (FAME) Study [J]. J Atheroscler Thromb, 2022, 29(5): 608-38.
[18] HIRANO K, IKEGAMI C, TSUJII K, et al. Probucol enhances the expression of human hepatic scavenger receptor class B type I, possibly through a species-specific mechanism [J]. Arterioscler Thromb Vasc Biol, 2005, 25(11): 2422-7.
[19] YOKOTE K, AKO J, KITAGAWA K, et al. Safety and Effectiveness of Low-Density Lipoprotein Cholesterol-Lowering Therapy With Evolocumab for Familial Hypercholesterolemia/Hypercholesterolemia in Japan: A Real-World, Postmarketing, Single-Arm Study [J]. J Am Heart Assoc, 2024, 13(21): e035809.
[20] KASTELEIN J J, HOVINGH G K, LANGSLET G, et al. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 monoclonal antibody alirocumab vs placebo in patients with heterozygous familial hypercholesterolemia [J]. J Clin Lipidol, 2017, 11(1): 195-203.e4.
[21] BRANDTS J, DHARMAYAT K I, VALLEJO-VAZ A J, et al. A meta-analysis of medications directed against PCSK9 in familial hypercholesterolemia [J]. Atherosclerosis, 2021, 325: 46-56.
[22] PéREZ DE ISLA L, DíAZ-DíAZ J L, ROMERO M J, et al. Alirocumab and Coronary Atherosclerosis in Asymptomatic Patients with Familial Hypercholesterolemia: The ARCHITECT Study [J]. Circulation, 2023, 147(19): 1436-43.
[23] SANTOS R D, WIEGMAN A, CAPRIO S, et al. Alirocumab in Pediatric Patients With Heterozygous Familial Hypercholesterolemia: A Randomized Clinical Trial [J]. JAMA Pediatr, 2024, 178(3): 283-93.
[24] RAY K K, WRIGHT R S, KALLEND D, et al. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol [J]. N Engl J Med, 2020, 382(16): 1507-19.
[25] RAAL F J, KALLEND D, RAY K K, et al. Inclisiran for the Treatment of Heterozygous Familial Hypercholesterolemia [J]. N Engl J Med, 2020, 382(16): 1520-30.
[26] WRIGHT R S, RAAL F J, KOENIG W, et al. Inclisiran administration potently and durably lowers LDL-C over an extended-term follow-up: the ORION-8 trial [J]. Cardiovasc Res, 2024, 120(12): 1400-

ISSN 2706-6819 Vol. 7, Issue 1: 80-85, DOI: 10.25236/IJFM.2025.070113

10.
[27] WANG A, RICHHARIYA A, GANDRA S R, et al. Systematic Review of Low-Density Lipoprotein Cholesterol Apheresis for the Treatment of Familial Hypercholesterolemia [J]. J Am Heart Assoc, 2016, 5(7).
[28] VíšEK J, BLáHA M, BLáHA V, et al. Monitoring of up to 15 years effects of lipoprotein apheresis on lipids, biomarkers of inflammation, and soluble endoglin in familial hypercholesterolemia patients [J]. Orphanet J Rare Dis, 2021, 16(1): 110.
[29] HAJIGHASEMI S, MAHDAVI GORABI A, BIANCONI V, et al. A review of gene- and cell-based therapies for familial hypercholesterolemia [J]. Pharmacol Res, 2019, 143: 119-32.
[30] ZHAO H, LI Y, HE L, et al. In Vivo AAV-CRISPR/Cas9-Mediated Gene Editing Ameliorates Atherosclerosis in Familial Hypercholesterolemia [J]. Circulation, 2020, 141(1): 67-79.
[31] LI Z, ZHAO P, ZHANG Y, et al. Exosome-based Ldlr gene therapy for familial hypercholesterolemia in a mouse model [J]. Theragnostic, 2021, 11(6): 2953-65.
[32] YANG Z, JI P, LI Z, et al. Improved extracellular vesicle-based mRNA delivery for familial hypercholesterolemia treatment [J]. Theragnostic, 2023, 13(10): 3467-79.