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Treatment of Homozygous Familial Hypercholesterolemia (HoFH): A Case Series Study and Mini Review of PCSK9 Inhibitor for HoFH

Jia-Ling Lin[1,2], Po-Tseng Lee[2], Pei-Yin Chen[3], Kai-Pi Cheng[3], Yen-Wen Liu[2], Ping-Yen Liu[2,4], Ting-Hsing Chao[2], and Yi-Heng Li[2]

[1]Division of Cardiology, Department of Internal Medicine, National Cheng Kung University Hospital Dou-Liou Branch, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [2]Division of Cardiology, [3]Division of Endocrinology and Metabolism, Department of Internal Medicine,National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [4]Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Abstract

Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disorder that increases the level of low-density lipoprotein cholesterol (LDL-C) and causes premature coronary artery disease. HoFH is usually undiagnosed until the cardiac events occur. Most patients with asymptomatic HoFH are also not treated adequately. Proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitor is a powerful LDL-C-lowering agent. In this review, we described the treatment experiences of eight patients with HoFH in our hospital. We also reviewed the clinical trials of PCSK9 inhibitor therapy for HoFH and discussed the current challenges of HoFH treatment in Taiwan. (J Intern Med Taiwan 2022; 33: 155-163)

Key Words: Familial hypercholesterolemia, PCSK9 inhibitor

Introduction

Homozygous familial hypercholesterolemia (HoFH) is a genetic disorder that is associated with high level of low-density lipoprotein cholesterol (LDL-C) and high-risk of coronary artery disease (CAD). It is the most severe form of familial hypercholesterolemia (FH) and was traditionally considered a rare disease with an estimated prevalence of 1:1,000,000 populations. However, recent studies have shown that the prevalence of HoFH was much higher than previously thought, with an estimated

Reprint requests and correspondence：Dr. Yi-Heng Li
Address：Department of Internal Medicine, National Cheng Kung University Hospital, No.138, Sheng Li Road, Tainan, Taiwan

frequency of 1:160,000-300,000 in general population[1-3]. The identification of HoFH without clinical events is usually difficult because the clinical and biochemical phenotypic expressions are highly variable, leading to underdiagnoses and undertreatment[4]. Definitive diagnosis of HoFH needs genetic testing. The commonly involved mutations in FH are genes encoding the low-density lipoprotein receptor (LDLR), apolipoprotein B (Apo-B), and proprotein convertase subtilisin/kexin 9 (PCSK9)[5]. The mutations in low-density lipoprotein receptor adapter protein 1 (LDLRAP1) mediating the interaction of LDLR with clathrin were also reported[6]. In addition to true homozygous (the same mutation on the same gene in both alleles), patients with compound heterozygous (different mutations on the same gene in both alleles) and double heterozygous (mutations on different genes in both alleles, for example, mutations in LDLR + Apo-B or LDLR + PCSK9) also have high LDL-C levels. Generally, patients with true homozygous in LDLR mutations or compound heterozygous in LDLR mutations have the highest LDL-C levels. The typical clinical features of HoFH are characterized by extremely high levels of LDL-C leading to premature CAD and/or other atherosclerotic cardiovascular disease (ASCVD)[1]. Therefore, the primary goal of management of HoFH is the early control of elevated LDL-C level to prevent CAD and other complications. Unfortunately, HoFH is commonly diagnosed when acute cardiac events or severe coronary atherosclerosis has already occurred. Given its very high levels of LDL-C, HoFH usually requires combination lipid-lowering therapy with statin, ezetimibe, and/or PCSK9 inhibitor to decrease the level of LDL-C to a reasonable range and to reduce the risk of CAD/ASCVD. This paper aimed to retrospectively analyze the genetic, biochemical, and clinical data of eight patients with HoFH who were treated in our hospital in the recent 3 years and to perform a minireview on the use of PCSK9 inhibitors in HoFH.

Case series

We retrospectively collected and analyzed the data of eight patients with HoFH (5 men; mean age, 52.1 years) confirmed by genetic testing in our hospital from March 2017 to February 2020 (Table 1). Half of these patients were asymptomatic and referred to our hospital for very high levels of LDL-C, while the other half came to our hospital for chest pain. On physical examination, 3 of the 8 patients had evident xanthoma. We were unable to obtain the untreated cholesterol levels in all patients because some of them had already been treated with lipid-lowering agents before they were referred to our hospital. For the initial cholesterol levels in our hospital, seven of them had LDL-C level >190 mg/dL. Patient 5 had a relatively lower level of initial LDL-C (139 mg/dL). However, his LDL-C level remained high (166 mg/dL) while under statin and ezetimibe treatment, raising the suspicion of FH. All those patients who presented with chest pain had established diagnosis of severe CAD. Patients 1 and 3 underwent coronary angiography after positive non-invasive stress test for myocardial ischemia. Both of them had high SYNTAX score (patient 1 had 51.5 and patient 3 had 54.5) and received coronary artery bypass graft (CABG) in our hospital. Patient 5 presented with ST elevation myocardial infarction and had two-vessel disease. He received primary percutaneous coronary intervention (PCI). Patient 7 had undergone CABG surgery more than 10 years ago. His coronary angiography showed severe triple-vessel disease with patency of left internal mammary artery (LIMA) to left anterior descending artery (LAD), but stenosis in LAD just distal to LIMA anastomosis site, so he also received PCI. The diagnoses of FH for these eight patients were all confirmed by genetic testing. Genetic testing was performed in the Taipei Veteran General Hospital by Dr. Min-Ji Charng. A custom-made mass spectrometry assay was used for genotype screening. The assay detected 68 known

FH genes in Taiwan. If the mass spectrometry showed negative result and the level of LDL-C was >250 mg/dL, a targeted next generation sequencing (NGS) was performed to detect novel variations not included in the panels of mass spectrometry. If the targeted NGS was also negative, multiplex ligation-dependent probe amplification analysis would be performed to detect LDLR large gene rearrangement[7]. In these eight cases, the genetic mutations were mainly located in the LDLR and Apo-B genes. One patient was a true homozygote, two patients were double heterozygotes, and the remaining five

Table 1. Baseline characteristics & clinical presentation

Case	1	2	3	4	5	6	7	8
Age	47	45	47	63	55	31	58	71
Sex	M	M	F	F	M	M	M	F
Reason for the first visit	Chest pain	Referred for hyperlipidemia	Chest pain	Referred for hyperlipidemia	Chest pain (STEMI)	Referred for hyperlipidemia	Chest pain	Referred for hyperlipidemia
Physical examination	--	--	--	--	--	Tendon xanthoma	Eyelid xanthoma	Xanthoma; eye: lipid ring
Initial medication	Untreated	Possibly untreated*	Untreated	Rosu 5mg	Untreated	Rosu 5mg	Sim 20mg +Eze 10mg	Statin*
Initial data%								
TC (mg/dL)	377	472	352	276	212	237	291	475
HDL (mg/dL)	40	34	NA	58	36	49	NA	53
LDL (mg/dL)	306	396	287	216	139	192	225	406
TG (mg/dL)	229	195	224	NA	150	53	152	123
Clinical phenotype	Homo	cHete	dHete	cHete	dHete	cHete	cHete	cHete
Gene	LDLR	LDLR	LDLR ApoB	LDLR	LDLR ApoB	LDLR	LDLR	LDLR
Mutation	H562Y	R236W D568N	D69N R3500W	G457R F179C	D69N R3500W	R236W A410T D568N I602V	R236W D568N G457R	E207Q G457R
Nucleotide change	c.1747C>T	c.769C>T c.1765G>A	c. 268G>A c.10707C>T	c.1432G>A c.599T>G	c. 268G>A c.10707C>T	c.769C>T c.1291G>A c.1765G>A c.1867A>G	c.769C>T c.1765G>A c.1432G>A	c.682G>C c.1432G>A

* According to medical record: statin was used before but stopped due to muscle pain (case 2); dose and type not recorded (case 8).
% Lipid profiles were initial data, not untreated data.
ApoB: Apolipoprotein B; cHete: compound heterozygous; dHete: double heterozygous; Eze: ezetimibe; F: female; HDL: high density lipoprotein; Homo: homozygous; LDL: low density lipoprotein; LDLR: LDL receptor; M: male; NA: not available; Rosu: rosuvastatin; Sim: simvastatin; STEMI: ST-elevation myocardial infarction; TC: total cholesterol; TG: triglyceride.

were compound heterozygotes. Since HoFH is a genetic disease, the disease is highly likely present within family members. To screen family members of the proband of HoFH, plasma lipid profile test and/or genetic analysis should be performed[5,8]. However, cascade screening was only performed in one of these patients (patient 5). We did not know the definite causes why cascade screening was not performed in other patients.

For lipid-lowering therapies in our hospital, one patient did not receive statin because of severe muscle pain. The other seven patients were treated with high-intensity statin (atorvastatin 40–80 mg or rosuvastatin 20 mg) plus ezetimibe. According to the 2017 Taiwan lipid guidelines for high-risk patients, the target of LDL-C for FH was <100 mg/dL and should be <70 mg/dL for those with ASCVD[7]. As expected, these patients could not achieve the LDL-C target under statin and ezetimibe. Therefore, all of them were indicated for PCSK9 inhibitor. However, only three patients received PCSK9 inhibitor. Patient 1 received evolocumab 140 mg every 2 weeks initially, and evolocumab was later titrated to 420 mg every month. Patient 2 requested self-paid PCSK9 inhibitor. After sufficient explanation, he was prescribed with alirocumab 75 mg every 3 weeks. Neither alirocumab nor evolocumab was available in our hospital when patient 2 started the medication. We did not know why the physician chose alirocumab and where the patient got the medication. Patient 5 participated in a randomized clinical trial of alirocumab. One year after the trial completed, he received alirocumab 75 mg every 2 weeks for 48 weeks as compassionate use. In Taiwan's National Health Insurance (NHI) regulation, the dosage of evolocumab for HoFH is 420 mg every month. The dose of alirocumab used in the study for HoFH was 150 mg every 2 weeks, but it is not approved for HoFH in Taiwan yet. In NHI's regulation, the dose of alirocumab for patients with major cardiovascular event is 75 mg every 2 weeks. A possible reason why patient 2 received alirocumab 75 mg every 3 weeks is that physicians in Taiwan were not familiar with the use of PCSK9 inhibitor for FH. Other possible reasons included economic issue and convenience. They all responded well to PCSK9 inhibitor, and the average reduction of LDL-C was 47.3% compared with the baseline before PCSK9 inhibitor treatment. Patient 5 was off PCSK9 inhibitor again after the amount of compassionate use was completed, and his LDL-C increased to the level before use of PCSK9 inhibitor. Patient 3 was regularly followed up at cardiovascular surgeon's clinic but PCSK9 inhibitor was not used. Patients 4 and 7 were lost during follow-ups while waiting for the approval of using PCSK9 inhibitor from the NHI Administration. Patient 6 did not return to the clinic after the second visit, before the result of genetic testing was known. Patient 8 was still in our clinic, under evaluation, and was waiting for the approval for PCSK9 inhibitor use, while we were writing this article. The management of these patients is summarized in Table 2.

Diagnosis of HoFH

The diagnosis for FH in all major guidelines and recommendations is based on the scoring system. In Taiwan's FH diagnostic criteria, there are four clinical parameters: family history, clinical history, physical examination, and LDL-C level[8]. When there is positive finding in these parameters, FH should be considered. More precisely, these are patients with a family history of hypercholesterolemia, premature cardiovascular disease, tendon xanthoma, and severe hypercholesterolemia. For HoFH, diagnosis is established by either positive genetic testing or fulfillment of all of the following: (1) skin/tendon xanthoma, or corneal arcus, (2) untreated LDL-C >330 mg/dL and/or total cholesterol (TC) >500 mg/dL, and (3) parents with hypercholesterolemia (untreated TC >250 mg/dL) or premature CAD. For the complete description for the diagnosis of FH,

Table 2. Management & response to medication

Case	1	2	3	4	5	6	7	8
Statin	Ator 40mg	Ator 40mg	Ator 80mg	Not used	Rosu 20mg	Ator 40mg	Ator 40mg	Ator 80mg
Ezetimibe	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg
PCSK9i	Evolocumab 140mg q2w	Alirocumab 75mg q3w	Not used	Not used	Alirocumab 75mg q2w	Not used	Not used	Not used
Reasons why PCSK9i not used	--	--	Not known	Lost while application	--	Lost after the 2nd visit	Lost while application	Under application
LDL before PCSK9i	91	281	--	---	125	--	--	--
LDL while on PCSK9i	44	148	--	--	72	--	--	--
LDL reduction	51.6%	47.3%	--	--	42.4%	--	--	--
Management of CAD	CABG	No known CAD	CABG	No known CAD	PCI for STEMI	No known CAD	PCI (post CABG)	No known CAD
Cascade screening #	N	N	N	N	Y	N	N	N

#As documented in medical record, but no further detail.
Ator: atorvastatin; LDL: low density lipoprotein (mg/dL); N: no; PCSK9i: Proprotein convertase subtilisin/kexin type 9 inhibitor; q2w: every 2 weeks; q3w: every 3 weeks; Rosu: rosuvastatin; STEMI: ST-elevation myocardial infarction; Y: yes.

please refer to the 2017 Taiwan lipid guidelines for high-risk patients[8]. Figure 1 shows a simplified and modified algorithm for the diagnosis of HoFH from Taiwan's guideline.

Treatment of HoFH

Observational studies have shown grave outcomes of HoFH if untreated, and treatment delays the onset of ASCVD[9,10]. Therefore, major guidelines or recommendations, such as European Society of Cardiology's consensus and Taiwan's guideline, suggest initiation of treatment as early as possible[1,8]. Although statin is less effective in lowering LDL-C for patients with HoFH because of a lack of functional LDLR, it remains the first-line therapy. The average LDL-C reduction in HoFH is approximately 20% with high-intensity statins[10,11]. Even if the reduction of LDL-C level was not as good as in usual hypercholesterolemia, statins effectively delayed the cardiovascular event and reduced the mortality in HoFH compared with the era before statin was widely used[10]. The second-line therapy is ezetimibe, providing another 10%–15% LDL-C reduction[12]. Together, statin and ezetimibe reduce LDL-C by 30%–40%. Further therapy is therefore required to lower the extremely high level of LDL-C to the target level. Combining other conventional drugs, such as bile acid sequestrants or niacin, could be considered, but their use may be limited by adverse events[1,8].

Among novel pharmacological therapies for HoFH, PCSK9 inhibitor is the most promising agent because of its efficacy in reducing LDL-C level based on scientific evidence from clinical trials. This agent will be discussed further in the following section. Other new agents include mipomersen and lomitapide. They both reduce production of LDL by inhibiting the production of Apo-B containing protein. This mechanism is favored in HoFH since it does not involve LDLR. Only lomitapide, an oral agent, is approved in Taiwan. Besides medical therapy, lipoprotein apheresis should be considered in HoFH. While standard lipid-lowering agents act by increasing LDLR, lipoprotein apheresis works by extracorporeal removal of LDL-C. Apheresis enhances plaque regression and/or stabilization and

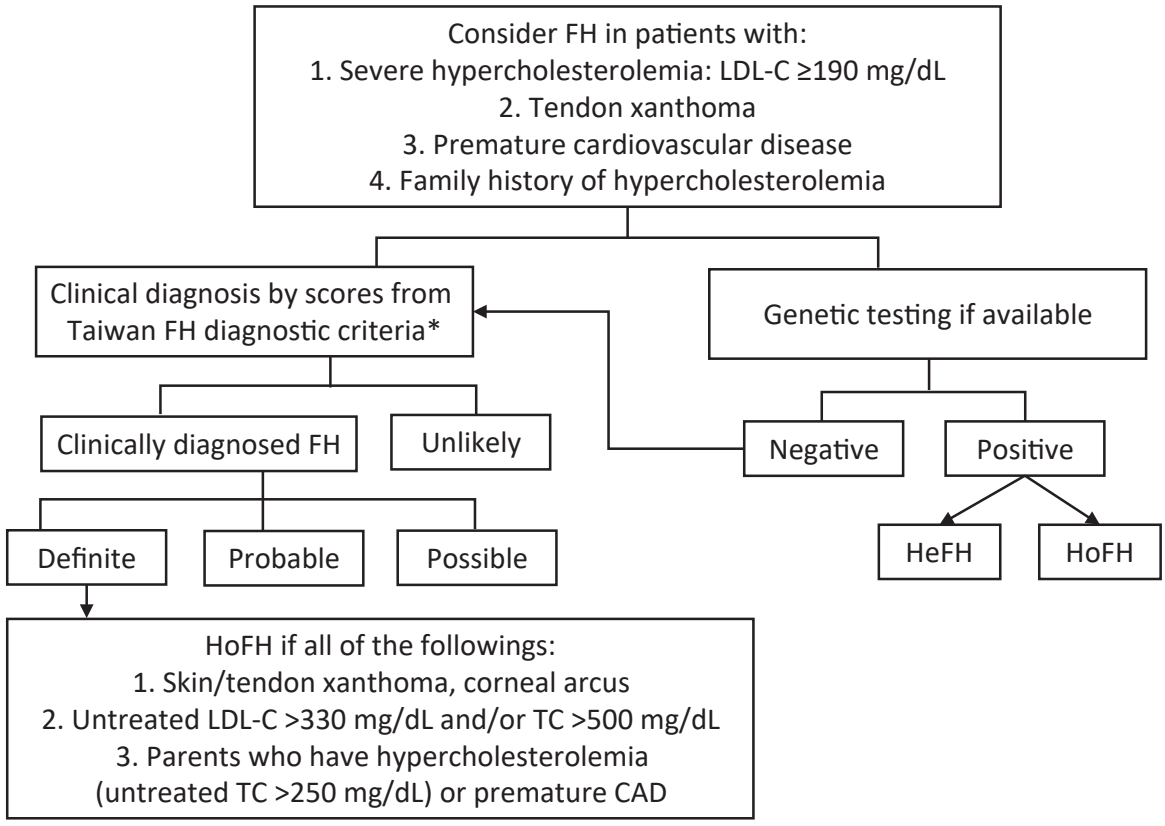

Figure 1. Simplified and modified algorithm for diagnosis of HoFH from 2017 Taiwan lipid guidelines for high-risk patients. * Please refer to 2017 Taiwan lipid guidelines for high-risk patients for details of scores in Taiwan FH diagnostic critieria[7]. CAD: coronary artery disease. FH: familial hypercholesterolemia; HeFH: heterozygous familial hypercholesterolemia; HoFH: homozygous familial hypercholesterolemia; LDL-C: low density lipoprotein cholesterol; TC: total cholesterol.

improves prognosis although there is no randomized trial[1]. Limitations include high-cost, time-consuming, unavailability in some regions, and the need of vascular access[8].

PCSK9 inhibitor for HoFH

Two PCSK9 inhibitors are available in Taiwan: evolocumab and alirocumab.

Evolocumab demonstrated its efficacy and safety in treating HoFH in the clinical trial, TESLA Part B[13]. In this study, 50 patients aged ≥12 years with HoFH were randomized in a 2:1 ratio to evolocumab 420 mg or placebo every 4 weeks. At week 12, the rate of change in LDL-C level from the baseline was −23.1% for the evolocumab group and 7.9% for placebo group. The treatment difference was −30.9%. In our series, patient 1 received evolocumab 420 mg every month, and his LDL-C reduction rate was 51.6%, better than the average of the evolocumab group in TESLA Part B. Although the average LDL-C reduction was 23.1% in TESLA Part B, supplemental data showed that about one-third in the evolocumab group had LDL-C reduction between 40% and 60%, similar to patient 1. The response of patient 1 to evolocumab appeared not rare.

For alirocumab, the ODYSSEY HoFH trial enrolled 69 patients with HoFH and randomized in a 2:1 ratio into alirocumab 150 mg or placebo every 2 weeks for 12 weeks in double-blind period[14]. Then, all subjects received alirocumab 150 mg every 2 weeks for another 12 weeks in open-labeled period. At week 12, alirocumab reduced LDL-C for 26.9%, while LDL-C increased for 8.6% in placebo group,

leading to a 35.6% LDL-C reduction difference. In our case series, patients 2 and 5 received alirocumab; and their LDL-C reduction were 47.3% and 42.4%, respectively; both better than the average LDL-C reduction of the alirocumab group in ODYSSEY HoFH. Looking into the details of ODYSSEY HoFH, analysis of percentage change in LDL-C according to genotyping showed that alirocumab performed better in compound heterozygous, compared with true homozygous. LDL-C reduction in patients 2 and 5, both compound heterozygous, were similar to those with compound heterozygous in ODYSSEY HoFH, although dose in patients 2 and 5 were lower.

Another possible reason for a good response to PCSK9 inhibitors in our case series might be ethnic difference. This issue had been demonstrated well in statin. For trials of PCSK9 inhibitors dedicated to HoFH, few Asians were included. No Asian participated in the TESLA Part B trial while Taiwan and Japan joined in the ODYSSEY HoFH trial[15]. The ODYSSEY KT trial, which was performed in South Korea and Taiwan, showed that alirocumab reduced the level of LDL-C for 57.1% at week 24 for patients with high cardiovascular risk. In this trial, alirocumab was given at 75 mg every 2 weeks, with dose titration to 150 mg every 2 weeks only if LDL-C was ≥70 mg/dL at week 8. The dose of alirocumab used in the ODYSSEY KT trial was similar to patients 2 and 5, with a better effect on LDL-C lowering. This was as expected since PCSK9 inhibitors worked better in usual hypercholesterolemia compared with HoFH.

Both evolocumab and alirocumab were well tolerated with no treatment-emergent adverse event leading to discontinuation. A comparison of the two randomized trials of PCSK9 inhibitors dedicated for

Table 3. Comparison of trials for PCSK9 inhibitors on HoFH

	TESLA Part B[13]		ODYSSEY HoFH[14]	
Year published	2015		2020	
PCSK9 inhibitor	Evolocumab		Alirocumab	
Trial design	Double-blind placebo control		Double-blind placebo control	
Age of subjects	≥ 12 years		≥ 18 years	
Primary outcome	LDL reduction		LDL reduction	
Case number	Evolocumab 33	Placebo 16	Alirocumab 45	Placebo 24
CAD	46%	38%	46.7%	37.5%
High-intensity statin*	93.9%	93.8%	84.4%	87.5%
Ezetimibe	91%	94%	68.9%	79.2%
LDL apheresis	Excluded	Excluded	13.3%	16.7%
Baseline LDL (mg/dL)	355.8	336.4	295.0	259.6
Change in LDL after 12 weeks	-23.1%	+7.9%	-26.9%	+8.6%
Treatment difference	-30.9%		-35.6%	
95% CI	-43.9% to -18.0%		-51.2% to -19.9%	
p-value	<0.0001		<0.0001	
AE leading to discontinuation	0%	0%	0%	0%

*High-intensity statin: atorvastatin ≥40mg, or rosuvastatin ≥20mg.
AE: adverse event; CAD: coronary artery disease; CI: confidence interval; HoFH: homozygous familial hypercholesterolemia; LDL: low density lipoprotein (mg/dL); PCSK9: Proprotein convertase subtilisin/kexin type 9.

HoFH is summarized in Table 3.

Despite its efficacy in LDL-C reduction, PCSK9 inhibitor is under-used because of its high cost and reimbursement issue[16]. Taiwan NHI approved the reimbursement of PCSK9 inhibitor for HoFH since 2018. From 2020, PCSK9 inhibitors are also reimbursed by Taiwan NHI for patients with recent ASCVD events (within 1 year) who receive high-intensity statins plus ezetimibe, but LDL-C level is still higher than 135 mg/dL. However, given the lack of awareness of the importance of controlling high LDL-C level to prevent premature ASCVD in HoFH, some patients did not or refuse to receive PCSK9 inhibitor treatment[17,18]. Therapeutic inertia is also common in the physicians taking care of patients with high-risk status and failed to intensify treatment with PCSK9 inhibitors[19]. Awareness should be raised not only in the general public but also in the medical community to emphasize the importance of LDL-C control and the availability of PCSK9 inhibitor for HoFH. Treatment for HoFH to prevent premature ASCVD should be initiated early and continue over the life course because LDL-C reduction could avoid the risk of ASCVD and lead into favorable clinical outcomes[20]. PCSK9 inhibitors are undoubtedly the drug of choice in HoFH on top of statin and ezetimibe before more robust evidence of other agents presents.

Conclusion

From our experience and studies worldwide, underdiagnoses and undertreatment are common issues of HoFH. Many patients present too late and present with severe CAD. Prevention is better than treatment, so the aim is to identify these patients and start treatment immediately. After diagnosis, make sure these patients are adequately treated. Currently, the choice of combination treatment is statin, ezetimibe, and PCSK9 inhibitor. Continuing education to enhance awareness and knowledge of HoFH is important.

References

1. European atherosclerosis society consensus panel on familial hypercholesterolaemia. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the consensus panel on familial hypercholesterolaemia of the european atherosclerosis society. Eur Heart J 2014; 35: 2146-57.
2. Vallejo-Vaz AJ, Ray KK. Epidemiology of familial hypercholesterolaemia: community and clinical. Atherosclerosis 2018 ;277: 289-97.
3. Vallejo-Vaza AJ, Marcoa MD, Stevensa CAT, et al. Overview of the current status of familial hypercholesterolaemia care in over 60 countries - The EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). Atherosclerosis 2018; 277: 234-55.
4. Alonso R, Diaz-Diaz JL, Arrieta F, et al. Clinical and molecular characteristics of homozygous familial hypercholesterolemia patients: Insights from SAFEHEART registry. J Clin Lipidol 2016; 10: 953-61.
5. Sturm AC, Knowles JW, Gidding SS, et al. Clinical genetic testing for familial hypercholesterolemia JACC Scientific Expert Panel. J Am Coll Cardiol 2018; 72: 662-80.
6. Soutar AK, Naoumova RP. Mechanisms of disease: genetic causes of familial hypercholesterolemia. Nat Clin Pract Cardiovasc Med 2007; 4: 214-25.
7. Huang CC, Niu DM, Charng MJ. Genetic analysis in a Taiwanese cohort of 750 index patients with clinically diagnosed familial hypercholesterolemia. J Atheroscler Thromb 2021; 28: 000-000. doi: 10.5551/jat.62773. Online ahead of print.
8. Li YH, Ueng KC, Jeng JS, et al. 2017 Taiwan lipid guidelines for high risk patients. J Formos Med Assoc 2017; 116: 217-48.
9. Kolansky DM, Cuchel M, Clark BJ, et al. Longitudinal evaluation and assessment of cardiovascular disease in patients with homozygous familial hypercholesterolemia. Am J Cardiol 2008; 102: 1438-43.
10. Raal FJ, Pilcher GJ, Panz VR, et al. Reduction in mortality in subjects with homozygous familial hypercholesterolemia associated with advances in lipid-lowering therapy. Circulation 2011; 124: 2202-07.
11. Marias AD, Raal FJ, Stein EA, et al. A dose-titration and comparative study of rosuvastatin and atorvastatin in patients with homozygous familial hypercholesterolaemia. Atherosclerosis. 2008; 197: 400-6.
12. Gagne C, Gaudet D, Bruckert E. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. Circulation 2002; 105: 2469-75.
13. Raal FJ, Honarpour N, Blom DJ, et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. Lancet 2015; 385: 341-50.
14. Blom DJ, Harada-Shiba M, Rubba P, et al. Efficacy and safety of alirocumab in adults with homozygous familial hy-

percholesterolemia: the ODYSSEY HoFH trial. J Am Coll Cardiol 2020; 76: 131-42.
15. Koh KK, Nam CW, Chao TH, et al. A randomized trial evaluating the efficacy and safety of alirocumab in South Korea and Taiwan (ODYSSEY KT). J Clin Lipidol 2018; 12: 162-72.
16. Cohen JD, Cziraky MJ, Jacobson TA, Maki KC, Karalis DG. Barriers to PCSK9 inhibitor prescriptions for patients with high cardiovascular risk: results of a healthcare provider survey conducted by the National Lipid Association. J Clin Lipidol. 2017; 11: 891-900.
17. Marusic T, Sustar U, Sadiq F, et al. Genetic and clinical characteristics of patients with homozygous and compound heterozygous familial hypercholesterolemia from three different populations: case series. Front Genet 2020; 11: 572176.
18. Taranto MDD, Giacobbe C, Buonaiuto A, et al. A real-world experience of clinical, biochemical and genetic assessment of patients with homozygous familial hypercholesterolemia. J Clin Med 2020; 9: 219.
19. Reda A, Almahmeed W, Dobrecky-Mery I, et al. A narrative review and expert panel recommendations on dyslipidaemia management after acute coronary syndrome in countries outside western Europe and north America. Adv Ther 2020; 37: 1754-77.
20. Bruckert E, Kalmykova O, Bittar R, et al. Long-term outcome in 53 patients with homozygous familial hypercholesterolaemia in a single centre in France. Atherosclerosis. 2017; 257: 130-7.

同合子家族性高膽固醇血症治療困境與進展：佐以單一中心個案經驗與PCSK9抑制劑回顧

林佳淩[1,2] 李柏增[2] 陳沛吟[3] 鄭凱比[3] 劉嚴文[2]
劉秉彥[2,4] 趙庭興[2] 李貽恆[2]

[1]國立成功大學醫學院附設醫院斗六分院內科部心臟血管科
國立成功大學醫學院附設醫院內科部 [2]心臟血管科 [3]內分泌與新陳代謝科
[4]國立成功大學臨床醫學研究所

摘 要

家族性高膽固醇血症是造成高濃度低密度膽固醇之基因遺傳疾病，患者常因此產生早發性冠狀動脈疾病。此篇迷你綜論著重討論家族性高膽固醇血症中最為嚴重之次分型：即基因型同合子變異、複合異合子變異、與雙重異合子變異，臨床表型統稱同合子家族性高膽固醇血症。以下包含兩部分：第一部分簡述來自單一醫學中心之系列病例、第二部分探討現今治療準則與困境並回顧新型降血脂藥物PCSK9抑制劑針對同合子家族性高膽固醇血症之臨床試驗。總結來說，及早治療家族性高膽固醇血症，並給予足夠降血脂藥物來達到治療目標，以預防冠狀動脈疾病生成，仍需藉由多方教育來達成。