Switching from lipoprotein apheresis to evolocumab in FH siblings on hemodialysis: case reports and discussion

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Abstract

Familial hypercholesterolemia (FH) and chronic kidney disease, especially end-stage renal disease (ESRD), are common and put patients at a high risk of developing atherosclerotic cardiovascular disease (ASCVD). ESRD concomitant with FH may further increase the risk of ASCVD. Achieving target levels of low-density lipoprotein cholesterol (LDL-C) is difficult owing to the limitations of statin administration due to its side effects in ESRD. Therefore, some FH patients with ESRD require lipoprotein apheresis for the prevention of secondary ASCVD events. Although proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors may offer a safe and effective option for lowering lipid levels in such patients, no guidelines are available for their use. Here, we report the case of two male siblings with FH in secondary prevention undergoing hemodialysis combined with PCSK9 inhibitor treatment. The siblings, who showed a heterozygous c.1846-1G>A mutation in the *LDLR* gene, underwent hemodialysis. In combination with the lipoprotein apheresis, siblings were administered evolocumab, a PCSK9 inhibitor. Both the siblings had coronary artery disease, diabetes, and ESRD, and received hemodialysis. Their LDL-C levels did not reach the target values despite administering statin, ezetimibe, and biweekly lipoprotein apheresis. On the introduction of evolocumab treatment, their LDL-C levels were significantly reduced without any adverse effects, resulting in successful withdrawal from lipoprotein apheresis therapy. Although the effects of switching from lipoprotein apheresis to PCSK9 inhibitors for cardiovascular protection remain unclear in FH patients with and without ESRD, our case report will be helpful in guiding future therapeutic decisions.

Keywords Proprotein convertase subtilisin kexin 9 · Evolocumab · Heterozygous familial hypercholesterolemia · Hemodialysis

Introduction

Familial hypercholesterolemia (FH) is the most frequent hereditary metabolic disorder, with an estimated prevalence of 1 heterozygote per 200–300 individuals [1]. FH is caused by mutations in the *LDLR*, *APOB*, and *PCSK9* genes that decrease the clearance of low-density lipoprotein (LDL), leading to an elevated plasma LDL-C concentration, and an increased risk of premature atherosclerotic cardiovascular disease (ASCVD). Patients with a confirmed *LDLR* or *APOB* mutation possess risk estimate ORs of 1.99 (95% CI 1.22 to 3.26) for CKD compared with those without FH [2].

Patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) are also at high risk of ASCVD. It was reported that age-adjusted ASCVD mortality was 1.5% in the general population vs 41.58% in a dialysis population in

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Japan and in US [3]. Unfortunately, statins have shown no benefit on ASCVD outcomes in several previous trials [4].

A recent study revealed that individuals with FH showed increased risk of CKD, and a low estimated glomerular filtration rate (eGFR) was associated with high risk of myocardial infarction in patients with FH. ESRD concomitant with FH may further increase the risk of ASCVD. Additionally, to make the case worse, LDL-C target achievement is difficult due to the limitation in high dose statin use. Therefore, some FH patients in secondary prevention with ESRD require lipoprotein apheresis. Although proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors may offer a safe and effective option for lipid lowering in such patients, standard guidelines for their use are not available.

Here, we report two siblings with FH in secondary prevention undergoing hemodialysis combined with lipoprotein apheresis. Both patients were able to discontinue lipoprotein apheresis using evolocumab, a PCSK9 inhibitor, and achieved the target LDL-C levels.

Case report

The clinical features of our cases are based on retrospective data retrieved from medical files. Genetic testing for *LDLR* and *PCSK9* genes was carried out as previously reported [5].

Patient 1

The patient was a 61-year-old man. He was diagnosed with FH at the age of 38 based on having high LDL-C levels (210 mg/dL), thickened Achilles tendon (25 mm), and a family history of early-onset of coronary artery disease (Fig. 1a) when he underwent coronary stenting due to angina pectoris. Xanthelasma palpebrarum was also pointed out. He also had diabetes mellitus, hypertension, abdominal aortic aneurysm, and progressive renal failure (Fig. 1a, b). Although the patient had not undergone renal biopsy, the cause of renal failure was supposedly nephrosclerosis due to hypertension and diabetic nephropathy given the history of hypertension and diabetes. He began hemodialysis combined with biweekly lipoprotein apheresis at the age of 50.

Despite the administration of rosuvastatin calcium (7.5 mg/day), ezetimibe (10 mg/day), and eicosapentaenoic acid (900 mg/day), his pre-apheresis plasma LDL-C level was 140 mg/dL (Table 1). Genetic testing for FH revealed a heterozygous c.1846-1G>A mutation in the *LDLR* gene, which affects splicing and generates a truncated LDLR (Fig. 2a). Based on these findings, biweekly subcutaneous injection of 140 mg evolocumab was initiated, and then changed to monthly subcutaneous injection of 420 mg

evolocumab. Serum creatinine level at the initiation of evolocumab treatment was 12.8 mg/dL before dialysis.

Serum LDL-C decreased rapidly from 140 to 34 mg/dL 1 month after first injection and was controlled under 50 mg/dL without any adverse effects.

The CAG history of the patient was unclear. Coronary CT performed in February 2021 revealed RCA segmental calcification (Agatston score, 2634.23), but there was no LCA calcification. Skin perfusion pressure (SPP) in the foot dorsal area was assessed, and the findings were as follows: SPP (evolocumab start), rt 76-lt 144 mmHg; SPP (2 years), rt 72-lt 84 mmHg; and SPP (4 years), rt 78-lt 69 mmHg. Lipoprotein apheresis was discontinued and 3.5 years after administration of evolocumab, there have been no evidence of progression or new onset of ASCVD.

Patient 2

The second patient was a 65-year-old man, the elder brother of patient 1. He was diagnosed with FH at the age of 38 when he underwent coronary intervention due to acute myocardial infarction. He had tendon xanthomas at the metacarpophalangeal (MP) joints, elbows, knees, and Achilles tendons. After diagnosis with FH (Fig. 1a, c), monthly lipoprotein apheresis was initiated. Consistent with his younger brother, genetic testing for FH revealed a splicing error caused by a heterozygous c.1846-1G>A in the *LDLR* gene (Fig. 2b). He also had diabetes and had been treated with insulin. As his renal function gradually deteriorated due to diabetic nephropathy, hemodialysis was initiated when he was 62 years old.

Despite the administration of rosuvastatin calcium (5 mg/day) and ezetimibe (10 mg/day), his pre-apheresis plasma LDL-C level was 111 mg/dL (Table 1). Based on these findings, biweekly subcutaneous injection of 140 mg evolocumab was initiated, and then changed to monthly subcutaneous injection of 420 mg evolocumab. Serum creatinine level at the initiation of evolocumab treatment was 7.08 mg/dL before dialysis.

Serum LDL-C was rapidly decreased and stably maintained under 50 mg/dL by evolocumab. CAG was performed in 1993: PCI 1993 LAD#6 RCA#4 POBA 2010 RCA #1 Endeavor SAPT. Coronary CT performed after 3.5 years of LDL-A therapy revealed LCA calcification (Agatston score, 3347.12), but there was no RCA calcification. SPP was assessed and the findings were as follows: SPP (evolocumab start), rt 71-lt 63 mmHg; SPP (1.5 years), rt 61-lt 49 mmHg; and SPP (2.5 years), rt 80-lt 93 mmHg. Lipoprotein apheresis was discontinued and 2 years after administration of evolocumab, there have been no evidence of progression nor new onset of ASCVD.

Fig. 1 Heterozygous c.1846-1G>A mutation in the *LDLR* gene, pedigree, and Achilles tendon thickness. **a** A pedigree of siblings with familial hypercholesterolemia with a heterozygous c.1846-1G>A mutation in the *LDLR* gene. The mother was free from CVD events and died at 89 years old. The father died at 54 years old by cerebral infarction and was diagnosed with myocardial infarction at age 52 years. The aunt (father's sister) had hyperlipidemia and was

treated with dialysis. Their female cousins had hyperlipidemia with medication. A brother was free from dyslipidemia and CVD events but had obesity. The arrow indicates present cases. *MI* myocardial infarction, *AP* angina pectoris, *HL* hyperlipidemia, *CI* cerebral infarction, *HD* hemodialysis, *LDL-A* low-density lipoprotein cholesterol apheresis; **b** Achilles tendon thickness with calcification (patient 1); **c** Achilles's tendon thickness with calcification (patient 2)

Discussion

In this article, we present two siblings with FH in secondary prevention undergoing hemodialysis who discontinued regular lipoprotein apheresis using evolocumab with no newly diagnosed ASCVD events for 3 years. The siblings had FH with a heterozygous *LDLR* mutation, resulting in poor response to statins. Additionally, in Japan, statins could only be prescribed from 1/3 to 1/4 of the maximum dose to patients with ESRD on dialysis due to an increased risk of adverse events. Therefore, in our cases, it was difficult to achieve the target LDL-C levels (less than 70 mg/dL) set by the Japanese Guidelines for Diagnosis

and Treatment of Familial Hypercholesterolemia 2017 and therefore, evolocumab was initiated.

In a prespecified analysis of the FOURIER randomized controlled trial [6], evolocumab significantly reduced the cardiovascular risk with and without diabetes at baseline. Evolocumab did not increase the risk of new-onset diabetes, nor did it worsen the glycemia. Both of our cases had diabetes at the time of evolocumab initiation, and their condition of diabetes did not worsen during the course.

Our patients continued statin plus ezetimibe treatment after transition to chronic dialysis. The 2013 Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline for lipid management [7] as well as the 2019 European Society of Cardiology (ESC)/European

Table 1 Laboratory data for PCSK9 inhibitor administration and after 3.5 years

	Case 1	Case 1 (3.5y)	Case 2	Case 2 (3.5y)	Units
UN	62	65	52	67	mg/dL
Cre	12.78	10.84	7.08	10.11	mg/dL
eGFR	4	4	7	7.6	mL/min/1.73m ²
UA	8.2	4.9	6.9	7.6	mg/dL
Na	144	144	140	139	mEq/L
K	5.4	4.5	3.6	5.2	mEq/L
Cl			102	102	mEq/L
Ca	8.1	8.1	8.3	7.6	mg/dL
IP	7.2	4.2	4	6.5	mg/dL
TP	6.6	6.4	6.4	6.7	g/dL
Alb	3.7	3.2	3.4	3.1	g/dL
CPK	149				IU/L
AST(GOT)	18	13	9	7	IU/L
ALT(GPT)	13	13	9	8	IU/L
LDH	267	177	143	144	IU/L
γGTP(IU)	24	27	18	14	IU/L
Glu	94	142	330	208	mg/dL
GA	11.9	12	19.9	17.4	%
T-cho	229	136	175	75	mg/dL
TG	109	73	151	78	mg/dL
LDL-C	140	50	111	21	mg/dL
HDL-C	63	64	31	38	mg/dL
PCSK 9	535		291		ng/mL

Atherosclerosis Society (EAS) Guidelines for the management of dyslipidemia state that statins or statin plus ezetimibe should not be initiated for CKD patients with chronic dialysis, and also suggest that statins or statin plus ezetimibe should be continued at the time of dialysis initiation if it is already being taking prior to initiation of dialysis. A recent retrospective large cohort study of US veterans demonstrated that the continuation of statin therapy after transition to dialysis was associated with reduced all-cause mortality and cardiovascular mortality [8].

Our patients had received chronic hemodialysis, and then initiated evolocumab therapy. Recently, the safety and tolerability of evolocumab in patients on hemodialysis were studied in a single-center, open-label, single-dose study in the United States. In the study, mean systemic evolocumab exposure was lower in patients with severe renal impairment and ESRD receiving hemodialysis than in patients with normal renal function after a single 140 mg dose of evolocumab. The authors also reported that evolocumab effectively lowered LDL-C levels in patients on dialysis, and the safety results of evolocumab in patients with ESRD receiving hemodialysis were similar to those in patients with normal renal function. Actually, the serum LDL-C of our patients was decreased rapidly by evolocumab and maintained stably without adverse events.

Greater cardiovascular protection with evolocumab has been reported in a retrospective analysis of the FOURIER study among stage 3 CKD patients [9]. However, there have been no reports investigating the effect of PCSK9 inhibitors on cardiovascular protection in patients receiving hemodialysis.

The effect of LDL lowering therapy in ESRD during long-term dialysis therapy is unclear. This is because atherosclerosis in ESRD is not necessarily caused by high LDL-C levels. In this regard, it is not clear whether therapeutic intervention for hyperlipidemia in ESRD is necessary. Nevertheless, if FH is complicated in ESRD, LDL-C lowering therapy should be administered, but there is no guideline for this issue. Many clinicians will face the issue of managing LDL-C in ESRD + FH patients in the future due to high rate of FH diagnosis. Therefore, it is important to report cases of this nature.

Our patients discontinued lipoprotein apheresis because their LDL-C levels reached recommended treatment targets using evolocumab. In the ODYSSEY ESCAPE trial, a double-blind study of the effect of alirocumab (150 mg) in 62 heterozygous FH patients undergoing regular biweekly lipoprotein apheresis, 63.4% of the patients on alirocumab avoided all and 92.7% avoided at least half of the apheresis treatments. Another trial from Japan reported that 11

Fig. 2 Course of laboratory data after administration of evolucumab. LDL-C (mg/dL) and serum PCSK9 (ng/mL). Hemodialysis was performed 3 times per week. Before the administration of evolucumab, LDL-A had been performed once a month; evolucumab was started at 280 mg /month and then 420 mg/month. After starting evolucumab, serum PCSK9 was upregulated and coronary CT was performed 3.5 years after administration of evolucumab

heterozygous FH patients undergoing lipoprotein apheresis could switch to subcutaneous injection of evolucumab safely. However, it has been reported that lipoprotein apheresis improves coronary outcomes, progression of ASCVD [10]. ASCVD in ESRD cannot be prevented by statins, and it is unclear whether ASCVD can alternatively be prevented with LDL lowering therapy; however, if FH is complicated with ESRD, LDL-C lowering therapy should be administered. Further studies are needed to assess the cardiovascular outcome of patients who switched from lipoprotein apheresis to PCSK9 inhibitors.

In terms of cost, the total cost for LDL-A 15 times/year is 2,414,700 yen and that for evolucumab 12 times/year is 645,240 yen. The difference is 16,086 USD (1 USD = 110 yen). Thus, the cost of LDL-A is higher than that of the PCSK9 inhibitor. Further, administration of the PCSK9 inhibitor is both less time-consuming and energy-demanding. Taken together, the PCSK9 inhibitor is superior in terms

of social and economic benefits. Before the PCSK9 inhibitor, the LDL-C level was over 100–150 mg/dL, but the PCSK9 inhibitor, which is cost-effective, reduced it to 70 mg/dL.

To conclude, we encountered two siblings with FH in secondary prevention undergoing hemodialysis combined with lipoprotein apheresis. Both patients were able to discontinue lipoprotein apheresis using evolucumab and achieved the target LDL-C levels. CKD is increasing all over the world, and we will encounter more FH patients with ESRD as the diagnostic rate of FH increases. As there are no guidelines for aggressive lipid-lowering treatment by PCSK9 inhibitors in heterozygous FH patients on hemodialysis, we believe that increasing numbers of documented cases, such as the ones we present here, will be helpful to guide future therapeutic decisions.

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Declarations

Competing interests The authors declare that they have no competing interests.

Ethical approval This case report was approved by the Ethical Committee of the Yokohama Daiichi Hospital (IRB approval number 2016–02) and that of National Cerebral and Cardiovascular Center (M17-56) and was conducted in compliance with the ethical guidelines of the 1975 Declaration of Helsinki.

Informed consent Informed consent was obtained from all individual participants included in the study. Written informed consents were obtained from the patients for publication of this case report and any accompanying images.

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