



Case Report

Use of Alirocumab for the Secondary Prevention of Cardiovascular Disease in a Patient with End-stage Renal Disease on hemodialysis

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ABSTRACT

Introduction: Cardiovascular diseases (CVDs) are quite prevalent globally, with atherosclerotic being a predominant CVD in Asia. Well-controlled low-density lipoprotein cholesterol (LDL-C) level is crucial in both primary and secondary prevention of these conditions, particularly in patients with chronic kidney disease (CKD). Lipid management in this setting is a major concern for physicians and patients. Here, we report the case of a man with previous hypertension, type 2 diabetes mellitus, dyslipidemia, peripheral artery disease, CKD, heart failure, and coronary artery disease post multiple stent implantations. He was initiated on rosuvastatin treatment, during which he developed rhabdomyolysis, and subsequently received regular hemodialysis. Since the patient was at a very high risk of cardiovascular events and adverse drug reactions, treatment with alirocumab (a proprotein convertase subtilisin / kexin type 9 inhibitor) was initiated for further controlling LDL-C level. Although there is a lack of evidence on the use of alirocumab in patients on hemodialysis, the drug demonstrated a favorable efficacy and safety profile in our patient.

INTRODUCTION

Cardiovascular diseases (CVDs) are common in the general population worldwide. Of these, atherosclerotic CVDs (ASCVDs) are predominant in Asia [1]. Ensuring adequate control of low-density lipoprotein cholesterol (LDL-C) is one of the most important strategies in both primary and secondary prevention of these conditions. It is estimated that long-term LDL-C reduction (over 40 years) might even be associated with a reduction in cardiovascular mortality by 50% – 55% [2]. Traditionally, statins have been the main treatment for hypercholesterolemia and the cornerstone of ASCVD prevention. However, certain factors, such as intolerance or drug–drug interactions, might restrict their use [3]. Furthermore, in adults on dialysis, Kidney Disease : Improving Global Outcomes guideline recommends avoiding initiation of statins or statin/ezetimibe combinations. However, there is no recommendation to stop therapy in dialysis patients who are already receiving statins or statin/ezetimibe combinations [4].

Recently, a new drug class of proprotein convertase subtilisin / kexin type 9 (PCSK9) inhibitors has been increasingly used, and these agents can decrease LDL-C in a dose-dependent manner by as much as 70% and by as much as 60% in statin-treated patients [5]. Currently, two PCSK9 inhibitors (i.e., alirocumab and evolocumab) are commercially available. These are fully humanized monoclonal antibodies indicated for secondary prevention of cardiovascular events. Nevertheless, evidence on the use of these agents in patients with end-stage renal disease (ESRD, defined as estimated glomerular filtration rate [eGFR] of < 15 mL / min / 1.73 m²) or those requiring hemodialysis (HD) is limited. In addition, relevant dosage recommendation has not been provided in manufacturer's labeling or international guidelines, as this aspect has not yet been studied. Here, we report the case of a man with dyslipidemia, multiple comorbidities, and chronic kidney disease (CKD) on regular HD treated with alirocumab.

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CASE PRESENTATION

A 60-year-old man with a history of hypertension, type 2 diabetes mellitus, dyslipidemia, peripheral artery disease, chronic kidney disease, heart failure, and coronary artery disease after multiple stent implantations presented with lower limb edema and chronic diabetic wound ulcer. As the patient was at a very high risk of future cardiovascular events, secondary prevention with high-intensity statin therapy was indicated. He was prescribed rosuvastatin 20 mg / day with an eGFR of 102 mL / min / 1.73 m² (calculated by CKD Epidemiology Collaboration equation). However, his renal function declined gradually throughout the treatment course, and he unexpectedly developed rhabdomyolysis after 9-year use of rosuvastatin and started undergoing HD. As a result, we discontinued the statin; however, total cholesterol and LDL-C levels were still 7.1 and 5.2 mmol/L, respectively. Under such circumstances observed in our patient, PCSK9 inhibitors might efficiently control LDL-C level, although there is a lack of evidence on the use of this agent in patients with stage 5 CKD on HD. As a result, we initiated alirocumab at a dose of 75 mg every 4 weeks. After 3 months of treatment, the patient's LDL-C level was 3.29 mmol / L. However, as the LDL-C target (<1.4 mmol / L, European Society of Cardiology guideline) was not achieved, we up-titrated the dosing interval of alirocumab to 75 mg every 2 weeks. Three months later, LDL-C level decreased to 2.5 mmol / L but eventually increased to 3.29 mmol / L. Incidentally, the triglyceride level had significantly decreased. Thus, we decided to maintain the current dose of alirocumab, and the patient denied any adverse drug reactions. In the most recent follow-up, patient's ischemic heart disease has been stable. Moreover, coronary angiography revealed patent stents without significant stenosis. The dynamic variation in the lipid profile before and after alirocumab treatment is summarized in Table I below.

Table I. Lipid profile before and after treatment with alirocumab

Parameters	Before Treatment	After Treatment				
		150 mg every 4 weeks			150 mg every 2 weeks	
		Jul 2020	Aug 2020	Sept 2020	Jan 2021	Feb 2021
SCr (μmol/L)	529	626	517	413	555	459
TotChol (mmol/L)	7.1	5.2	4.2	5.2	4.3	5.2
LDL-C (mmol/L)	5.17	3.07	2.45	3.29	2.5	3.29
HDL-C (mmol/L)	1.08	1.07	0.72	1.36	1.23	1.46
TG (mmol/L)	1.87	2.33	2.27	1.2	1.25	1.0

SCr-Serum creatinine; TotChol-Total cholesterol; LDL-C-Low-density lipoprotein cholesterol; HDL-C-High-density lipoprotein cholesterol; TG -triglyceride

DISCUSSION

As PCSK9 monoclonal antibodies are composed of proteins and carbohydrates, elimination is expected to occur via saturable binding to PCSK9 enzyme and nonsaturable proteolysis of small peptides and amino acids. In addition, monoclonal antibodies are not eliminated by the kidneys but by the reticuloendothelial system; therefore, a significant alteration in exposure in patients with renal impairment is not expected [6]. However, alirocumab is unlikely to be filtrated via hemodialysis owing to the small pore size of the hemodialysis filter. Moreover, relevant available data on patients with severe renal impairment are limited; in these patients, the exposure to alirocumab was approximately 2-fold higher compared with that in subjects with normal renal function [7]. Hence, we set the initial dosing frequency of alirocumab to 75 mg every 4 weeks, which was up-titrated as needed.

Suboptimal responders to PCSK9 inhibitors are defined as individuals with < 50% – 60% LDL-C reduction after treatment. As described in our case, after increasing the initial dosing frequency to 75 mg every 2 weeks, LDL-C level reduced to 36% – 52% from that at the baseline. Impaired renal function may be responsible for the suboptimal response to PCSK9 inhibitors in patients with ESRD. Moreover, without use of statins cannot increase the PCSK9 levels and may correlate with the suboptimal clinical response [8].

In the present case, a significant decrease was noted in triglyceride level. PCSK9 may play a role in the metabolism of triglyceride-rich lipoproteins in patients on hemodialysis [9]. However, further studies are warranted to confirm this finding.

CONCLUSION

Lipid management is a key component of the secondary prevention of CVDs. Although data on the use of PCSK9 inhibitors in patients with dialysis are lacking, our case report revealed that alirocumab is safe and effective in these patients. However, further investigations (e.g. clinical trials) are required to validate this finding.

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CONFLICT OF INTEREST

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