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HEART FAILURE AND CARDIOMYOPATHIES

CASE REPORT: CLINICAL CASE

Use of Evolocumab in Familial Hyperlipidemia With Isolated Heart Transplant

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ABSTRACT

We describe a novel use of evolocumab for successful postoperative lipid control in a patient with familial hyperlipidemia who underwent isolated heart transplantation. We believe that this case carries valuable lessons regarding post-transplant proprotein convertase subtilisin kexin 9 inhibitor use with implications for the future of combined organ allocation and transplantation waitlist times. (JACC Case Rep 2024;29:102426) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Among candidates for heart transplantation (HT), familial hyperlipidemia (FH) has been suggested as a contraindication to single-organ HT.[1,2] While there are no consensus guidelines, there is precedent for pursuing simultaneous heart-liver transplantation (SHLT) in patients with FH. This precedent was established to address the underlying cause of severe lipid derangements driving ischemic cardiomyopathy, and the improvements seen in cholesterol levels after liver transplantation in patients with FH have served to reinforce the practice.[2-4]

However, novel lipid-lowering agents have shown efficacy in treating statin-resistant hyperlipidemia and are safe in patients post-HT.[5] We describe a successful case of isolated HT in a patient with FH who experienced normalization and control of his lipid profile postoperatively with the use of evolocumab, a proprotein convertase subtilisin kexin 9 inhibitor (PCSK9i).

LEARNING OBJECTIVES

- To understand the novel lipid-lowering therapy options for patients with FH and post-transplant patients receiving immunosuppressive medications.
- To consider how precedent regarding indications for SHLT may be affected by novel lipid-lowering therapies.

HISTORY OF PRESENTATION

A 39-year-old man with a past medical history of FH and a previous ST-segment elevation myocardial infarction (STEMI) at age 19 years that was treated with coronary intervention, complicated by ischemic cardiomyopathy, was transferred from an outside hospital to the cardiac intensive care unit of our institution (University of Utah, Salt Lake City, Utah, USA) in cardiogenic shock secondary to recurrent STEMI.

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ABBREVIATIONS AND ACRONYMS

CAV = cardiac allograft vasculopathy

FDA = Food and Drug Administration

FH = familial hyperlipidemia

HT = heart transplantation

LDL = low-density lipoprotein

PCSK9i = proprotein convertase subtilisin kexin 9 inhibitor

SHLT = simultaneous heart-liver transplantation

STEMI = ST-segment elevation myocardial infarction

tMCS = temporary mechanical circulatory support

PAST MEDICAL HISTORY

In the years before presentation, he was found to have a Dutch lipid clinic score of 19, a total cholesterol value of 440 mg/dL, and a low-density lipoprotein (LDL) value of 359 mg/dL despite high-intensity statin therapy. Because of insurance authorization difficulties, he had only intermittently taken a PCSK9i. He presented to our hospital with a total cholesterol value of 374 mg/dL, a triglyceride value of 95 mg/dL, and an LDL value of 322 mg/dL, with historically normal liver function.

DIFFERENTIAL DIAGNOSIS

On presentation, the initial differential diagnosis included acute myocardial infarction complicated by cardiogenic shock, myocarditis, endocarditis, or arrhythmia.

INVESTIGATIONS

At an outside hospital, the patient underwent left-sided heart catheterization demonstrating severe multivessel disease. However, because of hemodynamic instability he underwent venoarterial extracorporeal membrane oxygenation with Impella device (Abiomed) support, and he was transferred to our institution for consideration of advanced therapies. A lipoprotein (a) level was not obtained during the admission.

MANAGEMENT

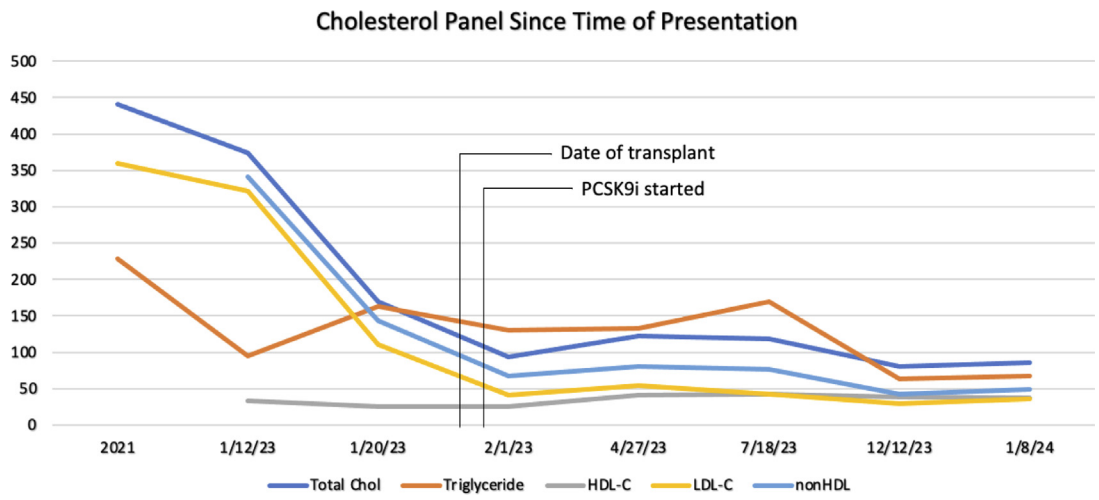
On admission to our institution, the patient's vital signs included an arterial line mean arterial pressure of 78 mm Hg, a heart rate of 65 beats/min, a

TABLE 1 Novel Lipid-Lowering Agents With FDA Approval

Medication or Medication Class	Mechanism of Action	Expected Impact on LDL	Dosing	Post-Transplant Safety	Additional Notes
PCSK9 inhibitors	The PCSK9 protein reduces LDL receptor expression; inhibition of this protein increases LDL receptor expression, which is associated with lower circulating LDL levels	Typical reduction by 60% from baseline[9,10]	Evolocumab: biweekly injection Alirocumab: injection every 4 weeks, can be increased to biweekly depending on LDL response	No interaction with cytochrome P450 avoiding many drug-drug interactions experienced by statins; no large RCTs have been completed on PCSK9i use in transplant patients[10]	Statin therapies increase PCSK9 levels and pose an opportunity for increased therapeutic potential when the 2 medication classes are used simultaneously
Inclisiran	Small interfering RNA that inhibits PCSK9 production, thus decreasing LDL receptor degradation	Approximately 50% reduction from previous baseline on maximally tolerated statin therapy[11]	Injectable formulation, first dose on days 1 and 90, then every 6 months	No large RCTs have been completed on inclisiran use in transplant patients	FDA approved as adjunct to statin therapy
Lomitapide	Inhibits the microsomal triglyceride transfer protein involved in hepatic VLDL synthesis	50% reduction from baseline at 26 weeks and 44% reduction at 56 weeks in single-arm, open-label phase III study[9]	Orally daily	Lack of data in post-transplant patients; potential for significant drug-drug interaction because of metabolism by CY3PA4[12]	FDA approved exclusively for use in familial hyperlipidemia
Mipomersen	Antisense oligonucleotide that selectively binds and degrades ApoB-100 messenger RNA	Randomized double-blind multicenter study found 37% reduction from baseline[13]	Weekly injection	Lack of data in post-transplant patients	FDA approved for use in familial hyperlipidemia
Bempedoic acid	Inhibits the ATP-citrate lyase enzyme responsible for cholesterol synthesis upstream from HMG-CoA reductase	Approximately 25%-30% reduction from baseline as monotherapy, 50% reduction when combined with ezetimibe; 15%-18% reduction in high-risk groups when combined with statins[9,14]	Orally daily	Lack of data in post-transplant patients; no cytochrome P34A interaction	Administered as a prodrug activated in the liver but not muscle cells, thus potentially generating fewer muscle-related symptoms than statins alone
Evinacumab	Monoclonal antibody inhibitor of ANGPTL3, a lipoprotein lipase involved in lipoprotein breakdown and lipid metabolism	47% reduction from baseline in phase III trial consisting of 65 patients with familial hyperlipidemia receiving either evinacumab or placebo[15]	Once monthly IV infusion	No large RCTs have been completed on evinacumab use in transplant patients	FDA approved as lipid-lowering adjunct therapy in familial hyperlipidemia

ApoB = apolipoprotein B; ATP = adenosine triphosphate; FDA = Food and Drug Administration; HMG-CoA = β-Hydroxy β-methylglutaryl-coenzyme A; IV = intravenous; LDL = low-density lipoprotein; PCSK9 = proprotein convertase subtilisin kexin 9; RCT = randomized controlled trial; VLDL = very low-density lipoprotein.

FIGURE 1 Post-Transplantation Lipid Stabilization With PCSK9i Therapy



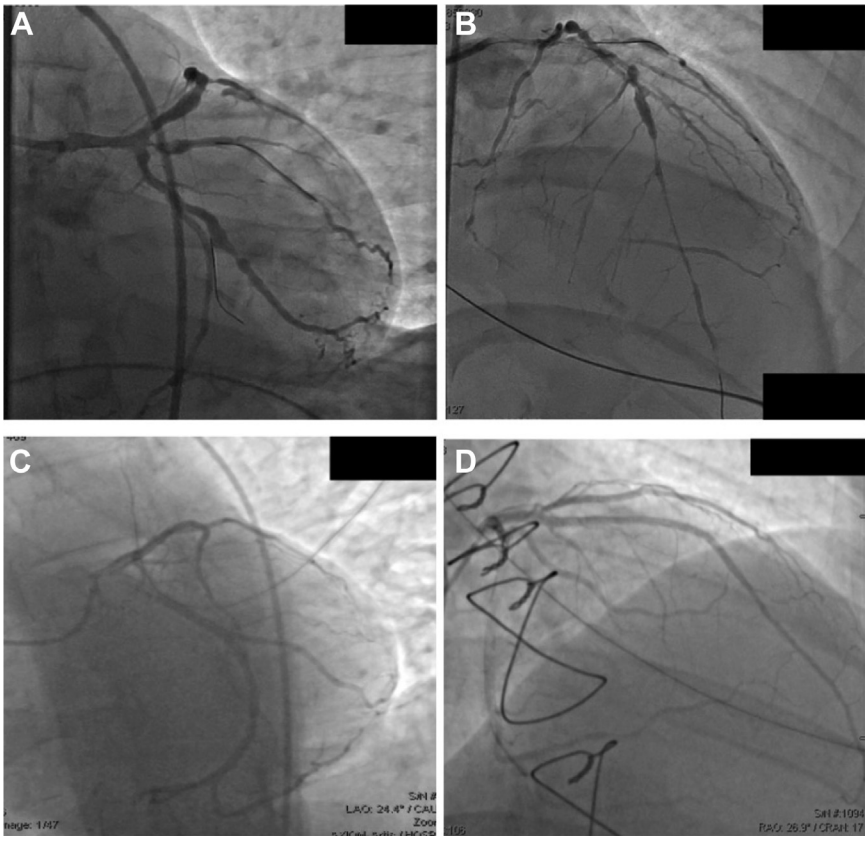
The patient's heart transplantation date was January 28, 2023, and he was started on proprotein convertase subtilisin kexin 9 inhibitor (PCSK9i) therapy on January 30, 2023. Note the rapid decline to normal levels after starting therapy and the lipid profile stabilization since transplantation. Chol = cholesterol; HDL = high-density lipoprotein; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

respiratory rate of 12 breaths/min, oxygen saturation of 100% on a 100% fraction of inspired oxygen, and a temperature of 36.5 °C. He underwent temporary mechanical circulatory support (tMCS)-assisted coronary revascularization with 7 stents. The patient remained stable but was unable to be weaned from tMCS. He was evaluated by transplant hepatology and was determined to be an appropriate transplantation candidate with minimal hepatic dysfunction, and he was subsequently listed for SHLT given his FH. A suitable donor was found; however, an unsuspected hepatic artery thrombus of the donor liver was discovered during procurement. The urgent decision was made to pursue isolated HT with aggressive PCSK9i therapy to control his cholesterol level in the setting of his FH. The patient was maintained on high-dose statin therapy from admission to the time of HT. Postoperatively, the patient was started on rosuvastatin (40 mg daily), ezetimibe (10 mg daily), and evolocumab (420 mg monthly) for management of hyperlipidemia. The transplantation program helped arrange appropriate insurance for the patient that included coverage of evolocumab. He was discharged on an immunosuppression regimen of tacrolimus (5 mg twice daily), mycophenolate mofetil (1,500 mg twice daily), and prednisone (20 mg daily), in addition to sulfamethoxazole-trimethoprim, valganciclovir, and fluconazole for infection prophylaxis.

DISCUSSION

This case and the few other published cases like it draw into question the scope of the recommendation for SHLT in all cases of FH. PCSK9is have been demonstrated to lower LDL in patients unable to tolerate statins and in patients unable to achieve target lipid levels with statin therapy alone. At present, 2 monoclonal antibody PCSK9is, evolocumab and alirocumab, have received U.S. Food and Drug Administration (FDA) approval as lipid-lowering therapy. This class of medication can be administered safely in combination with immunosuppressive therapy following HT. The 2022 International Society for Heart and Lung Transplantation guidelines for the care of heart transplant recipients continue to recommend statins as first-line therapy for post-transplant management of hyperlipidemia and for primary prevention of cardiac allograft vasculopathy (CAV) while acknowledging the increasing role for PCSK9i therapy in patients intolerant to statins or whose lipid levels remain uncontrolled.[6] Limited case series and retrospective cohort studies suggest that PCSK9i therapy may effectively assist in the management of coronary intimal hyperplasia in HT recipients.[6-8] Additional studies, including the EVOLVD (Cholesterol lowering with EVOLocumab to prevent cardiac allograft Vasculopathy in De-novo heart

FIGURE 2 Pre- and Post-Transplant Cardiac Catheterization Findings



(A) The patient's native, pretransplantation left anterior oblique (LAO) caudal (CAU) view demonstrating severe, proximal left-sided coronary artery disease. (B) The patient's native, pretransplantation left anterior oblique cranial (CRAN) view, which again demonstrates severe multivessel coronary artery disease. (C) The patient's 1-year post-transplantation left anterior oblique caudal view without evidence of coronary artery disease. (D) The patient's 1-year post-transplantation right anterior oblique cranial view without evidence of coronary artery disease.

transplant recipients) randomized controlled trial, are seeking to understand more clearly how PCSK9i therapy may affect CAV prevention in the year following HT.

Table 1 contains a list of novel lipid-lowering agents with FDA approval.[9-15]

FOLLOW-UP

Lipids were monitored every 1 to 3 months for 6 months and then every 3 to 6 months. Almost immediately, the patient experienced normalization of his lipid profile, and he has remained at goal, with LDL values below 55 mg/dL (**Figure 1**). Surveillance echocardiography and right- and left-sided heart catheterization have consistently demonstrated normal filling pressures and cardiac output, with no evidence of coronary atherosclerosis (**Figures 2A to 2D**).

CONCLUSIONS

The safety and efficacy of PCSK9i therapy raise hope that the pathologic cardiohepatic interaction generated by FH can be uncoupled, thereby avoiding the need for SHLT, preserving scarce resources, and potentially reducing time on transplantation waitlists.

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