JACC: CASE REPORTS VOL. 2, NO. 3, 2020

MINI-FOCUS ISSUE ON HEART FAILURE

ADVANCED

CASE REPORT: CLINICAL CASE SERIES

Use of PCSK9 Inhibitors in Solid Organ Transplantation Recipients

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ABSTRACT

Standard lipid-lowering therapies in solid organ transplantations pose challenges due to interactions with immunosuppressants. Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) represent a new class of lipid-lowering therapies with potential promise in this population. We describe PCSK9i as an efficacious and safe option for management of hypercholesterolemia in solid organ transplantations. (**Level of Difficulty: Advanced.**)
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Solid organ transplantation (SOT), encompassing heart, kidney, liver, pancreas, and lung transplants, has revolutionized treatment of end-stage disease (1). Advances in care post-SOT have led to reduced rejection rates, improved graft survival, and patient longevity. Improved patient survival after transplantation unmasked cardiovascular disease (CVD) as the leading cause of morbidity and mortality. A particularly aggressive form of CVD in patients who have undergone transplantation is allograft vasculopathy. Among heart transplant recipients, cardiac allograft vasculopathy (CAV) manifests as a progressive form of arteriosclerosis in the transplanted heart. Although risk factors for the development of CVD after transplantation are numerous, dyslipidemia is one of the strongest, most prevalent, and eminently modifiable factors. Standard lipid-lowering therapies (LLT) pose challenges in the SOT population due to potential toxicity resulting from drug-drug interactions with immunosuppressants. Readers are referred to a more comprehensive evaluation of the precautions and monitoring parameters involved with the coadministration of LLT and immunosuppressants (1).

In 2015, a new class of LLT, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (PCSK9i),

LEARNING OBJECTIVES

- Management of dyslipidemia in solid organ transplantation patients is discussed.
- Safety and effectiveness of PCSK9i in transplant patients are highlighted.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, or patient consent where appropriate. For more information, visit the *JACC: Case Reports* author instructions page.

Manuscript received August 15, 2019; revised manuscript received September 16, 2019, accepted September 27, 2019.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2019.09.026

was approved for use in patients with familial hypercholesterolemia (FH) and/or established atherosclerotic CVD (ASCVD) who require additional low-density lipoprotein-cholesterol (LDL-C) lowering after standard therapy. Two large randomized controlled trials that tested PCSK9i demonstrated large reductions in LDL-C (50%–60%) and improvement in cardiovascular outcomes (2,3). Enthusiasm has grown within the transplantation community for use of PCSK9i as an adjunctive treatment in patients who have failed to achieve LDL goals with standard therapies. This is exemplified in recent reports of the use of PCSK9i among SOT recipients (4–8). These reports leave additional questions, for example, are these agents effective and safe in different forms of SOT? Are the pharmacokinetics of PCSK9i in cases of SOT similar to those in non-SOT patients? Do PCSK9i affect immunosuppression? This case series aims to shed light on these aspects.

PRESENTATION

Our clinical case series involved a group of 12 adult SOT recipients with concurrent hypercholesterolemia who were inadequately treated with standard LLTs. At baseline, 25% of patients were not taking LLT, and more than half were deemed statin intolerant. Statin treatment was predominantly low or moderate intensity, as recommended for transplantation patients (**Table 1**).

MEDICAL HISTORY. The majority of patients had undergone heart transplantation (75%), but kidney, liver, and lung transplantation recipients were also represented. One-half of the patients had FH (n = 6), 75% had ASCVD (n = 8), and 18% had mild CAV (n = 2).

INVESTIGATIONS. All patients were initiated on PCSK9i therapy (alirocumab [n = 2], evolocumab [n = 9], or both sequentially [n = 1]). To assess the efficacy, safety, and tolerability of PCSK9i in SOT recipients in the present cohort, data collection was performed before and after PCSK9i treatment and included measurements of plasma concentrations of LDL-C, PCSK9, and immunosuppressants. The proportion meeting immunosuppression goals (9), rates of organ rejection, hospitalizations, emergency department visits, and infections were collected. All outcomes were continuously monitored during a mean observation period of 12 months starting 6 months prior to PCSK9i initiation (pre-PCSK9i) and ending 6 months after PCSK9i initiation (post-PCSK9i).

MANAGEMENT. Median LDL-C levels decreased 60% from 142 mg/dl to 57 mg/dl post-PCSK9i. All patients achieved optimal LDL-C levels of ≤70 mg/dl at some point during therapy. The median plasma PCSK9 concentration was 9.3-fold increased from 408 ng/dl to 3,404 ng/dl post-PCSK9i. Median plasma levels of immunosuppressants decreased for cyclosporine (37%) and sirolimus (27%) but increased for tacrolimus (6%). However, the proportion of time within therapeutic ranges for immunosuppressants did not change post-PCSK9i compared with pre-PCSK9i. Moreover, no cases of rejection occurred post-PCSK9i. Rates of hospitalization, emergency department visits, and infections pre-PCSK91 were similar to those post-PCSK9i. Only 33% (n = 4) underwent post-PCSK9i coronary artery catheterizations, but none demonstrated progression of atherosclerosis or CAV. One death occurred as the result of respiratory complications from a newly diagnosed advanced stage adenocarcinoma of the lung and was deemed unrelated to ASCVD, use of the drug, or transplantation failure. PCSK9i was well tolerated, with 25% of patients experiencing mild and self-limiting adverse drug events consisting of injection site reactions, rhinorrhea, and nausea. No patients discontinued treatment because of adverse events.

ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

CAV = cardiac allograft vasculopathy

CVD = cardiovascular disease

FH = familial hypercholesterolemia

LDL-C = low-density lipoprotein cholesterol

LLT = lipid-lowering therapy

PCSK9 = proprotein convertase subtilisin/kexin type 9

PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor

SOT = solid organ transplantation

DISCUSSION

This report describes the efficacy, safety, and tolerability of PCSK9i in a cohort of SOT patients. As expected for this population, most patients at baseline had uncontrolled dyslipidemia perpetuated by lipid-altering effects of immunosuppressant drugs required to prevent organ rejection and concerns about possible LLT toxicity after transplantation (1).

The 9.3-fold rise in PCSK9 levels after PCSK9i therapy in this SOT cohort was comparable to the 7-fold increase previously reported in non-SOT hyperlipidemic patients (10). The 60% reduction in LDL-C was comparable to the 50% to 60% reduction observed in cardiovascular outcome trials (2,3). Compared with standard LLT, which have heightened risk for significant drug-drug interactions with immunosuppressants, medication-related toxicity, and/or reduced immunosuppression levels, PCSK9i seemed to have a favorable safety profile for lipid management in SOT patients. The present study demonstrated negligible effects of PCSK9i therapy on plasma immunosuppressant concentrations. Additionally, there were no changes in rates of organ rejection, progressive atherosclerosis, hospitalization, emergency department visits, or infection.

Although other reports of PCSK9i use in SOT recipients have been published (4–8), the present

JACC: CASE REPORTS, VOL. 2, NO. 3, 2020
MARCH 2020:396–9

TABLE 1 Characteristics of Solid Organ Transplant Patients Receiving PCSK9i Therapy (N = 12)

Baseline Characteristics	
Age, yrs	63 ± 11
Males	4 (33.3)
Females	8 (66.7)
Type of solid organ transplant	
Heart	9 (75.0)
Kidney	1 (8.3)
Liver	1 (8.3)
Lung	1 (8.3)
Time between transplantation and injection, months	80.5 (21.5–158.5)
FH	6 (50.0)
Without known ASCVD	2 (33.3)
With ASCVD	4 (66.7)
ASCVD (includes CAD diagnosed by CACS)	8 (66.7)
CAD	6 (75.0)
Cerebrovascular disease	0 (0.0)
PAD	2 (25.0)
CAV*	2 (18.2)
Diabetes mellitus	4 (33.3)
Chronic kidney disease (stage 3-ESRD)	9 (75.0)
HIV	1 (8.3)
LLT use	9 (75.0)
High = intensity statin	1 (8.3)
Statin-intolerant†	7 (58.3)
Statin monotherapy	1 (8.3)
Statin + ezetimibe	4 (33.3)
Additional LLT	3 (25.0)

Continued on the next column

TABLE 1 Continued

Clinical Characteristics	Pre-PCSK9i	Post-PCSK9i
LDL-C, mg/dl	141.5 (113.5–149.0)	57 (27–69) (change: −50% [−58% to −23%])
PCSK9, ng/dl	407.5 (330.5–591.4)	3,404.3 (2,976.7–4,863.8) (change: 932% [661% to 1,025%])
Cyclosporine, ng/ml‡	102.2 (93.4–111.0)	64.5 (57.4–71.6) (change: −37% [−39% to 36%])
Tacrolimus, ng/ml	6.8 (6.0–7.4)	7.6 (6.1–9.8) (change: 6% [−3% to 12%])
Sirolimus, ng/ml‡	3.9 (3.9–3.9)	2.8 (2.6–3.0) (change: −27% [−32% to −21%])
Rejection episodes	0 (0.0)*	0 (0.0)§
Hospitalizations	2 (18.2)*	1 (8.3)§
Emergency department visits	3 (27.3)*	1 (8.3)§
Infections	3 (27.3)*	3 (25.0)§
Progression of atherosclerosis documented by post-PCSK9i catheterization		
Yes	-	0 (0.0)§
No	-	4 (33.3)§
Unknown (no catheterization)	-	8 (66.7)§
New cases ASCVD	-	0 (0.0)§
New cases CAV	-	0 (0.0)§
Mortality	-	1 (8.3)§

Values are mean ± SD, n (%), or median (interquartile range), unless otherwise indicated. *Out of 11 total patients as one patient received PCSK9i prior to transplantation. †Unable to tolerate lowest therapeutic daily dose. ‡Levels only drawn in 2 patients. §Events post-PCSK9i initiation and post-transplant.

ASCVD = atherosclerotic cardiovascular disease; CACS = coronary artery calcium score; CAD = coronary artery disease; CAV = cardiac allograft vasculopathy; ESRD = end-stage renal disease; FH = familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; PCSK9 = proprotein convertase subtilisin/kexin type 9; PAD = peripheral arterial disease; Pre = pre-PCSK9 inhibitor; Post = post-PCSK9 inhibitor.

cohort is unique for several reasons and aims to improve the understanding of the efficacy and safety of PCSK9i in this setting. This study describes the use of PCSK9i in a diverse cohort of SOT patients, including those who underwent heart, kidney, liver, and lung transplantations, the most diverse cohort evaluated to date. Additionally, prior reports insufficiently characterized the pharmacokinetic and pharmacodynamic response to PCSK9i and its effect on immunosuppression. The present study comprehensively describes the effect of PCSK9i on both of these fronts, detailing the percentage of LDL-C reduction, post-treatment LDL-C values, LDL-C goal attainment, and plasma PCSK9 levels, as well as degree of immunosuppression by evaluating average values and percentage of goal attainment. The present results indicate that PCSK9i in SOT patients perform similarly in non-SOT patients. This report adds significant granularity to the interplay between PCSK9i and immunosuppression and contributes to the growing published reports that support use of PCSK9i among SOT recipients.

FOLLOW-UP. All surviving SOT patients remained well managed on PCSK9i therapy, with frequent (6-month) follow-up examinations in the authors' PCSK9i clinic to assess response and tolerability.

CONCLUSIONS

These results suggest that PCSK9i are an efficacious and safe treatment for hypercholesterolemia in SOT recipients. Further studies of PCSK9i in SOT are needed to assess long-term LDL-C lowering, prevention of graft vasculopathy and ASCVD, and safety.

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REFERENCES

1. Warden BA, Duell PB. Management of dyslipidemia in adult solid organ transplant recipients. J Clin Lipidol 2019;13:231–45.

2. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713–22.

3. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379:2097–107.

4. Di Nora C, Sponga S, Livi U. Safety and efficacy of PCSK9 inhibitor treatment in heart transplant patients. Transplantation 2019;103:e58.

5. Uyanik-Uenal K, Stoegerer-Lanzenberger M, Auersperg K, et al. Treatment of therapy-resistant hyperlipidaemia after heart transplant with PCSK9-inhibitors (abstr). J Heart Lung Transplant 2019;38:S213–4.

6. Ordonez-Fernandez L, Rodriguez-Ferreras A, Carriles C, et al. Pneumonia in a patient with kidney transplant treated with alirocumab and everolimus. Farm Hosp 2019;43:74–6.

7. Moayedi Y, Kozuszko S, Knowles JW, et al. Safety and efficacy of PCSK9 inhibitors after heart transplantation. Can J Cardiol 2019;35.104.e1–.e3.

8. Kuhl M, Binner C, Jozwiak J, et al. Treatment of hypercholesterolaemia with PCSK9 inhibitors in patients after cardiac transplantation. PLoS One 2019;14:e0210373.

9. Costanzo MR, Dipchand A, Starling R, et al. The International Society of Heart and Lung Transplantation guidelines for the care of heart transplant recipients. J Heart Lung Transplant 2010;29:914–56.

10. Shapiro MD, Miles J, Tavori H, Fazio S. Diagnosing resistance to a proprotein convertase subtilisin/kexin type 9 inhibitor. Ann Intern Med 2018;168:376–9.

KEY WORDS **dyslipidemia, proprotein convertase subtilisin/kexin type 9 inhibitors, solid organ transplantation**