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Case Report

Safety and Efficacy of PCSK9 Inhibitors After Heart Transplantation

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See editorial by Noel and Genest, pages 17–18 of this issue.

ABSTRACT

Dyslipidemia is common in patients undergoing heart transplantation and is associated with the progression of cardiac allograft vasculopathy. Two monoclonal antibodies directed against PCSK9i—evolocumab and alirocumab—are currently available. However, their use, safety and efficacy in the post-transplant setting have not been studied. We present our experience with 6 heart transplant recipients treated with a PCSK9i. A > 70% reduction in LDL-cholesterol was observed after evolocumab therapy. PCSK9 inhibitors are a potentially lipid-lowering therapeutic option for heart transplant patients with suboptimal LDL despite maximal tolerated statin doses.

RÉSUMÉ

La dyslipidémie, couramment observée chez les patients subissant une transplantation cardiaque, est associée à la progression de la vasculopathie du greffon cardiaque. Deux anticorps monoclonaux dirigés contre la protéine PCSK9 — l'évolocumab et l'alirocumab — sont actuellement offerts. Toutefois, leur utilisation, leur innocuité et leur efficacité lorsqu'ils sont administrés après une transplantation n'ont pas été étudiées. Nous présentons les observations tirées de notre expérience auprès de six patients traités par un inhibiteur de la PCSK9 après une transplantation cardiaque. Une réduction > 70 % du taux de cholestérol LDL a été observée après le traitement par l'évolocumab. Les inhibiteurs de la PCSK9 représentent une option thérapeutique hypolipidémiante envisageable chez les patients ayant subi une transplantation cardiaque qui affichent une concentration de cholestérol LDL sous-optimale malgré la prise de statines à la dose maximale tolérée.

Cases

Dyslipidemia is common in patients undergoing heart transplantation and is associated with the progression of cardiac allograft vasculopathy (CAV). High-intensity statin therapy after transplant is limited by increased intolerance and adverse effects due to potential interactions with calcineurin inhibitors and other transplant-related medications (eg, triazole antifungals) that increase serum statin levels. Therefore, the use of statins may be contraindicated, as patients can be at increased risk of myalgias and rhabdomyolysis.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a circulating protein that increases the degradation of low-density lipoprotein receptors (LDLRs). PCSK9 inhibition results in recycling of LDLRs and increased hepatic removal of circulating LDL-cholesterol (LDL-c). Monoclonal antibodies inhibiting PCSK9 have emerged as potent lipid-lowering agents. Two humanized monoclonal antibodies directed against PCSK9, evolocumab and alirocumab, are currently available as subcutaneous injections administered every 2 to 4 weeks in adults with established cardiovascular disease and/or familial hypercholesterolemia (FH).[1,2] PCSK9 inhibitors were well tolerated, durable, and effective in reducing LDL-c levels to guideline-based criteria in real- world practice in high-risk patients.[2,3] However, their use, safety, and efficacy in the post-transplant setting have not been studied. In this case series, we describe our short-term experience with 6 patients

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Table 1. Clinical and demographic data in patients initiated on a PCSK9 inhibitor (evolocumab 140 mg sc q2wk) following heart transplantation

Age	Sex	Time post- transplant at PCSK9i initiation	Indication	Statin (dose)	LDL before initiation mmol/L (mg/dL)	LDL at FU mmol/L (mg/dL)	Duration of PCSK9i therapy at time of repeat LDL	Total duration of PCSK9i therapy
38	F	2.5 years	FH and elevated transaminases	Pravastatin (40 mg daily)	4.7 (181)	2.5 (98)	2 months	11 months
54	M	8.2 years	FH and myositis on atorvastatin	Pravastatin (40 mg daily)	4.9 (188)	1.05 (38)	2 months	8 months
49	M	10.6 years	Statin intolerant with severe CAV	None	4.2 (162.4)	1.1 (42.5)	1 month	10 months
55	M	17.4 years	Myositis with statin and severe CAV	None	2.96 (114.5)	0.5 (19.3)	1 month	5 months
67	M	16.9 years	FH with poorly controlled lipids on maximum tolerated statin	Atorvastatin (30 mg daily)	6.5 (251.4)	0.4 (15.5)	31 months	35 months
61	M	9.8 years	Myositis with statin	None	3.90 (150.8)	2.14 (82.8)	1 month	2 months

FH, familial hypercholesterolemia; FU, follow up; CAV, cardiac allograft vasculopathy; PCSK9, proprotein convertase subtilisin/kexin type 9.

Figure 1. Pre- and post-treatment LDL cholesterol with PCSK9 inhibitors in 6 heart transplant recipients.

treated with evolocumab after heart transplantation at 3 North American centres including Stanford University; Ottawa Heart Institute; and University Health Network, Toronto.

Table 1 shows the clinical characteristics of 6 heart transplant recipients treated with a PCSK9 inhibitor. Among the cohort, the median age is 55 years (interquartile range [IQR] 50.3,59.5 years), 5 are male at a median 11 years (IQR 8,16 years) post-transplant. Three patients were on tacrolimus and mycophenolate mofetil maintenance immunosuppression, and 2 patients were treated with tacrolimus and sirolimus for CAV. One patient was on prednisone, cyclosporine, and mycophenolate mofetil. The treatment indication for starting a PCSK9 inhibitor was related to FH in 3 of 6 recipients and statin intolerance in 3 of 6 recipients. One recipient (Patient 5) had a kidney transplant 19 years following his initial heart transplant. All patients tolerated evolocumab without reported side effects or adverse events. There were no hospitalizations, episodes of infection or rejection during the 9-month median follow up period. A $> 70\%$ reduction in LDL-c, was observed with a mean level of 4.5 ± 1.2 mmol (179.9 ± 45.8 mg/dL) before and 1.28 ± 0.9 mmol/L (49.6 ± 33.3 mg/dL) after evolocumab therapy (Fig. 1).

Neither of the 2 patients with CAV has undergone repeat coronary angiography since initiation of therapy.

Discussion

In the nontransplant population, treatment with PCSK9 inhibitors in combination with statins has been demonstrated to reduce LDL-c by 60% and cardiovascular events by 50%.[4] Dyslipidemia occurs in 60% to 80% of heart transplant recipients treated with contemporary immunosuppression, including corticosteroids and calcineurin inhibitors.[5] Aggressive treatment of dyslipidemia in heart transplant recipients is important for prevention of systemic atherosclerosis and slowing progression of CAV. The International Society for Heart and Lung Transplantation provides a class IA recommendation for initiating statins postoperatively in heart transplant recipients, regardless of lipid levels.[5] Pravastatin is the preferred statin, given its limited drug interactions and lower incidence of intrinsic muscle toxicity. It is estimated

that 5% to 10% of heart transplant recipients are either intolerant to statins or have persistently elevated LDL-c despite maximized statin therapy.

We report on 6 patients initiated on evolocumab after heart transplantation with a median follow-up of 9 months. All patients displayed dramatic rapid reduction in LDL-c levels and tolerated treatment well without reported side effects or requirements for immunosuppression dose adjustments. At present, at least 1 randomized control trial (NCT3537742) is scheduled to begin enrollment evaluating the safety and efficacy of PCSK9 inhibitors in heart transplantation.

Conclusions

PCSK9 inhibitors are a potentially well tolerated and potent lipid-lowering therapeutic option for heart transplant patients with suboptimal LDL-c despite maximal tolerated statin doses. Future larger studies assessing the role of PCSK9 inhibitors in this population are encouraged and warranted.

Disclosures

Joshua Knowles has received research grants from Amgen Inc US and the AHA, both of which have been paid to Stanford University, for a project centred on using artificial intelligence to identify patients with familial hypercholesterolemia in electronic health records. The other authors have no conflicts of interest to disclose.

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