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Editorial

Smashing Low-Density Lipoprotein Levels and Preventing Coronary Allograft Vasculopathy: One Heart Transplant Patient at a Time

Aimee Noel, MD, and Jacques Genest, MD

From Queens University and Research Institute of the McGill University Health Center, Montréal, Québec, Canada

See article by Moayedi et al., pages 104.e1–104.e3 of this issue.

Along with graft failure and malignancy, coronary allograft vasculopathy (CAV) is one of the major leading causes of mortality in heart-transplant recipients. Unlike traditional atherosclerotic coronary artery disease, CAV is characterized by concentric and longitudinal intimal hyperplasia, culminating in diffuse, multiterritory stenosis of epicardial and more distal coronary arteries. Its pathogenesis has been linked to humoral and cellular immunological processes, cytomegalovirus infection as well as more traditional risk factors such as diabetes and dyslipidemia.

Even recipients with previously normal lipid profiles and nonischemic type of cardiomyopathy pretransplant tend to develop significant dyslipidemia and become at risk for CAV shortly after starting immunosuppressive therapy. In large part, the increase in low-density lipoprotein (LDL)-cholesterol (LDL-c) and triglyceride levels (reflecting an increase in remnant lipoproteins cholesterol content) are related to the unavoidable use of medications such as corticosteroids and calcineurin inhibitors.

The impact of CAV on post-heart transplant patients is not negligible. According to the International Society for Heart and Lung Transplantation (ISHTL) registry of 135,000 adult patients post-heart transplant, the prevalence of CAV was 7.6% at 1-year post-transplant, climbing to 47% after 10 years.[1] The incidence of the disease tends to decrease with time, highlighting the importance of effective early prevention. Patients who develop CAV within 3 years post-transplant have a 5.4% and 10% increased mortality at 5 and 10 years after diagnosis, compared with recipients who do not develop CAV.[2] Diagnosis of CAV post-transplant has also been associated with higher morbidity with the development of graft failure, arrhythmia, and acute myocardial infarction.

There are no treatments or cures for CAV, except for retransplantation. The best approach to limit its impact on the patient's health is prevention and early detection. Because of denervation post-transplant, ischemic symptoms are not reliable indicators of disease. Routine screening for CAV by noninvasive means or coronary angiography have proven difficult and of low diagnostic yield; the focus has therefore shifted to broad preventive strategies to reduce the incidence of graft vasculopathy.

Since the advent of statin therapy, small clinical trials have demonstrated significant benefits in reducing CAV and prolonging event-free survival. A meta-analysis of 9 studies of reporting on 2295 heart-transplant recipients revealed that the use of statins was associated with a significant reduction in mortality (odds ratio [OR], 0.26; 95% confidence interval [CI], 0.20-0.35; $P < 0.0001$), a decrease in the risk of hemodynamically significant or fatal rejection (OR, 0.37; 95% CI, 0.21-0.65; $P = 0.0005$), and a decreased incidence of coronary vasculopathy (OR, 0.33; 95% CI, 0.16-0.68; $P = 0.003$).[3] These results are explained not only by their ability to lower LDL and other atherogenic lipoproteins but also because of their pleiotropic effects linked to decreased inflammatory activity and endothelial dysfunction.

Despite their proven role in the care of heart-transplant recipients, there are factors limiting the widespread use of statins. Most significantly, the potential risk of statin-associated myositis or rhabdomyolysis is higher in this population because of the use of calcineurin inhibitors that reduce the activity of CYP3A4 enzyme, thus decreasing statin metabolism.[4] Although the risk is reported to be less with pravastatin, intolerance due to myalgia or myopathy can lead to suboptimal dosage or discontinuation. Other options—such as bile sequestrants, fibric acid derivatives, or nicotinic acid—are also ill advised, as they have the potential to diminish the immunosuppressant activity of calcineurin inhibitors or have significant drug–drug interactions.

More recently, the use of PCSK9 inhibitors evolocumab and alirocumab to lower LDL-c has shown incremental benefit over statins in reducing cardiovascular outcomes.[5,6] These are fully human monoclonal antibodies that prevent

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Corresponding author: Dr Jacques Genest, McGill University Health Center/Royal Victoria Hospital, 1001 boul. Decarie, Bloc E, Office EM12212, Montréal, Québec H4A 3J1, Canada. Tel.: +1-514 934-1934, ext 34630.

E-mail: Jacques.genest@mcgill.ca

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the interaction between the LDL receptor protein and PCSK9. In the relatively short term of clinical trials, PCSK9 inhibitors have shown excellent safety profiles and have demonstrated a significant reduction of major adverse cardiovascular events. Moreover, compared with other antihyperlipidemic drugs, PCSK9 inhibitors have very limited drug—drug interactions and apparently do not interact with immune- suppressive therapies post-transplant. It seems natural, therefore, to test their applicability in heart-transplant recipients who have developed goal-inhibiting statin intolerance or statin- associated myopathy or those who have failed to achieved target LDL-c levels despite maximally tolerated doses or because of such conditions as familial hypercholesterolemia.

Moayedi et al.[7] described 6 heart transplant patients who were otherwise treated with modern standard immunosuppressive therapies but were unable to tolerate or achieve therapeutic goals with statin therapy.[8] Three of their patients had familial hypercholesterolemia, and 3 others had goal-inhibiting statin intolerance. They reported impressive reductions of LDL-c shortly after the initiation of PCSK9 inhibitors without significant side effects and excellent tolerability profiles, at least during the short duration of exposure. They observed a $> 70\%$ reduction in LDL-c, from a mean level of 4.5 ± 1.2 mmol to 1.28 ± 0.9 mmol/L after evolocumab therapy. One of their patients was a recipient of both heart and lung transplant and, like others, benefited from a more than 70% reduction in LDL-c with no adverse events and no adjustment in dose of immunosuppressive treatment.

Donor hearts are a scarce resource for patients with end-stage heart failure, and investing in preserving heart function—and, by extension, the quality and quantity of life of donor-heart recipients—is of outmost importance. CAV is an important cause of graft failure and mortality in heart-transplant patients and—given the absence of satisfactory treatment options and considering the scarcity of resources to permit retransplant—prevention, including LDL-c reduction with statin therapy, is paramount. In their retrospective analysis, Moayedi et al.[7] have opened the door to new possibilities for effective management of CAV. PCSK9 shows little to no interaction with other drugs, especially corticosteroids and calcineurin inhibitors, making them a suitable add-on or substitute for statins in heart-transplant recipients. The authors highlight the need for a clinical study to determine the benefits of PCSK9 inhibitors and measure the clinical impact of their lipid-lowering capabilities. Ashleh et al. have shown the importance of timing for the initiation of statins to prevent CAV; thought should be given to introducing this new therapy early on when statins are shown to be insufficient or not tolerated.[9] It will be interesting to test PCSK9 inhibitors not only in heart transplant recipients but also to other solid-organ recipients for whom lipid control is critical to reduce mortality, risk of cardiovascular events, graft failure, and mortality. The Canadian heart-transplant community could certainly benefit from the creation of a national registry to study patients who are candidates for PCSK9-inhibitor treatment and examine efficacy and safety outcomes.

Disclosures

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