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Statin therapy in cardiac allograft vasculopathy progression in heart transplant patients: Does potency matter?

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A B S T R A C T

Cardiac allograft vasculopathy (CAV) is a unique multi-factorial pathologic process encountered following heart transplantation. Several risk factors have been identified including a combination of immunologic and non-immunologic processes. Significant research has been conducted to elucidate the driving forces of CAV as well as improved identification, prevention and treatment strategies. Statin therapy following transplant remains the standard of care to help prevent the progression of CAV. The benefits of statin therapy following transplantation correspond to cholesterol control, anti-inflammatory and immunomodulatory mechanisms as well as potentially unknown mechanisms. Despite known drug interactions with calcineurin inhibitors, the use of statins is highly recommended in the current International Society for Heart and Lung Transplantation guidelines. Limited research has been conducted on the impact of higher intensity statin therapy following heart transplant and the relative risks and benefits are unknown. This review focuses on risk factors and pathophysiology of CAV, the role of statin therapy in heart transplantation, and the potential added benefit of more intense statin therapy to limit the progression of this graft-limiting complication.

1. Introduction

Cardiac allograft vasculopathy (CAV) is a unique pathologic process commonly encountered in heart transplant patients. Despite advances in maintenance immunosuppressive regimens and continuously evolving strategies for the detection and treatment of cellular and antibody-mediated rejection, CAV continues to be a limiting factor for long-term graft survival. The use of statin therapy for CAV has become standard of care based on numerous clinical studies demonstrating reduction in rejection and improved mortality [1–4].

Unlike coronary artery disease which is seen in a variety of patients, CAV is a pathologic process unique to cardiac transplant. Coronary artery disease is largely characterized by atherosclerosis manifesting as eccentric, proliferative, and degenerative lesions of the intimal layer while CAV affects the epicardial and intramural arteries and presents with concentric intimal layer thickening (Fig. 1) [5]. Pathological changes within the arterial vasculature following transplantation were first described in 1910 by Alexis Carrel following carotid arterial allograft transplantation in a canine [6]; however, CAV was not fully described as a pathological entity until the late 1960s and early 1970s [7,8]. Current International Society for Heart and Lung Transplantation (ISHLT) registry reports that CAV affects approximately 8%, 30%, and 50% of patients who survive 1, 5, and 10 years post-transplant, respectively [9]. Survival after development of CAV is significantly lower compared to patients who do not develop CAV [9]. Graft failure from CAV eventually accounts for 30% of heart transplant deaths [10]. Initial presentation of CAV may be myocardial infarction, congestive heart failure, or sudden cardiac death [11]. Because these symptoms may have a very acute onset, surveillance strategies should be encouraged to prevent late discovery of allograft vasculopathy. Annual or biannual coronary angiography should be considered to help assess developing CAV. In addition to other imaging modalities, IVUS may help further characterize the extent and severity of the disease [12]. This review aims to describe some of the known pathogenesis mechanisms of cardiac allograft disease, evaluate the utility of statin therapy in heart transplant patients and explore the potential for more potent statin therapy to slow the progression of CAV in this population.

2. Pathogenesis of cardiac allograft vasculopathy

Research has shown that the pathogenesis of CAV is a multifactorial process with both immune-mediated and non-immune mechanisms contributing to the progression of the disease [13,14]. The presence of pre-transplant donor specific anti-HLA antibodies as well as the development of *de novo* donor specific anti-HLA antibodies significantly increases mortality, specifically due to CAV [15–17]. Additionally, antibody development to cardiac myosin, vimentin and major histocompatibility complex (MHC) class I-related chain A (MICA) all have relevance in the pathogenesis of rejection and vasculopathy [18–20]. Timing of rejection as well as the number and severity of rejection episodes are associated with an increased risk of CAV [1,21–24]. Patients

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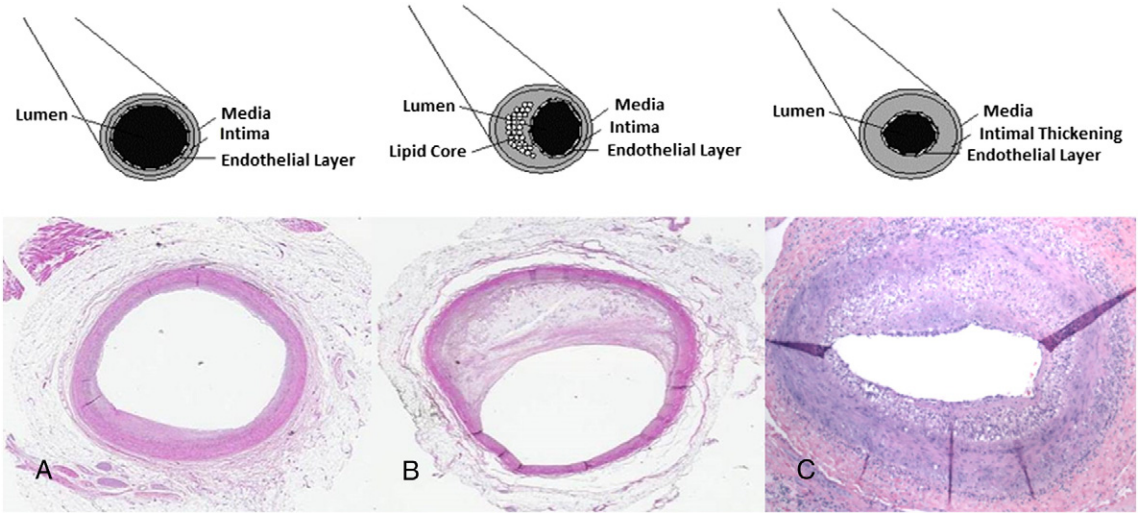

Fig. 1. (A) Normal coronary artery with age-related intimal hyperplasia (B) atherosclerotic plaque within a coronary artery characteristic of coronary artery disease (C) concentric intimal hyperplasia with lymphocyte proliferation in a patient with cardiac allograft vasculopathy. Image reprinted with permission. *Hypothesis*. 2006;4 (1):19–27. Available online at http://www.hypothesisjournal.com/?p=623

with three or more episodes of AMR have a shorter onset and experience a significant increase in the incidence of CAV and cardiovascular death with each subsequent AMR occurrence [21]. At one year post-transplant, the presence of AMR increases the incidence of CAV by 10% and up to 36% five years post-transplant [25].

Current ISHLT guidelines recommend strict control over potentially modifiable (non-immune) risk factors including hypertension, diabetes, hyperlipidemia, smoking, and obesity [12]. Results from 114 heart transplant patients showed a strong correlation between a combined elevated c-reactive protein (CRP) with elevated triglyceride (TG) to high density lipoprotein (HDL) ratio and the frequency of CAV [26]. Freedom from CAV at 5 years was 65% of patients with CRP < 3 mg/dL and TG/HDL < 3 compared to 9% of patients with CRP > 3 mg/dL and TG/HDL > 3 [26].

The development of cytomegalovirus (CMV) has been associated with a significant increase in the risk of CAV development, even in patients with subclinical and low-grade systemic viral replication [27–29]. It is unclear whether this association is a result of changes to immunosuppression common in significant CMV disease or by infecting endothelial cells directly, resulting in NF-kappa B activation and extensive cytokine release [30].

Donor factors including brain death, intracranial hemorrhage, and donor management strategies may have a direct impact on CAV development after transplant [30–32]. Heart transplant recipients from explosive brain death donors (defined by the authors, as death from a gunshot wound or other accidental trauma to the head and other causes of fatal intracranial hemorrhage that progressed rapidly to brain death) demonstrated a greater degree of maximum intimal thickness, decreased graft survival and more cardiac events [31].

3. The role of statin therapy in heart transplant patients

The use of statin therapy to lower cholesterol, slow progression of atherosclerosis, and prevent cardiovascular events has been demonstrated in several clinical trials and angiographic studies [33–36]. Based on the rate of cholesterol reduction, statin therapy may elicit benefits through modulation of vascular function, plaque growth/rupture, or thrombosis [33]. The beneficial effects of statin therapy on cholesterol control is an essential component of post-transplant management with 60–80% of heart transplant patients developing hyperlipidemia [1]. Hyperlipidemia, as early as 6 months following transplantation, has been shown to be a strong risk factor for CAV [37,38]. When transplanted vasculature of animals were exposed to the same level of hyperlipidemia as native vessels, there was a significant increase in intimal thickness, greater angiogenesis and higher accumulation of T-lymphocytes within the allograft [39,40]. These findings suggest that additional benefits of statins may be through immunomodulatory and anti-inflammatory mechanisms in combination with lipid lowering effects.

Activation of T-lymphocytes is an essential aspect of the immune system which requires specific antigen recognition in concert with costimulatory molecules CD40, CD80, and CD28 [36]. The use of statin therapy has been shown to inhibit lymphocytes, macrophages, and endothelial cells through the disruption of costimulatory molecules (CD40, CD80, and CD86) [41]. Additional studies have shown that statin therapy may affect interferon gamma (IFN-γ) induction of MHC class II (MHC-II) molecules and reduce expression in a dose-dependent manner [42,43]. The effect of statins on MHC-II expression is abolished in the presence of L-mevalonate, indicating that the alteration is truly driven by HMG-CoA reductase inhibitors [42,43]. The repression of MHC-II significance in organ transplantation stems from their direct involvement in the immune response, reduction in T-lymphocyte activation, and subsequent reduction in rejection risk [42]. These benefits were not limited to a single statin, but were seen utilizing atorvastatin, lovastatin, simvastatin, and pravastatin. Also, statins have been shown to block binding of β-2 integrin, leukocyte function antigen 1 (LFA-1) to intracellular adhesion molecule-1 (ICAM-1) which prevents necessary signals for leukocyte migration and co-stimulation of T cells [44]. An animal study evaluating allograft vasculopathy in rat models demonstrated the significance of monocyte chemoattractant protein-1 (MCP-1), regulated on activation, normal T-cell expressed and secreted (RANTES) protein and interferon inducible protein 10 (IP-10) and their accompanying chemokine receptors CCR2, CCR5 and CXCR3 in the pathogenesis of this disease [45]. This study also showed that simvastatin reduced the presence of MCP-1-CCR2 and RANTES-CCR5 complexes and concentration of IP-10 levels detectable in the allograft.

4. Statins: Pharmacokinetics, adverse effects, and drug interactions

The beneficial effects seen with statin therapy are well described; however continued use of these medications will be evaluated carefully due to significant concerns for adverse effects, including symptomatic or asymptomatic CPK elevations, elevated transaminase levels, myalgias, and rhabdomyolysis. The implications of elevated CPK levels with statin therapy are unclear and while common practice, current American College of Cardiology (ACC) /American Heart Association (AHA) cholesterol guidelines recommend against routine measurements in individuals receiving statins; however, it may be useful at baseline in patients who are at high risk for myopathy [46]. Myositis