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OBM Transplantation

Review

Management of Cardiac Allograft Vasculopathy

Rama Bindu Manchikalapudi *

Huntington Heart Center, Huntington, NY, USA; E-Mail: rbindum@gmail.com

***Correspondence:** Rama Bindu Manchikalapudi; E-Mail: rbindum@gmail.com

Academic Editor: Nandini Nair

OBM Transplantation
2017, volume 1, issue 3
doi:10.21926/obm.transplant.1703005

Received: May 31, 2017
Accepted: September 18, 2017
Published: September 29, 2017

Abstract

Cardiac allograft vasculopathy is one of the leading causes of death following the first 5 years after orthotopic heart transplantation along with late graft failure, likely secondary to undiagnosed CAV. Currently there is no single medical treatment available for this condition except modification of risk factors and immunosuppression. Retrasplantation remains the hope for this entity with some limitations.

Keywords

Cardiac allograft vasculopathy; orthotopic heart transplantation; graft failure

Introduction

Cardiac allograft vasculopathy (CAV) is one of the leading causes of death following the first 5 years after orthotopic heart transplantation (OHT) along with late graft failure, likely secondary to undiagnosed CAV [1]. The prevalence of CAV increases from the time of OHT affecting 8% recipients by a year and more than half of all the recipients by 10 years after transplant [2, 3]. Therefore, it is of utmost importance to prevent and treat CAV aggressively post OHT.

Etiology and risk factors

Various alloimmune and non-immune mechanisms contribute to endothelial injury in the setting of impaired host repair mechanisms post OHT leading to development of CAV [4].

The alloimmune factors identified for development of CAV after transplant include the number of HLA mismatches, the number of rejection episodes, their duration and their time of onset posttranplantation. Acute rejection prior to discharge from the hospital is considered a significant risk factor for development of CAV [3, 5].

Alloimmune-independent risk factors include diabetes mellitus, hypertension (donor and recipient), hyperlipidemia, older donor age, certain recipient/donor gender combinations including female without prior pregnancy/female vs. male/male, obesity, hyperhomocysteinemia, CMV infection (Cytomegalovirus (CMV)–negative recipients of CMV-positive donor organs), ischemia/reperfusion injury, brain death, use of certain immunosuppressant medications (like OKT3 for induction, azathioprine vs. mycophenolate and cyclosporine vs. tacrolimus for maintenance) [3, 5].

Hyperlipidemia and insulin resistance are the most significant non immunologic factors occurring in 50-80% of the heart transplant population [5].

Prevention

Certain risk factors for CAV are modifiable. Therefore prevention and management of the risk factors in a timely fashion is crucial when not many therapies exist for the management of this entity.

Ischemia-reperfusion (I/R) injury

I/R injury at the time of cardiac transplantation is known to contribute significantly to endothelial dysfunction and pathophysiology of CAV [5]. Ischemia contributes to graft injury during transplantation as well reperfusion with associative oxidative outburst contributes to the onset and progression of CAV. Therefore, attenuation of I/R injury as much as possible during transplantation will be beneficial to prevent the development of CAV. With the available newer technologies, it seems feasible to decrease the ischemia time to a certain extent.

Brain death

The leading cause of donor death had been head trauma (40-50%) according to the recent report from International Society for Heart and Lung Transplantation (ISHLT) [6]. Brain death is considered a catastrophic central injury that triggers increase in catecholamine levels and

oxidative stress that may contribute to CAV [5]. Avoiding organs from the donors with brain death does not seem to be a feasible option at this time when there is already known shortage of donor hearts, but this has to be noted as a risk factor for the development of CAV.

Donor age

Increasing donor age is correlated with the development of CAV [3]. It is not clear if the increasing donor age represents occult pretranplant coronary artery disease (CAD) or an age-related predisposition to CAV. In the prior studies, it was noted that there was no significant difference in the rate of intimal thickening between patients with donor hearts having preexisting CAD and those without CAD [7]. Certainly with the shortage of donor hearts, older donors were being accepted in the recent years.

Hypertension

Traditional risk factors for coronary artery disease, hypertension (HTN), hyperlipidemia, diabetes, insulin resistance, and obesity, seem to be prevalent in transplant recipients either pretransplantation or develop posttransplantation. Tobacco smoking although less prevalent in patients after OHT, should be noted as a risk factor for the development of CAV.

Certain factors like drugs used posttranplantation like calcineurin inhibitors can cause or exacerbate the preexisting HTN, insulin resistance or hyperlipidemia. Early identification and aggressive treatment of these risks can mitigate the progression of CAV.

Hypertension is very common post OHT. Hypertension causes endothelial injury by promoting intimal hyperplasia. Hypertension was shown to be an independent factor for atherosclerotic plaque progression in prior studies [8]. Certain factors influence the development of HTN after OHT or worsen the HTN that was already present prior to OHT. These factors include the use of immunosuppressive medications like cyclosporine, corticosteroids, denervation of the cardiac volume receptors that happens with OHT and failure to suppress renin-angiotensin–aldosterone system (RAAS). Diltiazem had been shown to slow or prevent decrease in the diameter of the coronary artery vessel lumen at one year although the mechanism was unclear [9]. Inability to suppress the RAAS in OHT recipients was shown to cause blunted diuretic and natriuretic responses to volume expansion and thereby causing hypertension. High-dose angiotensin converting enzyme inhibition was shown to be effective in treatment of hypertension post OHT [10]. Oftentimes more than one antihypertensive medication is required for treatment. Combination of angiotensin converting enzyme inhibitors and calcium channel blockers has been shown to decrease the degree of intimal hyperplasia at one year post OHT [11]. Despite this evidence, a report from 2010 showed that in the OHT population, only 43% of subjects achieved the target blood pressure [12] which highlights the real world challenges in adequate treatment of hypertension in this population.

Hyperlipidemia

Hyperlipidemia and hypertriglyceridemia are known risk factors for the development of CAV [13]. Prednisone and cyclosporine used for immunosuppression posttransplantation can cause or worsen the preexisting hyperlipidemia.

3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase inhibitors (statins) have proven beneficial by the lipid lowering effects as well as by restoration of endothelial-dependent vasodilator function [5]. In a randomized controlled trial, pravastatin was shown to have beneficial effects in the first year cholesterol levels, survival, development of CAV (evaluated by coronary angiography and intracoronary ultrasound) and the incidence of rejection causing hemodynamic compromise [14]. These beneficial effects were noted to be persistent at 10-year follow-up [15]. Similar beneficial effects were noted with simvastatin [16, 17]. In a 12-month observational study comparing simvastatin 20mg to pravastatin 40 mg, both agents resulted in comparable reduction in lipid levels and lipid profile, but pravastatin group had lesser side effects of rhabdomyolysis and myositis compared to the simvastatin group [18].

Statin therapy has been shown to reduce CAV and improve long-term outcomes regardless of lipid levels and should be considered for all HT recipients. Statin therapy has been demonstrated to have immunomodulatory effects thereby reducing the number of rejection episodes with hemodynamic consequences [14, 15, 19-21].

There are some adverse effects of statins like myositis and rhabdomyolysis that are more pronounced in the posttranplant population secondary to the drug-drug interactions especially if used in conjunction with calcineurin inhibitors [22-24].

Diabetes, insulin resistance and metabolic syndrome

Diabetes is considered coronary artery disease equivalent in nontransplant coronary artery disease. Diabetes and insulin resistance are noted to be prevalent in OHT recipients either pretransplant or post OHT [25]. Certain immunosuppressive medications including corticosteroids and calcineurin inhibitors (cyclosporine and tacrolimus) are frequently attributed to the development of diabetes post OHT [26, 27]. Metabolic syndrome with hyperglycemia, hypertriglyceridemia, hyperinsulinemia, high very low density lipoprotein (VLDL) levels and low high density lipoprotein levels together cause the progression of atherosclerotic vascular disease [28]. CAV is noted to be accelerated in animal models with insulin resistance in prior studies independent of an alloimmune response [29].

Good glycemic control pretransplant, close vigilance for early identification of hyperglycemia post OHT, prompt treatment of diabetes and adjustment of the immunosuppressive medications are the crucial steps in the management of this risk factor for the development of CAV.

Infections and CMV

Opportunistic infections are the Achilles heel of the immunosuppression post OHT. Various bacterial, viral, fungal, parasitic infections that develop post OHT have been implicated in the development of accelerated CAV, acute rejection, increased mortality and posttransplant lymphoproliferative disorder [30, 31].

CMV is the most frequent and most studied infecting organism after OHT playing a significant role in development of CAV [32], although other viral and fungal agents were studied and shown to have modest role. It accelerates CAV by increasing the host immune response to the allograft, induces procoagulant state and affects various factors involved in angiogenesis, smooth muscle cell migration and vessel remodelling [4]. Close attention to the CMV positive status of the

recipient and donor as well as aggressive CMV prophylaxis and monitoring for CMV viremias warranted. CMV–negative recipients of CMV-positive donor were at higher risk of CAV [3].

Prophylaxis against CMV with Ganciclovir with or without CMV hyperimmune globulin early after transplantation may reduce the risk of CAV [33].

Antibodies and rejection

The current immunosuppressive regimens are effective in interfering with the T cell signaling pathways that are known to mediate cellular rejection. However donor specific antibodies (DSA) and nondonor specific antibodies contribute to the clinical challenging entity of antibody mediated rejection in OHT recipients. Circulating antibodies predispose the OHT recipients to graft loss, accelerated CAV and death [34]. Certain factors like pregnancy, blood transfusions, transplantation, retransplantation, ventricular assist device complications, cardiac repairs with homograft material predispose patients to the development of alloantibodies.

In the study by Kobashigawa et al in 523 OHT recipients, compared to the untreated sensitized group (PRA > 10%) and the control group (PRA < 10%), the treated sensitized group (PRA > 10%) had similar five-year survival (81.1% and 75.7% vs. 71.4%, respectively, $P = 0.523$) and freedom from cardiac allograft vasculopathy (74.3% and 72.7% vs. 76.2%, respectively, $P = 0.850$) [35].

In a recent study by Kobashigawa et al, it was shown that there was a lower subsequent 4-year freedom from CAV in the persistent DSA group when compared to the no DSA group ($P = 0.061$) and the transient DSA group ($P = 0.152$). Of note this was a study with 109 subjects and the *P* value was not statistically significant [36]. This has to be looked into further with large multicenter studies.

The risk of infection in pretransplantation patients should be carefully weighed against the benefits of treatment of the sensitized patients' pretransplanatation.

Larger studies are required to further asses the relationship of the donor and non-donor specific antibodies in the development and progression of CAV as well as the management.

The risk of antibody mediated rejection can be mitigated by careful selection of a donor toward whom the patient does not have DSA or removal of the DSA via desensitization protocols. Currently there were no randomized controlled trials comparing the clinical efficacy of different desensitization strategies [37].

Modification and optimization of immunosuppression

Certain immunosuppressive medications were noted to be better compared to others in decreasing the incidence of CAV and in decreasing the progression of already established CAV.

Mycophenolate mofetil (MMF) was noted to have significantly less progression of the first-year intimal thickening. In the initial randomized active-controlled trial in heart transplant recipients, there was no difference in the intravascular ultrasound (IVUS) score between the MMF and azathioprine treated group [38]. Subsequent reanalysis of this multicenter trial, matching site- to-site comparisons showed first-year change in maximal intimal thickness (MIT) ≥ 0.3 was significantly greater in the AZA-treated group compared to the MMF-treated group. Also, more AZA-treated patients had a first-year change in MIT of ≥ 0.4 and 0.5 mm compared to the MMF-treated patients; however, this did not reach statistical significance ($P = 0.05$ and 0.10, respectively). At 1 year, the mean vessel area decreased in the AZA group and actually increased in

the MMF group (P = 0.03) [39]. The 36-month results of a randomized, double-blind, active-controlled trial of Mycophenolate mofetil (MMF) vs. Azathioprine (AZA) in heart transplant patients did not demonstrate significant differences between the groups in coronary angiographic or IVUS assessments. The inability to show significant benefits of MMF using vascular assessments was attributed to the fact that only approximately 20% of patients in each treatment group had complete sets of IVUS data by the authors [40].

Proliferation signal inhibitors (PSI) have been shown to markedly decrease the intimal thickness. In an open-label, prospective, randomized study by Mancini et al, treatment with rapamycin versus continued current immunosuppression was studied. Treatment with rapamycin was shown to effectively slow the progression of graft vasculopathy and reduced the incidence of clinical significant cardiac events namely death, acute myocardial infarction, need for angioplasty or bypass surgery, and/or a > 25% increase in the catheterization score [41].

In another randomized, open-label study, sirolimus/rapamycin was compared with azathioprine in combination with cyclosporine and steroids administered from the time of cardiac transplantation. Intracoronary ultrasound performed at 6 weeks, 6 months, and 2 years demonstrated highly significant progression of transplant vasculopathy in azathioprine-treated patients whereas at 6 months, a highly significant absence of progression in intimal plus medial proliferation and significant protection against luminal encroachment was evident in sirolimus-treated patients, and these effects were sustained at 2 years [42].

Everolimus in a two-year, prospective, randomized, double-blind trial was shown to limit progressive intimal thickening and decrease the frequency of vasculopathy [43].

Sirolimus and everolimus were shown to decrease the progression of already established CAV as well as decrease in incidence of CAV. Both sirolimus and everolimus were shown to cause worsening of the renal function and hyperlipidemia.

In a randomized pilot study of 23 patients, prophylactic photopheresis was shown to significantly reduce coronary artery intimal thickness. However data from larger trials is lacking [44].

Antioxidants

The effect of vitamin C and E were evaluated in a double blind prospective study with 40 subjects which showed that OHT recipients who received Vitamin C 500 mg plus Vitamin E 400 IU, each twice daily showed no change in the intimal index compared to the placebo group where intimal index was noted to have increased justifying their use in the current management of OHT population [45].

Coronary revascularization

CAV involves the vascular bed of the allograft including the epicardial, intramyocardial coronary arteries and veins. CAV is primarily a diffuse process and the coronary arteries dilate as a compensatory mechanism to the intimal hyperplasia [5]. Therefore, routine angiography which is most commonly employed fails at times to diagnose the presence and can underestimate the severity of CAV given the morphology of CAV lesions. Intravascular ultrasound is an invaluable, most sensitive tool and is most often applied technology for the angiographic diagnosis of CAV [46-49].

Revascularization is used as a palliative procedure for CAV. Percutaneous coronary intervention (PCI) is used to treat discrete lesions in Type A CAV [50]. The intervention with PCI was not clinically or symptom driven in CAV but driven by angiographic stenosis unlike in the setting of nontransplant CAD where it is primarily symptom driven. The restenosis rate of the CAV lesions after angioplasty or PCI is noted to be higher in long term [51-53]. With the advent of drug eluting stents the restenosis rates were noted to be lower especially with the second generation drug eluting stents (DES) [54, 55]. The restenosis rates were noted to be lower in patients on clopidogrel, statin therapy and higher doses of immunosuppression [49, 50].

Coronary artery bypass grafting (CABG) was often limited by absence of distal vessel targets for revascularization of CAV. The periprocedural mortality was noted to be extremely high making it almost abandoned procedure for CAV revascularization [56].

Retransplantation

This remains the only hope for survival of the transplant recipients with severe CAV at the current time. However the survival after retransplantation for severe CAV is similar compared to survival after initial transplantation past the 30 days of retransplantation. Survival after retransplantation is related to the time from initial transplantation, with better survival if the time from initial transplantation is longer [56-59].

Future directions

Cardiac allograft vasculopathy remains a serious complication post OHT despite our current efforts to modify and treat the risk factors. The current available therapies have shown modest benefits in slowing the progression and to treat CAV. Currently retransplantation remains the hope for severe CAV with outcomes dependant on the time from initial transplantation. With the shortage of donor hearts retransplantation poses ethical dilemmas in management of these patients.

There is a tremendous need for us to further investigate novel therapies that must address the multitude of mechanisms underlying CAV for this deadly condition in prospective randomized controlled trials and to assess longitudinal clinical outcomes in long term.

There is also a need to refine the assessment tools for CAV and to show the role of endothelial function in the clinical outcomes in patients with CAV. In a study by Fearon et al, ACE inhibitor Ramipril was shown to improve microvascular function based on improvement in index of microcirculatory resistance and coronary flow reserve. Ramipril has also been shown to improve the number of circulating endothelial progenitor cells compared to placebo although the clinical significance of this finding is unclear at this time and yet to be proven. Ramipril was not shown to significantly affect the progression of plaque or endothelial function but appeared to be safe and effective in lowering blood pressure [60].

Various HLA and non HLA antibodies have gained interest in their role in development and progression of CAV and there is a need for further studies in this area given the potential for the development of new pharmacological therapies [61, 62].

Competing Interests

The author has declared that no competing interests exist.

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