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Suppressive effects of conversion from mycophenolate mofetil to everolimus for the development of cardiac allograft vasculopathy in maintenance of heart transplant recipients☆,☆☆

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ABSTRACT

Background: Whether converting to everolimus (EVL) from mycophenolate mofetil (MMF) during the maintenance period after heart transplantation (HTx) reduces cardiac allograft vasculopathy (CAV) progression remains unclear. We sought to determine the effect of converting from MMF with standard-dose calcineurin inhibitors (CNIs) to EVL with low-dose CNIs on CAV progression.

Methods: We retrospectively reviewed the medical records of 63 HTx recipients who survived at least at 1 year after HTx. Twenty-four recipients were converted from MMF to EVL (EVL group, 2.2 ± 2.3 years after HTx), while 39 recipients were maintained on MMF (MMF group, 2.4 ± 2.2 years after HTx). The EVL group underwent three-dimensional intravascular ultrasound (3D-IVUS) analysis before and 1 year after conversion to EVL, and these data were compared with data from 2 consecutive IVUS in the MMF group.

Results: IVUS indices in the EVL group at 1 year after conversion did not show increased CAV development, whereas a significant increase in %plaque volume ($p = 0.006$) and decrease in lumen volume ($p < 0.001$) were observed in the MMF group. EVL conversion was significantly associated with smaller increases in %plaque volume ($p = 0.004$) and smaller decreases in lumen volume ($p = 0.017$). IVUS indices in the late EVL conversion group (≥2 years) also did not exhibit increased CAV development, while those in the MMF group did.

Conclusions: Conversion to EVL from MMF in maintenance periods after HTx may decrease the rate of CAV progression based on IVUS indices.

Abbreviations: %PVI, percent plaque volume index; 3D-IVUS, three-dimensional intravascular ultrasound; AZA, azathioprine; CAV, cardiac allograft vasculopathy; CMV, cytomegalovirus; CNIs, calcineurin inhibitors; EEM, external elastic membrane; EVL, everolimus; GFR, glomerular filtration rate; HTx, heart transplantation; ISHLT, International Society of Heart and Lung Transplantation; LVI, lumen volume index; MIT, maximal intimal thickness; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; NCVC, National Cerebral and Cardiovascular Center; PVI, plaque volume index; VVI, vessel volume index.

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1. Introduction

Cardiac allograft vasculopathy (CAV) is the leading cause of late morbidity and mortality in heart transplant recipients, accounting for one-third of all-cause mortality at 5 years [1]. The pathophysiology of CAV is closely linked to both immunologic factors, such as alloreactive T-cell and antibody activation, and non-immunologic factors, including pre-transplant coronary artery disease, cytomegalovirus (CMV) infection, older age of the donor and recipient, recipient's conventional risk factor (e.g. hyperlipidemia, hypertension and diabetes mellitus) and ischemia/reperfusion injury [2]. This complex etiology makes it difficult to prevent and suppress the development of CAV.

Immunosuppression after heart transplantation (HTx) has traditionally consisted of calcineurin inhibitors (CNIs) combined with mycophenolate mofetil (MMF) or azathioprine (AZA) and corticosteroids [1]. Mammalian target of rapamycin (mTOR) inhibitors, the novel immunosuppressants such as everolimus (EVL) and sirolimus, are expected to suppress CAV progression [3,4]. Previous studies have examined the influence of mTOR inhibitors on CAV by comparing them with various baseline immunosuppressive drugs, such as AZA [4], AZA and MMF [3–5], CNI-free [6,7], and add-on regimens [8]. However, concomitant immunosuppression with EVL may affect the suppressive effects of EVL on CAV progression [8]. Recently, MMF has replaced AZA due to inferior outcomes [9], and so a direct comparison between MMF and EVL is required [10,11]. Recent clinical trials on de novo heart transplant recipients have indicated that EVL with reduced-dose CNIs is more effective than MMF with standard-dose CNIs for suppressing first-year CAV progression after HTx [10,11]. However, the effects of converting to EVL from MMF in maintenance periods after HTx are still controversial [3,5–8]; furthermore, the underlying mechanism for the suppressive effect of EVL on CAV progression remains unclear [10].

The aim of the present study was to elucidate the effect of converting from MMF with standard-dose CNIs to EVL with low-dose CNIs on CAV progression using three-dimensional intravascular ultrasound (3D-IVUS).

2. Methods

2.1. Patient management and selection

We retrospectively reviewed the medical records of all post-HTx recipients at the National Cerebral and Cardiovascular Center (NCVC) in Japan between July 1993 and March 2013.

All de novo heart transplant recipients in our institution received triple immunosuppressive therapy consisting of CNIs (i.e., cyclosporine or tacrolimus), MMF, and corticosteroids [12]. We regulated immunosuppressive drug dosage based on blood trough concentrations. Standard target trough levels were as follows: cyclosporine, 350–450 ng/mL for the first month, 250–350 ng/mL between 1 and 3 months, 200–300 ng/mL between 3 and 12 months, and 100–250 ng/mL after the 1-year follow-up; tacrolimus, 9–12 ng/mL for the first 3 months, 8–9 ng/mL between 3 and 6 months, and 6–8 ng/mL after the 6-month follow-up. Tacrolimus was used as an alternative to cyclosporine as the primary immunosuppressant beginning in 2005.

Since 2007, we have primarily considered converting from MMF with standard-dose CNIs to EVL with low-dose CNIs for the following recipients: 1) recipients with impaired renal function (glomerular filtration rate [GFR] <60 mL/min/1.73 m^2); 2) those with increases in or an initially large maximal intimal thickness (MIT) on routine IVUS examinations; and 3) those with MMF-related leukopenia. According to our protocol for EVL conversion with low-dose CNIs, the standard target trough levels were as follows: EVL, 6–8 ng/mL; reduced-dose cyclosporine, 50% of standard blood concentrations; and reduced-dose tacrolimus, 3–4 ng/mL. The conversion to EVL from MMF was initiated with EVL 1.0–1.5 mg/day while MMF was withdrawn. The trough levels of EVL were evaluated at 1 week after initiation. Once target trough levels of EVL (6–8 ng/mL) were achieved, the tacrolimus or cyclosporine dose was reduced to obtain target trough levels [13].

Routine endomyocardial biopsies were performed weekly for 3 weeks after HTx, every 2 weeks from 3 weeks to 2 months, at 3 months, every 1.5 months from 3 months to 6 months, every 3 months from 6 months to 12 months, and then at 6-month intervals until the end of the fifth year, after which we performed endomyocardial biopsy every year. An International Society of Heart and Lung Transplantation (ISHLT) grade of 2R or greater acute cellular rejection on routine endomyocardial biopsy was treated with augmented immunosuppression and intravenous steroids [12,14,15]. Follow-up endomyocardial biopsies were performed at 14 to 21 days in treated cases.

Coronary angiography and IVUS examinations were performed 5–12 weeks after HTx and repeated to evaluate CAV every year. Coronary angiography was used to classify the severity of CAV as ISHLT CAV 0 (not significant), CAV 1 (mild), CAV 2 (moderate), or CAV 3 (severe) on the basis of the ISHLT guidelines [16]. A 40-MHz mechanical ultrasound transducer (View it®, Terumo, Tokyo, Japan) was advanced into a distal portion of the left anterior descending artery. Continuous ultrasound imaging was acquired at a constant rate of 1.0 mm/s to evaluate the coronary artery. Images were digitized for analysis by a researcher (T.W.) who was blinded to the clinical characteristics and treatment status of the patients. IVUS images were stored on S-VHS tapes for offline 3D IVUS analysis (Nicoras T2000® Ver. 2.1, Terumo, Tokyo, Japan). Using cross-sectional IVUS images, we compared changes in the MIT, which is known to impact long-term outcome after HTx [17–19], and coronary vessel, plaque, and lumen volumes based on 3D-IVUS images in both the EVL and MMF groups.

Seventy-four recipients who survived more than 1 year post-HTx were initially screened for inclusion (Fig. 1). Of these, 11 recipients were excluded because they lacked data from two consecutive IVUS studies. Of the remaining 63 recipients, 24 were converted from MMF with standard-dose CNIs to EVL with reduced-dose CNIs (EVL group). Of these, 17 recipients (70.8%) were converted to EVL because of CAV development, and five (20.8%) and two recipients (8.3%) were converted to EVL because of CNI-induced nephropathy and MMF-related leukopenia, respectively. The other 39 recipients remained on MMF with standard-dose CNIs (MMF group). Baseline characteristics of the recipients included in this study were collected at "study entry," which was defined as the time of the earlier of the two most recent consecutive IVUS examinations in the MMF group and as the time of the last IVUS examination before conversion in the EVL group. We analyzed data from the two most recent consecutive IVUS examinations to include all recipients who continued taking MMF as the control group. In the EVL group, IVUS data before EVL conversion (study entry) and at the 1-year follow-up after conversion were analyzed. Therefore, changes in IVUS parameters before and after conversion in the EVL group were compared with changes in the parameters of the two most recent consecutive IVUS examinations in the MMF group. There were no significant differences in the length of time between HTx and study entry between the two groups (mean, 2.2 years after HTx for the EVL group [range, 0.1–9.0 years] and mean, 2.4 years for the MMF group [range, 0.1–7.9 years], $p = 0.614$). To account for the timing of EVL conversion, study subjects were sub-classified into two groups according to the length of time between HTx and study entry. The "early" cohort included subjects enrolled within 2 years post-HTx, and the "late" cohort included the other subjects, who were enrolled more than 2 years post-HTx.

Because 14 recipients (7 in each group) underwent HTx in other countries, detailed information on their donors (i.e., donor age, sex, status of CMV infection mismatch, and cold ischemia time) were unavailable. In Japan, the Organ Transplant Law was enacted in October 1997 [12,20], and the first HTx in Japan was performed in February 1999 from a brain-dead donor in accordance with this law. From then until March 2013, 185 HTxs were performed in Japan, including 54 cases at our institute. In the present study, we included 49 of those 54 patients who underwent HTx at our institute and 14 recipients who underwent HTx in the United States and Germany on the basis of official procedures between 1993 and 2009. The ethics committee of the NCVC of Japan approved this study. Informed consent was obtained from all participants (IRB number M25-020 at NCVC).

2.2. Intravascular ultrasound measurements (Fig. 2)

We compared changes in IVUS data obtained at study entry and at the 1-year follow-up between both groups. Cross-sectional images of the left anterior descending artery spaced precisely 1 mm apart were selected for measurement. The maximum length measured was 50 mm of the left anterior descending artery, from the distal portion to the ostium. MIT was measured at the site with the greatest intimal thickness in the observed length. Plaque area was defined as the difference between the area occupied by the lumen and external elastic membrane (EEM) borders. Volumetric analyses were calculated as the summation of each area (vessel, plaque, and lumen). Each volume was standardized to account for differences in segment length between different subjects (vessel, plaque, and lumen volume indexes; VVI, PVI and LVI, respectively), and was calculated as: volumetric value/measured length (mm^3/mm). Percent plaque volume index (%PVI) was calculated as: (PV/VV) × 100%. Change in percent plaque volume was calculated as: (percent plaque volume at follow-up) − (percent plaque volume at study entry). In order to adjust for differences in the initial IVUS data between the EVL and MMF groups, relative changes for each volumetric data measure were calculated as: [(volumetric index at follow-up − volumetric index at entry) / (volumetric index at entry)] × 100%.

2.3. Statin therapy

Statin therapy was generally initiated within 2 months after HTx for all post-transplant recipients, regardless of cholesterol level, except for recipients who experienced adverse effects due to statin therapy. Pravastatin was generally used [21], but if the lipid profile worsened or if CAV progression was observed with conventional statin use, the statin dosage was increased or pravastatin was exchanged for a more powerful agent (i.e., a "strong statin"). We used atorvastatin, rosuvastatin, and pitavastatin as strong statins. Doses of at least 20 mg/day for pravastatin, 20 mg/day for atorvastatin, 5 mg/day for rosuvastatin, and 4 mg/day for pitavastatin were classified as "high-dose" statins. "Intensive statin therapy" was defined as follows: (1) initiating statin therapy during the study period in recipients who did not take statins at study entry, (2) increasing the statin dosage during the study period, and (3) converting to a strong statin from pravastatin during the study period.