의학박사 학위논문

심장이식 수혜자에서 Everolimus의 심장 동종이식 혈관병에 대한 효과: Cyclosporine 기반 및 Tacrolimus 기반 protocol과 비교 연구

The Efficacy of Everolimus to Prevent Cardiac Allograft Vasculopathy in Heart Transplant Recipients: Comparison With Cyclosporine-Based and Tacrolimus-Based Protocols

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이 논문을 의학박사 학위 논문으로 제출함

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[여기에 입력]

Abstract

The Efficacy of Everolimus to Prevent Cardiac Allograft Vasculopathy in Heart Transplant Recipients: Comparison With Cyclosporine-Based and Tacrolimus-Based Protocols

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Background

Previous studies have reported the superiority of everolimus (EVL) over antimetabolites in mitigating cardiac allograft vasculopathy (CAV) after heart transplantation (HT). However, data on the long-term effect of *de novo* EVL immunosuppression on CAV progression and clinical outcomes are lacking.

Objective

The aim of this study was to determine the long-term safety and efficacy of EVL as *de novo* immunosuppressant therapy on CAV progression and outcomes after HT.

Methods

We retrospectively reviewed the medical records of 144 HT recipients (EVL group = 24, Cyclosporine (CSA) group = 48, Tacrolimus (TAC) group = 72) who survived at least at 1 year after HT. This study evaluated treatment failure defined as all-cause death, graft failure, retransplantation and treatment requiring rejection. CAV progression was assessed using serial coronary intravascular ultrasound (IVUS) in recipients who underwent at least 2 IVUS studies.

Results

A significant attenuation in percent atheroma volume progression was observed with EVL (1.2%) compared with CSA (7.3%; p = 0.005 vs EVL) or TAC (6.6%; p = 0.0052 vs EVL) at 1 year after HT, and this trend has remained unchanged for 3 years (4.7% vs 12.4% vs 12.5%

for EVL vs CSA vs TAC respectively, p = 0.006) and 5 years (7.9% vs 14.9% vs 14.9% for EVL vs CSA vs TAC respectively, p = 0.02) after HT. The remodeling index was greater in the EVL (1.08) group than in CSA (0.23) or TAC (-0.25) groups at 1 year after HT. Kaplan-Meier analysis over a median follow-up period of 8 years did not show a statistical difference in primary endpoint event-free survival between the three groups. No death or re-transplantation occurred in the EVL group while 10 (21.8%) and 14 (20.6%) occurred in CSA and TAC group respectively.

Conclusions

De novo immunosuppression with EVL is associated with attenuated CAV progression during 5 years of IVUS follow up and with comparable long-term clinical outcomes compared with CSA or -TAC based protocols.

Key Words: heart transplantation, cardiac allograft vasculopathy, immunosuppressive therapy, intravascular ultrasound, treatment outcome

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Abbreviations

CAV = cardiac allograft vasculopathy

CNI = calcineurin inhibitor

CSA = cyclosporine

EVL = everolimus

HT = heart transplantation

ISHLT = International Society for Heart & Lung Transplantation

IVUS = intravascular ultrasound

LV = lumen volume

MMF = mycophenolate mofetil

mTOR = mammalian target of rapamycin

PAV = percent atheroma volume

SRL = sirolimus

TAC = tacrolimus

TAV = total atheroma volume

VV = vessel volume

Introduction

Over the past 50 years, heart transplantation (HT) has been consolidated as the therapy of choice for patients with end-stage heart disease. In HT recipients, cardiac allograft vasculopathy (CAV) is the leading cause of late morbidity and mortality, accounting for one-third of all-cause mortality at 5 years [1]. CAV mechanisms are not fully understood, but probably driven by immune and nonimmune mechanisms that cause inflammation, endothelial injury, and smooth muscle cell hyperplasia in the epicardial vessels as well as in the microvasculature [2]. CAV is characterized by endothelial injury and exaggerated repair response, leading to diffuse intimal hyperplasia and luminal stenosis that can involve the entire coronary arterial tree. Given the negative impact of CAV on the duration of HT graft survival, prevention remains the most effective strategy for optimizing long-term outcomes.

To prevent CAV, various medications have been studied. Studies have demonstrated the benefits of statins in improving patient survival and reduced the incidence and severity of CAV and allograft rejection [3]. Among immunosuppressants, mammalian target of rapamycin (mTOR) inhibitors has antiproliferative effects on fibroblasts and smooth muscle cells, thus they hold the potential of reducing intimal hyperplasia in coronary arteries, preventing CAV and its progression [4]. Previous studies have shown mTOR inhibitors to attenuate the progression of CAV when used as secondary immunosuppression in place of either azathioprine or mycophenolate mofetil (MMF) and in combination with a reduced dose of calcineurin inhibitor (CNI) as primary immunosuppression [5-8]. However, intravascular ultrasound (IVUS) data from large randomized trials present short to mid-term follow-up and [8, 9], there are limited long-term data regarding these patients. Also, published experience with *de novo* use of EVL in HT in routine clinical practice is currently relatively limited [10, 11]. Moreover, as far as we know, there has been no study regarding the effect and safety of *de novo* EVL based protocol in the Asian population.

The purposes of this study were to investigate the long-term effect of everolimus (EVL) as primary immunosuppressant on CAV progression as assessed by serial IVUS examinations

and to investigate the long-term safety and efficacy of an EVL-based regimen on clinical events compared with maintenance on a cyclosporine (CSA) -based and tacrolimus (TAC) -based regimen.

Methods

Study population

This study included patients ≥ 18 years who underwent HT at Asan Medical Center from 2005 to 2015 and survived for at least one year. Multiorgan transplant recipients were excluded. Since 2005, a total of 24 patients used the EVL-based protocol as a *de novo* immunosuppressant, and although all patients who used EVL as a *de novo* immunosuppressive regimen also received a calcineurin inhibitor (CNI), we will refer to this group of patients as the EVL group. Forty-eight and seventy-two patients, two and three times the number of patients in the EVL group respectively, were consecutively included from the patients using the CSA-based protocol (CSA group) and the TAC based protocol (TAC group).

Demographic, clinical follow-up, and laboratory data were obtained by review of the patients' medical records and from a prospectively collected clinical database. Immunosuppressive medications were reviewed and recorded at each outpatient visit post-HT.

Immunosuppression and management

All HT recipients received induction therapy with interleukin-2 monoclonal antibody (rituximab) as part of a standard induction protocol and a 3-drug maintenance immunosuppressive regimen consisting of a CNI (CSA or TAC), an antimetabolite agent (MMF), and tapering doses of prednisone post-HT. Withdrawal or continuance of the steroid (at the maintenance dose) was based on the attending physician's discretion and the patient's clinical status. Patients in stable condition at least 2 weeks post-HT, without evidence of rejection, or infection, MMF was replaced with EVL (trough level, 3-8 ng/mL) 0.5 mg bid orally. CSA was the major CNI used until 2007, and TAC was predominantly used after 2007. The CNI target trough concentration in first 3 months after HT was 300-350 ng/mL for CSA and 10-15 ng/mL for TAC. The target trough concentration was adjusted between 100 and 200 ng/mL for CSA and between 5 and 10 ng/mL for TAC 12 months after HT. Trough levels of CSA, TAC, and EVL were measured using high- performance liquid chromatography with tandem mass spectroscopy (XEVO TQ-S, Waters, Milford, USA) or microparticle enzyme

immunoassay (Dimension® EXL™ 200 Integrated Chemistry System; SIEMENS, Munich, Germany) and adjusted according to institutional protocols.

All patients underwent serial endomyocardial biopsies at regular intervals until 1 year after HT. 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].

Statin therapy was generally initiated within 2 weeks after HT for all post-HT recipients, regardless of cholesterol level, except for recipients who experienced adverse effects due to statin therapy. Lipid-lowering therapy with statins (initial daily dose, 10 mg of pravastatin) was mandatory [13], but if the lipid profile worsened with conventional statin use, the pravastatin dosage was increased, or pravastatin was exchanged for a stronger statin. "Intensive statin therapy" was defined as follows: (1) increasing the statin dosage during the study period, and (2) converting to a strong statin from pravastatin during the study period.

The Cytomegalovirus (CMV) antigenemia assay was performed weekly during hospitalization and during every visit at the outpatient clinic until 1 yr after HT. Gancyclovir prophylaxis was prescribed for all patients. Trimethoprim/sulfamethoxazole prophylaxis was prescribed for all patients for 1 yr after HT.

CAV and IVUS assessment

Coronary angiography with 3-dimensional IVUS as part of the surveillance for CAV progression has been performed since 2004 in most HT recipients. Baseline coronary angiography was performed within 3 months after HT unless patients had contraindications to coronary angiography. And 1, 3, 5, 8, 10 years after HT, or with any change in clinical status, follow-up coronary angiography was performed as routine surveillance. CAV was classified according to the ISHLT criteria [14]. For assessment of CAV progression, as measured by IVUS, patients with 2 or more IVUS examinations were included for analysis. IVUS was performed during routine coronary angiography after intracoronary administration of 100 to 200 mg nitroglycerin. Core laboratory analysts at the Asan Medical Center, blinded to treatment status

and sequencing of imaging studies (baseline vs. follow-up) defined the leading edges of the lumen and outer vessel wall by manual planimetry in images spaced 1-mm apart and where there is no artifact obscuring >90 º of the contiguous outer vessel wall, with reproducibility as previously reported [15, 16]. A number of measures of plaque burden were determined. Percent atheroma volume (PAV) was calculated as follows:

$$\frac{\Sigma\,(EEM_{area} - Lumen_{area})}{\Sigma\,EEM_{area}} \times 100$$

where EEM_{area} was the cross-sectional area of the external elastic membrane and $Lumen_{area}$ was the cross-sectional area of the lumen.Normalized total atheroma volume (TAV) was calculated as follows to compensate for differences in the examined vessel to the examined segment length:

$$\frac{\Sigma\,(EEM_{area} - Lumen_{area})}{Number\ of\ Images\ in\ Pullback} \times \text{Median number of images in a group}$$

where the average plaque area in each image was multiplied by the median number of images analyzed in each group to compensate for differences in segment length between patients. The vessel volume (VV) and lumen volume (LV) were also calculated to normalized values. CAV progression was assessed by calculating the changes in PAV, TAV, VV, and LV between the baseline and 1, 3, and 5 years of follow-up IVUS examinations for each patient. The remodeling index, a quantitative measure of extent and direction of remodeling, was calculated as the ratio of the change in the vascular area at the lesion site relative to the change in intimal area [17]. An index ≥ 1 indicates positive remodeling that adequately compensated (=1) or overcompensated (>1) for the intimal growth, whereas a remodeling index >0 and <1 indicates positive remodeling inadequate for intimal growth. An index <=0 indicates negative remodeling with no compensation (=0) or shrinkage (<0).

Outcome endpoints

The primary outcome endpoint was treatment failure defined by the composite of all-cause death, graft failure, retransplantation, and treatment requiring rejection in median follow-up.

Biopsy-proven rejection of at least grade 2R or any episode of rejection associated with hemodynamic compromise was defined as treatment requiring rejection.

Post-transplant diabetes mellitus (PTDM) was diagnosed using the American Diabetes Association criteria [18]. Post transplant hypertension was defined as systolic blood pressure > 140/diastolic blood pressusre > 90 mmHg/or use of antihypertensive medication. Patients receiving intensive statin therapy was defined to have hyperlipidemia. CMV antigemia was defined as > 50 CMV-positive cell per 200,000 leukocytes and CMV treatment with ganciclovir was started when > 100 CMV-positive cells per 200,000 and/or CMV disease was diagnosed. The study outcome "non-CMV infection" was defined as any infectious disease needing hospitalization and/or more than 2 weeks of treatment.

Statistical analysis

Quantitative data are summarized as mean standard deviation (SD) unless heavily skewed, in which case we used the median and interquartile range (IQR). Categorical data are expressed as counts and percentages. Baseline variables were compared using Student's t-test, Wilcoxon test, or chi-square test as appropriate. We estimated Kaplan-Meier survival curves and the log-rank test was used to compare survival function and clinical event incidence. Some adverse events were evaluated using a logistic regression model. A linear mixed model was used to assess the absolute change in PAV, TAV, VV, and LV between treatment groups. All P values were two-sided, and a value of $P < 0.05$ was considered significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

Results

Patient characteristics

Table 1 shows baseline demographics, medications, and laboratory data for the three groups. Mean recipient age at HT was 48 years old, and most patients were male. Median follow duration was 8.3 years (8.0 years for EVL group, 11.1 years for CSA group and 7.9 years in TAC group). At the time of HT, baseline characteristics were not significantly different between the three groups. Sixty percent of patients were diagnosed with dilated cardiomyopathy before transplantation, and 18% were diagnosed with ischemic cardiomyopathy. Patients in the TAC group had more preoperative mechanical circulatory support use, but there was no statistically significant difference between the other groups. The TAC group showed a slight difference from the CSA group, with fewer female to male transplants and lesser use of statins. Our post-HT management protocol recommended to use statin in every patient except those with contraindications; most of the patients used statin at 5 years after HT. In the TAC group, 80% of patients used statins at 5 years of follow-up, which was statistically less than the CSA group. The average trough level of CSA and TAC during the follow-up period was significantly lower in the EVL group than in the CSA group or TAC group (**Table 2**). EVL trough levels remained within the target range (3– 8 ng/mL) throughout the study and the mean dose at 5 years was 0.9 ± 0.3 mg/day (**Table 3**).

Effect of immunosuppression on plaque progression and vascular geometry

For the analysis of volumetric measures and progression of CAV, we identified 107 patients with a baseline and at least one more IVUS examination after HT (23 patients in the EVL group, 29 patients in the CSA group, and 55 patients in the TAC group). We excluded poor-quality images or images which could not be analyzed from the IVUS analysis. A total of 376 coronary IVUS examinations (median 4 [range: 3.4 to 4.6] per patient) were included for analysis of CAV progression in each group of patients. Volumetric measurements of plaque progression by 3-dimensional IVUS at baseline and at 1, 3, and 5- year follow-up IVUS are summarized in Table 4. At baseline, left anterior descending artery normalized TAV, VV, PV,

Table 1. Baseline characteristics of the patients according to immunosuppressant regimen

Characteristics	Everolimus (N=24)	Cyclosporine (N=48)	Tacrolimus (N=72)
Recipient characteristics			
Age, years	48.9 ± 13.0	47.0 ± 8.93	48.4 ± 13.2
Male (no. %)	20 (83.3%)	40 (83.3%)	45 (62.5%)
BMI, kg/m²	22.6 ± 4.30	22.2 ± 3.22	22.5 ± 3.60
Comorbidities			
CMV IgG-positive	24 (100%)	48 (100%)	71 (98.6%)
Diabetes	4 (16.7%)	4 (8.33%)	8 (11.1%)
Diagnosis			
DCMP	17 (70.8%)	25 (52.1%)	44 (61.1%)
ICMP	1 (4.17%)	11 (22.9%)	14 (19.4%)
Others	6 (25.0%)	12 (25.0%)	14 (19.4%)
Preoperative MCS	0 (0.00%)	1 (2.08%)	7 (9.72%)
Laboratory data			
Creatinine, mg/dl	1.03 ± 0.42	1.30 ± 0.50	1.39 ± 1.50
Bilirubin, mg/dl	1.17 ± 0.75	1.72 ± 1.01	1.73 ± 1.36
Donor characteristics			
Age of donor, years	34.7 ± 9.56	31.4 ± 9.31	34.4 ± 11.0
Donor male	18 (75.0%)	39 (81.2%)	57 (79.2%)
Female to Male	2 (8.33%)	7 (14.6%)	1 (1.39%)*
Weight difference	-9.09 ± 19.2	-7.78 ± 19.6	-10.83 ± 20.9
Total ischemic time, minutes	169 ± 72.3	163 ± 59.4	155 ± 53.1
Medications at 5 years after HT			
Statin	22 (91.7%)	47 (97.9%)	58 (80.6%)†
Aspirin	14 (58.3%)	37 (77.1%)	42 (58.3%)

Steroid	8 (33.3%)	11 (22.9%)	15 (21.1%)

* p = 0.02 for the comparison with the cyclosporine group.

† p = 0.03 for the comparison with the cyclosporine group

BMI, body mass index; CMV, cytomegalo virus; IgG, immunoglobulin G; DCMP, dilated cardiomyopathy; ICMP, ischemic cardiomyopathy; MCS, mechanical circulatory support; HT, heart transplantation

Table 2. Calcineurin inhibitor trough level during follow up

	Everolimus (N=24)	Cyclosporine (N=48)	Tacrolimus (N=72)	*P*
Tacrolimus trough level during follow up, ng/ml				
At 1 month	11.0	-	11.5 ± 3.65	NS
At 1 year	4.15 ± 2.05	-	8.08 ± 5.51	NS
At 3 years	4.60 ± 0.71	-	7.41 ± 2.33	NS
At 5 years	-	-	5.95 ± 2.20	NS
Cyclosporine trough level during follow up, ug/L				
At 1 month	290 ± 60.8	327 ± 110	-	NS
At 1 year	113 ± 36.6	268 ± 119	-	<0.001, vs CSA
At 3 years	105 ± 152	304 ± 273	-	0.01, vs CSA
At 5 years	94.4 ± 149	217 ± 146	-	NS

CSA, cyclosporine

Table 3. Everolimus dose and trough level during follow-up

	Everolimus (N=24)
Everolimus dose during follow up (mg/day)	
At 1 month	1.08 ± 0.34
At 1 year	1.07 ± 0.50
At 3 years	1.00 ± 0.48
At 5 years	0.90 ± 0.28
Everolimus trough level during follow up (ng/ml)	
At 1 month	4.75 ± 1.97
At 1 year	5.70 ± 2.18
At 3 years	5.24 ± 1.83
At 5 years	4.28 ± 1.03

patient) were included for analysis of CAV progression in each group of patients. Volumetric measurements of plaque progression by 3-dimensional IVUS at baseline and at 1, 3, and 5-year follow-up IVUS are summarized in **Table 4**. At baseline, left anterior descending artery normalized TAV, VV, PV, LV and PAV were not significantly different between groups. During follow-up, PAV was significantly increased in all three groups, but the change between 1, 3, and 5-year IVUS and the baseline measurement was significantly lower in the EVL group compared with those patients with CSA or TAC. A significant attenuation in PAV progression was observed with EVL (+1.2%) compared with CSA (+7.3%; p = 0.005) or TAC (+6.6%; p = 0.0052) at 1 year after HT, and this trend has remained unchanged for 3 years (+4.7% vs +12.4% vs +12.5% for EVL vs CSA vs TAC respectively, p = 0.006) and 5 years (+7.9% vs +14.9% vs +14.9% for EVL vs CSA vs TAC respectively, p = 0.02) after HT. Interestingly, after 1 year of treatment, EVL decreased TAV (-3.8 mm^3) while treatment with CSA (+24.2 mm^3; P = 0.005) or TAC (+19.3 mm^3; p = 0.007) showed an increase in TAV. Three and five years after HT, the TAV in the EVL group also increased, but the level of increase was statistically less than that of the other two. The efficacy of EVL to attenuate the progression of CAV was maintained at 5 years as presented by changes in PAV (**Figure 1A**) and TAV (**Figure 1B**) as compared with CSA and TAC groups.

Figure 2 shows the remodeling patterns (vessel changes in response to intimal changes) observed over the 1, 3, and 5-year follow up. In the EVL group, positive correlations between the changes in the vessel and atheroma volumes (i.e., adaptive vessel response) were observed through the entire period. However, the changes in VV were only weakly, inconsistently, or even inversely correlated to the changes in TAV in the CSA or TAC groups throughout the follow-up periods. The remodeling index was greater in the EVL (1.08) group than in CSA (0.23) or TAC (-0.25) groups. At 1-year post-HT, negative vessel remodeling (intimal increase with negative vessel remodeling) was observed in 30.4 %, 63.0% and 46.3 % for the EVL, CSA, and TAC group respectively.

Table 4. Assessment of cardiac allograft vasculopathy progression by IVUS during follow-up

	Everolimus	Cyclosporine	Tacrolimus	Overall *P*	*P* between EVL-CSA	*P* between EVL-TAC	*P* between CSA-TAC
% atheroma volume change from baseline							
Baseline	23.8 ± 1.6	21.9 ± 1.4	22.1 ± 1.1	0.62	0.39	0.37	0.92
1 year after HT	25 ± 2.2	29.4 ± 1.9	28.7 ± 1.4	0.27	0.13	0.16	0.76
1 year change from baseline	1.2 ± 1.6	7.3 ± 1.4	6.6 ± 1	0.008	0.005	0.005	0.68
p value	0.45	<0.001	<0.001				
3 years after HT	28.5 ± 2.6	34.6 ± 2.4	34.6 ± 1.7	0.13	0.09	0.05	0.99
3 year change from baseline	4.7 ± 2.1	12.4 ± 1.9	12.5 ± 1.4	0.006	0.01	0.003	0.97
p value	0.03	<0.001	<0.001				
5 years after HT	31.7 ± 2.7	37.1 ± 2.4	37.1 ± 1.7	0.22	0.14	0.1002	0.95
5 year change from baseline	7.9 ± 2.2	14.9 ± 1.9	14.9 ± 1.3	0.018	0.02	0.0072	0.99
p value	<0.001	<0.001	<0.001				
Total atheroma volume change from baseline							
Baseline	123.9 ± 10.4	125.1 ± 9.3	127.8 ± 6.7	0.94	0.94	0.7568	0.81
1 year after HT	120.1 ± 12.4	149.4 ± 11.1	147.3 ± 8	0.14	0.08	0.068	0.88

1 year change from baseline	-3.8 ± 7.3	24.2 ± 6.5	19.3 ± 4.7	0.01	0.005	0.0088	0.55
p value	0.60	<0.001	<0.001				
3 years after HT	143.7 ± 14.1	180.5 ± 12.7	176.3 ± 9.2	0.10	0.06	0.05	0.794
3 year change from baseline	19.8 ± 9.5	55.1 ± 8.5	48.3 ± 6.2	0.02	0.007	0.01	0.52
p value	0.04	<0.001	<0.001				
5 years after HT	151.8 ± 15.8	192.3 ± 13.7	184.5 ± 9.8	0.13	0.05	0.08	0.64
5 year change from baseline	26.9 ± 11.4	67 ± 9.5	56.3 ± 6.8	0.02	0.01	0.03	0.36
p value	0.01	<0.001	<0.001				
Total vessel volume change from baseline							
Baseline	518.6 ± 26.1	576.3 ± 23.2	582.3 ± 16.9	0.11	0.10	0.04	0.84
1 year after HT	471.9 ± 24.5	515 ± 22.1	518.5 ± 15.9	0.26	0.19	0.11	0.89
1 year change from baseline	-46.7 ± 19.9	-59.8 ± 18.0	-64.1 ± 12.9	0.77	0.63	0.47	0.84
p value	0.02	0.001	<.0001				
3 years after HT	506.8 ± 23.7	519.9 ± 21.7	523.7 ± 15.5	0.84	0.68	0.55	0.89
3 year change from baseline	-11.9 ± 22.1	-55.0 ± 20.1	-58.7 ± 14.5	0.19	0.15	0.08	0.88
p value	0.59	0.006	<0.001				
5 years after HT	471.2 ± 26.7	517 ± 22.7	506.6 ± 16.2	0.40	0.19	0.26	0.71

5 year change from baseline	-39.7 ± 26.5	-59.5 ± 22.4	-75.2 ± 16.0	0.51	0.57	0.26	0.57
p value	0.07	0.009	<0.001				
Total lumen volume change from baseline							
Baseline	394.7 ± 23.1	451.3 ± 20.6	454.5 ± 15	0.08	0.07	0.03	0.90
1 year after HT	351.8 ± 22.1	365.8 ± 20	371.5 ± 14.3	0.76	0.64	0.46	0.82
1 year change from baseline	-42.9 ± 21.3	-83.7 ± 19.3	-83.5 ± 13.8	0.25	0.16	0.11	0.99
p value	0.05	<0.001	<0.001				
3 years after HT	363.1 ± 22.9	339.5 ± 21	347 ± 15	0.74	0.45	0.56	0.77
3 year change from baseline	-31.6 ± 23.5	-110.4 ± 21.3	-107.0 ± 15.4	0.02	0.01	0.008	0.90
p value	0.18	<0.001	<0.001				
5 years after HT	319.9 ± 22.9	326.8 ± 19.6	322.9 ± 14	0.97	0.82	0.91	0.87
5 year change from baseline	-64.3 ± 25.3	-127.4 ± 21.7	-131.6 ± 15.5	0.07	0.06	0.02	0.87
p value	0.003	<0.001	<0.001				

EVL, everolimus; CSA, cyclosporine; TAC, tacrolimus; HT, heart transplantation

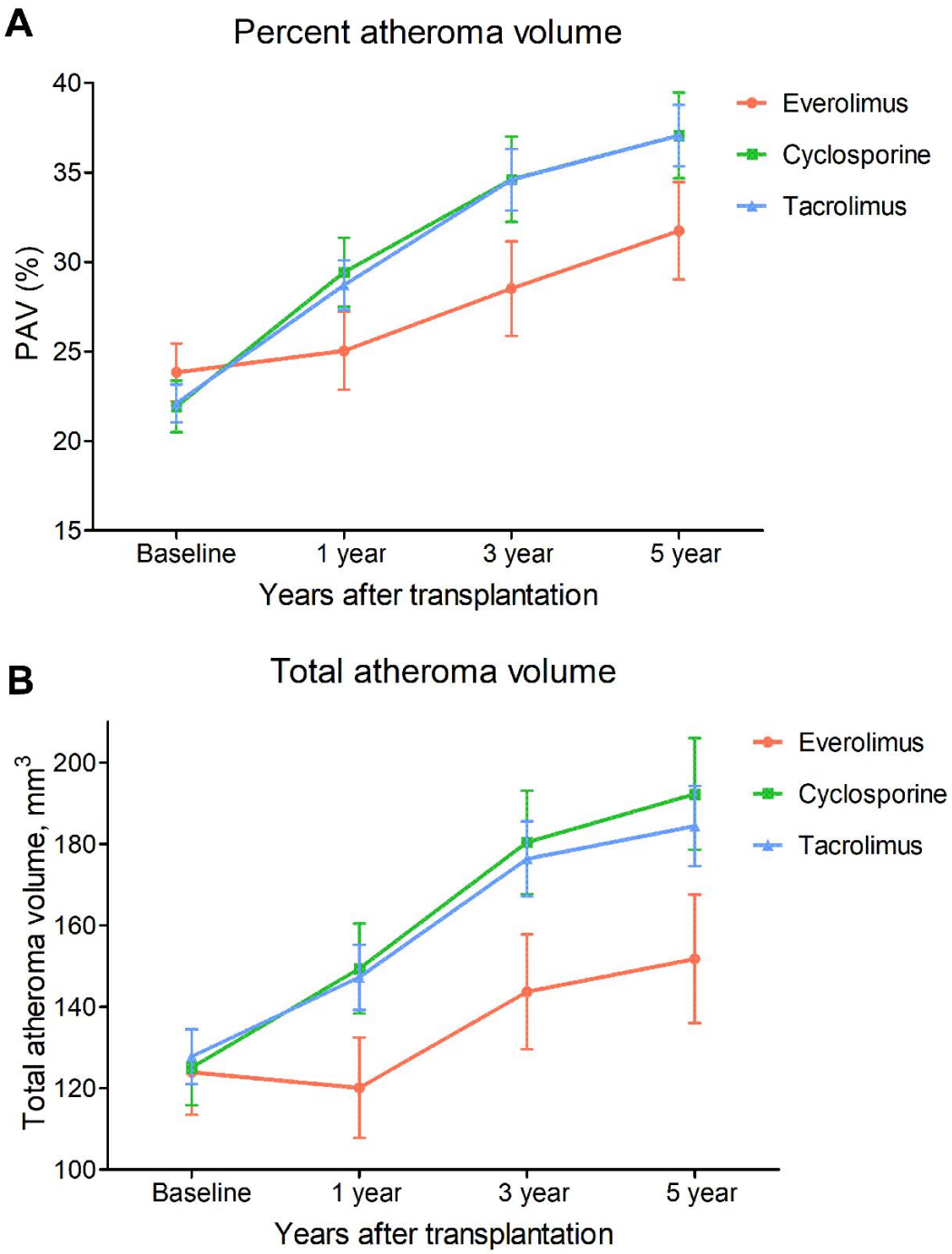

Figure 1. Changes in PAV (A) and TAV (B) as assessed by serial IVUS examinations during follow-up, stratified by type of immunosuppressive regimen. Values are mean ± SEM for each treatment group.

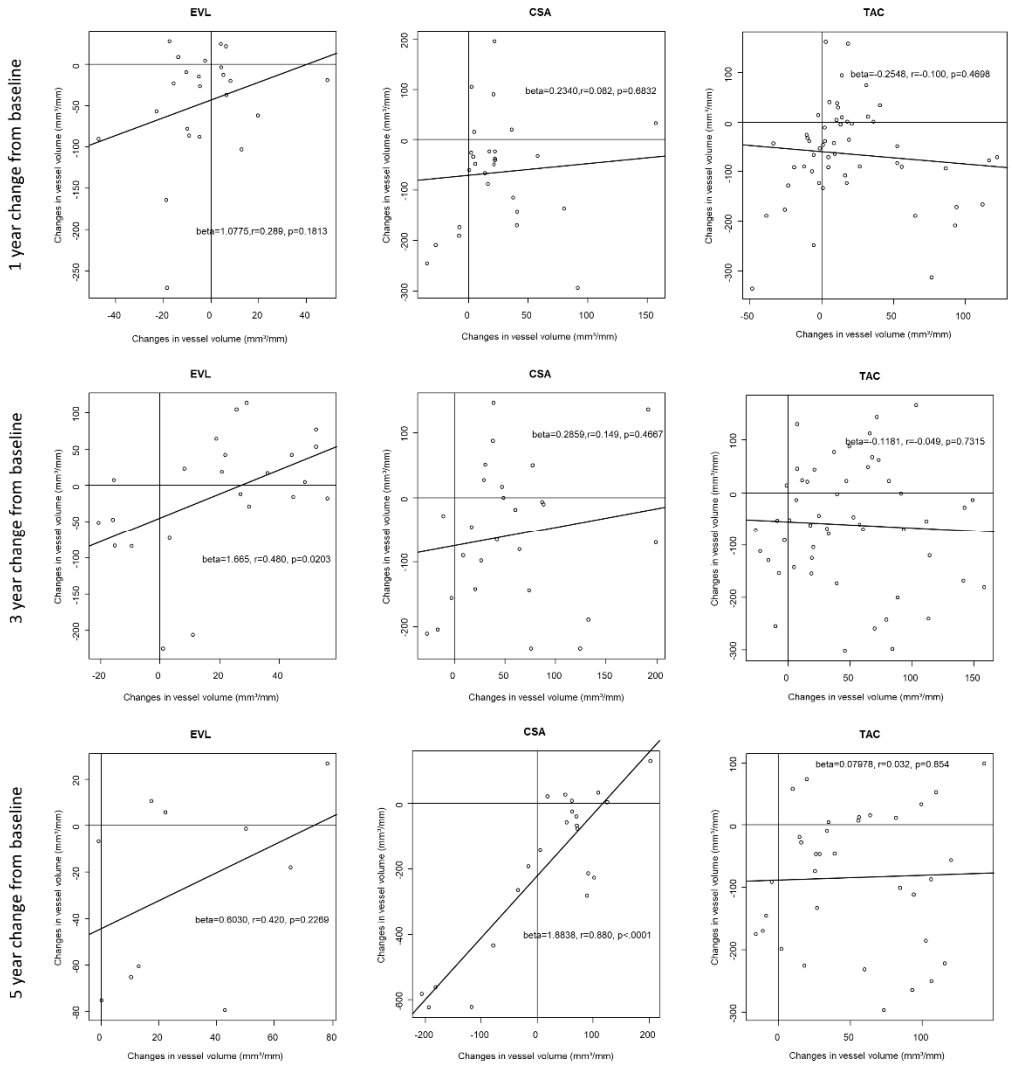

Figure 2A Remodeling patterns (Vessel changes in response to intimal changes) during follow up according to immunosuppressant regimen.

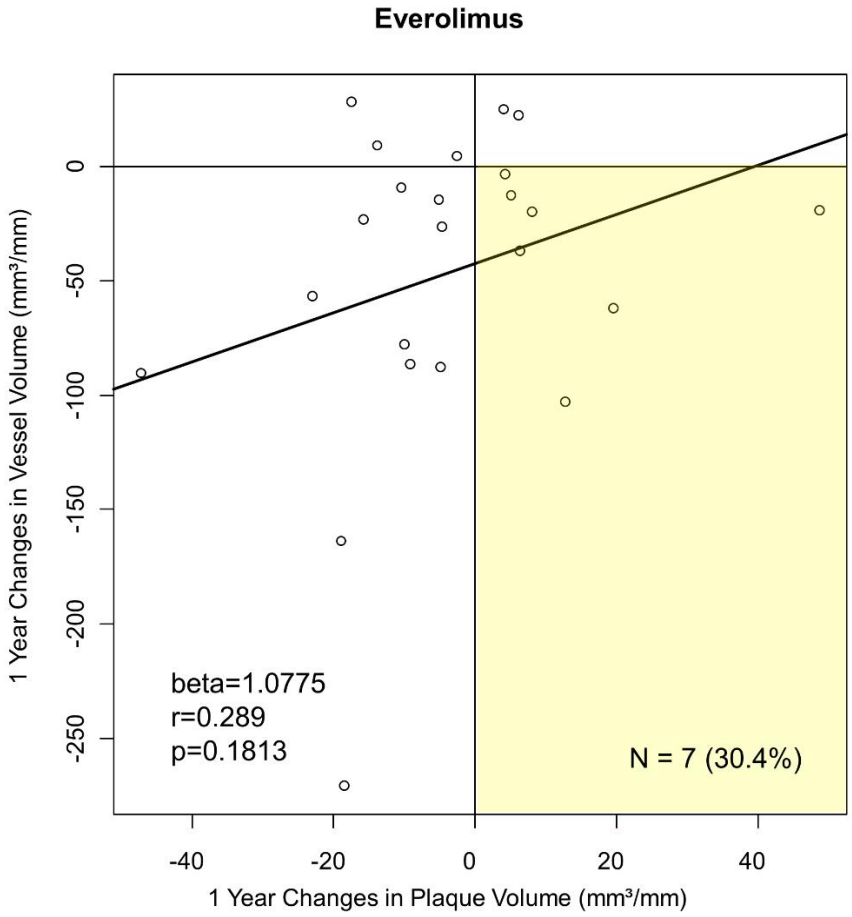

Figure 2B. 1 year change from baseline in everolimus group.

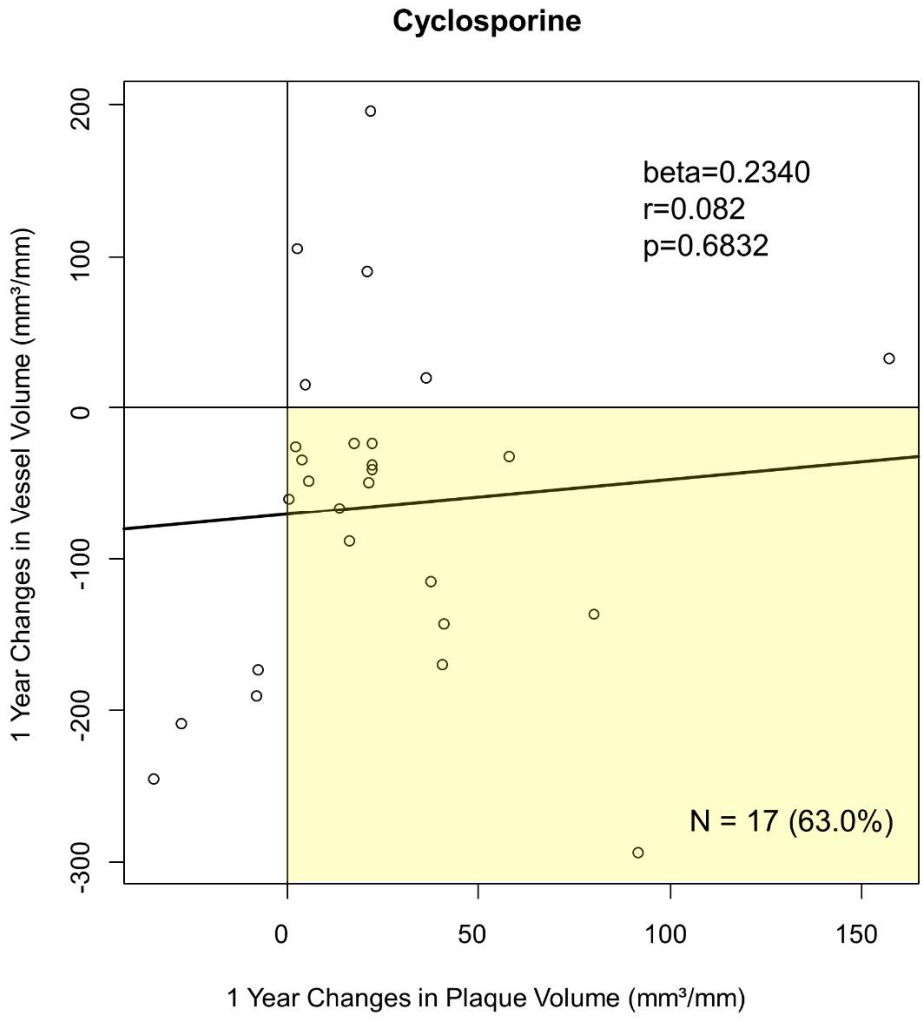

Figure 2C. 1 year change from baseline in cyclosporine group.

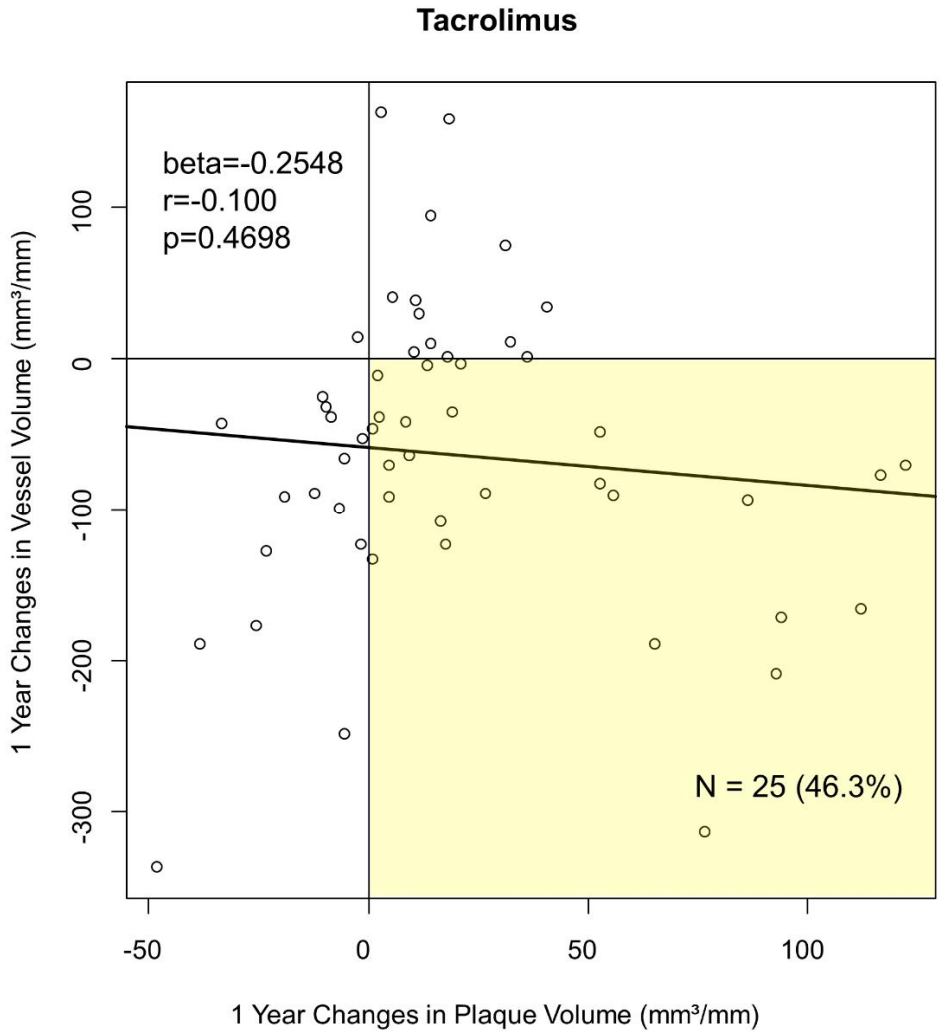

Figure 2D. 1 year change from baseline in tacrolimus group.

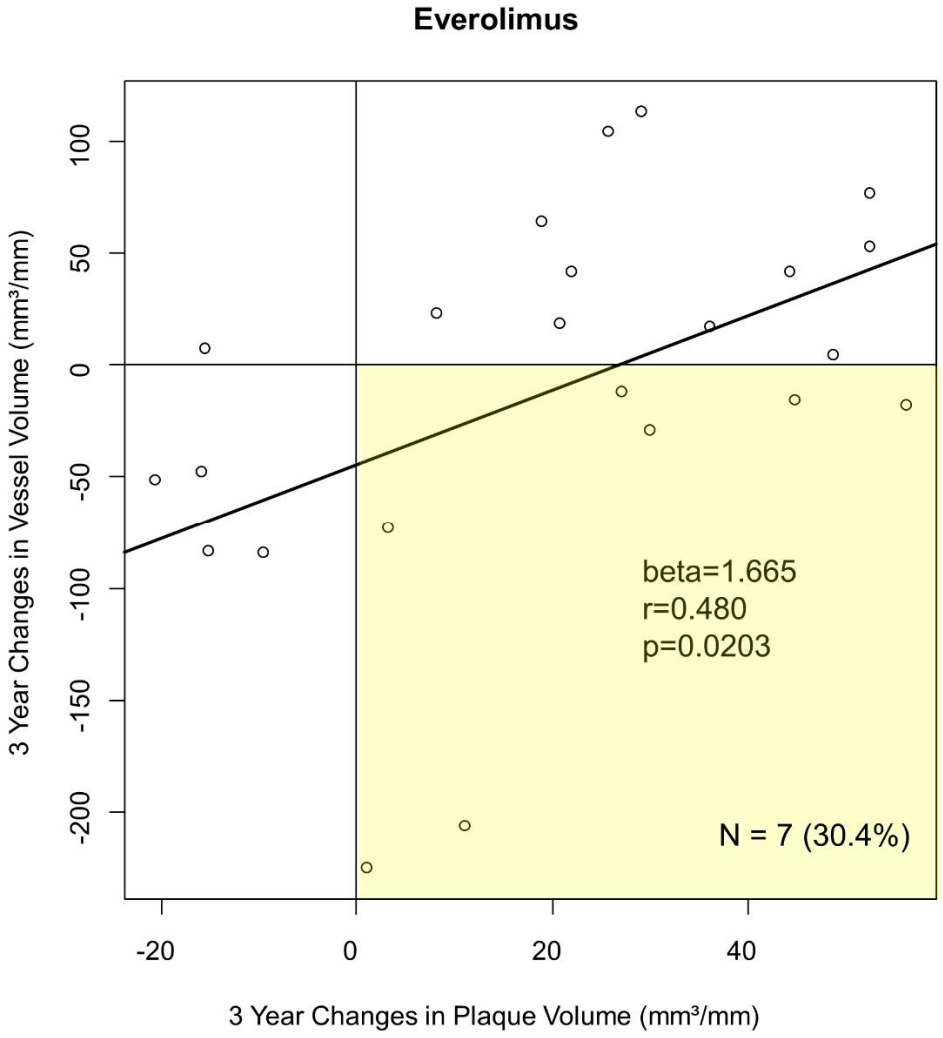

Figure 2E. 3 year change from baseline in everolimus group.

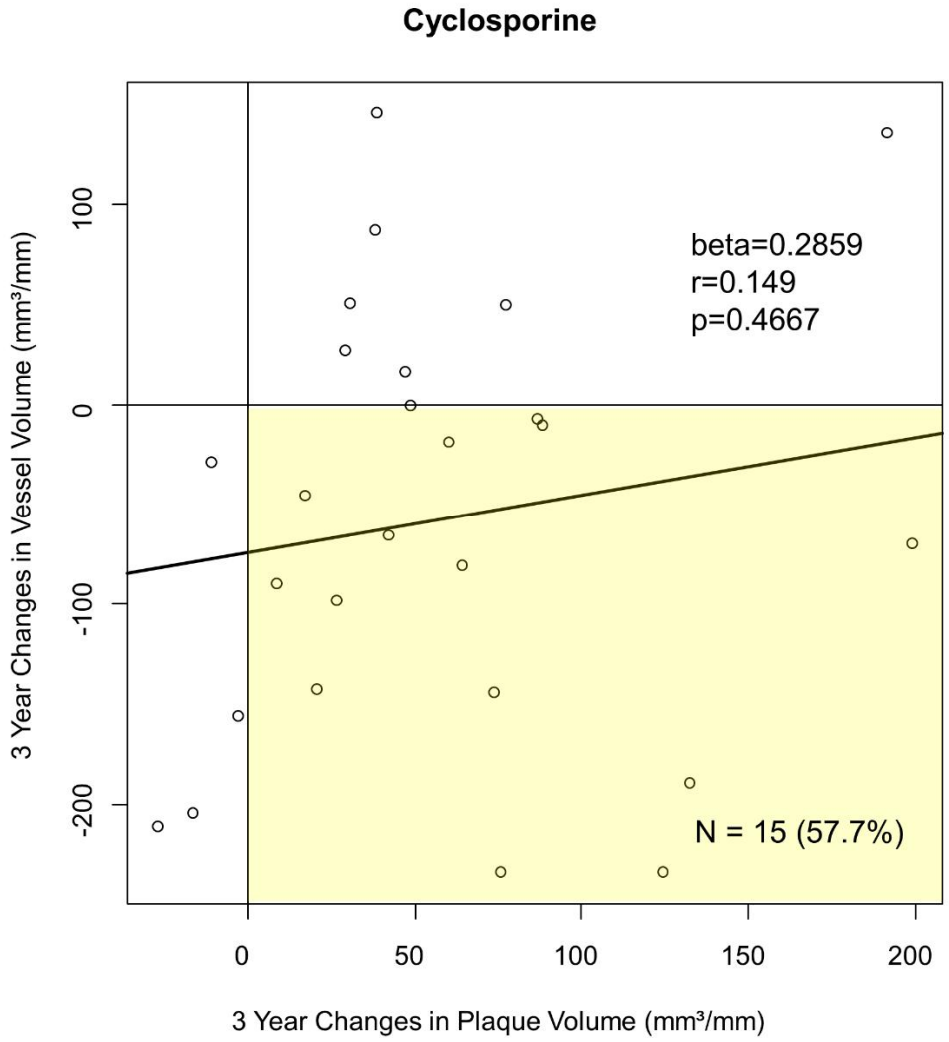

Figure 2F. 3 year change from baseline in cyclosporine group.

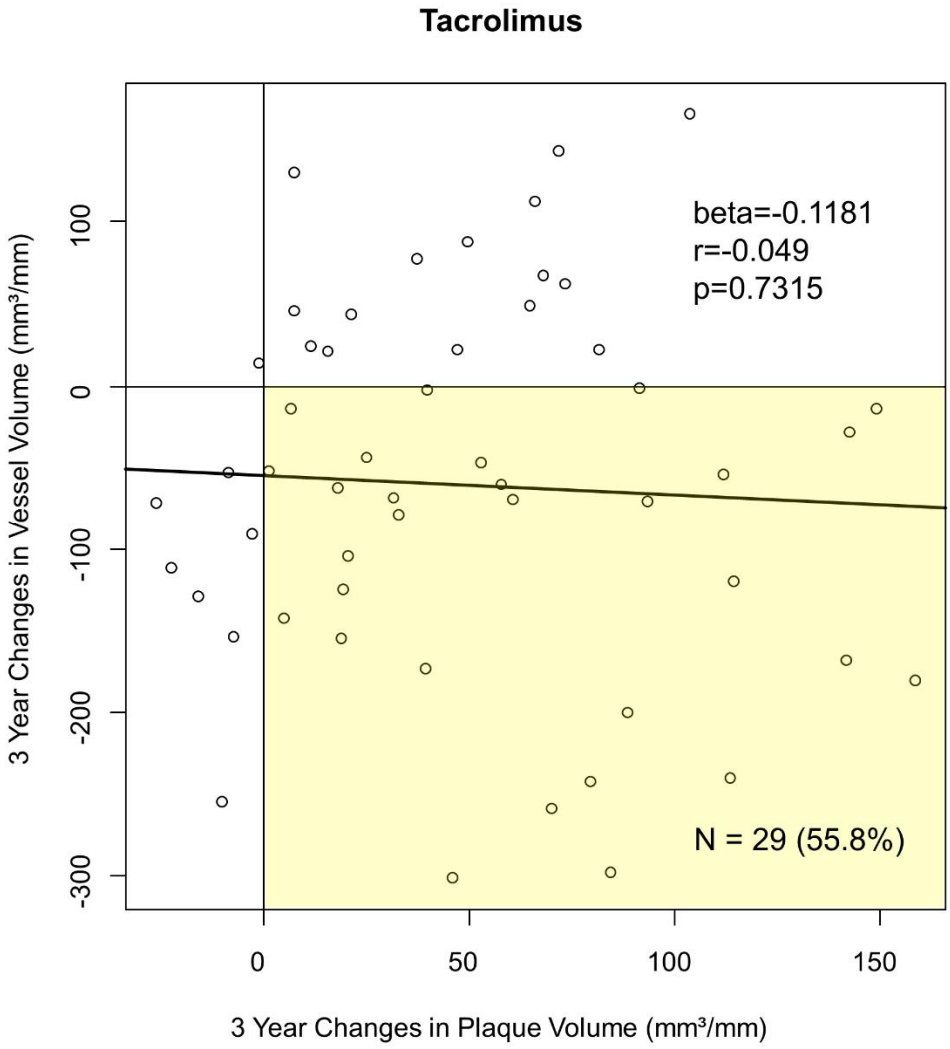

Figure 2G. 3 year change from baseline in tacrolimus group.

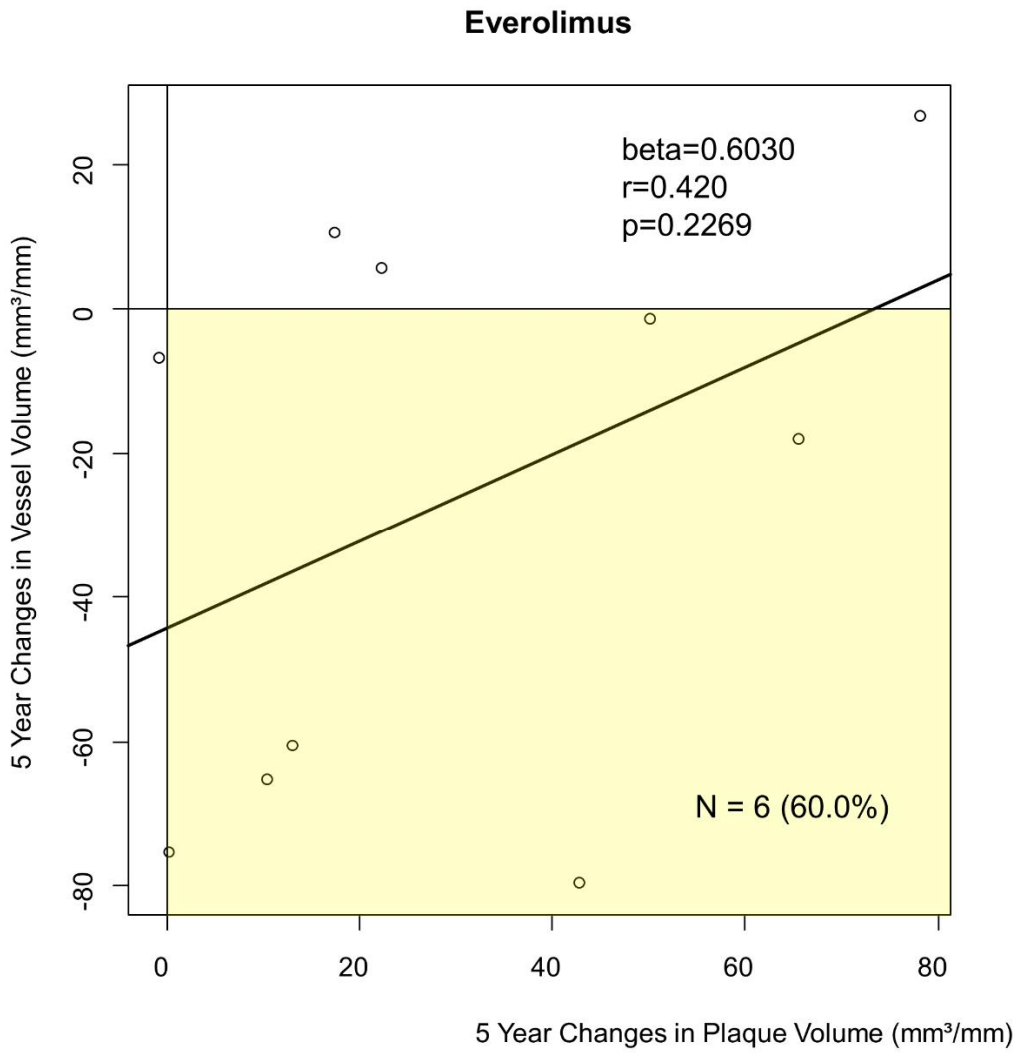

Figure 2H. 5 year change from baseline in everolimus group.

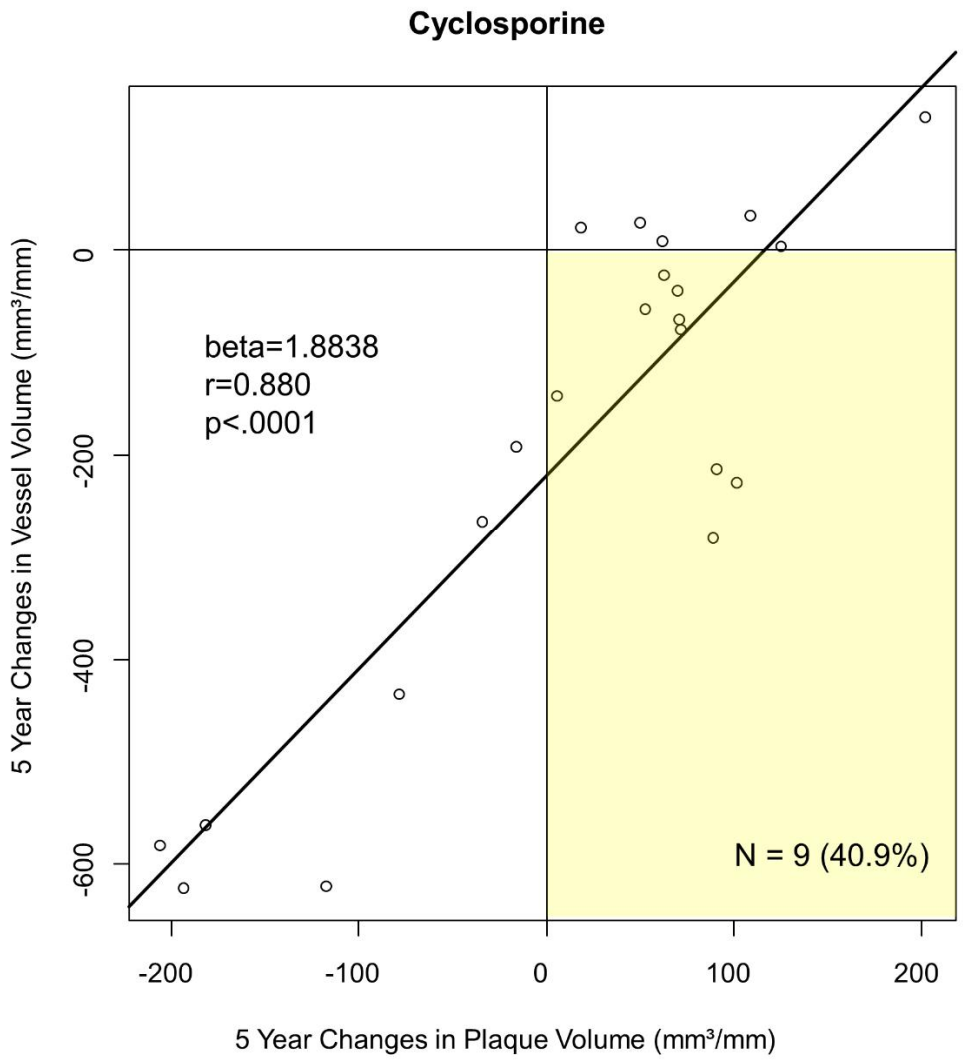

Figure 2I. 5 year change from baseline in cyclosporine group.

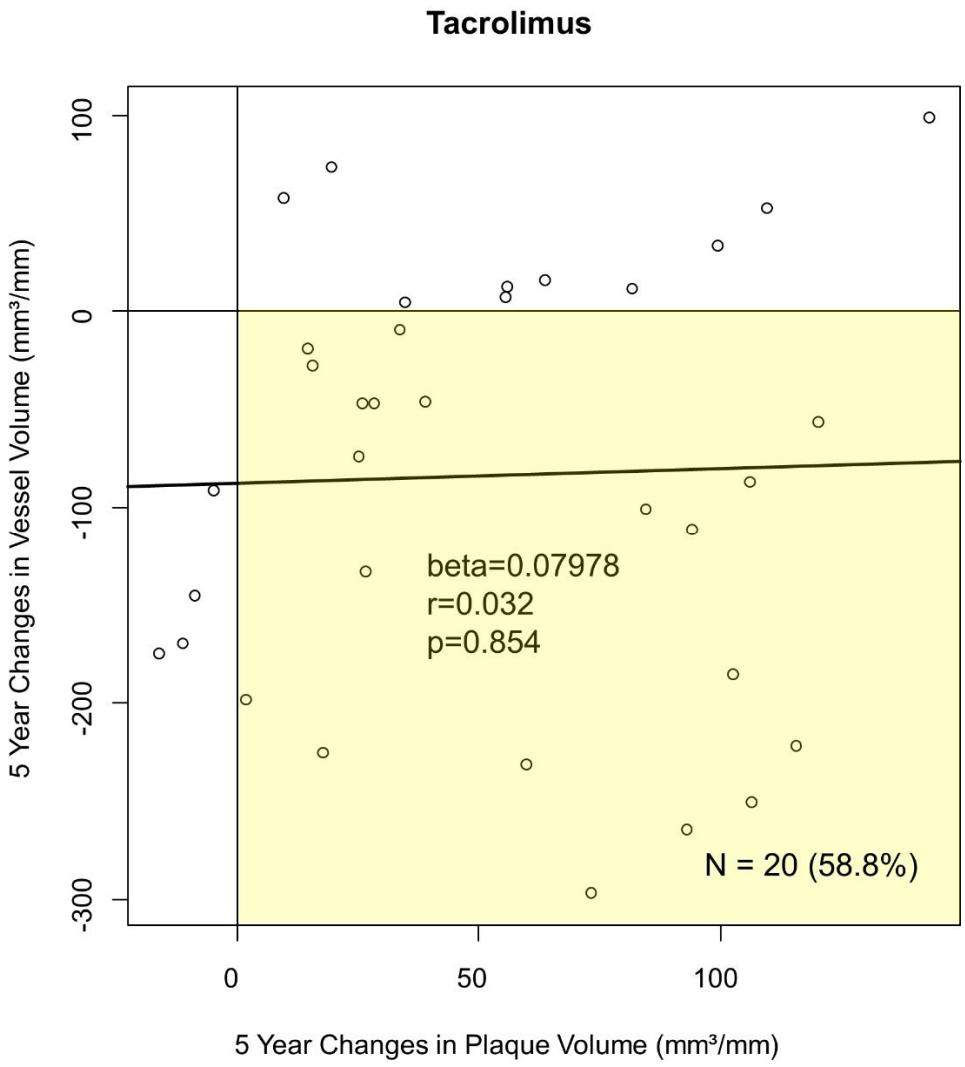

Figure 2J. 5 year change from baseline in tacrolimus group.

Effect of immunosuppression regimens on clinical outcomes

Kaplan-Meier analysis over a median follow-up period of 8 years did not show a statistical difference in event-free survival between the three groups (**Figure 3**). No death or re-transplantation occurred in the EVL group during the follow-up period while 10 (21.8%) and 14 (20.6%) occurred in the CSA and TAC group respectively (**Table 5**). We did not identify any difference in rates of treatment requiring rejection among patients treated with EVL-based protocol and those treated with CSA-based or TAC-based protocol during follow-up (0% vs 19.9% vs 19.4 in EVL, CSA and TAC group respectively; $p = 0.1$). In the CSA group, 9 patients (19.7%) had moderate-to-severe (ISHLT grade 2R or 3R) cellular rejection and in the TAC group, 7 patients (11.1%) had moderate-to-severe cellular rejection, while no patients in the EVL group had moderate-to-severe cellular rejection. Regarding the metabolic effects of immunosuppressant protocols, the prevalence of PTDM was not significantly different between groups at baseline and at 8 years of follow-up. A patient who received intensive statin therapy was numerically higher in the EVL group compared to the CSA or TAC group (87.5% vs. 69.9% vs. 54.8% in EVL, CSA, and TAC group respectively) but statistical significance was not made. The incidence of CMV infections was less with EVL-based protocol treatment (0 (0%)) than treatment with either CSA-based protocol (9 (18.8%), $p=0.27$) or TAC-based protocol (13 (18.8%), $p = 0.16$); the incidence of non-CMV infections did not differ between groups. The patients treated with EVL had less development in moderate-to-severe CAV (as assessed with the ISHLT nomenclature) compared to the other two groups. Changes in serum creatinine did not differ significantly over 5 years of follow up between the groups. However, the number of patients who ever had more than 2 mg/dl of serum creatinine was greater in the EVL group.

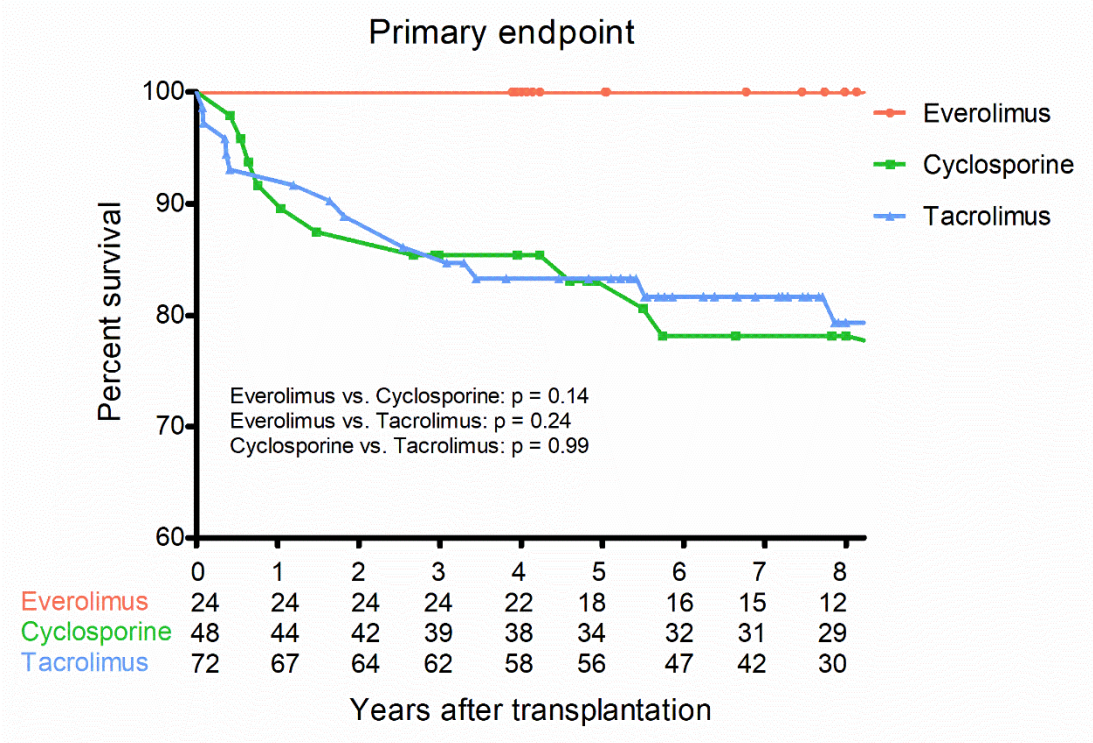

Figure 3. Event free survival in heart transplant recipients according to immunosuppressive regimen.

Table 5. Clinical endpoints at 8-year follow up according to groups

	Everolimus	Cyclosporine	Tacrolimus	Overall *P*	*P* between EVL-CSA	*P* between EVL-TAC	*P* between CSA-TAC
Primary endpoint	0 (0%)	10 (21.8%)	14 (20.6%)	0.07	0.14	0.24	0.99
Death	0 (0%)	3 (6.3%)	6 (9%)	0.40	0.68	0.46	0.94
Retransplantation							
Treatment requiring rejection	2 (8.3%)	9 (19.7%)	13 (19.4%)	0.30	0.33	0.32	0.99
PTDM	5 (20.8%)	14 (29.4%)	30 (42.1%)	0.22	0.95	0.19	0.46
Hypertension	17 (72.7%)	26 (58.8%)	26 (37.9%)	0.003	0.43	0.003	0.23
Hyperlipidemia	21 (87.5%)	33 (69.9%)	39 (54.8%)	0.001	0.33	0.002	0.26
CMV infection	0 (0%)	9 (18.8%)	13 (18.8%)	0.09	0.18	0.21	0.99
Treatment	0 (0%)	8 (16.8%)	13 (18.6%)	0.1	0.27	0.16	0.93
Viremia	0 (0%)	7 (14.6%)	6 (8.8%)	0.14	0.12	0.79	0.59
Non-CMV infection	10 (44.6%)	25 (52.1%)	40 (56.6%)	0.32	0.55	0.36	0.92
ISHLT CAV grade	1 (4.2%)	8 (19%)	17 (25.5%)	0.05	0.07	0.07	0.93
0	23 (95.8%)	37 (77.1%)	55 (76.4%)				

1	1 (4.2%)	6 (12.5%)	14 (19.4%)				
2	0 (0%)	3 (6.3%)	1 (1.4%)				
3	0 (0%)	2 (4.2%)	2 (2.8%)				
Changes of serum creatinine							
At 1 month	-0.05 ± 0.22	-0.17 ± 0.16	-0.29 ± 0.13	0.63	0.68	0.36	0.55
At 1 year	0.13 ± 0.24	-0.08 ± 0.17	0.04 ± 0.14	0.74	0.47	0.75	0.57
At 3 years	0.10 ± 0.24	0.11 ± 0.17	0.01 ± 0.14	0.88	0.99	0.72	0.64
At 5 years	0.14 ± 0.24	0.31 ± 0.17	-0.08 ± 0.14	0.19	0.57	0.41	0.07

EVL, everolimus; CSA, cyclosporine; TAC, tacrolimus; PTDM, post transplant diabetes mellitus

Discussion

The main findings of this study can be summarized as follows: 1) *de novo* use of EVL as secondary immunosuppression combined with reduced dose CNI was associated with attenuated progression of CAV to 5 years after HT; 2) EVL was not associated with significantly different all-cause mortality, graft failure, retransplantation, and treatment requiring rejection after 8 years of follow-up, although the trend of clinical benefit appeared in the EVL group patients; and 3) early adoption of EVL-based immunosuppression was safe and well tolerated for the long term compared with conventional CNI-based regimens. To the best of our knowledge, this is the first study to demonstrate long-term IVUS results of *de novo* EVL use and efficacy and safety in the Asian population.

In our study, the progression of CAV has been attenuated with the introduction of EVL, and these results can be sustained over 5 years after HT. EVL has been demonstrated to reduce first-year intimal thickening by IVUS in several clinical trials. The current study demonstrated that significant increases in plaque volume and vessel shrinkage were observed in the CSA and TAC group, resulting in a significant increase in PAV and reduced LV at the 5-year follow-up, whereas these worsening changes in the IVUS indices indicating CAV progression were attenuated in the EVL group. Our findings were consistent with the previously reported beneficial effects of mTOR inhibitors, including sirolimus (SRL) [7, 19] and its derivative EVL [8, 20] on the progression of CAV compared with azathioprine or MMF among *de novo* HT patients on full- or reduced-dose CNI. The IVUS substudy of A2310 (Everolimus Versus Mycophenolate Mofetil in HT: A Randomized Multicenter Trial) found that the increase in maximal intimal thickness 12 months post-HT and the incidence of CAV were significantly lower in the EVL and reduced-dose CSA group compared with the MMF and standard-dose CSA group [8]. Recently, Asleh et al [21] showed that primary immunosuppression with SRL with complete withdrawal of CNI was related to significant attenuation of plaque volume progression (SRL: 2.8 ± 2.3; CNI: 0.46 ± 1.8; $p < 0.0001$) and plaque index (SRL: 12.2 ± 9.6%; CNI: 1.1 ± 7.9%; $p < 0.0001$), compared to the CNI group. Interesting findings of our study

include the decrease in TAV at 1 year in follow-up IVUS compared to baseline IVUS and positive remodeling appeared with EVL-based immunosuppression. A growing body of evidence supports mTOR inhibitor-mediated mechanisms of CAV attenuation beyond its immunosuppressive properties, and suggests that the primary mechanism is derived from its antiproliferative and anti-migratory effects on vascular smooth muscle cells, as demonstrated with *in vitro* and *in vivo* studies [14, 22]. The mTOR inhibitors also reduce extracellular matrix accumulation and fibrosis [23] and induce production of nitric oxide [24], both of which can result in positive vascular remodeling and less obliteration of the coronary artery lumen. Regarding remodeling of the coronary artery, vessel responses of heart transplants seem to be different from native coronary arteries. [25-27] Based on these results, EVL is thought to cause positive remodeling in the coronary arteries of HT patients.

In our study, the primary composite endpoint of all-cause death, retransplantation, and treatments requiring rejection were not different between EVL-based protocols and CSA or TAC-based protocols. Individual variables responsible for the benefit were the reduction in all-cause mortality and treatment-requiring rejection, although statistical significance was not reached. Previous randomized trials on mTOR inhibitors showed favorable rejection and efficacy results in EVL combined with standard- or reduced dose CNI [10, 20, 28]. Two randomized trials have assessed the use of EVL with reduced-dose CSA versus MMF with standard-dose CSA in *de novo* HT populations [5, 10] showed than EVL with reduced-dose CSA offers equivalent efficacy to standard-dose CSA. Using an EVL target range of 3-8 ng/mL, the primary composite efficacy endpoint and the incidence of biopsy-proven acute rejection were similar in the EVL and MMF treatment arms at 12 months post-tranplant in each study. However, complete withdrawal of CNI should be carefully considered since studies on CNI-free regimen demonstrated conflicting results on allograft rejection [29, 30]. Although a recent large retrospective study [21] showed lower all-cause mortality (adjusted hazard ratio [HR]: 0.46; 95% confidence interval [CI]: 0.30 to 0.68; p = 0.0001), and fewer CAV-related events (adjusted HR: 0.35; 95% CI: 0.21 to 0.59; p <0.0001) in complete withdrawal cohort, routine

use after HT to reduce mortality is not supported by a preponderance of the evidence [20, 31]. Despite a trough level of CNI in the EVL group that was lower than comparable groups, there were no significant differences in changes of serum creatinine. Recent evidences relating to a renal benefit of EVL with reduced CNI in HT recipient is less convincing. Most of the patients (22, 91.7%) were using CSA as the conjunctive primary immunosuppressant. During the study period, the trough level of CSA was maintained at about half that of the CSA group. A recent study with Asleh et al [21] had shown that an mTOR inhibitor, SRL did not cause nephrotoxicity compared to CNIs. These results suggest that the level of CNI used in combination with EVL mainly influenced renal function rather than EVL itself and nephrotoxicity can be prevented by reducing CNI trough level. In addition to the well-established manifestations of CMV syndrome and potentially organ-invasive CMV disease, CMV infection increases the risk of acute rejection [32] and is associated with accelerated development of CAV [33],with an increased risk for secondary infections [34]. The mTOR inhibitors appear to inhibit CMV amplification by blocking the phosphatidylinositol 3-kinase pathway, a critical step for viral signaling and replication [35, 36]. The most robust data relating to an effect of EVL on CMV infection and CMV-related events following HT are derived from three randomized studies of *de novo* EVL therapy with standard CNI [20], reduced-dose CNI [5, 10], or reduced CNI with early CNI withdrawal [30]. EVL was again observed to reduce the incidence of CMV infection may reduce CAV development. CNIs are known to promote hypertension because they increase oxidative stress and sympathetic activation, which may cause afferent arteriolar vasoconstriction [37]. CNI minimization with mTOR inhibition may reduce the incidence of hypertension compared with standard-dose CNI, but data are conflicting. In our result, hypertension was more common in the EVL group. Although hypertension is a common side effect of mTOR inhibitors [38-40], further studies are needed to confirm this effect. In the EVL group, MMF was replaced with 0.5mg bid EVL at 2 to 4 weeks after HT. A previous systematic review of randomized controlled trials of either SRL or EVL concluded that the risk of wound complications is increased in patients receiving an mTOR inhibitor with CNI therapy [41], but included early

trials in which large SRL loading doses and high exposure levels were used with standard-exposure CSA. Randomized trials of delayed initiation of EVL and reduced dose CSA with MMF as a bridge appears to provide a better safety profile than immediate initiation, by reducing the incidence of pericardial effusions, especially those requiring pericardiocentesis, and by improving overall drug tolerability, with less adverse event-driven discontinuations, without compromising antirejection efficacy [42].

Limitations

The main limitations of this study were the small sample size and the observational, retrospective design without randomization. Patients were switched to EVL only when stable, for example, when not actively undergoing rejection, though they could be subsequently converted to EVL. Also, some patients could not convert to EVL because of side effects were excluded. Patients who did not undergo serial 3D IVUS were excluded from IVUS analysis. Furthermore, patients with rapidly progressive CAV without serial IVUS examinations were excluded from the analysis.

Conclusion

De novo immunosuppression with EVL is associated with attenuated CAV progression during 5 years of IVUS follow up and with comparable long-term clinical outcomes compared with CSA- or TAC-based protocols. In addition, this 3D-IVUS study suggests that the suppressive effects of EVL on CAV progression may be induced not only by reducing plaque progression but also by suppressing vessel shrinkage. Early introduction of EVL can provide adequate immunosuppressive potency in selected patients, but it should be borne in mind that numerous exclusion criteria were applied.

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국문요약

배경: 이전 연구에서 심장 이식 후 발생하는 동종 이식 혈관병증 (Cardiac allograft vasculopathy, CAV)의 진행을 완화하는데 대한 antimetabolite 대비 everolimus (EVL)의 우월성이 보고된 바 있다. 그러나 de novo EVL 면역억제 프로토콜이 CAV의 진행과 임상 효과에 미치는 장기적인 영향은 보고된 바 없다.

연구 목적: 본 연구를 통해 de novo EVL 면역억제 프로토콜이 CAV의 진행과 임상 경과에 미치는 장기적인 효과와 안정성을 확인하고자 하였다.

연구 방법: 심장이식 후 적어도 1년 이상 생존한 144 명의 심장이식 수혜자 (EVL군 24명, Cyclosporine (CSA)군 48명, Tacrolimus (TAC)군 72명)의 의무기록을 후향적으로 분석하였다. 사망, 이식심의 상실, 재이식 및 치료가 필요한 거부 반응으로 정의된 치료 실패를 1차 연구종료점으로 평가하였다. CAV의 진행은 최소 2회 이상 혈관내 초음파를 시행한 수혜자에서 연속적 혈관내 초음파 영상을 비교 분석하여 평가하였다.

결과: 심장이식 후 1 년째 혈관내 초음파 상에서 CSA군 (7.3 %, p = 0.005 vs EVL) 이나 TAC군 (6.6 %; p = 0.0052 vs EVL)에 비해 EVL군 (1.2 %)에서 % 죽상경화반 증가에 대한 유의한 감소가 관찰되었으며, 이 감소 효과는 심장이식 후 3년 (4.7% vs 12.4% vs 12.5% for EVL vs CSA vs TAC, p = 0.006)과 5년 (7.9% vs 14.9% vs 14.9% for EVL vs CSA vs TAC, p = 0.02)째 혈관내 초음파에서도 유의하게 유지되었다. Remodeling 지수는 EVL군에서 1.08로 CSA군의 0.23과 TAC군의 -0.25에 비해 높은 것으로 관찰되었다. Kaplan-Meier 분석 결과 8년의 추적 관찰 기간 중 세 그룹 간의 1차 연구종료점 발생에는 통계적으로 유의한 차이가 없었다. EVL군에서는 사망 또는 재이식이 발생하지 않았으며 CSA군과 TAC군에서 각각 10명 (21.8 %)과 14명 (20.6 %)에서 사망 또는 재이식이 발생하였다.

결론: De novo EVL 면역억제 프로토콜은 5년째 혈관내 초음파 상 CAV 진행의 감소와 관련이 있으며, CSA 또는 TAC 기반 면역억제 프로토콜과 비교하여 유사한 정도의 장기 임상 결과를 보인다.

중심단어: 심장이식, 동종이식 혈관병증, 면역억제요법, 혈관내 초음파, 치료 결과