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# The Effect of Statins on Cardiac Allograft Survival

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ABSTRACT

Purpose. In addition to having a lipid-lowering effect, statins also have an anti-inflammatory effect that may reduce allograft dysfunction by preventing cardiac allograft vasculopathy (CAV) and play an immunomodulatory role. We studied the effect of statins on cardiac allograft survival at the National Taiwan University Hospital (NTUH).

Materials and Methods. We retrospectively reviewed the patients undergoing heart transplantation at NTUH in the last 6 years. After transplantation, all patients received biochemical monitoring every month and echocardiographic examination regularly at NTUH. Protocol biopsy was performed in all except 18 pediatric patients. All patients received immunosuppressants, including tacrolimus or cyclosporine, everolimus or mycophenolate acid, and prednisolone. They were divided into statin and nonstatin groups according to whether or not a statin was taken.

Results. At NTUH, from 2007 to 2012, 168 heart transplantations were performed. The ages of the patients ranged from 6 to 74 years old with male predominance. The etiology was mainly dilated cardiomyopathy (52.4%) and ischemic cardiomyopathy (39.3%), including 7 retransplantations from severe CAV with heart failure. Twenty-three patients (17%) suffered from acute rejection. The overall 1-year actuarial survival rate was 86% ± 2% and the 5-year survival rate was 79% ± 3%. Seventy-eight patients (57.4%) took statins and the statin group has a better 5-year survival rate and freedom from cardiac death survival rate ($P < .01$).

Conclusion. Our study showed that the use of statins after transplantation was associated with better survival.

SEVERAL mechanisms for dyslipidemia have been suggested, such as pre-existing lipid abnormalities, use of immunosuppressant drugs, and insulin resistance [1,3]. The association between dyslipidemias and development of coronary allograft vasculopathy (CAV) following heart transplantation is well established [1,4,5], and CAV is the main reason leading to chronic cardiac allograft failure. With the development of hydroxyl-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors and statins, their potent effects have helped usher in a new era of widespread acceptance for lipid-lowering in heart transplantation and in the treatment of cardiac disease [6,7]. In addition to their lipid-altering mechanisms, evidence exists to suggest that statins have other important properties, such as improving endothelial function and reducing endothelial permeability, depressing thrombotic pathways, and inhibiting the inflammatory response [9–12]. Importantly, HMG-CoA reductase inhibitors (statins) initiated after heart transplantation exert beneficial effects on the incidence of cardiac allograft rejection, transplant vasculopathy, and survival rates [1,2,6]. However, the purposes of our study were primarily to assess the effects of statins on overall survival and cardiac allograft

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rejection, to confirm their lipid-lowering effects, to determine their safety, and to report on 5-year clinical outcomes.

## MATERIALS AND METHODS

Between January 2007 and June 2012, 132 patients who underwent heart transplantation and were discharged from the admission for heart transplantation at National Taiwan University Hospital were included in this prospective observational study. Immunosuppressive therapies followed a standardized protocol in all patients according to the International Society for Heart and Lung Transplantation Guidelines and there was a regular follow-up of the drug levels every month.

The principle of statin use was also defined according to the Heart and Lung Transplantation guidelines [13]. In adults, the use of statins beginning 1 to 2 weeks after heart transplantation has been recommended regardless of cholesterol levels since the publication of the International Society for Heart and Lung Transplantation Guidelines for the care of heart transplant recipients in 2010. Owing to pharmacological interactions with calcineurin inhibitors (CNIs) and risk for toxicity, initial statin doses should be lower than those recommended for hyperlipidemia [13]. The statin doses we used for heart transplantation patients are listed in Table 1. After January 2011, we also routinely used statins for the pediatric patients with evidence of hyperlipidemia, CAV, or after retransplantation according to the 2010 guidelines [13]; before January 2011, statins were prescribed if hyperlipidemia was present. However, if poor hepatic function or elevated liver enzyme were noted after heart transplantation, use of statins was avoided and regularly followed up with creatine kinase (CK) and liver enzyme was prescribed to prevent drug side effects.

Endomyocardial biopsy (EMB) was performed in adults and adolescents every week in the first month after cardiac transplantation and then 6 to 12 months after heart transplantation. After the first postoperative year, EMB surveillance was carried out for an extended period of time around once a year given the higher risk for late acute rejection. In younger children, especially infants, we routinely used echocardiography every 3 months as a screening tool to reduce the frequency of EMB.

The study protocol was reviewed and approved by the institutional review board of the National Taiwan University Hospital.

### Statistical Analysis

Descriptive results were given as median with interquartile range and number with percentage. For group comparison in univariate analysis, chi-square test was used for categorical variables and Mann-Whitney *U* test was used for continuous or ordinal variables. Kaplan-Meier estimates and log-rank tests were used for overall survival and noncardiac death survival. Hazard ratios were estimated using Cox regression. A significance level of $>.05$ was adopted throughout the study, and all confidence interval (CIs) were computed with a confidence level of 95%. All statistical analysis was carried out using the Stata/SE 8.0 (College Station, Tex, United States).

## RESULTS

### Patient Population

Of the 142 eligible patients who underwent heart transplantation during the study period, 10 (7%) were excluded because of severe sepsis (n = 6), persistent multiple-organ failure (n = 3), and postoperative surgical complication (n = 1) leading to death. The remaining 132 patients were enrolled in the study. The mean age at transplantation year was 43.6 +/− 18 years (range, 6–73 years), and 112 (84.8%) patients were male. The pretransplantation diagnoses were mainly dilated cardiomyopathy (52.4%) and ischemic cardiomyopathy (39.3%), and there were 2 (1.5%) patients who underwent retransplantations due to severe coronary artery vasculopathy with heart failure (Table 1). The overall 1-year actuarial survival rate was 86% ± 2% and the 5-year survival rate was 79% ± 3%.

**Table 1. Patient Characteristics**

| Patient characteristics (n = 132) | |
|---|---|
| Male | 112 (84.8%) |
| Female | 20 (15.2%) |
| Age at heart transplantation (y) | 43.36 (6–73) |
| Diagnosis | |
| Ischemic cardiomyopathy | 42 (31.8%) |
| Dilated cardiomyopathy | 72 (54.5%) |
| Retransplantation | 2 (1.5%) |
| Myocarditis | 5 (3.8%) |
| Valvular heart disease | 7 (5.3%) |
| Congenital heart disease | 4 (3.0%) |
| Immunosuppressive drugs | |
| Calcineurin inhibitors | 132 (100%) |
| Tarcolimus | 95 (72.0%) |
| Cyclosporine | 40 (30.3%) |
| Everolimus | 76 (57.6%) |
| Azathioprine | 1 (0.8%) |
| Mycophenolic acid | 61 (46.2%) |
| Prednisolone | 122 (92.4%) |
| Immunosuppressive switch | 29 (22.0%) |
| Tumor | 4 (3.0%) |
| Survival | 113 (85.6%) |
| Death | 19 (14.4%) |
| Cause of death | |
| Infection, sepsis | 5 (26.3%) |
| Cardiovascular | 13 (68.4%) |
| Other | 1 (5.3%) |
| Rejection | 22 (16.7%) |
| Humoral rejection | 8 (6.1%) |
| Cellular rejection | 17 (12.9%) |
| Statin use | 74 (56.1%) |
| No statin use | 58 (43.9%) |
| Multiple statin switch | 13 (9.8%) |
| Statin (n = 74) | |
| Flucastatin | 39 (52.7%) |
| Atrovastatin | 31 (41.9%) |
| Rosuvastatin | 19 (25.7%) |
| Ezetimibe | 4 (5.4%) |
| Triglycerides drug use (Lipanthyl) | 9 (6.8%) |
| Diabetes mellitus | 37 (28.0%) |
| Hepatitis B virus carrier | 16 (12.1%) |
| Chronic cardiac vasculopathy | 5 (3.8%) |

### Immunosuppressant Treatment

CNIs (Tacrolimus 72% and Cyclosporine 30.3%) were prescribed to all patients. Seventy-six (57.6%) of them also took Everolimus for combined use and 61 (46.2%) patients