ELSEVIER

The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

Statin therapy is not associated with improved outcomes after heart transplantation in children and adolescents

Steven C. Greenway, MS, MD, FRCPC,[a] Ryan Butts, MD,[b] David C. Naftel, PhD,[c] Elizabeth Pruitt, MSPH,[c] James K. Kirklin, MD,[c] Ingrid Larsen, BScN,[a] Simon Urschel, MD,[a] Kenneth Knecht, MD,[d] and Yuk Law, MD[e]

From the [a]Department of Cardiac Sciences, University of Alberta, Edmonton, Alberta, Canada; [b]Department of Pediatrics, Medical University of South Carolina, Charleston, South Carolina; [c]Department of Surgery, University of Alabama at Birmingham, Birmingham, Alabama; [d]Cardiology Section, Arkansas Children's Hospital, Little Rock, Arkansas; and the [e]Division of Pediatric Cardiology, Seattle Children's Hospital, Seattle, Washington.

KEYWORDS:
pediatric heart transplantation;
rejection;
vasculopathy;
statin;
HMG-CoA reductase inhibitors;
PTLD

BACKGROUND: Although used routinely, the pleiotropic benefits of statins remain understudied in children after heart transplantation. We hypothesized that statin therapy would reduce the incidence of rejection, cardiac allograft vasculopathy (CAV) and post-transplant lymphoproliferative disease (PTLD).

METHODS: This study was a retrospective review of 964 pediatric (ages 5 to 18 years) heart transplant recipients in the multicenter Pediatric Heart Transplant Study registry from 2001 to 2012. Patients were excluded if they were undergoing re-transplantation, survived <1 year post-transplant, or had missing data regarding statin use. The effects of statins beyond the first year were estimated by Kaplan-Meier and Cox regression multivariable analysis for freedom from PTLD, rejection requiring treatment, any severity of CAV, and survival.

RESULTS: Statin use was variable among participating centers with only 30% to 35% of patients ≥ 10 years of age started on a statin at <1 year post-transplant. After the first year post-transplant, statin-treated children (average age at transplant 13.24 $\pm$ 3.29 years) had significantly earlier rejection (HR 1.42, 95% CI 1.11 to 1.82, $p = 0.006$) compared with untreated children (transplanted at 12 $\pm$ 3.64 years) after adjusting for conventional risk factors for rejection. Freedom from PTLD, CAV and overall survival up to 5 years post-transplant were not affected by statin use, although the number of events was small.

CONCLUSIONS: Statin therapy did not confer a survival benefit and was not associated with delayed onset of PTLD or CAV. Early (<1 year post-transplant) statin therapy was associated with increased later frequency of rejection. These findings suggest that a prospective trial evaluating statin therapy in pediatric heart transplant recipients is warranted.

J Heart Lung Transplant 2016;35:457–465

Drugs used to lower serum cholesterol levels by inhibiting the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase are collectively known as "statins," and were first demonstrated to be beneficial post-heart transplantation

Reprint requests: Steven C. Greenway, MS, MD, FRCPC, Section of Cardiology, Alberta Children's Hospital, 2888 Shaganappi Trail NW, Calgary, Alberta, T3B 6A8, Canada. Telephone: 403-955-5049. Fax: 403-955-7621.

E-mail address: steven.greenway@albertahealthservices.ca

1053-2498/$ - see front matter
http://dx.doi.org/10.1016/j.healun.2015.10.040

in adults. Early statin therapy lowered cholesterol as expected but also decreased the frequency of rejection with hemodynamic compromise, decreased the frequency of cardiac allograft vasculopathy (CAV), and improved survival.[1] These benefits were maintained at 10-year follow-up and the pravastatin-treated group showed significantly greater freedom from angiographic CAV and death compared with a control group.[2] Although the statin-treated group had a lower cholesterol, cholesterol itself was not a risk factor for CAV, raising the possibility of additional transplant-related benefits from the use of statins.[1,2] The initial observations of lipid abnormalities post-transplant and the efficacy of statins, both pravastatin and atorvastatin, for the treatment of hypercholesterolemia have since been extended to the pediatric heart transplant population.[3–7]

In addition to positive effects on lipid levels, pravastatin was also associated with a lower incidence of angiographic CAV in children after heart transplant.[8]

Statins may also have other beneficial effects related to immunomodulation, many of which remain poorly understood.[9,10] Improved cancer-free survival has been found in adults, including heart transplant recipients, among whom statin therapy reduced the hazard of occurrence of any malignancy (predominantly skin but including a variety of cancers) by 67%.[11,12] However, the impact of statin use on the development of malignancy has not been explored in pediatric recipients where post-transplant lymphoproliferative disease (PTLD) remains a serious problem.[13,14]

Although appreciation of the effects of statins has increased and these drugs are widely prescribed, their use in pediatric heart transplant recipients remains insufficiently studied. This retrospective study was designed to review the potential effects of statin therapy on outcomes post-transplant. Using the Pediatric Heart Transplant Study (PHTS) database, statin therapy was assessed in a population of children and adolescents having undergone heart transplantation. We hypothesized that statin therapy would be associated with a lower incidence of rejection, CAV and PTLD in pediatric recipients treated within the first year post-transplant.

Methods

Patient population

The PHTS registry prospectively collects pre- and post-transplant data from participating centers. The collection of annual follow-up data on transplant recipients was initiated on July 1, 1996. The available study population consisted of all children (age $\leq$18 years at listing) from 36 institutions in North America and the UK (see Appendix). Each center obtained approval from its respective institutional human investigational committee before data collection began. From this population we retrospectively reviewed recipients transplanted during childhood or adolescence (ages 5 to 18 years at time of transplantation) throughout the study period from 2001 to 2012. By 2001, a relatively large ($\sim$16%) and stable number of patients were receiving statins and this time period allows for at least 1 year of follow-up data. The statin group included patients who received a statin within the first year post-transplant. The non-statin group included patients who had not received a statin before an event. The occurrence of rejection was defined as any biopsy-proven or clinically identified rejection event (acute cellular or antibody-mediated rejection) that required treatment. The presence of CAV was defined as any degree of CAV documented by angiography, intravascular ultrasound or dobutamine stress echocardiography. Patients undergoing re-transplantation, whose survival was $<$1 year post-transplant, or for whom data regarding statin use were not available were excluded from the analysis.

Data analysis

We collected baseline patient characteristics from annual follow-up forms, which are reported as mean $\pm$ standard deviation. Descriptive statistics were used to present differences between those patients treated with statins and those who did not receive statin therapy. Freedom from rejection, PTLD and CAV were assessed by the Kaplan–Meier method and differences analyzed by log-rank test. Multivariable Cox proportional hazards models were used to determine risk factors for rejection and statin use and included recipient and donor demographics. Hazard ratios (HRs) were expressed with 95% confidence intervals (CIs), with $p \leq 0.05$ considered statistically significant. All statistical analyses were performed using SAS software (version 9, SAS Institute, Cary, NC).

Results

From the total study population of 4,017 patients we identified 964 primary heart transplant patients who were between 5 and 18 years of age, transplanted between 2001 and 2012, survived to the first year post-transplant, and had at least 1 year of follow-up data available (Figure 1). Of these patients, 317 received a statin within the first year after transplantation. There were missing data for statin use in 56 patients, but exclusion of these patients did not affect our results. Early statin therapy was relatively uncommon in children $<$5 years of age, with only 102 patients prescribed a statin in the first year after transplant. Demographic characteristics between statin-treated and untreated patients were similar with respect to diagnosis, gender and ethnicity, as well as the presence of pre-transplant morbidities and the absence of hepatic dysfunction (Table 1). Patients receiving a statin were slightly older and more likely to have panel-reactive antibodies (PRA) of $>$10% and had a statistically shorter ischemic time compared with patients who did not receive a statin. Patients receiving a statin were more likely to have received induction therapy and to have received steroids, either pre-transplant or at 30 days post-transplant, but there were no significant differences between the use of maintenance immunosuppressive drugs.

Statins were utilized more frequently in patients $>$10 years of age ($p < 0.0001$; Figure 2). In patients 5 to 9 years of age, 20% were being treated with a statin by 1 year post-transplant and 30% were receiving a statin by 2 years post-transplant. Statin use was similar in patients 10 to 14 and 15 to 18 years of age. In patients $\geq$10 years of age, 30% to 35% were receiving a statin by 1 year post-transplant and