Incidence of Cardiovascular and Cerebrovascular Events Associated With Sirolimus Use After Liver Transplantation

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ABSTRACT

Background. Sirolimus (SRL) is an immunosuppressant often used in liver transplantation (LT) to mitigate renal insufficiency associated with calcineurin inhibitors. Sirolimus can cause hyperlipidemia, but its association with coronary artery disease (CAD) and cerebrovascular accidents (CVAs) is unclear. The purpose of this study was to assess the risk of CAD and CVAs with the use of SRL in LT recipients.

Methods. We retrospectively reviewed all of our LT recipients from 2000 to 2011. Patients with multiorgan transplant, multiple liver transplants, everolimus therapy, or survival <3 months were excluded. The 803 remaining patients were divided into 3 groups: 1) 134 patients who received and tolerated SRL; 2) 604 patients who never received SRL; and 3) 65 patients who started but discontinued SRL. The primary outcome was the development of CAD or CVA beyond 4 months after transplantation with the use of time-dependent Kaplan-Meier analysis.

Results. In group 1, there were 6 CAD and 2 CVA events; in group 2, 27 CAD and 16 CVA events; and in group 3, 10 CAD and 2 CVA events. The event-free survival for CAD/CVA at 1, 3, and 5 years was 100%, 98.1%, and 97.2% respectively for group 1; 99.7%, 98.4%, and 96.1% for group 2; and 92.3%, 92.3%, and 85.6% for group 3. On an unadjusted basis, compared with group 2, there was no difference in CAD/CVA rates in group 1 (hazard ratio [HR] 0.92; not significant), but there was an increase in group 3 (HR 2.94; $P = .0019$). However, on multivariate analysis, only age at transplantation (HR 1.06; $P = .001$) and diabetes before transplantation ($P = .011$) were associated with increased CAD/CVA risk.

Conclusions. Our analysis showed that patients receiving SRL after LT had no increased risk of CAD/CVA events compared with patients maintained on a calcineurin inhibitor. The risk of CAD/CVA should not be a factor in avoiding SRL.

SIROLIMUS (SRL) is a potent immunosuppressive agent that inhibits the mammalian target of rapamycin (mTOR), a mechanism different than that of calcineurin inhibitors (CNIs). CNIs are associated with renal insufficiency after solid organ transplantation [1]. Sirolimus may be used as an alternative for CNIs when renal insufficiency develops or is of concern. It has been associated with improved renal function after transplantation [2–4].

The potential benefits of SRL do not come without risks. Numerous side effects have been linked to SRL, including delayed wound healing and hepatic artery thrombosis. Hyperlipidemia is another side effect that can be observed in up to 49% of patients on SRL long term [5,6]. The consequences of this increased incidence of hyperlipidemia have not been well established, especially in the post–liver transplantation community. One study has demonstrated that even with increased Framingham Risk Model scores for myocardial infarction risk, patients receiving SRL for liver transplant do not have increased incidence of myocardial infarction; however, that was not a time-dependent analysis [7]. The relationship between SRL and cerebrovascular accident (CVA) incidence was also evaluated in the heart transplant community, with no increased risk of CVA observed, but that evaluation was based more on a

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Table 1. Patient Demographics and Baseline Characteristics

Characteristics	Group 1	Group 2	Group 3	*P* Value, Group 1 vs Group 2
Age at transplantation, y	54.1 ± 10.5	53.5 ± 10.0	55.5 ± 8.4	.5097
Male	96 (71.6%)	391 (64.7%)	43 (66.2%)	.1268
Race				
White	90 (67.2%)	398 (65.9%)	46 (70.8%)	.3186
Black	37 (27.6%)	151 (25.0%)	15 (23.1%)	
Other	7 (5.2%)	55 (9.1%)	4 (6.2%)	
Hepatitis C virus	51 (38.4%)	276 (46.8%)	16 (24.6%)	.0775
Hepatocellular carcinoma	38 (28.6%)	155 (26.2%)	9 (13.9%)	.5806
Alcohol use	48 (35.8%)	205 (33.9%)	30 (46.2%)	.6782
NASH	5 (3.8%)	29 (4.9%)	3 (4.6%)	.5645
BMI, kg/m^2	28.0 ± 6.4	29.0 ± 6.1	28.2 ± 5.9	.1222
Diabetes before transplantation	35 (26.5%)	121 (20.5%)	26 (40.6%)	.1271
Hypertension before transplantation	48 (36.4%)	167 (28.3%)	25 (39.1%)	.0655
Hyperlipidemia before transplantation	16 (12.2%)	30 (5.1%)	5 (7.8%)	.0025
CVA before transplantation	1 (0.9%)	9 (1.8%)	1 (1.6%)	1.0000
CAD before transplantation	2 (1.9%)	26 (5.1%)	6 (9.2%)	.2015
MELD at transplantation	20.1 ± 8.5	19.6 ± 7.8	21.4 ± 8.3	.4966
Dialysis at transplantation	3 (2.2%)	19 (3.2%)	6 (9.2%)	.7809
Creatinine at transplantation (mg/dL)	1.4 ± 0.9	1.2 ± 0.7	1.7 ± 1.1	.0018
GFR at transplantation (mL/min/1.73m^2)	72.1 ± 43.6	80.2 ± 39.7	54.7 ± 31.4	.0136
Proteinuria at transplantation	7 (10.8%)	52 (14.7%)	7 (15.2%)	.4036
Donor age, y	42.0 ± 17.8	42.8 ± 17.0	45.1 ± 15.9	.6363
In hospital at transplantation	28 (20.9%)	117 (19.6%)	15 (23.1%)	.7336
Days from treatment to attempted sirolimus	472.8 ± 611.4		310.5 ± 417.2	

Note. Values are presented as mean ± SD or *n* (%).
Abbreviations: NASH, non-alcoholic steatohepatitis; BMI, body mass index; CVA, cardiovascular accident; CAD, coronary artery disease; MELD, Model for End-Stage Liver Disease score; GFR, glomerular filtration rate.

purported link between SRL and thrombotic microangiopathy rather than hyperlipidemia [8,9].

Given that hyperlipidemia is associated with increased risk of coronary artery disease (CAD) and CVA in the general population, we sought to assess the time-dependent risk of CAD and CVA with the use of SRL in our liver transplant population.

PATIENTS AND METHODS

We conducted a retrospective chart review of 1,053 patients who received a liver transplant at our center from the years 2000 to 2011 to allow for adequate follow-up. Patients were excluded as follows: 59 patients with combined liver-kidney transplant, 94 with multiple liver transplants, 19 who received everolimus therapy, 45 with post-transplantation survival <3 months, and 2 with follow-up <3 months. Thus, 803 patients were included in the final analysis and were divided into 3 groups. Group 1 included 134 patients (16.7%) who were converted to SRL, tolerated it, and were maintained on the drug. Group 2 included 604 patients (75.2%) who did not receive SRL at any point. Group 3 included 65 patients (8.1%) who were converted to SRL but did not tolerate it or discontinued it for any reason. The primary composite outcome was the development of CAD or CVA occurring beyond 4 months after transplantation with the use of time-dependent Kaplan-Meier analysis, meaning that patients were evaluated based on the group they belonged to at the time of CAD or CVA event. Demographic and transplant data were used to perform multivariate Cox regression modeling of significant factors. This study was reviewed and approved by the Institutional Review Board at the study facility.

RESULTS

Table 1 highlights demographic data for all 3 groups. *P* values are indicated within the table and reflect comparison between group 1 and group 2 only. For numeric values, means are reported with standard deviation in parentheses, and for categoric variables frequency is reported with percentage in parentheses. Patients in group 1 were more likely to have hyperlipidemia before transplantation than patients in group 2 and had higher creatinine and lower glomerular filtration rate

Table 2. Reasons for Discontinuing Sirolimus

Reason	*n* (%)
Surgery	11 (16.9%)
Recurrent hernia	9 (13.8%)
Hyperlipidemia	8 (12.3%)
Rash	7 (10.8%)
Rejection	6 (9.2%)
Poor wound healing	4 (6.2%)
Infection	3 (4.6%)
Malignancy	3 (4.6%)
Pneumonitis	3 (4.6%)
Diarrhea	3 (4.6%)
Recurrent Edema/ascites	3 (4.6%)
Neutropenia	2 (3.1%)
Recurrent DVTs	1 (1.5%)
Acute kidney injury	1 (1.5%)
Initiation of antiviral therapy	1 (1.5%)

Abbreviation: DVT, deep vein thrombosis.