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Everolimus Use for Intolerance or Failure of Baseline Immunosuppression in Adult Heart and Lung Transplantation

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Background: Everolimus can be utilized after heart or lung transplantation to reduce calcineurin inhibitor associated nephrotoxicity, due to cell cycle inhibitor adverse effects, and as adjunct therapy for rejection, cardiac allograft vasculopathy, and bronchiolitis obliterans syndrome.

Material/Methods: A single-center, retrospective cohort study was conducted including 51 adult heart transplant patients (n=32) and lung transplant patients (n=19) started on everolimus due to immunosuppressive therapy intolerance or failure, between 2010 and 2017. Everolimus indication, response, efficacy, and tolerability were assessed.

Results: Everolimus was most commonly initiated due to leukopenia/neutropenia (n=17, 33%) or renal dysfunction (n=13, 25%). Leukopenia/neutropenia resolved in 76% of patients (13 out of 17 patients). Renal function (GFR) increased 7.4 mL/min from baseline to 3 months after everolimus initiation (*P*=0.011). The most common adverse effects were edema (n=23, 45%) and hyperlipidemia (n=25, 49%). A high discontinuation rate was observed (n=21, 41%), mostly from edema.

Conclusions: Everolimus might be beneficial in heart and lung transplant patients with leukopenia or neutropenia and lead to modest, short-term renal function improvement. Patient selection is crucial because adverse effects frequently lead to everolimus discontinuation.

MeSH Keywords: **Heart Transplantation • Immunosuppressive Agents • Leukopenia • Lung Transplantation • Renal Insufficiency**

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Background

Standard maintenance immunosuppression after heart or lung transplantation typically consists of a calcineurin inhibitor (CNI), either tacrolimus (TAC) or cyclosporine (CSA), a cell cycle inhibitor, either mycophenolate or azathioprine (AZA), and prednisone. CNIs have reduced rejection rates and improved overall graft survival, but are associated with significant adverse effects including nephrotoxicity [1]. Chronic kidney disease remains one of the most common complications after heart and lung transplantation [2,3]. At 5-years post-transplantation, 14% of patients have a serum creatinine >2.5 mg/dL, which carries a 4.55-fold increased risk of mortality [2–4]. Cell cycle inhibitors can cause gastrointestinal adverse effects, leukopenia, and increased risk for cytomegalovirus infection [1,5–10]. These adverse effects frequently lead to dose adjustments or need for alternative immunosuppressant therapy.

In 2010, the Food and Drug Administration approved everolimus, with low dose CNI for immunosuppression in liver and kidney transplantation. Everolimus is increasingly utilized in heart and lung transplant patients to reduce CNI-associated nephrotoxicity, cell cycle inhibitor adverse effects, and as adjunct therapy for acute rejection, cardiac allograft vasculopathy (CAV), and bronchiolitis obliterans syndrome (BOS) [1,5–8,11–15].

CNI minimization studies with mammalian target of rapamycin (mTOR) inhibitors have demonstrated more renal benefit with earlier everolimus introduction post-transplantation [11,12,16]. The reported change in glomerular filtration rate (GFR) is variable; after 12 months of everolimus use, some studies report a statistically significant improvement of 5–10 mL/min [15–18]. Everolimus is also associated with less leukopenia compared to mycophenolate in large randomized trials [9,19]. Finally, there is documented benefit in reducing the progression of both CAV and BOS with everolimus [5,6,10,14,19,20]. While there are several potential benefits, everolimus has many adverse effects including edema, hyperlipidemia, proteinuria, and pneumonitis which might lead to discontinuation [12,17,21]. There are few published reports on the clinical utility of mTOR inhibitors as second-line immunotherapy for intolerance or failure of baseline immunosuppression in a diverse heart and lung transplant population. The purpose of this study was to assess everolimus indication, response, efficacy, and tolerability in heart and lung transplant patients.

Material and Methods

A single-center, retrospective cohort study of adult heart and lung transplant patients was conducted at Spectrum Health Richard DeVos Heart and Lung Transplant Program. Spectrum Health Institutional Review Board approved the protocol in accordance with the Helsinki Declaration of 1975. Adult patients (≥18 years old) who received a heart or lung transplant and were started on everolimus between November 2010 and February 2017 were included.

Baseline patient information that was gathered included: transplant type, everolimus initiation time post-transplantation, concomitant immunosuppression, reason for everolimus initiation, need for renal replacement therapy, history of CAV, history of BOS and grade, statin use, and rejection history prior to everolimus initiation. Everolimus was initiated at 0.75 to 1 mg by mouth every 12 hours and titrated to a goal 12-hour trough level of 3 to 8 ng/mL. CNI doses were reduced from baseline by 30% to 50% depending on the trough level at initiation and indication. After everolimus initiation, endpoints collected included: immunosuppression, renal replacement therapy requirement, CAV, BOS grade, statin use, rejection grade and biopsies, edema, wound healing complications, and reasons for everolimus discontinuation.

Renal function, defined as estimated GFR as measured by the Modification of Diet in Renal Disease (MDRD) equation was collected at baseline, 1, 3, 6, and 12 months after everolimus initiation. Renal replacement therapy was defined as the need for hemodialysis or continuous veno-venous hemofiltration. A value of 10 mL/min was assumed and utilized for patients requiring renal replacement therapy. Total cholesterol, triglycerides, and LDL were collected at baseline and 3 months after everolimus initiation. Hyperlipidemia was defined as total cholesterol >190 mg/dL, triglycerides >200 mg/dL, and LDL >160 mg/dL [22]. Nadir white blood cell (WBC) and absolute neutrophil (ANC) counts were assessed during the 3 months before and after everolimus initiation. Leukopenia was defined as a WBC count less than 3000 cells/mm^3 and neutropenia was defined as an ANC less than 1000 cells/mm^3. To determine incidence of new biopsy proven acute rejection, the last biopsy prior to everolimus initiation was compared to the first biopsy after everolimus initiation. Heart and lung allograft rejection was graded according to the International Society for Heart and Lung Transplantation definitions [23,24].

Descriptive statistics were completed on all variables including sample size, frequency for categorical data, mean and standard deviation (SD) for normal data, and median with interquartile range [IQR] for non-normal data. Categorical variables were compared before and after everolimus initiation, using McNemar's test. Continuous data was compared at baseline and at various time points after everolimus conversion using the paired *t*-test for normal data and Wilcoxon signed rank test for non-normal data. A Bonferroni correction was applied to account for multiple comparisons to the baseline using a *P*-value <0.013 for significance. A total sample size of 34 was needed to identify a statistical difference in renal function from baseline to

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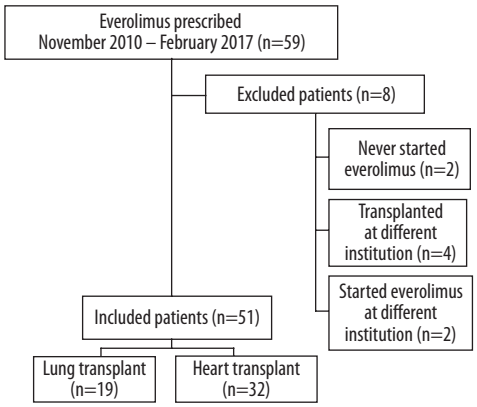

Figure 1. Patient enrollment.

Table 1. Demographics and baseline characteristics.

	n (%)
Type of transplant	
Heart	32 (63)
Lung	19 (37)
Males	38 (75)
Age at everolimus start (years), mean ±SD	60±10
Caucasian race	45 (88)
Concomitant immunosuppression	
Prednisone	47 (92)
Tacrolimus	44 (86)
Cyclosporine	7 (14)
Mycophenolate Mofetil	19 (37)
Azathioprine	3 (6)

Table 2. Immunosuppressant trough levels after everolimus initiation.

Agent	Goal trough*	1 month		3 months		6 months		12 months	
		N	Trough*	N	Trough*	N	Trough*	N	Trough*
Everolimus	4–6	48	4±2	41	5±2	29	5±2	17	5±1
Tacrolimus	4–6	41	6±3	35	6±4	25	5±2	13	5±2
Cyclosporine	75–121	7	95±35	6	111±53	4	88±8	4	80±7

* Mean ±SD (ng/ml).

predetermined time points for each individual patient, with medium effect size, and a power of 0.8. All *P*-values were 2-tailed and a *P*-value <0.05 was statistically significant. Statistical analysis was completed using SPSS, Version 23.0.

Results

Fifty-nine patients, between November 2010 and February 2017, were prescribed everolimus of which 51 patients met our study inclusion criteria: 32 heart transplant patients (63%) and 19 lung transplant patients (37%) (Figure 1). At our institution, there were 88 heart transplants and 77 lung transplants during this time period. Fifty of the 51 included patients received their transplant during the same time period when everolimus was prescribed. One patient received a heart transplant in 2007 but did not start everolimus until 7.5 years post-transplantation in 2015. Patient demographics and immunosuppression are summarized in Table 1. The median time from transplantation to everolimus initiation and duration of time on everolimus was 282 days [108–452 days] and 262 days [115–418 days] respectively. All patients were maintained on a CNI.

Table 3. Everolimus indication.

Indication	n (%)
Leukopenia/neutropenia	17 (33)
Renal dysfunction	13 (25)
Viral Infection	7 (14)
Rejection	5 (10)
Malignancy	3 (6)
Other immunosuppressant adverse effect	3 (6)
Cardiac allograft vasculopathy	3 (6)

The 2 most common regimens were: 1) everolimus with TAC and prednisone (n=23, 45%) and 2) everolimus with TAC, prednisone, and mycophenolate (n=11, 22%). Everolimus, TAC, and CSA mean trough levels were within specified target ranges at 1, 3, 6, and 12 months (Table 2). The reasons for everolimus initiation are described in Table 3.

Renal function from baseline to 1 month (n=49) and 3 months (n=42) significantly improved with an increase in GFR of

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Table 4. Renal function changes.

	n	GFR mean ±SD	Mean difference compared to baseline	P-value
1 month	49	51±21	+5.7 mL/min	.004*
3 months	42	52±22	+7.4 mL/min	.011*
6 months	30	53±19	+7.0 mL/min	.027
12 months	16	48±15	–0.9 mL/min	.836

* <.013 considered statistically significant based on Bonferroni correction.

Table 5. Lipid values.

Lab	N	Baseline [IQR] (mg/dL)	3 month [IQR] (mg/dL)	P-value
Total cholesterol	44	171 [142–205]	214 [185–246]	<.001
Triglyceride	44	151 [102–200]	200 [128–259]	.001
LDL	39	80 [64–101]	112 [83–134]	<.001

5.7 mL/min (*P*=0.004) and 7.4 mL/min (*P*=0.011), respectively (Table 4). GFR from baseline to 6 months increased by a mean of 7.0 mL/min for 30 patients, but did not reach statistical significance due to a Bonferroni correction (*P*=0.027). Twelve months after everolimus start, there were 16 patients with follow-up who experienced a 0.9 mL/min mean decrease in GFR (*P*=0.836).

Thirteen patients had renal dysfunction as their everolimus transition indication and experienced a statistically significant improvement in GFR from baseline to 3 months after everolimus initiation, (median 28 mL/min versus 42 mL/min, n=11, *P*=0.008). Five patients (10%) were on renal replacement therapy at everolimus initiation. These patients started everolimus at a median of 22 days [14-46 days] post-transplantation. At 3 months, 4 of the 5 patients (80%) no longer required renal replacement therapy.

Of the 17 patients (33%) who initiated everolimus for leukopenia or neutropenia, 13 patients (76%) did not have leukopenia or neutropenia after everolimus initiation. Nadir WBC and ANC was significantly higher 3 months after everolimus initiation as compared to 3 months prior to initiation; WBC was 4.1±1.2 versus 2.5±1.2 cells/mm^3, *P*=0.012 and ANC was 2.5±1.4 versus 1.2±0.9 cells/mm^3, *P*=0.015.

Three heart transplant patients (9%) started everolimus for CAV. Four patients (13%) had documented CAV at baseline and 1 additional patient (3%) developed CAV after everolimus initiation. There was not a statistically significant increase in CAV after everolimus compared to before everolimus (*P*>0.999). BOS was present in 3 lung transplant patients (16%) before everolimus initiation, 2 additional patients (11%) developed BOS after everolimus initiation. There was not a statistically significant increase in BOS after everolimus compared to before everolimus (*P*=0.480). No patients with BOS prior to everolimus transition had a change in BOS grade after everolimus.

No heart transplant patients experienced biopsy proven rejection 2R or greater after everolimus initiation. One lung transplant patient had a new A2 rejection episode, although maintenance immunosuppression at the time of rejection was suboptimal for this patient, with an everolimus trough level of 1.1 ng/mL, TAC trough level of 4.8 ng/mL, and 5 mg of prednisone.

The most common adverse effects documented after everolimus initiation were new or worsening hyperlipidemia, edema, and impaired wound healing. Almost half of the patients (n=25, 49%) experienced new or worsening hyperlipidemia after everolimus initiation. There were statistically significant increases in total cholesterol, triglycerides, and LDL from baseline to 3 months after everolimus start (Table 5). This occurred despite 42 patients (82%) taking a moderate intensity HMG-CoA reductase inhibitor. One-fourth of patients (13 patients) required an increase in HMG-CoA reductase inhibitor potency during the study. Edema occurred frequently in 23 patients (45%), overall. The median time from transplantation to everolimus initiation was numerically less in patients who had documented edema compared to those who did not, although this did not reach statistical significance (180 days [100–344 days] versus 372 days [137–564 days], *P*=0.112). Median baseline GFR was not significantly different in patients with or without edema (45 mL/min [34–57] versus 45 mL/min [32–56], *P*=0.834). Three heart transplant patients (6%) had documented impaired wound healing. These patients had slow healing after a skin cancer removal, groin incision, and ankle wound.

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Table 6. Everolimus discontinuation reason.

Discontinuation reason	n (%)
Edema	5 (10)
Wound healing concerns	4 (8)
Leukopenia/neutropenia	3 (6)
Gastrointestinal upset	2 (4)
Hyperlipidemia	2 (4)
Myalgia	1 (2)
Pulmonary toxicity	1 (2)
Non-healing mouth sores	1 (2)
Thrombotic microangiopathy	1 (2)
Cost	1 (2)

There was a high discontinuation rate of everolimus at 21 patients (41%) (Table 6). The median time to discontinuation was 145 days [56–316 days]. The most common reason for discontinuation was edema (n=5, 10%) and other reasons included prevention or concern for impaired wound healing, persistent leukopenia, gastrointestinal adverse effects, hyperlipidemia, myalgia, pulmonary toxicity, non-healing mouth sores, thrombotic microangiopathy, and cost.

Discussion

This study examined everolimus use for intolerance to baseline immunosuppression and subsequent response in heart and lung transplant patients. At our institution, approximately one-third of all heart transplant patients and one-fourth of all lung transplant patients during the study period were started on everolimus after intolerance to their baseline immunosuppression regimen. Interestingly, leukopenia or neutropenia was the most common reason for patients to transition to an everolimus regimen. The majority of patients who had leukopenia or neutropenia as their indication for starting everolimus experienced resolution with both WBC and ANC improving after everolimus initiation. Importantly, leukopenia did not resolve in the 1 patient who continued mycophenolate. Mycophenolate frequently causes leukopenia necessitating dose adjustment or alternative therapy. This effect is additive when combined with everolimus as described by Gullestad et al. where 97% of patient were on a cell cycle inhibitor and everolimus with low dose CNI or standard CNI. They found significantly more leukopenia with everolimus, CNI, and cell cycle inhibitor than with CNI and cell cycle inhibitor (11% versus 0%, $P<0.001$) [11]. There have been no studies investigating everolimus as an alternative for mycophenolate-related leukopenia in heart or lung transplantation. A study in kidney transplantation investigated everolimus as an alternative to mycophenolate for neutropenia and found neutropenia resolved in 65% of patient after transitioning from mycophenolate to everolimus [13]. Additionally, Eisen et al. found a relative risk reduction with everolimus use for both leukopenia 0.52 [0.36–0.74] and neutropenia 0.44 [0.33–0.59] compared to mycophenolate mofetil [9]. Based on the findings of this study and previous data, everolimus seems to be a reasonable alternative in patients who experience leukopenia or neutropenia with cell cycle inhibitors.

Renal dysfunction was the second most common reason for initiating everolimus in this study. Patients experienced a statically significant improvement in renal function from baseline to 1 month and 3 months after everolimus transition. Previous studies reported similar results with a statistically significant improvement of GFR of 5–10 mL/min after 12 months [15–18]. The present study is not able to report a statistically significant difference at 6 or 12 months likely related to the small sample size compared to previous trials. Even though a GFR change less than 10 mL/min can be due to natural variation, everolimus regimens with reduced CNI doses do appear to mitigate the renal toxicity associated with CNIs as evident by less decline in GFR [11,16]. Similar to previous studies, patients that transitioned to everolimus due to renal dysfunction in this study exhibited improved renal function after everolimus transition, but the small sample size limited assessment of the long-term effects [11,16,17]. The majority of patients who were on renal replacement therapy at everolimus initiation were able to come off within 3 months of starting everolimus. Notably, most of these patients started everolimus soon after transplantation.

There were statistically significant increases in total cholesterol, triglycerides, and LDL, which was consistent with earlier studies [5,9,11,17]. Despite most patients being maintained on a moderate dose HMG-CoA reductase inhibitor, patients experienced larger increases in cholesterol levels, compared with previous reports, within the first 3 months of everolimus use. However, as with other studies, this rise is driven by triglycerides. Patients might benefit from an increase in the HMG-CoA reductase inhibitor dose/potency at the time of everolimus initiation to mitigate everolimus associated hyperlipidemia, especially if they already have significant lipid abnormalities at baseline. In one study, omega-3 fatty acids have been associated with marked reduction in mTOR inhibitor associated hypertriglyceridemia and should be considered as adjunct therapy [25]. Edema occurred frequently in our patient population and was the most common reason for discontinuation in our study. Edema is typically the most common adverse effect of everolimus occurring in 30% to 50% of patients [9,11,15,17]. The patients who experienced edema tended to start everolimus earlier after transplantation. There were no notable trends associated with edema in our study

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population related to renal function, transplantation type, or concomitant immunosuppression.

Finally, there was a very high discontinuation rate for everolimus (41%) within our patient population, limiting the long-term use of this agent. Previous studies have reported a wide range of discontinuation rates from under 10% to over 30% [9–11,16–18].

Limitations of this study included the retrospective design that relied on chart documentation, and the lack of an unrelated comparator group. While enough participants were enrolled to meet power for our primary endpoint, the present study was from a single transplant center limiting the enrollment size and ability to extrapolate results to other centers. A limited duration of follow-up compounded with a high discontinuation rate prevented long-term safety and tolerability assessment. There was no everolimus initiation protocol in place before this study to describe thresholds for transitioning to everolimus in the setting of renal dysfunction or leukopenia; this contributed to a lack of concomitant immunosuppression standardization.

Conclusions

In conclusion, in our experience, everolimus was most commonly started for leukopenia/neutropenia or renal dysfunction. Leukopenia/neutropenia resolved in the majority of patients transitioned for that reason. Therefore, everolimus might provide a particular niche in management of these patients. There was modest improvement in renal function after everolimus initiation. Despite these benefits, high rates of edema occurred and led to early discontinuation in many patients. Careful patient selection is prudent prior to everolimus initiation due to its adverse effect profile. Further prospective, randomized trials are warranted to determine the potential benefits and risks of everolimus in heart and lung transplantation.

Conflict of interest

None.

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