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ORIGINAL RESEARCH

Characteristics, Predictors, and Outcomes of Early mTOR Inhibitor Use After Heart Transplantation: Insights From the UNOS Database

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BACKGROUND: The clinical characteristics of mTOR (mammalian target of rapamycin) inhibitors use in heart transplant recipients and their outcomes have not been well described.

METHODS AND RESULTS: We compared patients who received mTOR inhibitors within the first 2 years after heart transplantation to patients who did not by inquiring the United Network for Organ Sharing (UNOS) database between 2010 and 2018. The primary end point was all-cause mortality with retransplantation as a competing event. Rejection, malignancy, hospitalization for infection, and renal transplantation were secondary end points. There were 1619 (9%) and 15 686 (81%) mTOR inhibitors+ and mTOR inhibitors– patients, respectively. Body mass index, induction, cardiac allograft vasculopathy, calculated panel reactive antibody, and fewer days in 1A status were independently associated with mTOR inhibitors+ status. Over a follow-up of 10.4 years, there was no difference in all-cause mortality after adjusting for donor and recipient characteristics (adjusted subdistribution hazard ratio, 1.03 [0.90–1.19]; *P*=0.66). mTOR inhibitors+ were independently associated with increased risk for rejection (odds ratio [OR], 1.43 [1.11–1.83]; *P*=0.005) and basal skin cancer (OR, 1.35 [1.19–1.51]; *P*=0.012) but not for infection or renal transplantation.

CONCLUSIONS: mTOR inhibitors are used in <10% patients in the first 2 years after heart transplantation and are noninferior to contemporary immunosuppression regimens in terms of all-cause mortality, infection, malignancy, or renal transplantation. They are associated with risk for rejection.

Key Words: heart transplantation ■ immunosuppression ■ motor inhibitors

The mTOR (mammalian rapamycin receptor) inhibitors have been introduced in clinical practice as part of an immunosuppression regimen after heart transplantation (HTx) with the premise of reducing onset or progression of cardiac allograft vasculopathy (CAV) via inhibition of the proliferation of fibroblasts and smooth muscle cells and as alternatives to mycophenolate mofetil (MMF)/calcineurin inhibitors (CNIs) (ie, tacrolimus) when toxicities develop. Additionally, retrospective studies have suggested a lower risk for certain malignancies, lower mortality, fewer CAV-related events, and lower risk for renal dysfunction with mTOR inhibitor use.[1] On the other hand, they have been associated with higher risk for acute cellular rejection, especially upon discontinuation of CNIs, and their use remains limited to <15% of the cases in the United States.[2]

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CLINICAL PERSPECTIVE

What Is New?

- According to the data from the United Network for Organ Sharing database, mTOR (mammalian target of rapamycin) inhibitors are used in <10% patients in the first 2 years after heart transplantation.
- mTOR inhibitors were not found to be independently associated with increased risk of death, infection, non–skin cancer, or renal transplantation.
- mTOR use was independently associated with increased risk for rejection and cardiac allograft vasculopathy; the latter is unlikely a causal relationship.

What Are the Clinical Implications?

- The present study sheds light on a clinical matter where available literature is largely controversial.
- Concerns about mTOR use increasing the risk of all-cause mortality, infection, malignancy, or renal transplantation may be mitigated by the current findings, which suggest that they are noninferior to contemporary immunosuppressant regimens.
- However, the increased risk for rejection associated with mTOR use should be considered, and further prospective research is warranted to confirm these findings.

Nonstandard Abbreviations and Acronyms

CAV	cardiac allograft vasculopathy
CNI	calcineurin inhibitor
HTx	heart transplantation
MMF	mycophenolate mofetil
mTOR	mammalian target of rapamycin
SHR	subdistribution hazard ratio

In a randomized controlled trial of >700 HTx recipients, everolimus and reduced dose cyclosporine A demonstrated noninferiority for rejection, graft failure, and death compared with MMF and standard dose cyclosporine A. However, the use of the everolimus regimen was associated with increased risk for renal failure and rejection.[3] A recent meta-analysis showed that adding any mTOR inhibitor to the immunosuppressive regimen led to decreased CAV progression and cytomegalovirus (CMV) infection, at the expense of higher risk for drug toxicity. Combining an mTOR inhibitor with MMF can also spare CNI-induced nephrotoxicity, at the cost of increased rate of acute cellular rejection. A mortality benefit by adding an mTOR inhibitor was not evident in that study.[4]

However, limited data exist from large databases on the use and outcomes of mTOR inhibitors in contemporary clinical practice, whereas available literature is controversial. We therefore sought to analyze a contemporary cohort of the United Network of Organ Sharing (UNOS) database to (1) describe the epidemiologic and clinical characteristics of early mTOR inhibitor use and (2) compare outcomes between patients who were placed versus not placed on mTOR inhibitors early during their posttransplantation period.

METHODS

Study Population and Data Assembly

We queried the UNOS database for all adult patients who received an isolated HTx between 2010 and 2018. The following exclusion criteria were applied: candidates <18 years old, simultaneous lung or other organ transplantation, incomplete baseline or outcomes data.

The following data were assembled from several data sets of the UNOS database: baseline donor and recipient clinical and laboratory characteristics, index hospitalization variables, immunosuppression regimens at all recorded follow-ups, and clinical outcomes including all-cause mortality, hospitalization for rejection, cancer (posttransplant lymphoproliferative disease, lung cancer, skin cancer, and occurrence of any malignancy), CAV, hospitalization for infection, and renal transplantation.

The UNOS-derived study cohort contains deidentified information; therefore, it is considered institutional review board exempt.

Data are available upon reasonable request addressed to the corresponding author.

Study Design and Objectives

Based on early treatment with mTOR inhibitors, the study cohort was divided into 2 groups: patients who were placed on an mTOR inhibitor at discharge or within 2 years of index hospitalization (mTORi+) and all other patients (mTORi–). We compared immunosuppressive strategies between the 2 groups including induction therapy (defined as immunosuppressant medications given during the immediate posttransplant time period that would not be part of maintenance therapy, excluding steroids), duration of treatment with an mTOR inhibitor, and second or third immunosuppressive medication. For the mTORi– group, frequency of switch to mTOR after 2 years was derived. Baseline and index hospitalization characteristics were compared between groups to identify factors associated with mTOR inhibitor use.

The primary outcome was all-cause mortality, and our hypothesis was that early use of mTOR inhibitors is not inferior to standard immunosuppressants.

Secondary outcomes included hospitalization for rejection, hospitalization for infection, CAV, posttransplant lymphoproliferative disease, lung cancer, skin cancer, occurrence of any malignancy, and renal transplantation.

Statistical Analysis

Baseline characteristics were compared between groups using the Kruskal-Wallis ANOVA test for continuous variables and Pearson χ^2 test for categorical variables. Predictors of mTOR inhibitor use were analyzed using logistic regression. Because retransplantation is a competing event for all-cause mortality, we performed competing risk survival analysis and reported subdistribution hazard ratios (SHRs) from the Fine-Gray model to examine the relationship between mTOR inhibitor use and all-cause mortality.[4] We used Schoenfeld residuals to examine whether the proportional hazards assumption was met and examined our cumulative incidence function curves to determine any important departures from proportionality, which were not observed. Both univariate and multivariable analyses were performed. In the latter, we adjusted for the following covariates that were selected based on clinical expertise and literature review: donor and recipient age and sex, race, body mass index and recipient listing status, smoking history, creatinine, left ventricular assist device, intra-aortic balloon pump, extracorporeal membrane oxygenation, and ischemia time. The risks of rejection, cancer (posttransplant lymphoproliferative disease, lung cancer, skin cancer, and occurrence of any malignancy), CAV, and hospitalization for infection were analyzed using logistic regression. Similarly, both univariate and multivariable analyses were performed, adjusting for the same covariates as described above.

Analyses were performed using Stata 16.0 (StataCorp, College Station, TX). All tests were 2-sided, and $P<0.05$ was considered as statistically significant.

RESULTS

Patient Characteristics and Predictors of Early mTOR Inhibitor Use

Between 2010 and 2018, 17 305 HTx recipients (53 ± 13 years, 74% men) were eligible for our study. Of them, 1619 (9%) were treated with an mTOR inhibitor in the first 2 years after index hospitalization (Table 1). Patients with mTORi+ status were slightly younger (52.8 ± 0.3 versus 53.5 ± 0.1 years, respectively) with slightly lower body mass index (27.1 ± 0.1 versus 27.3 ± 0.1 kg/m^2, respectively), had higher calculated panel reactive antibody values (14.6 ± 1.1 versus 10.4 ± 0.3, respectively), fewer days in 1A status (31 versus 36 days, respectively), and received induction more frequently (56% versus 50%, respectively; $P<0.001$). Patients who received early mTOR inhibitors also received grafts from older donors (32.8 ± 0.3 versus 31.8 ± 0.1 years, respectively). There was no significant difference in terms of race, body mass index, prior cancer history, creatinine, or other comorbidities between the 2 groups. Ischemic time was similar in both groups. In multivariable regression analysis (Table S1), younger age, absence of prior cardiac surgery, non-UNOS 1A status, absence of intra-aortic balloon pump during listing, induction, and older donor age were independently associated with early mTOR inhibitor use.

Characteristics and Trends in mTOR Inhibitor Use

The mTOR inhibitor was started during the index hospitalization in only 5% of mTORi+ patients (Table 2). The most commonly prescribed immunosuppressant at discharge in this group was MMF (95% of patients). However, once patients were started on an mTOR inhibitor, they remained on it for at least 6 months (mean duration, 460 days). Only 2% of mTORi– patients were placed on an mTOR inhibitor after 2 years. Upon introduction of an mTOR inhibitor, the most commonly removed immunosuppressant was MMF (55%). However, multiple or other immunosuppressant switches occurred in the majority of mTORi+ patients at that point (69%). The most common induction agents were basiliximab and anti-thymocyte globulin (Table 2).

Trends in early mTOR inhibitor use for the study period based on the year of HTx are shown in Figure 1. The percent of mTORi+ patients during this time period ranged from 8% to 12% without any significant trend.

All-Cause Mortality

Over a follow-up period of 79 375 patient-years with median per patient follow-up 4.0 years and interquartile range of 2.3 to 6.6 years (last follow-up date December 31, 2019), there were 2401 deaths (14%). The incidence of all-cause mortality was 3.2 and 3.0 per 100 patient-years for mTORi+ and mTORi– patients, respectively. In competing risk regression analysis with retransplantation as competing event and adjusted for donor and recipient characteristics, all-cause mortality was not significantly different in mTORi+ versus mTORi– patients (adjusted SHR, 1.03 [95% CI, 0.90–1.19]; $P=0.656$) (Table 3) (Figure 2).

Secondary Outcomes

In unadjusted logistic regression analysis, mTORi+ patients more frequently developed basal carcinoma of the skin (5% versus 4%; $P=0.021$) and were more frequently hospitalized for rejection (14% versus 9%;

Table 1. Baseline Recipient and Donor Characteristics

Variable	mTOR inhibitors within the 2 first years, n=1619, mean or frequency (% or SD)	No mTOR inhibitors within the 2 first years, n=15 686, mean or frequency (% or SD)	*P* value
Recipient characteristics			
Male sex	1162 (71.7)	11 580 (73.8)	0.075
Age, y	52.8 (0.3)	53.5 (0.1)	0.046
Race			
White	1091 (67.4)	10 360 (66.0)	0.526
Black	331 (20.4)	3366 (21.5)	
Other	197 (12.2)	1960 (12.5)	
BMI, kg/m^2	27.1 (0.1)	27.3 (0.1)	0.115
UNOS status, d*			
1A	30.7 (1.3)	36.4 (0.5)	<0.001
1B	108.7 (5.0)	115.9 (1.7)	0.201
1, old allocation	0 (0)	0 (0)	0.707
2, old allocation	62.6 (5.4)	48.9 (1.5)	0.006
Device type			
None	904 (55.8)	8240 (52.5)	0.036
LVAD	661 (40.8)	6956 (44.3)	
RVAD	0 (0)	23 (0.2)	
BiVAD	17 (1.2)	158 (1.1)	
TAH	37 (2.2)	309 (1.9)	
ABO blood group types			
A	674 (41.6)	6279 (40.0)	0.938
B	239 (14.7)	2328 (14.8)	
AB	96 (5.9)	940 (5.9)	
O	610 (37.6)	6139 (39.1)	
Prior cardiac surgery	571 (35)	6333 (40)	<0.001
History of malignancy	127 (7.8)	1298 (8.3)	0.600
Creatinine, mg/dL	1.3 (0.1)	1.2 (0.1)	0.089
CPRA value	14.6 (1.1)	10.4 (0.3)	<0.001
Cardiac output, L/min	4.5 (0.1)	4.5 (0.1)	0.157
PCWP, mm Hg	18.1 (0.2)	17.6 (0.1)	0.041
sPAP, mm Hg	39.8 (0.1)	39.7 (0.4)	0.984
IABP	90 (5.5)	1058 (6.7)	0.068
ECMO	14 (0.8)	88 (0.6)	0.129
Inotropes	585 (36.1)	5655 (36.1)	0.948
Mechanical ventilation	10 (0.6)	145 (0.9)	0.212
Donor characteristics			
Male sex	1160 (71.6)	10 986 (70.0)	0.177
Age, y	32.8 (0.3)	31.8 (0.1)	<0.001
Transplantation characteristics			
Ischemic time, h	3.1 (1.0)	3.1 (1.0)	0.514
Induction	912 (56%)	7909 (50%)	<0.001

BiVAD indicates biventricular assist device; BMI, body mass index; CPRA, calculated panel reactive antibody; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; mTOR, mammalian target of rapamycin; PCWP, pulmonary capillary wedge pressure; RVAD, right ventricular assist device; sPAP, systolic pulmonary artery pressure; TAH, total artificial heart; and UNOS, United Network for Organ Sharing.

*The UNOS status is assigned at the time of transplant candidacy evaluation. Status code 1A is designated for candidates on the waiting list who have the highest priority on the basis of medical urgency.

P<0.001) compared with mTORi– patients (Table 4). CAV was associated with mTORi+ status (17% versus 6%; *P*<0.001). There was no difference between the groups in the overall incidence of solid malignant tumors including lung cancer and other types of skin cancer. Incidence of posttransplant lymphoproliferative

Table 2. Immunosuppression Characteristics of Recipients on Early mTOR Inhibitors (Within 2 Years After Heart Transplant)

Variable	Early mTOR inhibitors, n=1619, N (% or interquartile range)
Immunosuppressives at discharge	
mTOR inhibitor	79 (5)
CNI, tacrolimus	1493 (92)
MMF	1538 (95)
Tacrolimus and MMF	1431 (88)
mTOR inhibitor median duration, d	372 (350–430)
mTOR inhibitor duration <6 mo	3 (0–185)
Immunosuppressive removed upon introduction of mTOR inhibitor	
MMF	882 (55)
Tacrolimus	274 (17)
Other	1110 (69)
Induction	912 (56)
Thymoglobulin	473 (29)
Basiliximab	424 (26)
Alemtuzumab	17 (1)
Rituximab	9 (0.5)
Daclizumab	5 (0.3)

CNI indicates calcineurin inhibitor; MMF, mycophenolate mofetil; and mTOR, mammalian rapamycin receptor.

Table 3. Competing Risk Regression Analysis Adjusted for Donor and Recipient Characteristics

Covariate	SHR	95% CI	*P* value
Early mTOR inhibitors	1.03	0.89–1.19	0.656
Recipient			
Age, y	0.99	0.98–1.00	0.322
Female sex	1.06	0.95–1.18	0.301
BMI, kg/m^2	1.01	1.005–1.01	0.016
ECMO	0.61	0.28–1.32	0.213
IABP	1.16	0.95–1.41	0.144
Diabetes	0.99	0.98–1.01	0.543
Smoking	1.41	1.29–1.54	<0.001
Status 1A	1.00	0.99–1.00	0.385
Status 1B	1.00	0.99–1.00	0.285
Hispanic ethnicity	0.99	0.96–1.02	0.455
VAD	1.03	0.98–1.09	0.231
Donor			
Age, y	1.01	1.005–1.01	<0.001
Hispanic ethnicity	1.03	1.01–1.07	0.019
Female sex	0.88	0.79–0.98	0.019
BMI, kg/m^2	1.01	1.005–1.01	0.029
Ischemic time, h	1.05	1.01–1.09	0.028

BMI indicates body mass index; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; mTOR, mammalian target of rapamycin; SHR, subdistribution hazard ratio; and VAD, ventricular assist device.

disease was also similar between the groups. Finally, the 2 groups did not differ in the incidence of renal transplantation. After adjusting for baseline donor and recipient characteristics as well as ischemic time in multivariable logistic regression models, mTORi+ status was independently associated with hospitalization for rejection (*P*=0.006), CAV (*P*<0.001), and basal skin cancer (*P*=0.012). In a subgroup analysis of mTORi+ patients, there was no significant difference in mortality when comparing those who had tacrolimus versus MMF removed at the time of mTOR inhibitor initiation (unadjusted SHR, 1.55 [95% CI, 0.96–2.50]; *P*=0.08).

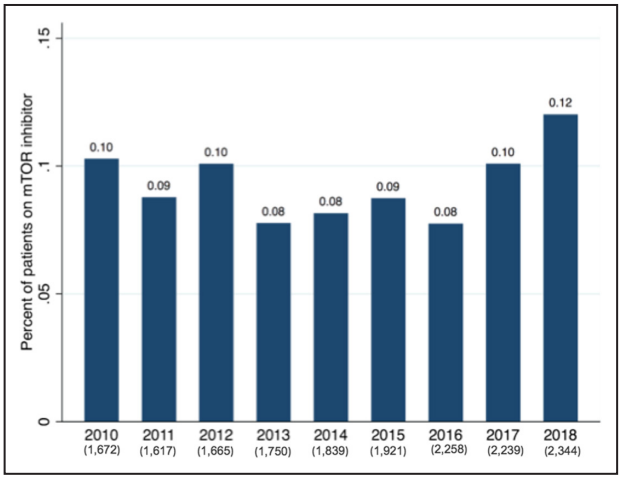

Figure 1. Trends in early use of mTOR inhibitors in the years 2010 to 2018 (percent of HTx recipients).
Numbers in parentheses below the year represent the total number of heart transplantations in that year. HTx indicates heart transplantation; and mTOR, mammalian target of rapamycin.

DISCUSSION

In the current retrospective analysis from the UNOS database of all adults who underwent isolated HTx between 2010 and 2018, we found that 9% of the HTx

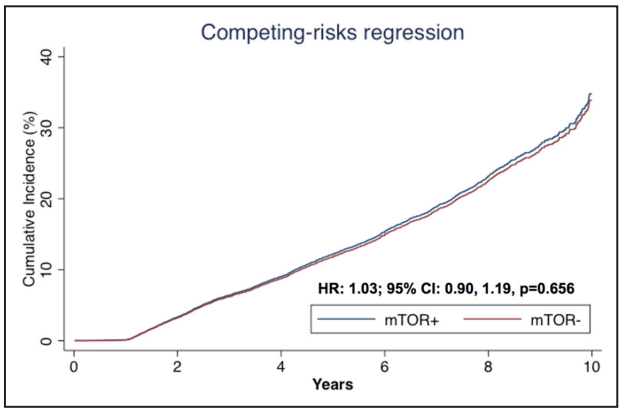

Figure 2. Fine-Gray analysis for all-cause mortality with retransplantation as competing event.
Multivariate analysis adjusted for variables listed in Table 3. HR indicates hazard ratio; and mTOR, mammalian target of rapamycin.

Table 4. Secondary Outcomes

Outcome	mTOR inhibitors within the first 2 years, n=1619	No mTOR inhibitors within the first 2 years, n=15 686	Univariate OR (95% CI)	*P* value	Multivariate OR (95% CI)	*P* value
Solid malignant tumor	223 (14%)	2162 (14%)	0.99 (0.92–1.06)	0.992		
PTLD	15 (0.9%)	157 (1%)	0.92 (0.67–1.17)	0.774	0.93 (0.68–1.18)	0.816
Skin cancer						
Squamous	123 (8%)	1061 (7%)	1.13 (1.02–1.24)	0.206		
Basal	85 (5%)	635 (4%)	1.31 (1.16–1.36)	0.021	1.35 (1.19–1.51)	0.012
Melanoma	13 (0.8%)	111 (0.7%)	1.13 (0.80–1.46)	0.665		
Lung cancer	22 (1.4%)	168 (1%)	1.27 (0.98–1.56)	0.290		
Hospitalization for infection	392 (24%)	3509 (22%)	1.1 (1.03–1.17)	0.091	1.13 (1.06–1.20)	0.055
Hospitalization for rejection	232 (14%)	1443 (9%)	1.65 (1.52–1.78)	<0.001	1.61 (1.49–72)	<0.001
CAV	280 (17%)	981 (6%)	3.13 (2.90–3.36)	<0.001	3.13 (2.90–3.36)	<0.001
Renal transplantation	0 (0%)	16 (0.1%)	N/A	N/A		

Multivariate analysis adjusted for variables listed in Table 1.
CAV indicates cardiac allograft vasculopathy; mTOR, mammalian target of rapamycin; OR, odds ratio; and PTLD, posttransplant lymphoproliferative disease.

recipients received mTOR inhibitors within the first 2 years after HTx. Over a follow-up of 10.4 years, mTOR treatment was not found to be independently associated with increased risk of death, infection, non–skin cancer, or renal transplantation. However, mTOR treatment was independently associated with increased risk for rejection and CAV.

The use of mTOR inhibitors has been investigated as de novo or as maintenance immunosuppressive therapy started early or late following HTx and with or without complete CNI withdrawal. The RAD B253 (Shift to Everolimus b253 study) trial included 634 HTx recipients who were randomly assigned to receive everolimus or azathioprine, in combination with cyclosporine and corticosteroids. The composite primary end point of death, graft loss or retransplantation, loss to follow-up, biopsy-proved acute rejection of grade 3A, or rejection with hemodynamic compromise was significantly smaller in the everolimus groups (both doses, 3.0 and 1.5 mg) than in the azathioprine group. Both the incidence of and progression of CAV were significantly lower in the 2 everolimus groups than in the azathioprine group. Moreover, the rates of CMV infection were significantly lower in the everolimus groups, but bacterial infection was significantly higher in the 3.0-mg everolimus group than in the azathioprine group.[5] The 24-month results of the RAD B253 trial showed that everolimus significantly reduced acute rejection and limited the progression of CAV compared with azathioprine. However, graft and patient survival were comparable at 24 months.[6]

In the SCHEDULE (Scandinavian heart transplant everolimus de novo study with early calcineurin inhibitors avoidance) trial, a multicenter, open-label randomized study, along with standard doses of MMF and steroids, de novo introduction of everolimus with complete withdrawal of cyclosporine by 7 to 11 weeks after HTx was prospectively compared with continued cyclosporine treatment. After 1 year of follow-up, a significant improvement in renal function as well as reduced incidence and progression of CAV were found in the everolimus-based compared with the cyclosporine-based groups.[7] Biopsy-proven acute rejection was more frequent with everolimus during the conversion process from cyclosporine, but these rejection episodes were mainly 1R rejections and without hemodynamic significance or reduction in allograft function. Long-term follow-up results of the SCHEDULE trial showed sustained improvement in kidney function and significantly reduced CAV progression. Despite increased incidence of treated biopsy-proven acute rejection in the everolimus group during the first year after HTx, no episode led to hemodynamic compromise, and long-term graft function was similar between the groups.[8]

In the 12-month, open-label MANDELA (A Study Investigating the Renal Tolerability, Efficacy, and Safety of a CNI-free Versus a Standard Regimen in de Novo Heart Transplant [HTx] Recipients) study, 145 patients were randomized at month 6 after HTx to convert to CNI-free immunosuppression with everolimus, MMF and steroids, or to continue reduced-exposure CNI, with everolimus and steroids. By 18 months, estimated glomerular filtration rate among the everolimus/MMF group was significantly higher than those on the reduced CNI/everolimus regimen. Biopsy-proven acute rejection was less frequent with a reduced CNI/everolimus regimen compared with the CNI-free regimen; all cases were without hemodynamic compromise. Notably, biopsy-proven acute rejection in the reduced

CNI/everolimus group was more common in those with low plasma everolimus levels (<5 ng/mL).[9]

In a recent large retrospective study from a single institution, we found that conversion from CNI to a sirolimus-based maintenance immunosuppressive regimen was associated with significant attenuation of CAV progression. We also found that sirolimus-based therapy was associated with reduced incidence of CAV-related adverse clinical events and improved late survival after HTx. There were no significant differences in the incidence of cellular, antibody-mediated, or hemodynamically significant rejections between patients converted to sirolimus-based and those continued on CNI-based therapy, and graft function was similar between the 2 groups at last follow-up.[10]

A recent meta-analysis of randomized controlled studies assessed the differential effects of the 3 commonly used immunosuppressive regimens with either CNI+ antimetabolite or mTOR + antimetabolite, or CNI + mTOR on outcomes following HTx. The meta-analysis showed no difference in all-cause mortality among the 3 immunosuppressive regimens, with CAV rates significantly lower with the CNI + mTOR combination. Acute rejection rates were significantly lower with CNI-based regimens compared with mTOR-based regimens. The mTOR-based regimes were associated with lower rates of CMV infections and better renal function than other regimens.[11]

Our results, in line with the accumulating data from randomized studies,[6,8,11] showed no difference in long-term mortality between HTx recipients based on mTOR status. However, late survival after HTx might be limited by multifactorial causes including CAV, rejection, malignancy, and infection. The balance between the benefit from potent immunosuppression to prevent rejection and CAV might be offset by the risk of infection and malignancy.

Our analysis showed higher rates of CAV in the mTOR group, which at first look contradicts numerous previous studies[5–11] that are in agreement that mTOR inhibitors are associated with lower incidence and progression of CAV. However, this finding is explained by selection bias, because UNOS patients are most likely selected for mTOR treatment after established CAV diagnosis.

In regard to rejection, previous randomized trials[8,9,11] showed increased risk of rejection with mTOR inhibitor-based immunosuppressive regimens, similarly to our results. However, these were usually mild rejection episodes with no hemodynamic compromise or graft dysfunction. Nevertheless, the benefit of reduced CAV in patients receiving mTOR inhibitors appears to be at the risk for rejection compared with patients receiving MMF/CNI regimens. The relationship between CAV and rejection does not appear to be causal but simply mTOR inhibitors protect against the first and introduce vulnerability toward the second. It would be clinically meaningful to detect patients who are at high risk for CAV and low risk for rejection to fully use mTOR inhibitors. Notably, in the MANDELA study,[9] the biopsy-proven acute rejection in the reduced CNI/everolimus group were more common in those with low plasma everolimus levels, suggesting that close monitoring of everolimus levels during the conversion process is important for minimizing the risk of allograft rejection. Interestingly, in our analysis we found that patients in the mTOR group had higher calculated panel reactive antibody values, which may confer higher risk of rejection.

Our analysis shows similar rates of malignancy (including skin, solid, and hematologic) between mTORi-treated patients versus those with no mTOR. However, in a recent large retrospective study from our institution, we found that conversion from a CNI- to a sirolimus-based maintenance immunosuppressive regimen was associated with a significantly decreased risk of all de novo malignancy, posttransplant lymphoproliferative disease, and primary occurrences of nonmelanoma skin cancer as compared with continued CNI therapy.[8] Notably, the study used time-dependent analysis because of the potential dependency on time of any effect associated with sirolimus.

Our results showed similar rates of infection between mTORi+ versus mTORi– groups. However, the type of infection was not specified in the UNOS database, and unfortunately the CMV infection data were not available, because mTOR inhibitors were previously shown to decrease the risk of CMV infection.[5,11,12]

Although numerous studies[7,8,11,12] showed improvement of renal function with mTOR-treated patients, especially when compared with their CNI-based immunosuppressive counterparts, our UNOS-based analysis shows that mTOR-treated patients were not at lower risk for renal transplantation as one may expect.

Our analysis is subject to limitations inherent to that of a retrospective study. The main limitation is the potential for selection bias, because patients with established CAV diagnosis are inherently selected to be treated with mTOR inhibitors. However, we have acknowledged this fact and do not support a higher risk for CAV with mTOR inhibitor treatment in our discussion. Additional limitations include the lack of data on different combinations of immunosuppressive agents and blood levels of these agents as well as the lack of data on CMV infection and rejection severity. Although we have used acceptable techniques to deal with missing data, missing information can still limit the power of our analysis.

In conclusion, mTOR inhibitors were used in <10% patients in the first 2 years after HTx and were noninferior to contemporary immunosuppression regimens in terms of all-cause mortality, infection, non–skin cancer,

or renal transplantation. However, they were associated with higher risk of rejection. Further prospective research is needed to validate these observations.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Table S1

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SUPPLEMENTAL MATERIAL

Table S1. Multivariable regression for early mTOR inhibitor use.

Variable	OR (95% CI)	p-value
Recipient characteristics		
Female gender	1.13 (1.05-1.21)	0.063
Age [years]	0.99 (0.98-0.99)	0.03
Hispanic	0.97 (0.95-0.99)	0.17
BMI [kg/m^2]	0.99 (0.98-1.01)	0.10
Diabetes	0.99 (0.985-0.995)	0.89
Prior cardiac surgery	0.82 (0.77-0.87)	0.001
History of malignancy	0.94 (0.85-1.03)	0.52
Creatinine [mg/dL]	1.06 (1.03-1.09)	0.053
UNOS status [days]		
1A	0.99 (0.985-0.995)	0.003
1B	0.99 (0.989-1.001)	0.77
VAD	0.95 (0.91-0.99)	0.30
IABP	0.70 (0.61-0.79)	0.01
ECMO	1.2 (0.84-1.55)	0.53
Donor characteristics		
Female gender	0.83 (0.77-0.84)	0.006
Age [years]	1.01 (1.008-1.012)	<0.001
Transplantation characteristics		
Ischemic time [hours]	1.01 (0.98-1.03)	0.56
Induction	1.25 (1.18-1.32)	<0.001