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Research Article

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Outcomes of Mammalian Target of Rapamycin Inhibitor Regimens in Kidney Transplant Recipients with Pre-Transplant Primary Diagnosis of Hypertension and Other Etiologies: An Observational Study

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Abstract

Objective: We aimed to examine the outcomes associated with the mammalian target of rapamycin inhibitor (sirolimus or everolimus), (m-TORi) regimens in kidney transplant recipients (KTR) with primary diagnoses of hypertension.

Methods: In this retrospective observational study, 187,381 adult KTRs were classified into the hypertension or non-hypertension cohort based on their primary renal diagnosis pre-transplant. Cox regressions were used to analyze the risks for death and graft loss associated with the following regimens: m-TORi with or without steroids combined with cyclosporine (m-TORi+CSA), mycophenolate (m-TORi+MPA) or tacrolimus (m-TORi+Tac); cyclosporine with or without steroids combined with mycophenolate (CSA+MPA); and other regimens.

Results: The risk of death-with-graft-function did not differ between mTORi regimens in KTRs with a primary diagnosis of HTN [mTORi+CSA vs: mTORi+MPA (HR=0.88; 95% CI=0.68-1.14) and mTORi+Tac (HR=1.16; 95% CI=0.91-1.47); and mTORi+MPA vs. mTORi+Tac (HR=1.31; 95% CI=1.00-1.72)]. However, in KTRs with a primary diagnosis other than HTN, mTORi+CSA is associated with a lower risk of death-with-graft-function than mTORi+MPA or mTORi+Tac [mTORi+CSA vs. mTORi+MPA: HR=0.81; 95% CI=0.71-0.92] and [mTORi+CSA vs. mTORi+Tac: HR=0.76; 95% CI=0.66-0.87]. In both primary diagnosis cohorts, the risks of overall and death-censored graft loss are higher with m-TORi+MPA than the other m-TORi regimens.

Conclusion: MTORi+MPA is associated with higher risks of graft loss regardless of pre-transplant primary diagnosis. MTORi+CSA is associated with a higher likelihood of survival with a functioning graft in KTRs with a non-HTN primary diagnosis, a benefit not seen among KTRs with a primary diagnosis of HTN. Therefore, outcomes associated with mTORi regimens vary with the pre-transplant primary diagnosis classification of hypertension or non-hypertension: these associations may be considered in mTORi regimen selection after kidney transplantation.

Keywords:

Graft survival; Hypertension; Immunosuppressant; Calcineurin inhibitor; MTOR inhibitor; Patient survival

Introduction

The success of modern immunosuppressant drugs in improving kidney transplant survival through prevention of rejection have been reflected in the reduction of acute rejection rates and increase in allograft survival rates [1]. However, the same agents have contributed to increased morbidity and mortality in kidney transplant recipients (KTR). Since the most common cause of renal allograft loss is death with a functioning graft, clinical measures aimed at decreasing this complication, including a systematic selection of immunosuppression regimen would be beneficial [2,3]. Hypertension, a leading cause of renal failure leading to kidney transplantation that commonly recurs after kidney transplantation is associated with multiple cardiovascular risk factors and morbidities that increase the risks of post-transplant mortality and allograft failure [4,5]. Post-transplant hypertension contributes to allograft and multi-system vasculopathy that can lead to poor patient and graft outcomes [6,7]. Calcineurin inhibitors (CNIs), the cornerstone of current immunosuppression regimen in kidney transplantation are implicated in the pathogenesis of post-transplant hypertension through multiple mechanisms [8]. On the other hand; other rejection prophylaxis drugs such as mycophenolic acid, azathioprine and the mammalian target of rapamycin inhibitors such as sirolimus and everolimus (m-TORi) are believed to be not intrinsically pro-hypertensive [9]; although, when combined with CNI's, mTOR-inihibitors could promote nephrotoxicity and hypertension [7,8]. In US, the triple drug combination of tacrolimus+mycophenolate+steroids has been the most utilized immunosuppression regimen in kidney transplantation [10]. However, when clinical indications dictate the use of alternative regimens, the m-TORi drugs have been combined with the CNIs, cyclosporine or tacrolimus or the antimetabolite, mycophenolate [10]. Hence, we aimed to study the kidney transplant and patient outcomes associated with the interactions between mTOR-i regimens and primary diagnosis classification of HTN or non-HTN. Utilizing existing data of the US Organ Procurement and Transplantation Network (OPTN) we conducted this observational study analyzing the risks of overall graft loss (OAGL), death-censored graft loss (DCGL), and death-with-graft-function (DWGF) associated with m-TORi regimens in KTR with a primary diagnosis classification of HTN or non-HTN. The study may be relevant in guiding the selection of an m-TOR inhibitor regimen for kidney transplant recipients.

Materials and Methods

Data source and study population

This was a retrospective observational cohort study based on the National UNOS STAR FILE data from the Organ Procurement

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Transplantation Network (OPTN) as of June 17, 2016. The study protocol was approved by the Institutional Review Board of the University of Florida. First time solitary-organ kidney transplant recipients (KTR) from 01/01/2000 through 12/31/2014 with a conditional three-month patient and graft survival were assigned to one of two cohorts based on the primary diagnosis at transplant waitlist enrolment: 1) the hypertension cohort included KTRs with hypertensive nephrosclerosis and 2) another etiology/non-hypertension cohort included KTRs with: glomerular diseases; tubular and interstitial disease; polycystic kidney disease; congenital, familial, and metabolic kidney diseases; diabetes mellitus; renovascular and vascular diseases; neoplasms; re-transplant/graft failure; or another kidney disease [11]. Inclusion criteria for this study included: KTR age 18 years or higher and receipt of a first-time kidney-only transplant. The exclusion criteria from this study included: kidney re-transplant, multiple organ transplants, death or graft loss within the first 3 months after transplant, missing primary diagnosis at transplant wait-list enrolment, and missing discharge immunosuppression regimen data. Baseline transplant recipient, donor and clinical data collected included those listed in Table 1.

Table 1: Baseline characteristics N=187,381.

Baseline Characteristics	Hypertension Cohort N=44803 (23.91%)	Non-Hypertension Cohort N=142578 (76.09%)
Recipient Age (years)		
18-49	18261 (40.76)	63037 (44.21)
50-64	17756 (39.63)	58126 (40.77)
65 and+	8786 (19.61)	21415 (15.02)
Gender, N (%)		
Male	29328 (65.46)	84602 (59.34)
Female	15475 (34.54)	57976 (40.66)
Recipient Race		
White	15920 (35.53)	84417 (59.21)
Black	19693 (43.95)	26988 (18.93)
Hispanic	6173 (13.78)	20451 (14.34)
Other	3016 (6.73)	10720 (7.52)
Missing	1 (0.00)	2 (0.00)
Recipient BMI		
<21 kg/m^2	3770 (8.41)	14158 (9.93)
21-24 kg/m^2	10942 (24.42)	34545 (24.23)
25-59 kg/m^2	16079 (35.89)	48821 (34.24)
≥30 kg/m^2	14012 (31.27)	45054 (31.60)
Recipient HCV Antibody		
Pos.	2695 (6.02)	5466 (3.83)
negative	38990 (87.03)	127571 (89.47)
Unknown	2537 (5.66)	8221 (5.77)
Missing	581 (1.30)	1320 (0.93)
Recipient CMV Antibody		
pos.	30242 67.50	85009 (59.62)
Neg.	12317 27.49	50502 (35.42)
unknown	2244 5.01	7067 (4.96)
Recipient History of Diabetes		
Yes	6026 (13.45)	54520 (38.24)
No	38133 (85.11)	86343 (60.56)
Unkown/Missing	644 (1.44)	1715 (1.20)
Induction Agent		
ATG	16932 (37.79)	51062 (35.81)
Alemtuzumab	4514 (10.08)	13985 (9.81)
IL-2 receptor blockers	12529 (27.96)	43576 (30.56)
Other agents	1503 (3.35)	5971 (4.19)
None	9325 (20.81)	27984 (19.63)
Maintenance Regimen		
CSA+MPA	4569 (10.20)	17021 (11.94)
Tac+MPA	33339 (74.41)	105189 (73.78)
mTori+MPA	695 (1.55)	1907 (1.34)
mTORi+Tac	1171 (2.61)	3804 (2.67)
mTORi+CSA	1593 (3.56)	2987 (2.09)
Other	3436 (7.67)	11670 (8.18)

Steroids Maintenance		
Yes	32606 (72.78)	104271 (73.13)
No	9786 (21.84)	31596 (22.16)
Missing	2411 (5.38)	6711 (4.71)
Delayed Graft Function		
Yes	8112 (18.11)	20347 (14.27)
No	36689 (81.89)	122230 (85.73)
Missing	2 (0.00)	1 (0.00)
Donor Race		
White	28276 (63.11)	102133 (71.63)
Black	8368 (18.68)	15553 (10.91)
Hispanic	6396 (14.28)	18824 (13.20)
Other Missing	1756 (3.92) 7 (0.02)	6055 (4.25) 13 (0.01)
Donor Age		
<50 year	32034 (71.50)	102570 (71.94)
≥50 year	12769 (28.50)	40008 (28.06)
Donor Gender		
Male	23930 (53.41)	73244 (51.37)
Female	20873 (46.59)	69334 (48.63)
Donor Type		
Living	13487 (30.10)	60699 (42.57)
Deceased	31316 (69.90)	81879 (57.43)
Cold Ischemia Time		
0-23 hr	37510 (83.72)	125152 (87.78)
24-41 hr	6638 (14.82)	16111 (11.30)
≥ 42 hr	655 (1.46)	1315 (0.92)
HLA Mismatch		
0-3	15962 (35.63)	59955 (42.05)
>3	28718 (64.10)	82063 (57.56)
Missing	123 (0.27)	560 (0.39)
Primary Insurance		
Private	13225 (29.52)	62056 (43.52)
Other	31576 (70.48)	80522 (56.48)

Exposure and outcomes

KTR were followed from the date of kidney transplant until the first of death or graft loss (defined as a return to dialysis or re-transplantation), end of the five-year observation or end of OPTN follow-up. The outcomes of the study were: 1) over-all graft loss (OAGL) defined as death from any cause or loss of renal allograft determined by return to dialysis or retransplantation. 2) death-censored graft loss (DCGL) defined as loss of renal allograft from any cause censored for death and 3) death with a graft function (DWGF) defined as death from any cause censored for graft loss. Cox multivariable regression analyses (also termed "Cox models") were conducted to study the risks of OAGL, DCGL and DWFG in the 5 years following transplant associated with the primary renal diagnosis classification of HTN or another (non-HTN) etiology and m-TORi immunosuppression regimens. The immunosuppression regimens used in the study were based on the UNOS STAR KIDPAN_IMMUNO_DISCHARGE_DATA and included: mammalian target of rapamycin inhibitor (sirolimus or everolimus), (m-TORi) with/without steroids and included the following: A) m-TORi+cyclosporine (also termed as m-TORi+CSA); B) m-TORi+mycophenolate (also termed as m-TORi+MPA); C) m-TORi+tacrolimus (also termed as m-TORi+Tac); D) cyclosporine+mycophenolate (also termed as CSA+MPA); E) tacrolimus+mycophenolate (also termed Tac+MPA); and F) all the other regimens not classified above were included under the category termed "other regimens". Clinically relevant recipient and donor demographics and transplant characteristics enumerated in Table 1 were used as covariates in the Cox models for OAGL, DCGL and DWGF [12]. Subsequent Cox regressions were performed to analyze relative risks for OAGL, DCGL, and DWGF associated with the interactions between primary diagnosis classification (HTN or non-hypertension) and discharge immunosuppression regimens (including steroid or non-steroid-containing CSA+MPA, m-TORi+CSA, mTORi+MPA, mTORi+Tac, or other regimens versus the reference regimen; Tac+MPA with or without steroids). Use of maintenance steroids and induction immunosuppression regimens were included among the covariates in the Cox models. Comparisons between m-TORi regimens and between CSA+MPA and m-TORi regimens were conducted based on point estimates and confidence limits in the main Cox models.

Statistical analysis

Baseline categorical covariates were reported in absolute counts and percentages. Cox multivariable regressions were conducted for a composite over-all graft loss outcome and 2 cause-specific outcomes of DCGL and DWGF. Results were expressed as hazard ratio (HR) accompanied by 95% confidence interval (CI) and P value. Discharge immunosuppression regimens that included m-TORi, CSA+MPA and "other" (versus Tac+MPA, as reference) were used as covariates

in the Cox models. Comparisons between m-TORi regimens and between CSA+MPA and m-TORi regimens were conducted by estimation of differences in the log of HRs and derivation of standard errors from the log of 95% CIs in the main Cox models. Results were presented as HRs and 95% CIs and P value, adjusted for multiple comparisons. All other statistical analyses in this study were performed using SAS software, version 9.2 (SAS Institute, Inc., Cary, NC, USA).

Results

Baseline patient demographics and clinical characteristics

We studied 187,381 adult kidney transplants from Jan. 01, 2000 through Dec. 31, 2014. Primary diagnosis at the time of transplant waitlist enrolment was hypertension in 44,803 (23.91%) and other kidney diseases in 142,578 (76.09%) of KTR included in the analysis. Discharge maintenance immunosuppression regimen was m-TORi+MPA in 1.55% and 1.34%, m-TORi+Tac in 2.61% and 2.67%, m-TORi+CSA in 3.56% and 2.09%, CSA+MPA in 10.20% and 11.94% and Tac+MPA in 74.41% and 73.78% in the HTN and other (non-hypertension) groups, respectively. The baseline demographic and clinical characteristics of recipients and donors as well as transplant-related variables are exhibited in Table 1.

Primary diagnosis of hypertension and immunosuppression regimens as risk factors for outcomes: Main Cox models

Compared with another primary renal diagnosis, hypertension was associated with a 10%, 6% and 15% higher relative risk of overall graft loss (OAGL), death-censored graft loss (DCGL) and death with a graft function (DWGF); respectively. Compared with the non-lymphocyte depleting agent, basiliximab, induction of immunosuppression with anti-thymocyte globulin was associated with a lower risk of OAGL, DCGL, and DWGF; while, alemtuzumab was associated with a higher risk of DCGL. The inclusion of steroids in the maintenance immunosuppression regimen was a risk factor for OAGL, DCGL, and DWGF. Other significant risk factors for OAGL, DCG, and DWGF are shown in Table 2.

Table 2: Risk factors for outcomes in the five years following kidney transplant [a]: Main Cox Multivariable Regression Results.

Risk Factor [reference]	Over-All Graft Loss HR[b] 95% CI[c] P LL[d] UL[e]				Death-Censored Graft Loss HR[b] 95% CI[c] P LL[d] UL[e]				Death with Graft Function HR[b] 95% CI[c] P LL[d] UL[e]			
Primary Diagnosis Hypertension [other diagnoses]	1.10	1.07	1.13	<.001	1.06	1.02	1.10	.001	1.15	1.11	1.19	<.001
Induction Agent [basiliximab]:												
Antithymocyte globulin	0.93	0.91	0.96	<.001	0.92	0.89	0.96	<.001	0.95	0.91	0.98	.005
alemtuzumab	1.04	0.996	1.09	.08	1.10	1.04	1.16	.002	0.98	0.92	1.04	.46
none	1.01	0.98	1.04	.67	0.99	0.95	1.04	.73	1.04	1.00	1.09	.052
other	1.09	1.03	1.15	.002	1.12	1.04	1.21	.002	1.08	1.00	1.17	.051
Maintenance Regimen [tacrolimus+ mycophenolate]												
CSA+MPA[f]	1.28	1.24	1.32	<.001	1.26	1.21	1.32	<.001	1.29	1.24	1.36	<.001
other regimens[g]	1.26	1.21	1.31	<.001	1.32	1.26	1.39	<.001	1.21	1.14	1.28	<.001
mTOR+CSA[h]	1.43	1.34	1.52	<.001	1.34	1.22	1.46	<.001	1.52	1.39	1.66	<.001
mTOR+MPA[i]	1.71	1.59	1.84	<.001	1.78	1.61	1.96	<.001	1.65	1.49	1.83	<.001
mTOR+Tac[j]	1.37	1.28	1.45	<.001	1.39	1.28	1.51	<.001	1.33	1.22	1.46	<.001
Missing	1.01	0.95	1.06	.81	1.05	0.97	1.13	.23	0.96	0.89	1.04	.38
Maintenance Steroids [no steroids]	1.11	1.08	1.14	<.001	1.06	1.02	1.11	.006	1.17	1.12	1.22	<.001
Recipient Age [18-49 years]												
50-64 years	0.996	0.97	1.02	.74	0.62	0.60	0.64	<.001	2.10	2.02	2.19	<.001
≥65 years	1.42	1.38	1.46	<.001	0.61	0.58	0.64	<.001	3.68	3.51	3.85	<.001
Recipient Race [Caucasian]												
African American	1.14	1.11	1.18	<.001	1.55	1.49	1.62	<.001	0.79	0.75	0.82	<.001
Hispanic	0.78	0.76	0.82	<.001	0.94	0.83	0.99	.03	0.65	0.61	0.68	<.001
Other	0.73	0.70	0.77	<.001	0.87	0.81	0.94	<.001	0.61	0.57	0.66	<.001
Unknown	2.29	0.32	16.3	.41	3.66	0.52	26.02	.19	0.01	0.00	4.571E22	.87
Recipient Female [male]	0.94	0.92	0.96	<.001	1.01	0.98	1.04	.54	0.87	0.84	0.90	<.001
Recipient BMI[k] (kg/m^2),[21-24]												
<21	1.14	1.09	1.19	<.001	1.13	1.07	1.20	<.001	1.17	1.10	1.24	<.001
25-29	0.98	0.95	1.01	.11	1.04	0.99	1.08	.09	0.91	0.87	0.95	<.001
≥30	1.04	1.01	1.07	.02	1.16	1.12	1.21	<.001	0.90	0.86	0.94	<.001
Recipient Prior Diabetes [absent]												
Unknown/Missing	1.09	0.99	1.20	.06	1.00	0.89	1.14	.94	1.27	1.10	1.46	<.001
Present	1.40	1.37	1.43	<.001	1.00	0.97	1.04	.99	1.97	1.90	2.04	<.001
Delayed Graft Function [absent]												
Missing	3.83	0.96	15.2	.06	2.89	0.41	20.47	.29	5.61	0.79	39.89	.08
Present	1.47	1.43	1.51	<.001	1.53	1.47	1.58	<.001	1.41	1.36	1.46	<.001

Donor Ethnicity/Race [Caucasian]												
African American	1.30	1.26	1.34	<.001	1.41	1.36	1.47	<.001	1.15	1.09	1.20	<.001
Hispanic	1.02	0.98	1.05	.37	1.06	1.01	1.12	.01	0.97	0.92	1.02	.20
Other	1.06	0.99	1.12	.08	1.06	0.97	1.15	.20	1.06	0.97	1.15	.22
Unknown	1.15	0.48	2.77	.75	0.77	0.19	3.06	.71	1.71	0.55	5.30	.35
Donor Age ≥50 years [18-49 yrs.]	1.36	1.33	1.39	<.001	1.55	1.51	1.61	<.001	1.20	1.16	1.24	<.001
Donor Gender, Female [male]	1.12	1.09	1.14	<.001	1.18	1.15	1.22	<.001	1.05	1.02	1.08	.003
Kidney Donor Type Living [deceased]	0.72	0.70	0.74	<.001	0.73	0.70	0.76	<.001	0.70	0.67	0.72	<.001
Recipient Hepatitis C Antibody [neg.]												
Missing	1.34	1.22	1.46	<.001	1.44	1.28	1.63	<.001	1.28	1.12	1.46	<.001
Positive	1.45	1.39	1.51	<.001	1.42	1.34	1.51	<.001	1.51	1.42	1.61	<.001
Unknown	1.03	0.98	1.08	.29	1.11	1.04	1.18	.002	0.96	0.90	1.03	.29
Cold Ischemia Time [<24 hr.]												
24-41 hours	1.06	1.03	1.09	<.001	1.08	1.03	1.12	<.001	1.05	1.00	1.09	.03
≥42 hours	1.20	1.09	1.31	<.001	1.30	1.16	1.47	<.001	1.11	0.97	1.27	.14
HLA[L] mismatch [0-3]												
4-6	1.09	1.06	1.11	<.001	1.15	1.12	1.19	<.001	1.03	1.00	1.07	.047
Missing	1.04	0.84	1.28	.73	1.11	0.84	1.46	.46	0.98	0.72	1.34	.92
Recipient CMV[m] Antibody [neg.]												
Positive	0.99	0.96	1.01	.30	0.98	0.95	1.01	.21	0.99	0.96	1.03	.88
Unknown	1.04	0.99	1.10	.11	0.99	0.92	1.06	.78	1.10	1.02	1.18	.02
Primary Insurance [private]												
Other than Private	1.31	1.28	1.34	<.001	1.24	1.20	1.29	<.001	1.36	1.31	1.41	<.001
Unknown	0.02	0.00	2.259E12	.80	0.01	0.00	1.048E1	.85	0.01	0.00	1.522E	.92

[a]Model based on Recipients Conditional 3 Months Patient and Graft Survival
[b]Hazard Ratio, [c] Confidence Interval, [d]Lower Limit, [e]Upper Limit
[f]cyclosporine+mycophenolate,
[g]All other regimens,
[h]mammalian target of rapamycin (sirolimus or everolimus)+cyclosporine,
[i] mammalian target of rapamycin (sirolimus or everolimus)+mycophenolate,
[j]mammalian target of rapamycin (sirolimus or everolimus)+tacrolimus
[k]body mass index, [L] human leukocyte antigen,
[m]Cytomegalovirus

Outcomes of calcineurin inhibitor-mycophenolate versus m-TORi regimens in hypertension and non-hypertension KTR groups

In both the HTN and non-hypertension KTR cohorts, the risks of all 3 outcomes were higher with the three m-TORi regimens, CSA+MPA, and other regimens compared with the standard (Tac+MPA) regimen (Table 2).

Outcomes associated with interactions between different m-TORi regimens and primary diagnosis classification of HTN or non-hypertension in KTRs

Cox models with interaction terms showed that in both the non-HTN and HTN cohorts, mTORi with mycophenolate was associated with higher risks of overall and death-censored graft loss than mTORi with cyclosporine or tacrolimus (Table 3). The risks of overall and death-censored graft loss associated with mTORi with cyclosporine or tacrolimus were not significantly different between the primary diagnosis cohorts.

On secondary analyses, the risk of death with graft function (DWGF) did not differ among KTRs with primary diagnosis of HTN on m-TORi+CSA, m-TORi+MPA, and m-TORi+Tac. In KTRs with a non-hypertension primary diagnosis, m-TORi+CSA was associated with a lower risk of death with graft function than m-TORi+MPA or m-TORi+Tac.

Discussion

In this study, we analyzed the risks of (overall and death-censored) graft loss and death with graft function associated with the mammalian target of rapamycin inhibitor regimens in KTRs stratified based on their primary diagnosis of hypertension or another etiology. The study found that the risks of graft loss and patient death varied between different m-TORi regimens used in kidney transplantation. Specifically, m-TORi+MPA was associated with higher risks of overall and death-censored graft loss than other m-TORi regimens irrespective of the primary renal diagnosis classification. On the other hand, m-TORi+CSA was associated with a lower risk of death-with-graft-function (DWGF) than other m-TORi regimens in KTRs with primary diagnoses other than hypertension. The risk of DWGF did not differ among the m-TORi regimens in KTRs with primary diagnoses of HTN.

Our analysis showed that the standard Tac+MPA regimen is superior to the other regimens studied (Table 2). This finding is consistent with the results of previous studies and could explain why Tac+MPA is the most frequently utilized regimen after kidney transplantation [12-17]. In a small minority of KTRs however, clinical indications dictate the avoidance or discontinuation of the standard Tac+MPA regimen and substitution therefor of an m-TORi regimen. Under prevailing clinical practice, m-TORi is being used in

Table 3: Comparisons of Risks for Outcomes in the Five Years Following Kidney Transplant [a] between Calcineurin Inhibitor+Mycophenolate and Sirolimus Regimens: Cox Multivariable Regression Results.

Maintenance Post-Transplant Immunosuppression Regimen	Over-All Graft Loss HR[b] 95% CI[c] LL[d] UL[e] P	Death-Censored Graft Loss HR[b] 95% CI[c] LL[d] UL[e] P	Death with Graft Function HR[b] 95% CI[c] LL[d] UL[e] P
Reference: tacrolimus+mycophenolate Non-Hypertension, Primary Diagnosis			
CSA+MPA[f]	1.26 1.22-1.31<.001	1.25 1.18-1.32<.001	1.27 1.21-1.34<.001
other regimens [g]	1.25 1.20-1.31 .009	1.32 1.24-1.40<.001	1.22 1.14-1.29<.001
mTOR+CSA [h]	1.42 1.31-1.54<.001	1.32 1.18-1.47<.001	1.33 1.20-1.48<.001
mTOR+MPA [i]	1.67 1.53-1.82<.001	1.75 1.55-1.98<.001	1.51 1.35-1.51<.001
mTOR+Tac [j]	1.36 1.27-1.46<.001	1.40 1.27-1.54<.001	1.61 1.43-1.82<.001
Secondary comparisons[k]:			
m-TOR+CSA vs. m-TOR+MPA	0.85 0.76-0.96 .01	0.75 0.64-0.89 .008	0.81 0.71-0.92 .004
m-TOR+CSA vs. m-TOR+Tac	1.04 0.94-1.16 .32	0.94 0.82-1.09 .29	0.76 0.66-0.87<.001
m-TOR+MPA vs. m-TOR+Tac	1.11 1.23-1.37 .02	1.25 1.07-1.46<.001	0.94 0.80-1.10 .31
Hypertension, Primary Diagnosis			
CSA+MPA[f]	1.32 1.24-1.41<.001	1.30 1.19-1.41<.001	1.39 1.26-1.52<.001
other regimens [g]	1.27 1.18-1.36<.001	1.34 1.22-1.47<.001	1.18 1.06-1.32 .002
mTOR+CSA [h]	1.45 1.31-1.61<.001	1.37 1.19-1.58<.001	1.55 1.32-1.82<.001
mTOR+MPA [i]	1.80 1.57-2.05<.001	1.82 1.54-2.16<.001	1.76 1.44-2.16<.001
mTOR+Tac [j]	1.38 1.23-1.54<.001	1.36 1.17-1.58<.001	1.34 1.12-1.61 .001
Secondary comparisons[k]:			
m-TOR+CSA vs. m-TOR+MPA	0.81 0.65-0.95 .02	0.75 0.60-0.94 .02	0.88 0.68-0.14 .25
m-TOR+CSA vs. m-TOR+Tac	1.05 0.90-1.32 .35	0.01 0.82-1.24 .52	1.16 0.91-1.72 0.19
m-TOR+MPA vs. m-TOR+Tac	1.30 1.10-1.55 .006	1.34 1.07-1.68 .002	1.31 1.00-1.72 0.053

[a]Model based on recipients with conditional 3-month patient and graft survival

[b]Hazard Ratio, [c] Confidence Interval, [d]Lower Limit, [e]Upper Limit

[f]cyclosporine+mycophenolate,

[g]All other regimens,

[h]mammalian target of rapamycin (sirolimus or everolimus)+cyclosporine

[i] mammalian target of rapamycin (sirolimus or everolimus)+mycophenolate

[j]mammalian target of rapamycin (sirolimus or everolimus)+tacrolimus

[k]Secondary comparisons: inv. log [HR1- HR2]+/- 1.96 × (sq. rt. [(inv log-Se1) ^{2}+(inv log-Se2) ^{2}]; P values corrected for multiple comparisons

KTR who are at increased risk for or have developed malignancies or are intolerant of the CNI-mycophenolate regimens [18-21]. Additionally, the m-TORi's are associated with the reduction of risks for some viral infections [22-29] and attenuation of nephrotoxicity by allowing either CNI discontinuation or dose reduction [30-34].

This study showed that compared with other primary renal diagnoses, hypertension is associated with 10%, 6% and 15% higher relative risks of overall graft loss, death-censored graft loss and death-with-graft-function; respectively. These results are expectable because pre-transplant hypertension is a risk factor for chronic post-transplant hypertension [35-37] and it has been independently correlated with reduced renal allograft survival and increased transplant recipient mortality. Our present finding of lower allograft survival associated with m-TORi regimens compared with Tac+MPA supports previous reports [38-42]. Isakova et al. [43] have shown that compared with m-TORi with CNI, m-TORi without CNI is associated with a greater risk of death and/or allograft loss. Our current findings are consistent with Isakova's findings as the m-TORi without CNI regimen represented by m-TORi+MPA showed inferior outcomes compared with the two m-TORi+CNI (CSA or Tac) regimens (Tables 2 and 3).

Our results showed that aside from being a predictor of higher risks of graft loss and mortality overall, a pre-transplant diagnosis of hypertension can also help predict the outcomes of specific m-TORi regimens after kidney transplantation. Among the m-TORi regimens, m-TORi+MPA appears to be the most inferior due to its association with higher risks of overall and death-censored graft loss than the other 2 m-TORi regimens (Table 3). The inferiority of m-TORi (SRL)+MPA compared with CNI+MPA and m-TORi (SRL)+Tac have been shown previously by other authors [40, 44]. Our results further showed that in KTRs with primary diagnoses of HTN, the risk of death with graft function were not different among the 3 m-TORi regimens. On the other hand, in KTRs with non-HTN primary diagnoses, the risk of DWGF was lower with m-TORi+CSA than the m-TORi (+MPA or Tac) regimens (Table 3). We hypothesize that m-TORi+Tac which has been associated with greater hyperglycemic effects than m-TORi+CSA [41] caused relatively more post-transplant diabetes exacerbations in the non-HTN cohort due to the higher percentage of diabetic patients in this cohort than in the HTN cohort at baseline (38.2% vs. 13.5%, respectively: p<.001), (Table 1). On the other hand, in the HTN cohort, CSA in the m-TORi regimens likely contributed to the post-transplant exacerbations of hypertension [6,45,46]. The foregoing mechanism is supported by Kumar et al. who has shown that biopsy-proven chronic allograft injury from HTN could be found in 36% of SRL+CSA-treated (vs. 16% of SRL+Tac-treated and 14% of Tac+MPA-treated) KTRs [47]. Additionally, the pro-dyslipidemic effect of SRL+CSA could have worsened the cardiovascular risk profile of KTRs in the HTN cohort [8]. Limitations of this study

include, 1) The lack of data on post-transplant hypertension. 2) Biases implicit in a database analysis. 3) The absence of data on drug doses and blood levels. On the other hand, the use of a large national data repository for all transplant centers in the US allowed the analysis of large numbers of kidney transplants over a fourteen-year period. This would have been very difficult to achieve through a randomized clinical trial due to logistical and financial constraints. Our findings are novel and clinically useful as no previous study has demonstrated the usefulness of primary diagnosis classification (into HTN or non-HTN) in tailoring m-TORi regimen prescriptions for KTR. As demonstrated by our analyses the risks of OAGL and DCGL were lower with m-TORi+CSA than m-TORi+MPA, similar between m-TORi+CSA and m-TORi+Tac and higher with m-TORi+MPA versus m-TORi+Tac regardless of the pre-transplant primary renal diagnosis classification (of hypertension or another etiology). The risk of death- with-graft-function was lower with m-TORi+CSA than m-TORi+MPA and m-TORi+Tac in KTRs with primary renal diagnosis of hypertension: this benefit was lost in KTRs with primary renal diagnoses other than hypertension.

Conclusion

In summary, our study suggests that in a kidney transplant recipient with clinical indication for an m-TORi (+/- steroids) immunosuppressant regimen, m-TORi+MPA is not a desirable choice due to its higher risks for overall and death-censored graft losses than m-TORi+CSA or m-TORi+Tac. When choosing between last two foregoing regimens, a primary diagnosis of HTN may indicate that either may be used; while, a primary diagnosis other than hypertension may indicate the preferential use of m-TORi+CSA. We conclude that the classification of the KTR's pre-transplant renal diagnosis into HTN or another (non-HTN) etiology could be a useful baseline pre-transplant factor to consider in the selection of an m-TORi regimen for maintenance immunosuppression.

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