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Outcomes of sirolimus regimens in 65-year-old and older kidney transplant recipients: a registry-based observational study

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Abstract

Purpose In large observational studies of adult kidney transplant recipients (KTRs) where older adults (65 years old and older) were not well represented, the mammalian target of rapamycin inhibitors (mTOR inhibitors) has poorer outcomes than the standard tacrolimus–mycophenolate–steroids (TAC–MPA–S) regimen. We conducted this study to compare the outcomes of regimens containing the common mTOR inhibitor, sirolimus (SRL) against TAC–MPA–S in older adult KTRs.

Methods Using the 2000–2016 Scientific Registry of Transplant Recipients, Cox multivariable regression models were conducted to analyze the patient and graft outcomes associated with regimens containing SRL, steroids (S) and cyclosporine (CSA), tacrolimus (TAC), or mycophenolate (MPA) vs. the standard (TAC–MPA–S) regimen in older adult KTRs.

Results Included in the analysis were 15,008 (95.19%) older adult KTRs on standard (TAC–MPA–S) regimen, 242 (1.53%) on SRL–MPA–S, 300 (1.90%) on SRL–TAC–S, and 217 (1.38%) on SRL–CSA–S. Compared with the standard regimen, the adjusted risks of all-cause death and overall graft loss over a maximum 5-year follow-up were highest with SRL–MPA–S, intermediate with SRL–TAC–S and not significantly different with SRL–CSA–S. The adjusted risks of all-cause death and overall graft loss were modified by a pre-transplant history of malignancy in older adult KTRs on SRL–TAC–S, not in those on SRL–MPA–S or SRL–CSA–S.

Conclusions In older adult kidney transplant recipients, SRL–TAC–S or SRL–MPA–S, but not SRL–CSA–S is associated with higher risks of death and allograft loss than standard TAC–MPA–S regimen and a pre-transplant malignancy history worsens these risks in patients on SRL–TAC–S. Confirmation of our findings by a prospective randomized trial is needed before translation into clinical practice can be recommended.

Keywords Sirolimus · Outcomes · Older adult kidney transplants

Introduction

Over the past decade, kidney transplantation in older adults (65 years old and older) has steadily increased. In 2017, 18.5% of KTRs were 65 years old and older [1]. The survival, quality of life, and economic advantages of kidney transplantation over dialysis seen in younger KTRs have also been demonstrated in older adult KTRs [2]. However, except for a few studies, the outcomes of specific immunosuppression regimens have not been well studied in older adult KTRs who were either under-represented or excluded in clinical trials of rejection prophylaxis drugs [3–6]. With the lack of evidence to support optimal immunosuppression regimen in older adult KTRs, it has been customary to use the standard immunosuppression regimen for patients in this age category [6, 7]. While the standard immunosuppression regimen (consisting of a calcineurin inhibitor, mycophenolate, and prednisone) is deemed efficacious and safe in preventing allograft rejection, in a minority of KTRs, compelling medical indications constrain the use of an alternative regimen such as an mTOR inhibitor [7–9].

mTOR inhibitor drugs have been used to reduce the risk of or adjunctly manage malignancies, viral infections, and

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calcineurin-induced nephrotoxicity in transplant recipients [9–12]. By their pleiotropic anti-atherosclerotic properties, the mTOR inhibitors prevent or delay the progression of vasculopathy after kidney transplantation [13–19]. Sirolimus (SRL) is the most common mTOR inhibitor given to KTRs in the US [8]. Despite its putative benefits mentioned above, large non-randomized studies have shown that SRL is associated with inferior graft and (or) patient outcomes in kidney transplantation [20–23]. The caveat though is those studies have not included enough 65-year-old and older KTRs, so that the patient and allograft survival outcomes of SRL regimens in older adult KTRs remains unclear [6]. It is crucial to determine the outcomes of SRLs in older adult KTRs who are predisposed to infections, malignancies, and progression of atherosclerotic diseases: complications of immunosuppression that could be attenuated by an mTOR inhibitor [10–12]. We hypothesized that by its anti-neoplastic, -atherosclerotic, and -viral properties, SRL provides greater patient and allograft survival benefits than the standard tacrolimus, mycophenolate and steroids (TAC–MPA–S) regimen in older adult KTRs. Therefore, we conducted this study to compare the outcomes of SRL regimens against standard TAC–MPA–S in older adult KTRs. We secondarily aimed to determine the modifying influence, if any, of a pre-transplant history of malignancy on the outcomes of SRL regimens in older adult KTRs. The findings of this research when confirmed by further studies could be useful in guiding the use of SRL-containing immunosuppression regimens in older adult KTRs with compelling indications for avoidance of the standard regimen.

Method

Study population

This study included 15,767 patients aged 65 years old and older that received a kidney-only transplant (KT) in the United States between January 1, 2000 and May 31, 2015 and survived with a functioning allograft in the first transplant year. Patients were included if they were on one of the study (sirolimus, tacrolimus and prednisone, SRL–TAC–S; sirolimus, cyclosporine, and steroids, SRL–CSA–S; or sirolimus, mycophenolate and steroids, SRL–MPA–S) or reference (TAC–MPA–S) maintenance immunosuppression regimens continuously for at least 6 months immediately preceding and including the 12th month of kidney transplant as previously described [23].

Data collection

This study used data from the Scientific Registry of Transplant Recipients (SRTR) as approved by the University of Rhode Island Institutional Review Board. The SRTR system includes data on all donors, waitlisted candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network and has been described elsewhere. The Health Resources and Services Administration provides oversight into the activities of the Organ Procurement and Transplantation Network and SRTR contractors.

Collected data on clinically relevant covariates chosen a priori [24] are enumerated in Table 1 including maintenance immunosuppression regimen, history of coronary artery disease or equivalent risk [25, 26]; era of transplantation 2000–2009 or 2010–2015; history of any type of malignancy pre-transplant; history of delayed graft function (DGF) defined as the need for dialysis within the 1st week following transplant; immunosuppression induction agent classified as anti-thymocyte globulin (ATG), alemtuzumab, interleukin-2-receptor blocker, none, or others; peak panel reactive antibody (PRA) percent before transplant stratified as < 50% or >/=50%; number of human leukocyte antigen (HLA) mismatches between donor and recipient, stratified as </=3, > 3, or unknown; primary native renal diagnosis classified as diabetes mellitus, glomerulonephritis, hypertension or other; duration of pre-transplant maintenance dialysis stratified into </=2 years, > 2 years, or none; and donor type classified as: (1) expanded criteria donor (ECD) if the deceased donor met the following criteria: age >/= 60 years or 50–59 years of age with any two of the following: terminal creatinine > 1.5 mg/dl, history of hypertension, or cardiovascular accident as the cause of death; (2) standard deceased donor, if the deceased donor does not meet the criteria for an ECD above; and (3) living donor [27].

Exposure and outcomes

Patients who received their kidney transplant between January 1, 2000 and May 31, 2015 and qualified for the study based on the inclusion and exclusion criteria were included in the analysis and followed after the 12th month of transplant until the first of the following events: death, end of 5-year maximum follow-up, end of SRTR follow-up, or 1 June 2016. The primary exposure was the use of a sirolimus regimen: (A) SRL–MPA–S, (B) SRL–TAC–S, or (C) SR–CSA–S consistently for at least 6 months immediately before and through the 12th month of transplant based on the SRTR immunosuppression records. TAC–MPA–S was the reference regimen. The primary study outcomes were: (1) overall graft loss, defined as death from all causes or non-death graft loss defined as the return to dialysis or re-transplantation; and (2) all-cause death. Secondary outcomes were overall graft loss and all-cause death in the subgroups with and without a pre-transplant history of malignancy. The methodology

Table 1 Demographic and transplant-related characteristics of 65-year-old and older kidney allograft recipients: overall and immunosuppression cohorts

Variables	Overall sample[a]	SRL–MPA–S[b]	SRL–TAC–S[c]	SRL–CSA–S[d]	TAC–MPA–S[e]	*p**
Acute rejection, early	963 (6.11)	10 (4.13)	18 (6.00)	9 (4.15)	926 (6.17)	0.36
HCV antibody+[f]	407 (2.58)	6 (2.48)	7 (2.33)	2 (0.92)	392 (2.61)	< 0.0001
CMV antibody+[g]	11,280 (71.54)	183 (75.62)	191 (63.67)	129 (59.45)	10,777 (71.81)	< 0.0001
Donor type						0.01
Expanded criteria	3719 (23.59)	74 (30.58)	66 (22.00)	45 (20.74)	3534 (23.55)	
Deceased, standard	7781 (49.35)	106 (43.80)	130 (43.33)	112 (51.61)	7433 (49.53)	
Living	4267 (27.06)	62 (25.62)	104 (34.67)	60 (27.65)	4041 (26.93)	
Recipient race						0.002
Caucasian	9522 (60.39)	158 (65.29)	187 (62.33)	124 (57.14)	9053 (60.32)	
Black	3283 (20.82)	40 (16.53)	55 (18.33)	32 (14.75)	3156 (21.03)	
Hispanic	1798 (11.40)	31 (12.81)	38 (12.67)	44 (20.28)	1685 (11.23)	
Other	1164 (7.38	13 (5.37)	20 (6.67)	17 (7.83)	1114 (7.42)	
Recipient sex						0.41
Male	9736 (61.75)	159 (65.70)	177 (59.00)	138 (63.59)	9262 (61.71)	
Female	6031 (38.25)	83 (34.30)	123 (41.00)	79 (36.41)	5746 (38.29)	
Year of transplant						< 0.0001
2000–2009	7992 (50.69)	227 (93.80)	294 (98.00)	200 (92.17)	7271 (48.45)	
2010–2015	7775 (49.31)	15 (6.20)	6 (2.00)	17 (7.83)	7737 (51.55)	
Previous transplant	794 (5.04)	8 (3.31)	19 (6.33)	11 (5.07)	756 (5.04)	0.46
BMI[h] >/= 30 kg/m^2	4632 (29.38)	64 (26.45)	66 (22.00)	36 (16.59)	4466 (29.76)	< 0.0001
Cardiovascular disease[i]	7962 (50.50)	125 (51.65)	157 (52.33)	86 (39.63)	7594 (50.60)	0.002
Malignancy history	1844 (11.70)	17 (7.02)	18 (6.00)	20 (9.22)	1789 (11.92)	< 0.0001
Delayed graft function	2943 (18.67)	75 (31.00)	47 (15.67)	33 (15.21)	2788 (18.58)	< 0.0001
Induction agent						< 0.0001
ATG[j]	6212 (39.40)	64 (26.45)	74 (24.67)	50 (23.04)	6024 (40.14)	
Alemtuzumab	605 (3.84)	0 (0.00)	1 (0.33)	0 (0.00)	604 (4.02)	
Basiliximab	5089 (32.28)	117 (48.35)	102 (34.00)	73 (33.64)	4797 (31.96)	
None	2026 (12.85)	30 (12.40)	60 (20.00)	28 (12.90)	1908 (12.71)	
Other	1835 (11.64)	31 (12.81)	63 (21.00)	66 (30.41)	1675 (11.16)	
Panel reactive antibody						0.47
< 50%, peak	15,141 (96.03)	234 (96.69)	293 (97.67)	209 (96.31)	14,405 (95.98)	
=> 50%, peak	626 (3.97)	8 (3.31)	7 (2.33)	8 (3.69)	603 (4.02)	
HLA[k] mismatch						< 0.0001
</= 3	5868 (37.22)	100 (41.32)	155 (51.67)	84 (38.71)	5529 (36.84)	
> 3	9866 (62.57)	141 (58.26)	143 (47.67)	133 (61.29)	9449 (62.96)	
Unknown	33 (0.21)	1 (0.41)	2 (0.67)	0 (0.00)	30 (0.20)	
Primary diagnosis						0.29
Diabetes mellitus	5288 (33.54)	79 (32.64)	101 (33.67)	59 (27.19)	5049 (33.64)	
Glomerulonephritis	2347 (14.89)	36 (14.88)	40 (13.33)	27 (12.44)	2244 (14.95)	
Hypertension	4717 (29.92)	67 (27.69)	87 (29.00)	71 (32.72)	4492 (29.93)	
Other disease	3415 (21.66)	60 (24.79)	72 (24.00)	60 (27.65)	3223 (21.48)	
Pre-transplant dialysis						0.15
None	5541 (35.14)	77 (31.82)	122 (40.67)	69 (31.80)	5273 (35.13)	
</= 2 years	7327 (46.47)	124 (51.24)	133 (44.33)	112 (51.61)	6958 (46.36)	
> 2 years	2899 (18.39)	41 (16.94)	45 (15.00)	36 (16.59)	2777 (18.50)	

Maintenance regimen: consistent immunosuppression drug regimens at discharge, 6th month and 12th month of transplant or at 6th month and 12th month of transplant

**p* significance of differences among maintenance immunosuppression regimen cohorts in columns 2–5

[a]Subjects are kidney transplant recipients who qualify based on the study inclusion and exclusion criteria (see text for details); $N = 15{,}767$ (100%)

Table 1 (continued)

[b] *SRL–MPA–S* sirolimus–mycophenolate–steroids; $N = 242$ (1.53%)

[c] *SRL–TAC–S* sirolimus–tacrolimus–steroids; $N = 300$ (1.90%)

[d] *SRL–CSA–S* sirolimus–cyclosporine–steroids; $N = 217$ (1.38%)

[e] *TAC–MPA–S* tacrolimus–mycophenolate–steroids; $N = 15{,}008$ (95.19%)

[f] Hepatitis C virus

[g] Cytomegalovirus

[h] Body mass index

[i] Defined as coronary artery disease, diabetes mellitus, angina pectoris, peripheral vascular disease, or cerebrovascular disease

[j] Anti-thymocyte globulin

[k] Human leukocyte antigen

used in defining primary exposure and following subjects for outcomes were adopted from a previously published SRTR-based study on sirolimus regimens in KTRs [23].

Statistical analysis

Baseline KTRs categorical variables characteristics were presented as frequency counts and percentages and compared using Chi square statistic. The risks of all-cause death and overall graft loss were analyzed using unadjusted and adjusted Cox multivariable hazards regression models (Cox models) with the sirolimus regimens (SRL–TAC–S, SRL–MPA–S, SRL–CSA–S) as main explanatory variables and the TAC–MPA–S regimen as the reference. The modifying effects of a pre-transplant history of malignancy on the associations between the SRL regimens and outcomes were analyzed using Cox models with interaction terms for pre-transplant history of malignancy and SRL regimens, and covariate terms for SRL regimens vs. TAC–MPA–S in the strata of KTRs with and without pre-transplant history of malignancy. The differences of the hazard ratios across subgroups with and without a pre-transplant history of malignancy were assessed by the method of Altman and Bland [28]. All covariates in the unadjusted and adjusted Cox models were selected a priori based on known clinical significance [24]. Indicator variables were used for missing data and no imputation method was used. The goodness of fit of models was assessed using Akaike's information criterion (AIC): a lower AIC indicated a better fit. Collinearity of covariates was analyzed with the Chi square test for independence standardized by Cramer's V statistic. Cox multivariable regression results were presented as unadjusted and adjusted hazard ratio (uHR and aHR, respectively) and 95% confidence interval (CI). The significance level for all analyses was set at $p \leq 0.05$. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

Based on the research inclusion criteria, 759 older adult (65 years old and older) KTRs from 1 January 2000 to 31 December 2015 were followed for a maximum of 5 years for outcomes associated with use of SRL regimens: (A) SRL–MPA–S [$n = 242$ (31.9%)]; (B) SRL–TAC–S [$n = 300$ (39.5%)]; or (C) SRL–CSA–S [$n = 217$ (28.6%)] for the specified duration in the first transplant year. Older adult KTRs on the standard regimen of TAC–MPA–S ($n = 15{,}008$) comprised the reference group. Therefore, of the 15,767 older adult KTRs included in the analysis, 4.8% were on a sirolimus regimen and 95.2% were on the standard regimen. The baseline characteristics of the cohorts are presented in Table 1.

Patient and overall graft outcomes

Results of unadjusted and adjusted multivariable Cox models showed that in older adult KTRs, SRL–MPA–S or SRL–TAC–S, but not SRL–CSA–S was associated with significantly higher risks of overall graft loss and all-cause death than the standard regimen (Tables 2, 3, respectively). A pre-transplant history of malignancy was associated with an 18% significantly higher risk of all-cause death (aHR 1.18, 95% CI 1.05–1.32) and a 9% suggestively higher risk of overall graft loss (aHR 1.09, 95% CI 0.98–1.22). A pre-transplant cardiovascular disease was associated with a 28% higher risk of 5-year all-cause death (aHR 1.28, 95% CI 1.16–1.41) and 24% higher risk of 5-year overall graft loss (aHR 1.24, 95% CI 1.13–1.35). The unadjusted and adjusted relative risk estimates and 95% confidence limits for the other covariates used in the Cox multivariable hazards regressions for overall graft loss and all-cause death are exhibited in Tables 2 and 3, respectively.

Table 2 Risk factors overall graft loss, 65-year-old and older kidney transplant recipients

Risk factor	Unadjusted Cox model			*p*	Adjusted Cox model			*p*
	HR[a]	95% CI[b]			HR[a]	95% CI[b]		
		LL[c]	UL[d]			LL[c]	UL[d]	
Maintenance regimen[e, f]								
SRL–MPA–S[g]	1.85	1.54	2.23	< 0.001	1.63	1.35	1.98	< 0.001
SRL–TAC–S[h]	1.45	1.21	1.73	< 0.001	1.32	1.10	1.58	0.003
SRL–CSA–S[i]	1.17	0.93	1.47	0.17	1.19	0.95	1.51	0.12
Regimen consistent	0.63	0.54	0.73	< 0.001	0.81	0.69	0.95	0.01
Acute rejection	1.97	1.77	2.19	< 0.001	1.86	1.67	2.07	< 0.001
HCV[j]+	1.32	1.09	1.59	0.005	1.26	1.04	1.52	0.02
CMV[k]+	1.01	0.93	1.09	0.90	0.99	0.91	1.08	0.82
Donor type								
ECD[l] donor	1.89	1.72	2.07	< 0.001	1.48	1.33	1.66	< 0.001
SCD[m] donor	1.39	1.27	1.51	< 0.001	1.23	1.11	1.35	< 0.001
Recipient race								
African American	1.09	1.00	1.18	0.05	0.84	0.77	0.92	< 0.001
Hispanic/Latino	0.93	0.83	1.04	0.18	0.77	0.69	0.87	< 0.001
Other	0.76	0.65	0.88	< 0.001	0.62	0.54	0.73	< 0.001
Recipient male	1.23	1.15	1.32	< 0.001	1.12	1.05	1.21	0.002
Previous transplant	1.21	1.05	1.40	0.01	1.35	1.17	1.57	< 0.001
BMI[n] >/= 30 kg/m^2	1.11	1.03	1.20	0.005	1.04	0.96	1.12	0.30
CVD[o] history	1.41	1.32	1.51	< 0.001	1.24	1.13	1.35	< 0.001
History, malignancy	1.09	0.98	1.21	0.12	1.09	0.98	1.22	0.11
DGF[p]	1.61	1.49	1.74	< 0.001	1.32	1.22	1.44	< 0.001
PRA[q] >=50%	0.98	0.84	1.14	0.74	0.99	0.85	1.17	0.94
HLA[r] mismatch, > 3	1.27	1.19	1.36	< 0.001	1.10	1.02	1.19	0.01
Primary disease								
Diabetes mellitus	1.43	1.30	1.57	< 0.001	1.25	1.11	1.40	< 0.001
Glomerulonephritis	0.95	0.85	1.08	0.44	0.97	0.86	1.09	0.62
Hypertension	1.21	1.10	1.34	< 0.001	1.19	1.08	1.32	< 0.001
Dialysis duration								
0–2 years	1.42	1.31	1.53	< 0.001	1.25	1.15	1.36	< 0.001
> 2 years	1.68	1.52	1.84	< 0.001	1.44	1.29	1.59	< 0.001
Transp. yr. 2010–2015 induction	0.82	0.76	0.89	< 0.001	0.86	0.79	0.94	< 0.001
Anti-thymocyte globulin	1.04	0.96	1.13	0.29	0.99	0.92	1.08	0.88
Alemtuzumab	1.23	1.02	1.49	0.03	1.13	0.93	1.37	0.21
None	1.00	0.90	1.12	0.97	0.95	0.85	1.06	0.37
Other	1.11	1.00	1.24	0.047	1.06	0.96	1.19	0.25

[a]Hazard ratio

[b]Confidence interval

[c]Upper limit

[d]Lower limit

[e]Maintenance regimen: consistent immunosuppression drug regimens at discharge, 6th month and 12th month of transplant or 6th month and 12th month of transplant

[f]Reference: *TAC–MPA–S* tacrolimus–mycophenolate–steroids

[g]*SRL–MPA–S* sirolimus–mycophenolate–steroids

[h]*SRL–TAC–S* sirolimus–tacrolimus–steroids

[i]*SRL–CSA–S* sirolimus–cyclosporine–steroids

[j]Hepatitis C virus

[k]Cytomegalovirus

[l]Expanded criteria deceased donor

Table 2 (continued)

[m]Standard criteria deceased donor

[n]Body mass index

[o]Defined as coronary artery disease, diabetes mellitus, angina pectoris, peripheral vascular disease, or cerebrovascular disease

[p]Delayed graft function

[q]Panel reactive antibody

[r]Human leukocyte antigen

[s]Reference: transplant year 2000–2009

Analyses stratified according to a history of malignancy pre-transplant

Relative to the standard regimen, SRL–TAC–S was associated with the doubling of the adjusted hazard ratios for all-cause death and overall graft loss in older adult KTRs with a history of malignancy pre-transplant compared to those without a similar history[(aHR 2.60, 95% CI 1.45–4.64) vs. (aHR 1.18, 95% CI 0.95–1.47); $p = 0.005$] and [(aHR 2.58, 95% CI 1.48–4.5) vs. (aHR 1.26, 95% CI 1.03–1.54); $p = 0.009$], respectively] (Fig. 1). Relative to the standard regimen, SRL–MPA–S was associated with significantly higher adjusted hazard ratios of overall graft loss and all-cause death in older adult KTRs without, not in those with a history malignancy pre-transplant [(aHR 1.66, 95% CI 1.36–2.04 and aHR 1.68, 95% CI 1.36–2.09) vs. (aHR 1.61 95% CI 0.83–3.12 and aHR 1.31, 95% CI 0.62–2.78), respectively] (Fig. 1). However, the differences in aHRs for overall graft loss and all-cause death associated with SRL–MPA–S in the pre-transplant malignancy history (present and absent) subgroups were not statistically significant. These results indicate that pre-transplant malignancy history did not modify the outcomes associated with SRL–MPA–S (Fig. 1). The unadjusted and adjusted risks of overall graft loss and all-cause death associated with SRL–CSA–S were not different from the standard regimen (Tables 2, 3, respectively) and the absence or presence of a pre-transplant malignancy history did not modify these relationships (Fig. 1).

Discussion

Main outcomes

Despite their weaker innate and adaptive immunity caused by "immune senescence", older adult (65 years old and older) KTRs typically receive the same standard immunosuppression regimen given to younger than 65-year-old KTRs. This practice is driven by the lack of evidence on optimal immunosuppression for older adult KTRs. Due to their anti-cancer, anti-viral and anti-atherosclerotic effects, mTOR inhibitors (such as sirolimus) can be hypothesized to be more beneficial than the standard TAC–MPA–S immunosuppression in the older adult KTRs [13–23]. We conducted this study to analyze the outcomes associated with sirolimus regimens in older adult KTRs. The main finding of our study is that two sirolimus regimens (SRL–TAC–S and SRL–MPA–S) are associated with higher risks of overall graft loss and all-cause death than standard TAC–MPA–S in KTRs 65 years old and older. And, in this older adult age group, a pre-transplant history of malignancy worsens the risk of mortality or graft loss associated with the SRL–TAC–S regimen. Among the three sirolimus regimens studied, only SRL–CSA–S is not associated with a higher risk of mortality or allograft loss compared with the standard regimen in the older adult KTRs. Therefore, if our findings are confirmed by further studies, SRL–CSA–S may potentially become a favorable substitute for TAC–MPA–S when an mTOR inhibitor is medically indicated in older adult KTRs. Additionally, a pre-transplant malignancy history would militate against the use of SRL–TAC–S in older adult KTRs.

Large non-randomized and meta-analytic studies with insufficient older adult subjects have shown that sirolimus is associated with inferior graft and (or) patient outcomes in kidney transplantation [20–23]. Our current study differs from the above studies in two important respects; (1) identification of outcomes of specific sirolimus regimens (SRL–TAC–S, SRL–MPA–S, and SRL–CSA–S) instead of reporting pooled outcomes of mTOR inhibitors or sirolimus without specifying the regimen, and (2) investigation of SRL regimen outcomes in KTRs aged 65 years old and older, an age group not well represented in past studies. Our main findings supported the superior patient and allograft outcomes of the standard TAC–MPA–S regimen over the two SRL regimens, SRL–MPA–S or SRL–TAC–S in the older adult KTRs. However, our results showed that not all SRL regimens are inferior to the standard regimen in older adult KTRs. We found that SRL–CSA–S was not associated with a different risk of death or overall graft loss compared with standard TAC–MPA–S in 65-year-old and older KTRs (Table 2). When confirmed by further clinical studies, our findings will have important clinical implications on the use of specific sirolimus regimens in older adult KTRs.

Table 3 Risk factors all-cause death, 65-year-old and older kidney transplant recipients

Risk factor	Unadjusted Cox model			*p*	Adjusted Cox model			*p*
	HR[a]	95% CI[b]			HR[a]	95% CI[b]		
		LL[c]	UL[d]			LL[c]	UL[d]	
Maintenance regimen[e,f]								
SRL–MPA–S[g]	1.87	1.53	2.29	< 0.001	1.64	1.33	2.02	< 0.001
SRL–TAC–S[h]	1.37	1.13	1.67	0.002	1.26	1.03	1.54	0.03
SRL–CSA–S[i]	1.14	0.89	1.47	0.30	1.14	0.88	1.47	0.32
Regimen consistent	0.71	0.60	0.85	< 0.001	0.88	0.74	1.06	0.19
Acute rejection	1.42	1.24	1.62	< 0.001	1.36	1.19	1.56	< 0.001
HCV[j]+	1.31	1.06	1.61	0.01	1.27	1.03	1.57	0.03
CMV[k]+	0.98	0.90	1.06	0.56	0.98	0.90	1.07	0.67
Donor type								
ECD[l] donor	1.67	1.50	1.85	< 0.001	1.38	1.22	1.56	< 0.001
SCD[m] donor	1.37	1.25	1.50	< 0.001	1.21	1.08	1.34	< 0.001
Recipient race								
African American	0.92	0.84	1.01	0.07	0.71	0.64	0.79	< 0.001
Hispanic/Latino	0.90	0.80	1.02	0.09	0.73	0.64	0.83	< 001
Other	0.74	0.63	0.87	< 0.001	0.61	0.52	0.72	< 0.001
Recipient male	1.24	1.15	1.33	< 0.001	1.12	1.04	1.22	0.004
Previous transplant	1.24	1.06	1.45	0.006	1.39	1.18	1.63	< 0.001
BMI[n] >/= 30 kg/m^2	1.06	0.98	1.15	0.17	0.98	0.90	1.06	0.61
CVD[o] history	1.48	1.38	1.60	< 0.001	1.28	1.16	1.41	< 0.001
History, malignancy	1.17	1.04	1.31	0.007	1.18	1.05	1.32	0.005
DGF[p]	1.55	1.43	1.69	< 0.001	1.32	1.20	1.44	< 0.001
PRA[q] >=50%	1.01	0.86	1.20	0.88	1.02	0.86	1.22	0.06
HLA[r] mismatch, > 3	1.20	1.11	1.29	< 0.001	1.09	1.01	1.19	0.03
Primary disease								
Diabetes mellitus	1.47	1.33	1.63	< 0.001	1.32	1.17	1.50	< 0.001
Glomerulonephritis	0.89	0.78	1.02	0.10	0.91	0.79	1.04	0.16
Hypertension	1.17	1.05	1.30	0.004	1.20	1.08	1.34	< 0.001
Dialysis duration								
0–2 years	1.40	1.29	1.53	< 0.001	1.26	1.15	1.38	< 0.001
> 2 years	1.67	1.50	1.85	< 0.001	1.48	1.32	1.66	< 0.001
Transp. yr. 2010–2015 induction	0.79	0.73	0.87	< 0.001	0.83	0.76	0.91	< 0.001
Anti-thymocyte globulin	1.02	0.93	1.11	0.70	0.99	0.90	1.08	0.77
Alemtuzumab	1.07	0.86	1.33	0.55	1.02	0.82	1.28	0.84
None	0.98	0.87	1.10	0.68	0.93	0.82	1.04	0.21
Other	1.10	0.98	1.23	0.11	1.05	0.94	1.18	0.41

[a]Hazard ratio

[b]Confidence interval

[c]Upper limit

[d]Lower limit

[e]Maintenance regimen: consistent immunosuppression drug regimens at discharge, 6th month and 12th month of transplant or 6th month and 12th month of transplant

[f]Reference: TAC–MPA–S, tacrolimus–mycophenolate–steroids

[g]SRL–MPA–S, sirolimus–mycophenolate–steroids

[h]SRL–TAC–S, sirolimus–tacrolimus–steroids

[i]SRL–CSA–S, sirolimus–cyclosporine–steroids

[j]Hepatitis C virus

[k]Cytomegalovirus

[l]Expanded criteria deceased donor

Table 3 (continued)

[m]Standard criteria deceased donor

[n]Body mass index

[o]Defined as coronary artery disease, diabetes mellitus, angina pectoris, peripheral vascular disease, or cerebrovascular disease

[p]Delayed graft function

[q]Panel reactive antibody

[r]Human leukocyte antigen

[s]Reference: transplant year 2000–2009

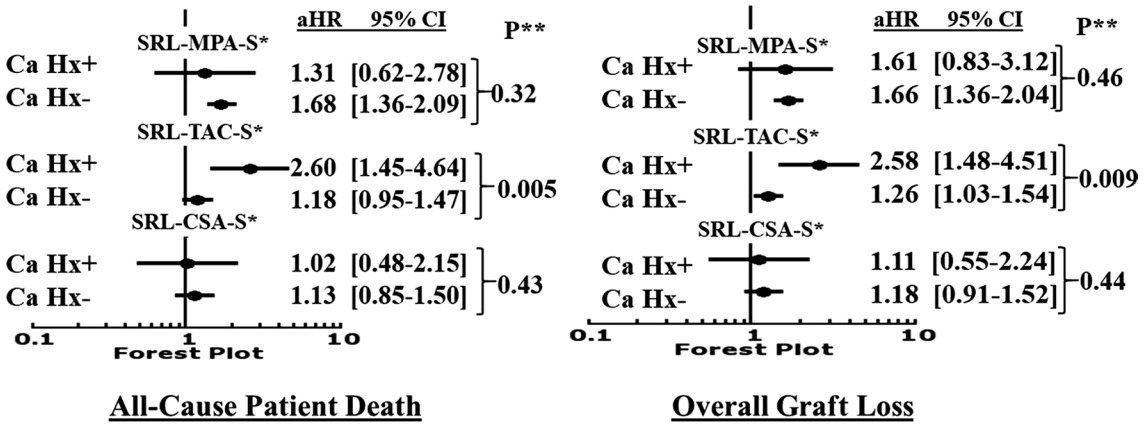

Fig. 1 Outcomes of sirolimus regimens in 65-year-old and older kidney transplant recipients with pre-transplant malignancy/ cancer history present ($CaHx^+$) or absent ($CaHx^-$). Cox models adjusted for acute rejection event before discharge following transplant; hepatitis C (HCV) and cytomegalovirus (CMV) antibody status; donor type categorized as expanded criteria deceased, standard deceased, or living; transplant recipient race/ethnicity classified as White, African American, Hispanic, or other; transplant recipient sex; year of transplant stratified as 2000–2009 or 2010–2016; history of previous kidney transplant; body mass index (BMI) stratified as >/=30 kg/m^2 or < 30 kg/m^2; history of cardiovascular disease, history of any type of malignancy pre-transplant; history of delayed graft function defined as the need for dialysis within the 1st week following transplant; immunosuppression induction agent classified as anti-thymocyte globulin (ATG), alemtuzumab, interleukin-2-receptor blocker, none, or others; peak panel reactive antibody (PRA) % before transplant stratified as < 50% or >/=50%: number of human leukocyte antigen (HLA) mismatch between donor and recipient, stratified as </=3, > 3, or unknown; primary diagnosis at transplant enrolment categorized as diabetes mellitus, glomerulonephritis, hypertension and other; and duration of pre-transplant maintenance dialysis stratified into </=2 years or > 2 years. *aHR* adjusted hazard ratio, *CI* confidence interval, *Reference regimen* TAC–MPA–S, tacrolimus, mycophenolate and steroids, *SRL–MPA–S* sirolimus–mycophenolate–steroids, *SRL–TAC–S* sirolimus–tacrolimus–steroids, *SRL–CSA–S* sirolimus–cyclosporine–steroids

The interaction between sirolimus regimens and pre-transplant history of malignancy

As the previous history of malignancy is a main reason for using a sirolimus regimen after kidney transplantation [9, 18, 20–23], we analyzed the interactions between SRL regimens and this risk factor on transplant outcomes in older adult KTRs. Our results showed that among the sirolimus regimens, SRL–TAC–S is associated with detrimental, instead of beneficial allograft and patient outcomes in older adults with a pre-transplant history of malignancy (Fig. 1). The outcomes associated with SRL–MPA–S and SRL–CSA–S are not modified by the pre-transplant malignancy history of older adult KTRs (Fig. 1). Cortazar et al. [29] have reported that sirolimus was associated with an increased risk of mortality in KTRs without a prior history of malignancy and this adverse outcome was not seen in KTRs with a prior history of malignancy. Our study differed from that of Cortazar et al., in that the mean age of KTRs in their study was 53.8 ± 10.6 years, while all patients in our study are 65 years old and older; they studied only 79 KTRs on sirolimus (and 22 KTRs on everolimus), while we studied 759 KTRs on sirolimus regimens. Their unadjusted analysis which showed that mTOR inhibitors were not associated with a higher risk of death in KTRs with a pre-transplant malignancy history was likely due to underpowering [29], on the other hand, our unadjusted and adjusted analyses showed that SRL–TAC–S is associated with higher risks of graft loss and death in KTRs with, not in those without a pre-transplant malignancy history (Fig. 1); conversely, SRL–MPA–S is associated with

higher risks of graft loss and death in KTRs without, not in those with a pre-transplant malignancy history. SRL–CSA–S was not associated with different risks of death and graft loss than the standard regimen irrespective of the KTRs' pre-transplant malignancy history.

Limitations and strengths of the study

The lack of data in SRTR on immunosuppressive doses and blood levels, monitoring and management of CMV and HCV infections, and treatment of acute rejections precluded a more detailed analysis. Disadvantages inherent in retrospective database analysis including selection bias and confounding by indication can be mitigated but not totally excluded [30]. The strengths of this study include the breadth of the analysis of a national transplant database spanning 15 years and the novelty of its findings, since older adult patients have not been well represented in previous studies on the use of sirolimus in KTRs.

Conclusions

In the older adult KTRs, SRL–TAC–S and SRL–MPA–S are associated with higher risks of overall graft loss and all-cause mortality than standard immunosuppression regimen: a pre-transplant malignancy history is associated with the worsening of these outcomes among those on SRL–TAC–S. On the other hand, SRL–CSA–S is not associated with higher risks of overall graft loss and all-cause mortality relative to standard immunosuppression regimen in older adult KTRs. Confirmation of the above findings by an adequately powered prospective randomized trial is needed.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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