ORIGINAL ARTICLE

Differential risks for adverse outcomes 3 years after kidney transplantation based on initial immunosuppression regimen: a national study

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SUMMARY

We examined integrated national transplant registry, pharmacy fill, and medical claims data for Medicare-insured kidney transplant recipients in 2000–2011 (n = 45 164) from the United States Renal Data System to assess the efficacy and safety endpoints associated with seven early (first 90 days) immunosuppression (ISx) regimens. Risks of clinical complications over 3 years according to IS regimens were assessed with multivariate regression analysis, including the adjustment for covariates and propensity for receipt of a nonreference ISx regimen. Compared with the reference ISx (thymoglobulin induction with tacrolimus, mycophenolate, and prednisone maintenance), sirolimus-based ISx was associated with significantly higher three-year risks of pneumonia (adjusted hazard ratio, aHR 1.45; $P < 0.0001$), sepsis (aHR 1.40; $P < 0.0001$), diabetes (aHR 1.21; $P < 0.0001$), acute rejection (AR; adjusted odds ratio, aOR 1.33; $P < 0.0001$), graft failure (aHR 1.78; $P < 0.0001$), and patient death (aHR 1.40; $P < 0.0001$), but reduced skin cancer risk (aHR 0.71; $P < 0.001$). Cyclosporine-based IS was associated with increased risks of pneumonia (aHR 1.17; $P < 0.001$), sepsis (aHR 1.16; $P < 0.001$), AR (aOR 1.43; $P < 0.001$), and graft failure (aHR 1.39; $P < 0.001$), but less diabetes (aHR 0.83; $P < 0.001$). Steroid-free ISx was associated with the reduced risk of pneumonia (aHR 0.89; $P = 0.002$), sepsis (aHR 0.80; $P < 0.001$), and diabetes (aHR 0.77; $P < 0.001$), but higher graft failure (aHR 1.35; $P < 0.001$). Impacts of ISx over time warrant further study to better guide ISx tailoring to balance the efficacy and morbidity.

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Key words
cancer, immunosuppression, infections, kidney transplant, Medicare, registries

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Introduction

Over the last several decades, the development of more potent immunosuppressive (ISx) therapies such as induction agents [1], cyclosporine A (CsA) [2], tacrolimus (Tac), mycophenolic acid (MPA) [3,4], and sirolimus (SRL) [5] has led to a reduction in the incidence of early kidney transplant acute rejection (AR) rates [6,7]. However, despite the reductions in AR with potent immunosuppressive regimens, longer-term graft survival has not substantially improved [8]. Ongoing graft loss from medication-related allograft injury,

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chronic immunologic injury, and recurrent disease limits kidney survival despite the decreased AR rates. Further, premature recipient death with a functioning allograft results from major infections, malignancies, and metabolic complications that exacerbate cardiovascular mortality.

Major infections and malignancies appear to be more common with more potent ISx [9–12]. Per the 2013 United States Renal Data System (USRDS) annual report, sepsis and pneumonia occur in 25–30% of all recipients in the first 2 years after a kidney transplant [13]. We have previously demonstrated the associations of hospitalizations for septicemia and pneumonia with substantially decreased patient and graft survival [14]. Queries of the USRDS and National Cancer Institute registries highlight the cumulative burden of cancer among immunosuppressed transplant recipients, especially the markedly increased risk for viral-linked cancers [15,16]. Also, some transplant ISx medications are associated with higher incidence of metabolic complications such as new-onset diabetes after transplant (NODAT), and we have demonstrated the associations of NODAT with an increased risk of post-transplant myocardial infarction and heart failure [17,18]. Individual antirejection medications associated with an increased risk of NODAT include glucocorticoids, calcineurin inhibitors (especially Tac), and SRL [11,19–21].

Importantly, the risks of infection, cancer, and metabolic complications with various ISx combinations have not been well quantified in a way that allows patients and practitioners to compare, simultaneously, the expected efficacy and toxicity of different regimens. Simultaneous assessments of efficacy and adverse effect endpoints are inconsistent in clinical trials [14]. Among recent transplant trials, one-year pneumonia rates were similar in some to the 25% rate from two-year USRDS data [22,23], lower in other studies [5,24–26], while not reported in the main publications of some trial experiences [1,20,27–29]. The sepsis rate was noted in the main public domain publication only in the BENEFIT trial [25] at 1%. Prospective trials, with one- or two-year follow-up, have reported low cumulative cancer incidences [20,23,24,27–30]. There was previously scant reporting of malignancy adverse events as in the preapproval SRL studies and MPA studies [3,4,31], only recently emphasized by the Food and Drug Administration, for example, in the BENEFIT study [25].

Combining the national U.S. transplant registry data and diagnostic information on billing claims submitted for clinical care affords an alternate strategy for assessing efficacy and adverse outcomes among large samples of transplant recipients in real-world practice. The objective of this study was to simultaneously examine the associations of early (within 90-day) kidney transplant ISx regimen with efficacy endpoints (as measured by AR and graft survival), measures of morbidity (major infections, cancer, NODAT), and mortality risk at 3 years post-transplant. Better understanding of the outcomes implications of ISx in real-world practice may guide tailoring of ISx regimen choice to balance efficacy and morbidity.

Methods

Data sources and study sample

Study data were drawn from USRDS records that integrate Organ Procurement and Transplantation Network (OPTN) records with Medicare billing claims. The primary study sample comprised recipients of kidney-only transplants in the United States in 2000 to 2011 with Medicare as the primary payer at the time of transplantation, followed to 3 years post-transplant. The similarities and differences of patients in the USRDS with and without Medicare as their primary payer are summarized in Table S1. Because our definition of the primary exposure was based on pharmacy claims for ISx, we also required Medicare reimbursed fills for ISx in the first 90 days after transplantation. The Institutional Review Boards of Washington University, Saint Louis University, and Johns Hopkins University approved this study, and all study activities were performed in accordance with the ethical standards of the 2000 Declaration of Helsinki and the Declaration of Istanbul 2008.

Definition of immunosuppression regimens

Early maintenance ISx regimen was defined by Medicare pharmacy claims for IS agents submitted within the first 90 days after transplant. Use of induction agents was defined by OPTN reporting. Patients were classified based on induction and maintenance ISx regimens into the seven study regimens (Fig. 1), as follows:

1 Tac + MPA (which included mycophenolate mofetil and mycophenolate sodium)/azathioprine (AZA) + prednisone after 30 days + antithymocyte globulin (thymoglobulin, TMG) induction – considered the reference

2 Tac + MPA/AZA + Pred after 30 days + IL2-receptor antibody (IL2R-Abs) induction

3 Tac + MPA/AZA + Pred after 30 days + no induction

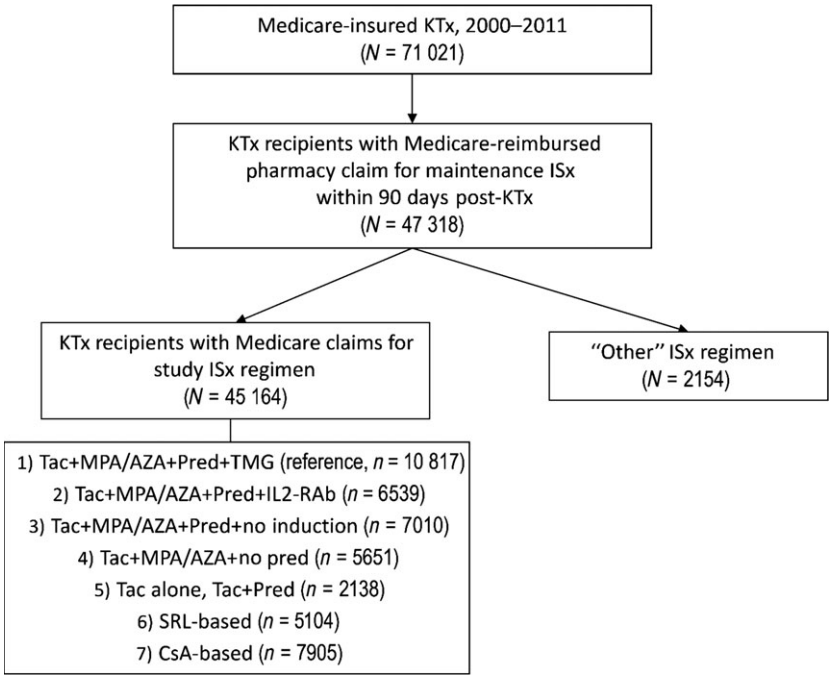

Figure 1 Sampling scheme used to categorize the study cohort. AZA, azathioprine; CsA, cyclosporine; IL2R, basiliximab or daclizumab; ISx, immunosuppressive agent; MPA, mycophenolic acid; No pred, no prednisone use after day 30 post-transplant; Pred, prednisone use documented after 30 days post-transplant; SRL, sirolimus; TMG, thymoglobulin; Tac, tacrolimus. Groups 4–7 were defined independent of induction. Patients in groups 1–5 did not receive SRL or CsA. SRL-based ISx was classified before CsA-based to enable the assignment of mutually exclusive regimens, as per previous methods [32].

4 Tac + MPA/AZA + no Pred after day 30 (steroid avoidance/withdrawal)
5 Tac alone, or Tac + Pred (antimetabolite avoidance)
6 *De novo* SRL-based regimens
7 *De novo* CsA-based regimens

Tac + MPA/AZA + Pred after 30 days + TMG, the most common regimen, was considered the reference. MPA included mycophenolate mofetil (MMF) and mycophenolate sodium. IL2R-Abs included the two agents available in the United States in the study period, basiliximab and daclizumab. Groups 4–7 were defined independent of induction. Patients in groups 1–5 did not receive SRL or CsA; SRL-based ISx was classified before CsA-based to enable the assignment of mutually exclusive regimens, as per previous methods [32]. SRL- and CsA-based regimens were not further subclassified due to low frequencies of patients treated with these regimens.

Outcome measures

Diagnoses of post-transplant infection, cancer, and NODAT events after the first 90 days and within the first 3 years after transplant were defined by the identification of billing claims with corresponding ICD9-CM diagnosis codes for pneumonia, sepsis, UTIs/pyelonephritis as leading categories of post-transplant infections, cancer [categorized as nonmelanoma skin cancer (NMSC), viral-linked, or other cancers], and diabetes mellitus (Table S2). The ICD-9 codes were chosen based on prior studies of these events in the transplant population [14,16,33,34]. Cancer was categorized as viral-linked cancer or not based on work by Grulich *et al.* [35]. To assess NODAT, analyses of the diabetes outcome were limited to patients without indications of diabetes as a primary cause of ESRD or comorbidity before the transplantation. We required one inpatient claim or two other claims on separate dates to define serious complications, and assigned the date of the first claim as the event date, as performed in previous studies of claims data to identify these conditions in the kidney transplant population [14,16,33,34]. Total observation was also limited to 3 years post-transplant, the time when Medicare coverage ends after kidney transplant in the absence of age older than 65 years or disability.

Acute rejection is not captured in billing claims. The OPTN queries centers for information on AR according to periods covered by specific reporting

forms (0–6, 7–12 months, then annual periods), but dates of acute rejection within reporting periods are not collected. We defined acute rejection from OPTN records according to center reports that an acute rejection event occurred in a reporting period, as per prior methods for identifying acute rejection from OPTN registry data [6,36].

Finally, death and graft failure events were defined by OPTN reports. Mortality included death from any cause. Cause of death reported to the registry was examined in a descriptive subanalysis. Graft failure was defined as the earliest reported date of return to maintenance dialysis or "preemptive" re-transplantation.

Statistical analyses

Data management and analysis were performed with SAS for Windows software, version 9.4 (SAS Institute Inc., Cary, NC, USA). Categorical data were summarized as proportions. Distributions of baseline trait proportions across the study regimens were compared using the chi-square test.

Multivariate Cox regression analysis was performed to quantify the adjusted hazard ratio (aHR) for the complications ascertained from Medicare claims and for graft loss and patient death, which are associated with exact event dates. At-risk time was censored at end of Medicare coverage, death not concomitant with a study event, 3 years post-transplant or end of study (December 31, 2011). Logistic regression analysis was used to assess the relative odds of any AR event by 3 years post-transplant. Multivariate models were adjusted for recipient (age, gender, race, body mass index, preemptive transplantation or not, cause of end-stage renal disease, diabetes pretransplant, previous transplantation history, peak panel reactive antibody level), donor [type (living, standard criteria deceased or expanded criteria deceased), race], and transplant factors [human leukocyte antigen (HLA mismatches), year of transplant]. Outcome models were also stratified by quintile of propensity for assignment to each ISx regimen compared with the reference regimen in binomial logistic regression analysis. A P-value <0.05 was considered statistically significant.

Results

Demographics

Figure 1 illustrates the sampling scheme used to identify the study cohort. The demographics of the final study sample of 45 164 kidney transplant recipients are shown in Table 1. Men comprised 57–62% of each group, and 49–63% of patients in each group were Caucasian. Diabetes mellitus and hypertension were the leading causes of end-stage renal disease across each group. Between 52% and 59% of transplants were from standard criteria donors in the study groups. The reference group Tac + MPA/Aza + Pred + TMG was the most common regimen, used in 24.1%; its use was more common in more recent transplant years, and among Black and among sensitized recipients. Steroid-free immunosuppression was more commonly used in patients with pretransplant diabetes. SRL-based and CsA-based regimens were more commonly used in the earlier study years and in white recipients. *De novo* SRL-based regimens were predominantly given with a CNI in 84.3%. The Tac + MPA/AZA + steroid withdrawal/avoidance IS group included the lowest proportion of repeat transplant recipients, while the Tac alone or Tac + Pred (antimetabolite avoidance) group had the highest proportion of preemptive transplant recipients. Delayed graft function affected 18–27% of transplants across the study groups. Use of induction among patients who received SRL-based immunosuppression was similar to the patterns of induction in the full study cohort, most commonly comprising TMG (58.7%), IL2R-Abs (37.7%), and no induction (27.2%).

Incidence of study events across is regimens

The incidence of many study events at 3 years post-transplant varied across the ISx regimens. Compared with the reference regimen, Tac + MPA/AZA + Pred + IL2R-Abs regimen was associated with significantly higher frequency of NODAT (19.0% vs. 17.5%) and NMSC (6.0% vs. 5.1%), but a significantly lower frequency of sepsis (21.3% vs. 23.0%) and UTI/pyelonephritis (48.2% vs. 51.3%; Fig. 2). Tac + MPA/AZA + Pred without induction was associated with significantly higher NODAT (24.1% vs. 17.5%) and less UTI/pyelonephritis (50.3% vs. 51.3%). Steroid withdrawal/avoidance was associated with less pneumonia (22.3% vs. 25.6%), less sepsis (18.4% vs. 23.1%), less UTI/pyelonephritis (47.5% vs. 51.3%), and less NODAT (12.6% vs. 17.5%). SRL-based ISx was associated with higher frequencies of pneumonia (34.5% vs. 25.6%), sepsis (28.9% vs. 23.1%), AR (14.9% vs. 12.0%), death-censored graft loss (9.4% vs. 6.3%), and patient death (18.8% vs. 15.2%).

Table 1. Distributions of recipient and donor characteristics according to immunosuppression regimen in the study sample of US kidney-only transplant recipients, 2000–2011 (*N* = 45 164).

Clinical factors	Tac +MPA/ AZA + Pred + TMG (*N* = 10 817) (Reference) %	Tac + MPA/ AZA + Pred + IL2R-mAbs (*N* = 6539) %	Tac + MPA/ AZA + Pred + No Induction (*N* = 7010) %	Tac + MPA/ AZA + No Pred (*N* = 5651) %	Tac alone, Tac + Pred (*N* = 2138) %	CSA-based (*N* = 7905) %	SRL-based (*N* = 5104) %	*P*-value
Recipient characteristics								
Age at transplant, years								<0.001
<18	2.6	4.9	3.0	4.2	4.3	2.3	2.1	
18–30	11.5	12.0	11.6	10.7	11.6	10.1	12.5	
31–44	26.6	25.0	26.4	22.9	25.1	23.8	26.5	
45–59	37.0	33.5	36.8	35.9	33.9	35.5	35.8	
≥60	22.3	24.6	22.3	26.4	25.2	28.3	23.0	
Male	57.4	61.9	59.5	62.1	60.0	62.3	62.3	<0.001
Race								<0.001
White	49.5	57.4	52.8	51.8	59.3	63.4	60.3	
Black	36.8	27.8	35.6	29.4	31.3	25.2	29.7	
Other race	13.7	14.8	11.5	18.8	9.4	11.4	10.0	
Body mass index, kg/m^2								<0.001
<18.5	3.6	5.1	3.7	4.4	5.1	3.7	3.7	
18.5–25	32.7	35.1	31.1	29.9	32.7	35.0	34.7	
25–30	31.7	32.3	29.2	30.5	30.6	31.5	32.1	
>30	27.6	25.1	23.9	29.8	24.3	25.6	24.8	
Unknown	4.4	2.4	12.1	5.3	7.3	4.2	4.7	
Cause of ESRD								<0.001
Diabetes	21.7	26.7	23.5	25.8	22.8	24.0	24.8	
Glomerulonephritis	18.6	19.3	17.5	17.5	17.8	18.4	15.7	
Hypertension	24.3	21.6	26.6	25.4	21.6	21.0	25.9	
Polycystic kidney disease	5.1	5.4	5.4	6.0	5.6	6.5	5.6	
Other/Unknown	30.3	27.0	27.0	25.4	32.2	30.1	27.9	
Any Diabetes	55.3	51.1	46.6	59.8	48.5	42.1	46.0	<0.001
Pretransplant dialysis								<0.001
Preemptive	3.4	4.8	5.4	5.0	6.6	5.0	4.3	
>0–24	15.8	23.9	21.1	22.2	23.0	24.7	21.3	
25–36	38.8	40.9	41.0	41.7	38.5	40.8	41.1	
≥37	41.7	30.2	31.9	30.7	31.4	29.3	33.1	
Unknown	0.3	0.3	0.6	0.4	0.7	0.2	0.1	
History of prior transplant	21.1	12.0	14.1	8.6	16.7	11.9	17.4	<0.001
Peak PRA level								<0.001
<10	69.1	85.3	80.9	83.2	80.5	86.2	80.6	
10–79	20.8	11.5	13.5	12.3	14.2	10.4	14.8	
≥80	10.1	3.3	5.6	4.5	5.2	3.4	4.6	
Transplant year								<0.001
2000–2002	11.3	25.4	31.0	2.2	25.2	49.8	32.0	
2003–2005	27.5	28.2	29.5	21.2	33.1	29.6	40.3	
2006–2008	34.4	28.5	25.8	44.4	27.9	14.8	19.7	
2009–2011	26.8	17.9	13.7	32.3	13.8	5.8	8.0	
Donor and transplant factors								
Donor Age, mean (SD)	38.3 (15.9)	37.3 (15.4)	37.7 (15.5)	38.7 (15.6)	37.7 (15.6)	38.1 (15.5)	39.3 (16.1)	<0.001
Donor Male	56.4	54.7	54.8	53.6	55.0	54.7	53.5	0.01
Donor Race								<0.001

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Table 1. Continued.

Clinical factors	Tac +MPA/ AZA + Pred + TMG (*N* = 10 817) (Reference) %	Tac + MPA/ AZA + Pred + IL2R-mAbs (*N* = 6539) %	Tac + MPA/ AZA + Pred + No Induction (*N* = 7010) %	Tac + MPA/ AZA + No Pred (*N* = 5651) %	Tac alone, Tac + Pred (*N* = 2138) %	CSA-based (*N* = 7905) %	SRL-based (*N* = 5104) %	*P*-value
White	70.8	72.4	72.6	68.7	74.1	79.2	76.1	
Black	15.1	14.1	15.5	14.9	15.2	12.4	14.1	
Other race	14.2	13.6	11.9	16.4	10.8	8.5	9.9	
HLA mismatches								<0.001
Zero A, B, DR	9.3	10.3	11.1	9.5	11.3	12.3	9.9	
Zero DR	15.0	16.1	16.4	16.3	17.1	16.7	16.1	
Other	75.7	73.7	72.5	74.2	71.6	71.0	74.0	
Cytomegalovirus sero-pairing								<0.001
Donor+/Recipient+	43.4	43.6	39.4	43.1	37.0	42.1	38.4	
Donor−/ Recipient+	24.1	22.1	20.8	21.5	23.0	21.9	21.0	
Donor+/ Recipient−	15.3	16.7	15.1	17.0	16.9	14.6	18.9	
Donor−/ Recipient−	11.8	12.4	11.3	12.7	13.0	12.1	12.9	
Missing	5.4	5.3	13.5	5.7	10.2	9.3	8.8	
Donor type								<0.001
Living	19.4	28.2	25.5	28.9	25.8	24.2	24.6	
Standard criteria deceased	59.5	55.9	56.4	52.1	56.1	53.5	53.7	
Expanded criteria deceased	21.1	16.0	18.2	19.0	18.1	22.4	21.7	

AZA, azathioprine; CsA, cyclosporine; HLA, human leukocyte antigen; IL2R mAbs, basiliximab or daclizumab; ISx, immunosuppressive agent; MPA, mycophenolic acid; No pred, no prednisone use after day 30 post-transplant; Pred, prednisone use documented after 30 days post-transplant; PRA, panel reactive antibody; SRL, sirolimus; TMG, thymoglobulin; Tac, tacrolimus.

P value for distributions of baseline trait proportions across the study regimens based on the chi-square test.

Independent associations of is regimen with study outcomes

Propensity models for use of each study regimen compared with the reference regimen are provided in Table S3.

After propensity adjustment, compared with the reference group, except the Tac + MPA/AZA + Pred + IL2R-Abs regimen, all the other ISx regimens showed at least one significant difference in risk of a study outcome at 3 years post-transplant (Fig. 3). The relative hazards of pneumonia (aHR 1.45, 95% CI 1.36–1.55) and sepsis (aHR 1.40, 95% CI 1.30–1.50) at 3 years were significantly higher with SRL-based ISx. The SRL-based regimen was also associated with higher risk for AR (aOR 1.33, 95% CI 1.20–1.48), death-censored graft failure (aHR 1.78, 95% CI 1.56–2.03), and patient death (aHR 1.40, 95% CI 1.28–1.53), but significantly lower risk for NMSC within 3 years (aHR 0.71, 95% CI 0.60–0.84). CsA-based ISx was associated with higher risk for pneumonia (aHR 1.17, 95% CI 1.10–1.25), sepsis (1.16, 95% CI 1.08–1.24), and death-censored graft failure (aHR 1.39, 95% CI 1.21–1.60), but lower risk for NODAT (aHR 0.83, 95% CI 0.77–0.90). An initial regimen that comprised Tac + MPA/AZA, but did not include steroids, was associated with lower risk of pneumonia (aHR 0.89, 95% CI 0.83–0.96), sepsis (aHR 0.80, 95% CI 0.74–0.87), and NODAT (aHR 0.77, 95% CI 0.70–0.85), but higher risk for graft loss (aHR 1.35, 95% CI 1.17–1.57). Finally, a three-drug maintenance drug regimen of Tac + MPA/AZA + Pred without induction had a higher risk of NODAT (aHR 1.23, 95% CI 1.15–1.32) compared with the reference regimen including TMG induction.

Cause of death across the immunosuppression groups

In the study period, we identified 6515 patient deaths. There was appearance of higher cardiovascular/cerebrovascular

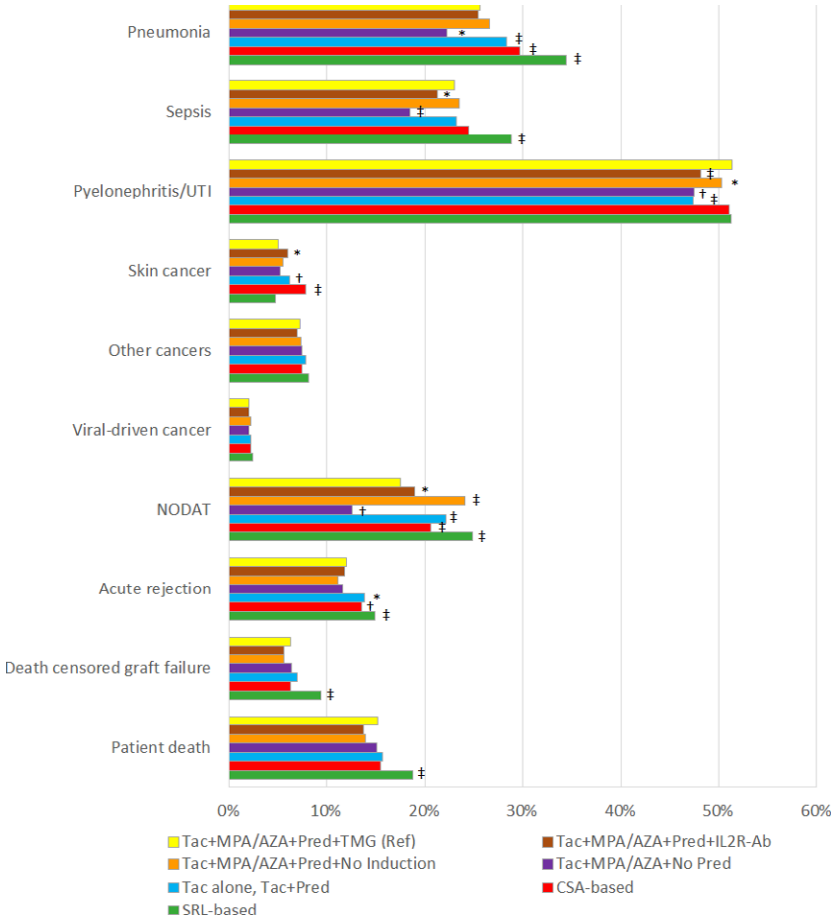

Figure 2 Incidence of clinical events at 3 years post-transplant according to early immunosuppression regimen of US kidney-only transplant recipients, 2000–2011 (N = 45 164). P value compared with reference regimen Tac + MPA/AZA + Pred + TMG: *P < 0.05–0.002; †P = 0.001–0.0002; ‡P < 0.0001. AZA, azathioprine; CsA, cyclosporine; IL2R, basiliximab or daclizumab; ISx, immunosuppressive agent; MPA, mycophenolic acid; No pred, no prednisone use after day 30 post-transplant; Pred, prednisone use documented after 30 days post-transplant; SRL, sirolimus; TMG, thymoglobulin; Tac, tacrolimus.

(Table S4) causes for deaths in patients treated with SRL-based (28.6%) or CsA-based (28.8%) regimens compared with Tac + MPA/AZA + Pred + TMG (25.8%); there was also appearance of higher infection-related causes for deaths in treated with SRL-based (19.7%) or CsA-based (18.8%) regimens compared with Tac + MPA/AZA + Pred + TMG (16.9%) (P = 0.0006 and P < 0.0001 for comparison of distributions of death vs reference for SRL- and CsA-based regimens, respectively). However, cause of death was missing in 25% of events.

Discussion

Based on this national cohort of US kidney transplant recipients, we found that each of the common categories of initial ISx regimens is associated not only with differing risks for AR, graft loss, and patient death over 3 years, but also with differing risks for key infection events such as pneumonia or sepsis, key malignancy events, or the development of NODAT. Notably, CsA-based and SRL-based regimens were associated with higher risks for AR, an event suggesting under-immunosuppression, and yet were also associated with higher risks of events reflecting over-immunosuppression, that is, major infections such as pneumonia and sepsis. These results suggest that intensity of the ISx is not the only driver of efficacy and morbidity and that AR and infections are not merely points on a linear spectrum.

Our results are in accord with prior data on well-characterized events such as graft survival, patient survival, and NODAT. For instance, in the ELITE-Symphony study, which simultaneously compared low- or high-dose CsA-based to Tac-based or SRL-based regimens, the AR rates and graft failure rates were much higher in the non-Tac-based arms [24]. Conversely, the

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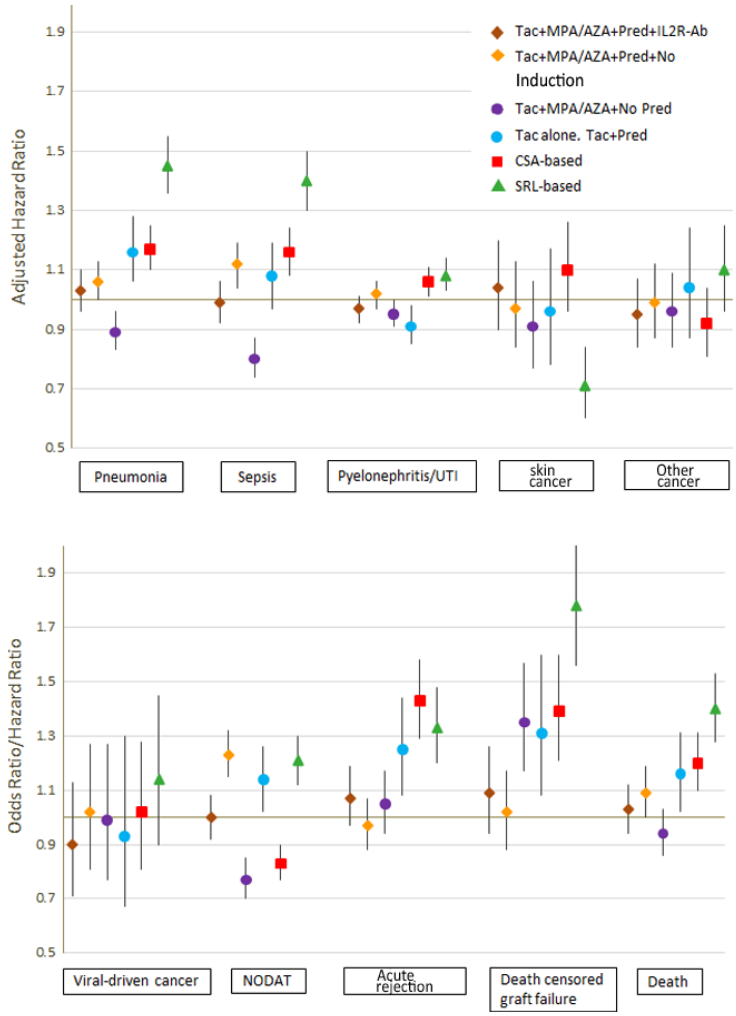

Figure 3 Relative risks of clinic events at 3 years post-transplant according to early immunosuppression regimen of US kidney-only transplant recipients, 2000–2011 (N = 45 164). P value compared with reference regimen Tac + MPA/AZA + Pred + TMG: *P < 0.05–0.002; †P = 0.001–0.0002; ‡P < 0.0001. AZA, azathioprine; CsA, cyclosporine; IL2R, basiliximab or daclizumab; ISx, immunosuppressive agent; MPA, mycophenolic acid; No pred, no prednisone use after day 30 post-transplant; Pred, prednisone use documented after 30 days post-transplant; SRL, sirolimus; TMG, thymoglobulin; Tac, tacrolimus. Models adjusted for recipient (age, gender, race, body mass index, preemptive transplantation or not, cause of end-stage renal disease, diabetes pretransplant, previous transplantation history, peak panel reactive antibody level), donor [type (living, standard criteria deceased or expanded criteria deceased), race], and transplant factors [human leukocyte antigen (HLA mismatches), year of transplant], and also stratified by propensity for assignment to each IS regimen compared with the reference regimen.

NODAT rate was much lower in the CsA-based arm. A Cochrane systematic review comparing IL2R-Abs with TMG showed that there was no difference in graft failure or AR rates between the two forms of induction, while the IL2R-Abs group had a slightly lower risk of malignancy than TMG in this Cochrane review [37]. Hall *et al.* [38] recently reported that IL2R-Abs and TMG were similar with respect to risk for overall cancer and viral-related cancer, but TMG had a slightly higher risk for melanoma. The risk for NODAT has been shown in prior studies to increase with the use of Tac and with steroids [24,39]; consistently, we observed a reduced NODAT risk with CsA-based and steroid-free ISx compared with the reference regimen. We also observed a higher risk of NODAT when a three-drug maintenance regimen of Tac + MPA/AZA + Pred was used without induction. In this situation, centers may have chosen to run higher Tac levels in the absence of induction, a practice we cannot assess as drug levels are not captured in any national-level database.

We observed the associations of SRL-based *de novo* ISx with a higher risk of pneumonia and sepsis, consistent with a prior report by Alangaden *et al.* [40] of 2.5-fold higher risk for bacterial infections with *de novo*

SRL-based regimens compared with Tac-based regimens. SRL-based ISx has been associated with an increased risk of infectious complications in a prior single-center retrospective study and in a randomized controlled trial [26,40], while other randomized trials (not powered for the assessment of complications) have reported numerically higher although statistically similar infection rates in patients receiving SRL compared with other maintenance regimens [24,28]. In the current study, SRL-based ISx was also associated with increased risks of AR, graft failure, and mortality. One advantage of SRL-based ISx appeared to be reduced risk of NMSC, although SRL was not associated with differences in the risk of viral-linked or other cancers. These results are consistent with recent meta-analyses demonstrating that lower overall cancer incidence associated with SRL appears to be attributable to a reduction in NMSC [41–43].

The current study was limited in objective to examining the outcome implications of initial ISx regimen choice. Patients may undergo changes in maintenance ISx dosing or regimen over time. While the impacts of ISx over time warrant further study, it is notable that early ISx regimen bore many prognostically important associations with outcomes at 3 years post-transplant. Billing claims are surrogate measures for clinical events. Although coding errors are possible and nonphysician billing coders may try to emphasize codes that are best reimbursed, these patterns should not be differential according to ISx regimen. The use of claims data provides a strategy for long-term, nationally representative collection of post-transplant infections and cancer events, complications that are not tracked in the national registry. The coding algorithms used in the current study have been applied previously to billing data from transplant population [14,16,33,34]. Kidney transplant recipients who have Medicare as their primary insurer may differ systematically from those who use other reimbursement systems. The population of Medicare-insured transplant recipients is slightly older and includes more African Americans, but fewer preemptively transplanted patients than US patients transplanted under other insurance systems (Table S1). However, Medicare claims are particularly relevant to research among kidney transplant recipients because, unlike the eligibility requirements of age >65 or disability in the general population, renal allograft recipients are offered disease-specific Medicare entitlement and Medicare is the largest single insurer in this population. As a result, Medicare billing claims have been used to study a variety of complications after kidney transplantation [14,17,33,44].

The study conclusions are also limited by the lack of data about uncaptured risk factors that may have affected the choice of ISx regimen and therefore confound the observed associations. For example, SRL-based *de novo* regimens may have been chosen to avoid calcineurin inhibitor toxicity to allografts considered "at-risk" based on biopsy data or other donor characteristics, contributing to premature graft failure or death based on selection rather than impact of the regimen itself. Similarly, steroid-free *de novo* regimens may have been used in patients with poor diabetic control or advanced atherosclerotic cardiovascular disease leading to the associations with increased rates of post-transplant mortality. ISx choice is also influenced by center practices [32], and these results may reflect, in part, the influence of center performance patterns. USRDS data do not include center identifiers. The numbers of patients treated with SRL- and CsA-based regimens were too small to examine for heterogeneity in risk associated with other concomitant agents. We did not attempt to investigate for common hematological toxicities (anemia, leucopenia) and gastrointestinal toxicities, as the major side effects of sepsis, pneumonia, and NODAT are more likely to be coded for in billing claims. Pharmacy data only tell us that prescriptions were filled, not whether they were taken as indicated, and adherence may differ by regimen given the differences in side effects. Finally, any associations reported in this study may not represent causation. Despite these caveats and limitations, given the strength of the observed associations, the consistency with prior clinical observations, and the adjustment for observed confounders including age, diabetes status, length of time on dialysis, and donor quality, it is likely the overall direction of the effect of ISx on outcomes would be robust to adjustment for more granular clinical information.

In summary, based on integrated analyses of multiple national-level databases, we demonstrate that graft outcomes, key morbidity events, and mortality vary as a function of each of the common categories of ISx regimens after kidney transplantation. Compared with a Tac-based triple maintenance ISx regimen with TMG induction, the use of SRL-based ISx regimens was associated with higher risks of pneumonia, sepsis, graft failure, and patient death at 3 years post-transplant, but less NMSC, while CsA-based therapy was associated with an increased risk of pneumonia, sepsis, AR, and graft failure, but less NODAT. Further study is warranted to better guide tailoring of ISx to balance efficacy and morbidity.

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Authorship

VRD, MAS and KLL: participated in study design, acquisition of data and regulatory approvals, data analysis, and writing of the manuscript. JC and JZ: participated in data analysis and manuscript preparation. DCB, DA, DLS and KBS: participated in study design, interpretation, and writing of the manuscript.

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Conflict of interest

Dr. Dharnidharka has received honoraria from Sanofi/Genzyme and receives research grant support from Novartis. Dr. Brennan receives research grant support from Pfizer, Veloxis, Astellas, Genentech, and Alexion and has received honoraria from Sanofi/Genzyme.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Characteristics of US transplant recipients with Medicare versus without Medicare as the primary insurer (2000–2011).

Table S2. ICD-9 diagnosis codes used for complications.

Table S3. Propensity models for use of each study regimen compared to reference (Tac + MPA/AZA + Pred + TMG) of US kidney only transplants performed between 2000 and 2011.

Table S4. Distribution of reported cause of death by ISx regimen ($N = 6515$ for patients died within 3-year post-transplant).

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