American Journal of Transplantation 2016; 16: 2453–2462
Wiley Periodicals Inc.

doi: 10.1111/ajt.13758

Brief Communication

National Variation in Use of Immunosuppression for Kidney Transplantation: A Call for Evidence-Based Regimen Selection

D. A. Axelrod[1,*], A. S. Naik[2], M. A. Schnitzler[3], D. L. Segev[4], V. R. Dharnidharka[5], D. C. Brennan[6], S. Bae[4], J. Chen[7], A. Massie[4] and K. L. Lentine[3,8]

[1]Section of Solid Organ Transplantation, Department of Surgery, Dartmouth Hitchcock Medical Center, Lebanon, NH
[2]Division of Nephrology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI
[3]Saint Louis University Center for Transplantation, Saint Louis University School of Medicine, St. Louis, MO
[4]Division of Abdominal Transplantation, Department of Surgery, Johns Hopkins University, Baltimore, MD
[5] Division of Nephrology, Department of Pediatrics, Washington University School of Medicine, St. Louis, MO
[6]Division of Nephrology, Department of Medicine, Washington University School of Medicine, St. Louis, MO
[7]Center for Outcomes Research, Saint Louis University School of Medicine, St. Louis, MO
[8]Division of Nephrology, Department of Medicine, Saint Louis University School of Medicine, St. Louis, MO
**Corresponding author: David Axelrod, david.a.axelrod@hitchcock.org*
Institution at which work was performed: Saint Louis University School of Medicine, St. Louis, MO.

Immunosuppression management in kidney transplantation has evolved to include an increasingly diverse choice of medications. Although informed by patient and donor characteristics, choice of immunosuppression regimen varies widely across transplant programs. Using a novel database integrating national transplant registry and pharmacy fill records, immunosuppression use at 6–12 and 12–24 mo after transplant was evaluated for 22 453 patients transplanted in 249 U.S. programs in 2005–2010. Use of triple immunosuppression comprising tacrolimus, mycophenolic acid or azathioprine, and steroids varied widely (0–100% of patients per program), as did use of steroid-sparing regimens (0–77%), sirolimus-based regimens (0–100%) and cyclosporine-based regimens (0–78%). Use of triple therapy was more common in highly sensitized patients, women and recipients with dialysis duration >5 years. Sirolimus use appeared to diminish over the study period. Patient and donor characteristics explained only a limited amount of the observed variation in regimen use, whereas center choice explained 30–46% of the use of non–triple-therapy immunosuppression. The majority of patients who received triple-therapy (79%), cyclosporine-based (87.6%) and sirolimus-based (84.3%) regimens continued them in the second year after transplant. This population-based study of immunosuppression practice demonstrates substantial variation in center practice beyond that explained by differences in patient and donor characteristics.

Abbreviations: ACR, acute cellular rejection; aOR, adjusted odds ratio; AZA, azathioprine; CI, confidence interval; CMV, cytomegalovirus; CNI, calcineurin inhibitor; COPD, chronic obstructive pulmonary disease; CsA, cyclosporine; EBE, empirical Bayes estimate; ECD, expanded-criteria donor; eGFR, estimated GFR; ESRD, end-stage renal disease; HRSA, Health Resources and Services Administration; ICC, intraclass correlation coefficient; ISx, immunosuppression; LRD, living related donor; LUD, living unrelated donor; MOR, median odds ratio; MPA, mycophenolate acid; mTOR, mammalian target of rapamycin; OPTN, Organ Procurement and Transplantation Network; Other, other regimens including CsA withdrawal or other trial medications; PCD, pharmaceutical claims data; PRA, panel reactive antibody; Pred, prednisone; SCD, standard-criteria donor; SRL, sirolimus; Tac, tacrolimus

Received 06 October 2015, revised 26 January 2016 and accepted for publication 31 January 2016

Introduction

Advances in immunosuppression (ISx) have substantially reduced the risk of early acute cellular rejection (ACR) in patients undergoing immunologically compatible kidney transplantation (1). The incidence of ACR has declined despite an increased prevalence of highly sensitized patients and retransplant recipients and the growing use of extended-criteria organs. Unfortunately, the marked reduction in ACR has come at the cost of rising rates of ISx-related complications including bacterial and viral infections (pneumonia, urinary tract infections, BK viruria), malignancy and accelerated cardiovascular disease (2–5). Furthermore, long-term survival remains limited by chronic transplant glomerulopathy, interstitial fibrosis/tubular atrophy, inflammation, and subclinical cellular and humoral rejection, despite apparently effective ISx (6,7).

In addition to complications associated with a globally immunosuppressed state, specific agents have well-described associations with metabolic and physiological derangements. Tailoring ISx based on patient characteristics, pharmacological side effects and donor factors to balance those toxicities with the need to maintain effective and durable long-term ISx remains a key challenge for transplant professionals (8–14). To develop an accurate assessment of current practices in the selection of maintenance ISx for kidney transplantation, we constructed a novel database integrating national transplant registry data with pharmacy fill records. Our primary goals were to examine associations of patient characteristics with regimen selection in a multilevel analytic framework and to quantify the contributions of center-level practice variation on ISx utilization.

Methods

Data sources

Study data were constructed by linking Organ Procurement and Transplantation Network (OPTN) records with a large U.S. pharmaceutical claims data (PCD) clearinghouse. The OPTN data system includes data on all donors, waitlisted candidates and transplant recipients in the United States, as submitted by the members of OPTN, and has been described elsewhere (15). The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services, provides oversight to the activities of the OPTN contractor. The PCD comprises National Council for Prescription Drug Program 5.1-format prescription claims aggregated from multiple sources including data clearinghouses, retail pharmacies and prescription benefit managers for ≈60% of U.S. retail pharmacy transactions, including those reimbursed by private payers, public payers and self-paid fills. After institutional review board and HRSA approvals, PCD records from 2005 to 2010 were linked with OPTN records for kidney transplant recipients. Because of the large sample size, the anonymity of the patients studied and the nonintrusive nature of the research, a waiver of informed consent was granted by the Department of Health and Human Services (45 CFR 46.116). Analyses were performed using Health Information Portability and Accountability Act–compliant limited data sets. This study was approved by the institutional review board of Saint Louis University.

Study sample

Eligible transplant recipients had an OPTN kidney transplant record and pharmacy claims during months 6–12 after transplantation to allow ISx regimen stabilization. A subset of the primary sample that also had PCD records at 12–24 mo after transplant were examined in a secondary analysis. ISx regimens were classified using pharmacy fill records into six mutually exclusive groups. Group 1 (reference) used standard triple therapy, defined as tacrolimus (Tac) with mycophenolic acid (MPA; mycophenolate mofetil or mycophenolate sodium) or azathioprine (AZA) and with prednisone (Pred), (Tac+MPA/AZA+Pred). Group 2 used a corticosteroid-sparing regimen (Tac+MPA/AZA). Group 3 used an MPA/AZA-sparing regimen (Tac alone, Tac+Pred). Group 4 used a regimen based on mammalian target of rapamycin (mTOR) that was defined by any fill for sirolimus (SRL) as the mTOR available in the study period, with or without other agents including calcineurin inhibitors (CNIs), (SRL-based). Group 5 used a cyclosporine (CsA)–based regimen, defined by CsA without SRL (CsA-based). Group 6 used other regimens including CsA withdrawal or other trial medications (Other). Patients in groups 1–3 did not receive SRL or CsA.

Analyses

Observed variation in regimen use across centers: To visually assess unadjusted variation in ISx regimen use at the center level across the United States, the observed proportion of patients receiving each regimen was computed for each center and displayed as stacked bar plots.

Combined center and case-level modeling: Bilevel hierarchical models were constructed to adjust for clustering effects: Level 1 comprised patient, donor and transplant (case) factors, and level 2 represented the center, wherein the use of each alternative regimen was compared individually to the reference regimen (pairwise). Empirical Bayes estimates (EBEs) provided the adjusted proportion (with 95% confidence intervals [CIs]) of use of a regimen of interest compared with the reference regimen, incorporating case-mix adjustment from the hierarchical model. If the 95% CI for a given center's EBE of use for a regimen of interest did not include the median national rate of use, this indicated a prescribing pattern that was statistically significantly different from the expected rate of use for that regimen.

Heterogeneity in ISx prescribing across centers was quantified using an intraclass correlation coefficient (ICC) and median odds ratio (MOR). ICC was defined as the ratio of cluster variance (center impact) to the total observed variance in ISx use, with contributions in our study framework defined as center-related, case-related, and other unmeasured impacts. In this context, the ICC quantified the proportion of total variance in ISx use that was accounted for by center. The MOR provided the median of the odds that patients with identical characteristics would receive the ISx regimen of interest when two centers were drawn at random (performed for all possible pairs of centers). A MOR of 2.0, for example, means that if we selected centers at random across all centers, then a patient with a given set of characteristics was, on an average, twice as likely to receive the ISx regimen of interest at one of the randomly selected centers than at the other selected center (16). The adjusted odds ratios (aORs) of being placed on an ISx regimen other than standard triple therapy was determined for patient and donor factors after accounting for the impact of center using the hierarchical model.

Secondary analyses were performed in the subgroup with available serum creatinine data at 6 mo for computation of 6-mo estimated GFR (eGFR). The eGFR was computed by the Chronic Kidney Disease Epidemiology Collaboration equation (17).

Data were analyzed using Stata 13 (StataCorp, College Station, TX). Hierarchical logistic regression modeling was done in Stata using the *xtmelogit* command with center as a random intercept. The ICC and the MOR were calculated using the *xtmrho* (third-party suite) command.

Contributions of case-level factors to variation in ISx use: To quantify the degree that variance in ISx regimen use was explained by recipient and donor characteristics, we performed multivariate logistic regression modeling with ISx regimen as the dependent variable and case factors as the predictors. Pairwise models were constructed to assess the relative likelihood of using each specific regimen (as outlined above) compared with standard triple-drug therapy.

Results

Integrated PCD and registry data were available for 22 453 kidney transplants performed at 249 centers in the study

Table 1: Comparison of recipient, donor and transplant characteristics among patients in the pharmacy claims data sample and OPTN registrants not included in the sample

Recipient characteristics	PCD study sample (n = 22 453) %	Other OPTN registrants (n = 61 109) %
Age, years		‡
<18	5.47	4.9
18–30	9.4	9.32
31–45	21.77	21.22
46–59	38.69	37.53
≥60	24.68	27.04
Sex		*
Male	60.13	61.11
Female	39.87	38.89
Race		‡
White	59.06	52.97
Black	22.08	25.36
Other	18.86	21.67
ESRD duration, mo		‡
None (preemptive)	19.33	17.45
>0–24	33.43	31.04
25–60	28.87	30.82
>60	16.67	19.1
Missing	1.69	1.59
BMI, kg/m^2		‡
<18.5	5.1	4.54
18.5–25	33.08	32.64
25–30	32.14	32.4
>30	29.04	29.44
Missing	0.65	0.97
Cause of ESRD		‡
Diabetes	21.61	22.75
Glomerulonephritis	21.2	21.09
Hypertension	20.94	22.53
Polycystic kidney disease	9.39	8.66
Other	26.86	24.97
Comorbidities		‡
Diabetes	30.85	32.45
Hypertension	53.92	52.16‡
Coronary disease/angina	3.59	3.52
COPD	0.98	0.95
Cerebral vascular disease	1.87	1.65*
Peripheral vascular disease	3.8	3.56
Highest level of education		†
Grade school	6.55	6.9
High school	38.08	38.17
Some college or higher	38.94	39.61
Unknown	16.43	15.32
Employment status		‡
Working	29.98	28.15
Not working	52.03	55.64
Unknown	17.98	16.21
Insurance type		‡
Public	56.02	60.58
Private	43.80	38.94
Other/unknown	0.17	0.47
Previous transplant		*
Yes	13.12	13.76
No	86.88	86.24
Peak PRA level		‡
<10	70.27	68.04
10–79	17.64	18.63
≥80	7.9	8.05
Missing	4.19	5.28
HLA mismatches		†
Zero A, B, and DR	10.47	9.9
Zero DR	46.32	45.79
Other	43.21	44.31
Transplant year		‡
2005	19.49	19.81
2006	22.46	19.72
2007	22.4	18.99
2008	20.22	19.61
2009	15.43	21.87
Donor race		‡
White	71.05	68.26
Black	12.42	13.26
Other	16.54	18.48
Donor sex		
Male	52.51	53.09
Female	47.49	46.91
CMV seropairing		‡
Recipient−, Donor−	17.2	15.55
Recipient+, Donor−	21.57	21.82
Recipient−, Donor+	17.39	16.96
Recipient+, Donor+	37	38.72
Not reported	6.84	6.95
Donor type		‡
Standard criteria deceased	50.51	53.13
Expanded criteria deceased	9.38	10.22
Living related	24.55	22.08
Living unrelated	15.56	14.57

CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; OPTN, Organ Procurement and Transplantation Network; PCD, pharmaceutical claims data; PRA, panel reactive antibody.
*p = 0.02–0.04.
†p = 0.0001–0.01.
‡p < 0.0001.

period. The study sample included 27% of all transplants performed. Compared with transplant recipients registered in OPTN who were not captured in the PCD, the proportions of patients with private insurance (44% vs. 39%, p < 0.001) and white race (59% vs. 53% p < 0.001) were increased in the study cohort (Table 1). Overall, 7.7% of patients experienced a reported acute rejection in the first 6 mo after transplant. Triple therapy (Tac+MPA/AZA+Pred) was the most frequently used regimen (33.8% patients overall), followed by steroid sparing (Tac+MPA/AZA) in 25.8%, MPA/AZA sparing (Tac alone, Tac+Pred) in 11.3%, SRL-based (with or without Tac/CsA) in 9.9% and CsA-based in 7.8%; Other regimens were filled for 11.6% of the sample. The majority of patients in the SRL group

also received CNIs (Tac 37.5%, CsA 15.3%). There was substantial variation in the unadjusted use of ISx regimens across centers (Figure 1). The use of triple ISx varied from 0% to 100% of patients across transplant centers; steroid-sparing regimens varied from 0% to 77%, SRL-based regimens varied from 0% to 100%, CsA-based regimens varied from 0% to 78%, and Other regimens varied from 0% to 100%.

Patient-level correlates of ISx regimen use

Patient characteristics were strongly correlated with differential use of maintenance ISx regimens at 6–12 mo after transplant (Table 2). Older patients were more likely to receive regimens without MPA/AZA than triple therapy (MPA/AZA sparing: aged >60 years, aOR 1.50, $p < 0.0001$; aged 49–60 years, aOR 1.20, $p < 0.01$). Compared with use in adults aged 31–45 years,

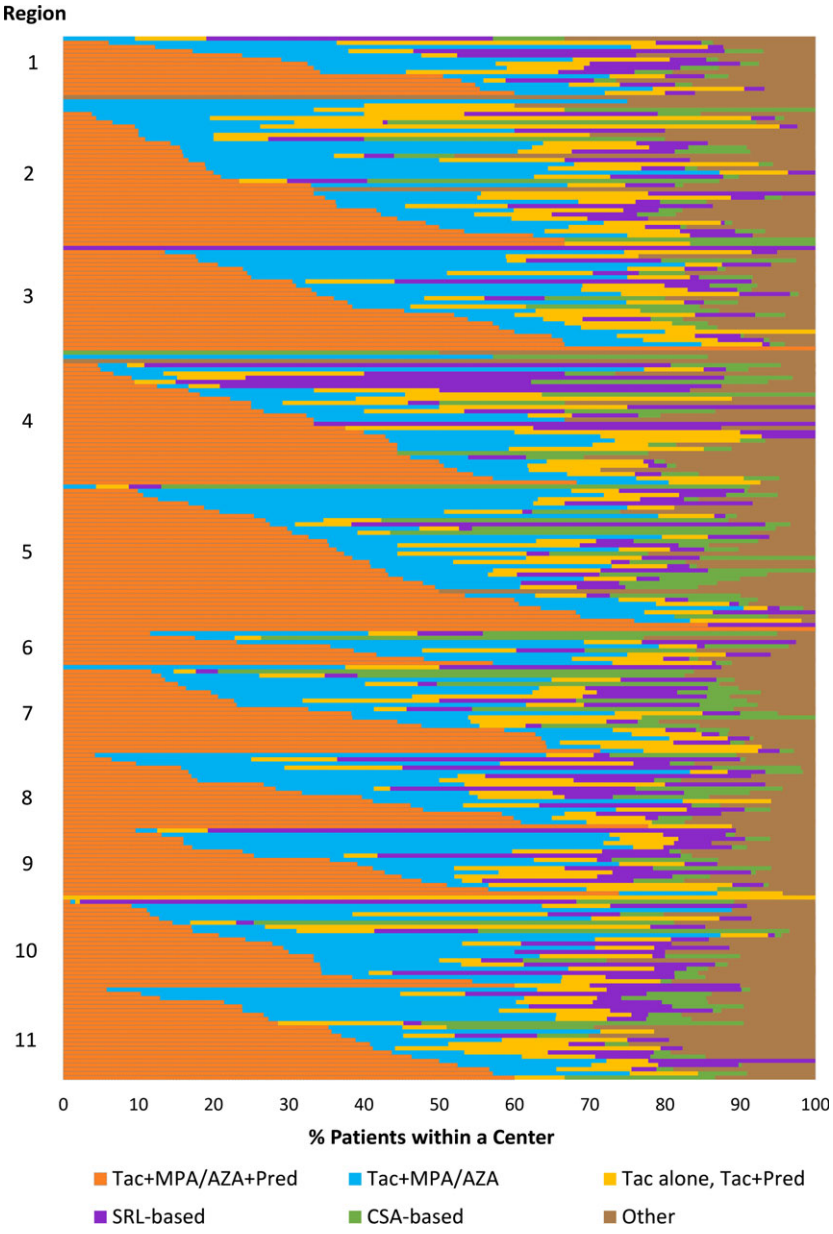

Figure 1: Proportion of patients receiving one of six mutually exclusive ISx regimens during months 6–12 after transplant. Each horizontal bar represents an individual center within U.S. regions ordered by the proportion of patients that received triple ISx (Tac+MPA/AZA+Pred; orange). Overall percentage of regimen use at patient-level across centers: Tac+MPA/AZA+Pred, 33.8%; Tac+MPA/AZA (no Pred), 25.8%; Tac without MPA/AZA, 11.3%; SRL-based, 9.9%; CsA-based, 7.8%; and Other regimens, 11.6%. AZA, azathioprine; CsA, cyclosporine; ISx, immunosuppression; MPA, mycophenolate acid; Other, other regimens including CsA withdrawal or other trial medications; Pred, prednisone; Tac, tacrolimus.

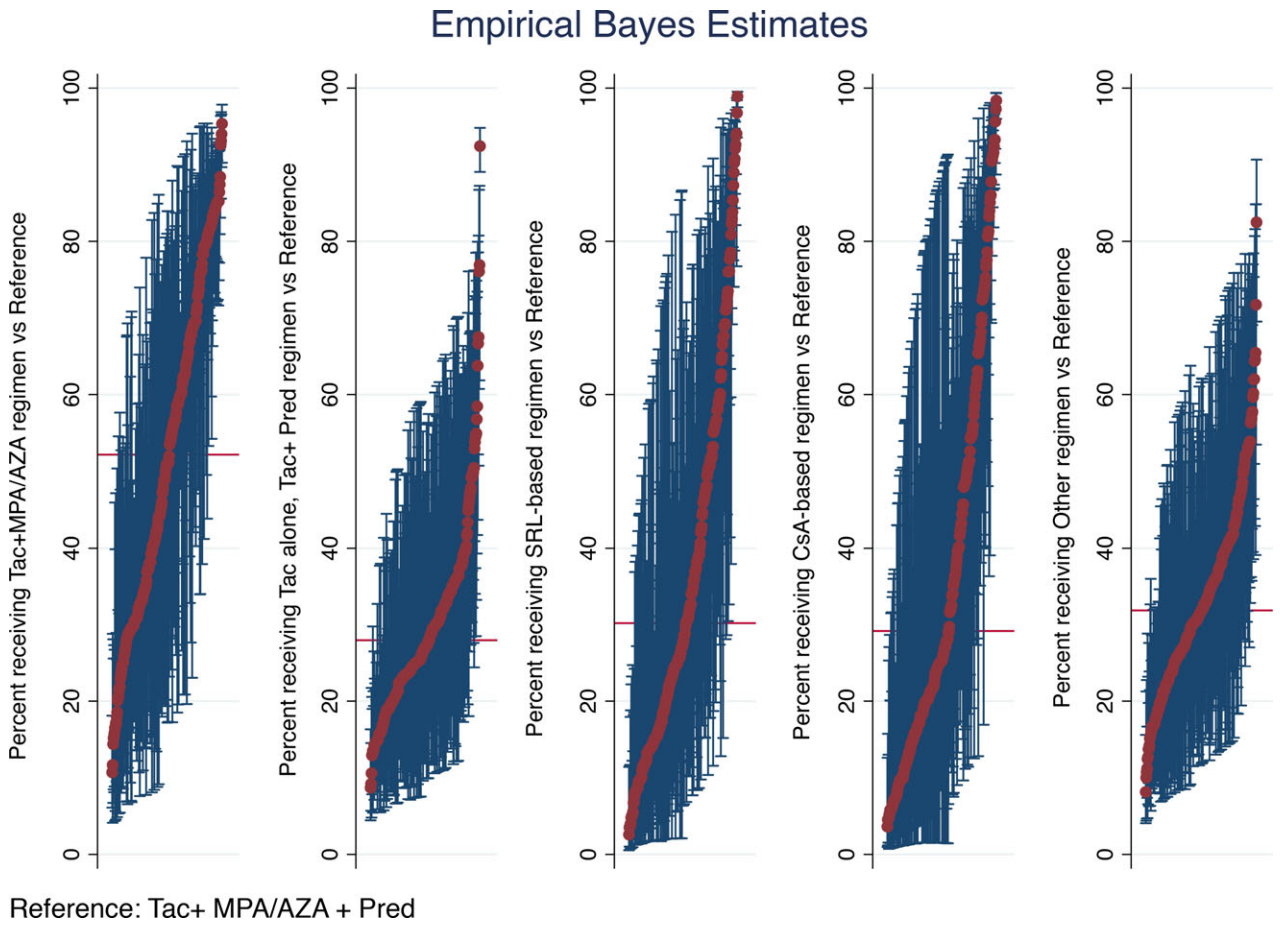

Figure 2: Empirical Bayes estimates for likelihood of regimen use compared with reference regimen. Red bar demonstrates national average rate of use of each regimen (within pairwise regimen comparisons). Each red dot represents adjusted use at one center, and the blue bars reflect 95% CI for use at the center determined by empirical Bayes estimates, adjusting for case factors of recipients at the center; exclusion of the national average by a 95% CI reflects adjusted center use significantly above or below the national average. AZA, azathioprine; CI, confidence interval; CsA, cyclosporine; MPA, mycophenolate acid; Other, other regimens including CsA withdrawal or other trial medications; Pred, prednisone; Tac, tacrolimus.

CsA-based regimens were more commonly used in patients aged 49–60 years (aOR 1.43, $p < 0.0001$) and especially in older patients aged >60 years (aOR 1.87, $p < 0.0001$) and were less likely to be used in younger adults aged 18–30 years (aOR 0.55, $p < 0.0001$) and children aged <18 years (aOR 0.42, $p < 0.0001$).

Women were more likely to be maintained on triple-ISx regimens than men. Although ISx regimens were generally similar in black patients compared with white patients, black patients were less likely to receive CsA-based regimens (aOR 0.69, $p < 0.01$). Obese patients were less likely to receive Tac without MPA/AZA (aOR 0.85, $p < 0.05$) or SRL-based therapies (aOR 0.84 $p < 0.05$).

Prolonged end-stage renal disease (ESRD) was also associated with a higher use of Other ISx regimens (aOR 1.25, $p < 0.01$). Compared with diabetic patients, patients with glomerulonephritis as the cause of their ESRD were more likely to receive triple therapy. There was also a trend for greater use of steroid-sparing ISx in patients with polycystic kidney disease (aOR 1.16, $p = 0.08$).

As expected, patients at a higher immunological risk for ACR, including those with prior transplantation, increasing levels of HLA mismatch and higher panel reactive antibody (PRA), were less likely to receive regimens other than the reference triple therapy. PRA ≥80, for example, was associated with less use of Tac+MPA/AZA (aOR 0.58, $p < 0.0001$), Tac alone or Tac+Pred (aOR 0.80, $p < 0.04$), SRL-based (aOR 0.61, $p < 0.0001$), CsA-based (aOR 0.51, $p < 0.0001$), or Other (aOR 0.77, $p < 0.01$) regimens. Induction therapy with depleting agents was associated with higher use of steroid-sparing, MPA/AZA-sparing and SRL-based regimens, whereas induction with IL-2R was associated with a statistically lower likelihood of receiving steroid-sparing and anti–metabolite-sparing regimens.

Table 2: Association of recipient and donor characteristics with immunosuppression regimens versus reference regimen (Tac+MPA/AZA+Pred) from multilevel models including center effects

	Tac+MPA/AZA	Tac alone, Tac+Pred	SRL-based	CsA-based	Other
			aOR (95% CI)		
Recipient characteristics					
Age, years					
<18	0.67 (0.52–0.86)†	1.13 (0.84–1.52)	0.77 (0.53–1.13)	0.42 (0.27–0.66)‡	0.70 (0.52–0.95)*
18–30	0.91 (0.78–1.07)	0.89 (0.72–1.10)	0.98 (0.77–1.24)	0.55 (0.40–0.74)‡	0.90 (0.74–1.09)
31–45	Reference	Reference	Reference		Reference
46–59	1.06 (0.95–1.19)	1.20 (1.04–1.39)†	1.11 (0.94–1.31)	1.43 (1.19–1.71)‡	1.16 (1.02–1.33)*
≥60	1.09 (0.96–1.25)	1.50 (1.28–1.76)‡	1.12 (0.93–1.37)	1.87 (1.53–2.30)‡	1.10 (0.95–1.29)
Female	0.98 (0.90–1.07)	0.87 (0.78–0.97)†	0.90 (0.79–1.03)	0.93 (0.81–1.07)	0.93 (0.84–1.03)
Race					
White	Reference	Reference	Reference	Reference	Reference
Black	0.90 (0.80–1.03)	1.00 (0.86–1.17)	0.98 (0.82–1.17)	0.69 (0.56–0.86)†	0.93 (0.80–1.07)
Other	0.93 (0.81–1.06)	0.91 (0.77–1.07)	0.76 (0.62–0.94)†	0.98 (0.80–1.21)	0.91 (0.78–1.07)
Cause of ESRD					
Diabetes	Reference	Reference	Reference	Reference	Reference
Glomerulonephritis	0.80 (0.70–0.92)†	0.82 (0.69–0.97)*	1.03 (0.84–1.26)	0.97 (0.79–1.19)	0.88 (0.75–1.02)
Hypertension	0.96 (0.84–1.10)	0.90 (0.77–1.06)	1.21 (0.99–1.48)	0.98 (0.80–1.21)	0.99 (0.85–1.15)
Polycystic kidney disease	1.16 (0.98–1.37)	1.00 (0.81–1.23)	1.23 (0.96–1.59)	0.98 (0.75–1.28)	0.95 (0.78–1.16)
Other	0.98 (0.86–1.12)	0.99 (0.84–1.16)	1.21 (0.98–1.48)	0.92 (0.74–1.14)	0.99 (0.85–1.16)
Previous kidney transplant	0.49 (0.41–0.56)‡	0.74 (0.63–0.88)†	0.81 (0.67–0.99)*	0.61 (0.48–0.77)‡	0.81 (0.69–0.99)†
ESRD duration, mo					
None	1.04 (0.92–1.17)	1.14 (0.98–1.32)	1.18 (0.99–1.41)	0.95 (0.78–1.17)	1.12 (0.97–1.29)
0–24	Reference	Reference	Reference	Reference	Reference
25–60	0.95 (0.85–1.06)	0.97 (0.84–1.12)	1.05 (0.89–1.25)	0.94 (0.78–1.13)	1.12 (0.98–1.28)
>60	0.87 (0.75–1.00)	1.06 (0.89–1.26)	1.17 (0.95–1.43)	1.13 (0.91–1.42)	1.25 (1.06–1.47)†
Missing	1.01 (0.73–1.40)	1.17 (0.80–1.71)	1.30 (0.83–2.06)	1.16 (0.69–1.95)	1.06 (0.72–1.59)
HLA mismatches					
Zero A, B, and DR	Reference	Reference	Reference	Reference	Reference
Zero DR	0.69 (0.60–0.80)‡	0.96 (0.79–1.16)	0.76 (0.61–0.95)*	0.67 (0.53–0.83)‡	0.74 (0.62–0.87)‡
Other	0.69 (0.60–0.80)‡	1.04 (0.86–1.26)	0.83 (0.67–1.04)	0.65 (0.52–0.82)‡	0.78 (0.66–0.92)†
Peak PRA level					
<10	Reference	Reference	Reference	Reference	Reference
10–79	0.84 (0.75–0.94)†	0.92 (0.80–1.06)	0.95 (0.80–1.12)	0.91 (0.76–1.10)	0.86 (0.75–0.99)*
≥80	0.58 (0.49–0.70)‡	0.80 (0.65–0.99)*	0.61 (0.47–0.78)‡	0.51 (0.38–0.69)‡	0.77 (0.63–0.93)†
Missing	0.99 (0.78–1.27)	0.82 (0.60–1.11)	0.58 (0.39–0.87)†	0.89 (0.59–1.34)	0.80 (0.59–1.09)
BMI, kg/m^2					
<18.5	1.12 (0.92–1.38)	1.03 (0.80–1.32)	0.82 (0.59–1.12)	1.20 (0.85–1.68)	0.97 (0.75–1.26)
18.5–25	Reference	Reference	Reference	Reference	Reference
25–30	1.00 (0.90–1.12)	0.90 (0.79–1.03)	0.93 (0.80–1.08)	1.02 (0.87–1.20)	1.05 (0.93–1.18)
>30	0.96 (0.87–1.08)	0.85 (0.74–0.97)*	0.84 (0.71–0.99)*	0.98 (0.82–1.16)	1.02 (0.90–1.16)
Missing	0.96 (0.59–1.56)	0.85 (0.46–1.58)	0.65 (0.27–1.60)	0.72 (0.28–1.84)	0.92 (0.52–1.62)
Hypertension	1.03 (0.93–1.14)	0.91 (0.80–1.03)	0.95 (0.81–1.10)	0.98 (0.83–1.15)	0.90 (0.80–1.01)
Highest level of education					
Grade school	1.04 (0.86–1.26)	0.94 (0.74–1.19)	0.87 (0.65–1.16)	0.92 (0.68–1.23)	0.88 (0.69–1.12)
High school	0.96 (0.87–1.05)	0.87 (0.77–0.98)*	1.00 (0.86–1.15)	0.98 (0.83–1.14)	1.02 (0.91–1.14)
College and higher	Reference	Reference	Reference	Reference	Reference
Unknown	0.98 (0.86–1.13)	0.99 (0.84–1.17)	1.08 (0.89–1.33)	0.91 (0.73–1.14)	1.20 (1.02–1.40)*
Donor and transplant factors					
Transplant year					
2005	Reference	Reference	Reference	Reference	Reference
2006	0.85 (0.74–0.97)*	0.83 (0.71–0.97)*	0.53 (0.44–0.63)‡	0.56 (0.46–0.67)‡	0.86 (0.74–0.99)*
2007	0.86 (0.75–0.98)*	0.72 (0.61–0.85)‡	0.35 (0.29–0.42)‡	0.44 (0.36–0.54)‡	0.73 (0.62–0.85)
2008	0.97 (0.84–1.12)	0.87 (0.73–1.03)	0.31 (0.25–0.39)‡	0.40 (0.32–0.50)‡	0.85 (0.72–1.00)
2009	0.97 (0.83–1.14)	0.92 (0.76–1.11)	0.29 (0.23–0.37)‡	0.34 (0.26–0.44)‡	0.98 (0.82–1.17)
Female donor	0.94 (0.86–1.02)	1.03 (0.93–1.14)	1.05 (0.93–1.19)	0.97 (0.85–1.11)	1.01 (0.92–1.12)

(Continued)

Table 2: Continued

	Tac+MPA/AZA	Tac alone, Tac+Pred	SRL-based	CsA-based	Other
			aOR (95% CI)		
Donor type					
SCD	Reference	Reference	Reference	Reference	Reference
ECD	0.88 (0.75–1.03)	1.12 (0.94–1.34)	1.73 (1.40–2.13)‡	0.94 (0.74–1.18)	1.17 (0.98–1.40)
LRD	1.34 (1.19–1.51)‡	0.89 (0.77–1.03)	1.16 (0.98–1.39)	0.98 (0.81–1.19)	1.11 (0.97–1.28)
LUD	1.01 (0.89–1.17)	0.86 (0.73–1.01)	0.95 (0.78–1.17)	0.75 (0.60–0.94)†	0.99 (0.84–1.15)
Donor race					
White	Reference	Reference	Reference	Reference	Reference
Black	0.98 (0.85–1.13)	1.07 (0.90–1.26)	0.96 (0.78–1.17)	1.06 (0.83–1.35)	1.01 (0.86–1.19)
Other	1.01 (0.89–1.15)	1.27 (1.09–1.48)†	0.89 (0.73–1.08)	1.07 (0.88–1.31)	1.00 (0.86–1.16)
Pharmacy payer					
Cash	1.43 (1.18–1.74)‡	1.73 (1.37–2.20)‡	1.11 (0.82–1.50)	1.00 (0.75–1.33)	1.69 (1.36–2.09)‡
Medicaid	1.18 (0.98–1.42)	0.92 (0.73–1.17)	0.75 (0.57–0.99)*	0.91 (0.67–1.25)	0.70 (0.54–0.91)†
Third party	1.07 (0.97–1.18)	1.34 (1.19–1.51)‡	1.13 (0.98–1.30)	1.03 (0.88–1.21)	1.25 (1.12–1.40)‡
Induction					
Depleting Abs	1.42 (1.26–1.60)‡	1.23 (1.07–1.42)†	1.21 (1.01–1.45)*	0.88 (0.73–1.07)	1.01 (0.88–1.16)
IL2R-Abs	0.83 (0.73–0.96)†	0.85 (0.72–0.99)*	1.13 (0.93–1.37)	1.05 (0.85–1.29)	1.21 (1.05–1.41)†
Acute rejection	0.39 (0.32–0.47)‡	0.92 (0.76–1.11)	1.09 (0.88–1.35)	0.64 (0.49–0.83)†	1.08 (0.91–1.28)

Abs, antibodies; aOR, adjusted odds ratio; AZA, azathioprine; CI, confidence interval; CsA, cyclosporine; ECD, expanded-criteria donor; ESRD, end-stage renal disease; ISx, immunosuppression; LRD, living related donor; LUD, living unrelated donor; MPA, mycophenolate acid; Other, other regimens including CsA withdrawal or other trial medications; PRA, panel reactive antibody; Pred, prednisone; SCD, standard-criteria donor; SRL, sirolimus; Tac, tacrolimus.

*p = 0.02–0.04.

†p = 0.0001–0.01.

‡p < 0.0001.

Over time, there have been alterations in the ISx landscape that in part may reflect changes in case characteristics. There was decreasing use of SRL compared with the reference ISx regimen (2006 vs. 2005: aOR 0.53, p < 0.0001; 2009 vs. 2005: aOR 0.29, p < 0.0001). Compared with recipients of transplants from standard-criteria donors, recipients from living related donors appeared to have higher rates of receiving steroid-sparing regimens (Tac+MPA/AZA; aOR 1.34, p < 0.0001), whereas recipients from expanded-criteria donors were more likely to receive SRL-based regimens (aOR 1.73, p < 0.0001). ISx regimen did not vary by donor race except that there was an increased use of Tac alone or Tac+Pred in recipients from other-race donors (aOR 1.27, p < 0.01). Economic factors appeared to influence prescription patterns, with cash payers appearing more likely to be taking "minimized" regimens (e.g. Tac+MPA/AZA [aOR 1.43, p < 0.0001], MPA/AZA-sparing [aOR 1.73, p < 0.0001] and Other [aOR 1.69, p < 0.0001] regimens). Patients with a history of acute rejection in the first 6 months were less likely to receive a steroid-sparing (aOR 0.39, p < 0.0001) or CsA-based (aOR 0.64, p < 0.01) regimen subsequently, during months 6–12 after transplant.

Associations between patient and donor characteristics and regimen choice during months 6–12 after transplant were also examined after adjusting for eGFR at 6 mo in the sample with available data for eGFR computation (n = 12 340). There were no changes in inferences across patient-level characteristics; however, there was an association of SRL use with eGFR, such that SRL use was less common (aOR 0.69, p < 0.0001) among patients with an eGFR >60 mL/min per 1.73 m^2 (vs. reference 30–60 mL/min per 1.73 m^2) but increasingly common with lower eGFR 15–30 mL/min per 1.73 m^2 (aOR 2.84, p < 0.0001) and <15 mL/min per 1.73 m^2 (aOR 3.28, p < 0.01).

Temporal trends

Among the subset of the primary sample that also had PCD records at 12–24 mo after transplant (n = 18 298), regimen selection in the second year was compared with the regimen at 6–12 mo. Compared with the initial regimen at 6–12 mo, the proportion of patients on triple therapy increased from 33.8% to 37.7% in year 2 after transplant (Table S1). The majority of patients who received triple therapy (79%) and CsA-based (87.6%) and SRL-based (84.3%) regimens continued them in the second year after transplant (Table S2). By comparison, only 55.8% of those on Other regimens at year 1 remained on Other regimens during year 2.

Center-driven variation in regimen use

Hierarchical logistic regression models demonstrated that between-center variation in use of specific ISx regimens was significantly greater than what would be expected based on differences in patient demographics or transplant characteristics (p < 0.0001) (Figure 2). Based on EBEs comparing the relative use of a specific alternative ISx regimen to triple therapy in two-way analyses, we identified 28% of centers in which frequency of Tac+MPA/AZA use

Table 3: Center-level empirical Bayes estimates adjusted for case-level characteristics[1] and for case-level characteristics including 6-month estimated GFR

ISx regimen (reference: Tac+MPA/AZA+Pred)	No. of centers in pairwise comparison	No. of centers significantly above reference probability	No. of centers significantly below reference probability
Adjusted for case-level characteristics			
Tac+MPA/AZA	244	68 (27.9%)	60 (24.6%)
Tac alone, Tac+Pred	243	31 (12.8%)	27 (11.1%)
SRL-based	241	61 (25.3%)	33 (13.7%)
CsA-based	242	64 (26.4%)	19 (7.9%)
Other	246	33 (13.4%)	31 (12.6%)
Adjusted for case-level characteristics including 6-month estimated GFR			
Tac+MPA/AZA	239	48 (20.1%)	39 (16.3%)
Tac alone, Tac+Pred	238	17 (7.1%)	18 (7.6%)
SRL-based	240	47 (19.6%)	18 (7.5%)
CsA-based	236	48 (20.3%)	11 (4.7%)
Other	240	18 (7.5%)	16 (6.7%)

CsA, cyclosporine; ISx, immunosuppression; MPA, mycophenolate acid; Pred, prednisone; Tac, tacrolimus.
[1]Constructed from pairwise comparisons of regimen of interest versus reference regimen (Tac+MPA/AZA+Pred).

was statistically higher than expected, whereas 13% used Tac alone or Tac+Pred at higher rates (Table 3). Addition of 6-mo eGFR in the model in secondary analysis reduced the variation in practice among centers (Table 3). In the fully adjusted model, including eGFR at 6 mo, 20.1% of centers prescribed Tac+MPA/AZA at rates significantly greater than expected. Similarly, 19.6% of centers had statistically significantly greater use of SRL, and 20.3% of centers had higher than expected use of CsA-based regimens.

Finally, the degree of heterogeneity in prescribing practice was assessed using the ICC. The ICCs for SRL-based, CsA-based and Tac+MPA/AZA regimens in models unadjusted for recipient, donor, and transplant factors were 0.40, 0.46 and 0.30, respectively, which suggests that 40%, 46% and 30% of the variation in the use of the "nonstandard" regimens was due to "center effect" (Table 4). The ICCs remained similar even after adjustment for case factors. These ICCs did not change over time when the sample was stratified into two eras. The MORs from case-factor–adjusted models for each regimen compared with reference triple therapy ranged from 2.08 to 5.15 (Table 4). Consequently, a patient with a given set of characteristics was, on average, 4.4 times as likely to receive an SRL-based regimen as triple therapy at specific centers.

Discussion

Using a novel linkage of the national transplant registry data and a large set of pharmacy fill records, we identified substantial variation in the choice of maintenance ISx regimen after kidney transplantation. Nationally, more than one-third of patients received triple maintenance ISx at 6–12 mo after transplant. In some centers, however, 100% of patients—regardless of characteristics—were placed on triple therapy, whereas other centers used this regimen rarely, if ever. After adjustment for recipient, donor, and transplant factors, ISx use varied markedly across centers, with two- to fivefold variation in the likelihood of use of non–triple-therapy–based regimens.

Although case-level factors are a weaker determinant of regimen choice than center practice, we identified a number of clinically rational associations between ISx regimen selection and clinical characteristics. Patients with increased immunological risk (glomerulonephritis,

Table 4: Heterogeneity across unadjusted and both adjusted models

ISx regimen (Ref: Tac+ MPA/AZA+Pred)	Proportion of variance in hierarchical model explained by center characteristics (unadjusted)	MOR	Proportion of variance in hierarchical model explained by center, adjusted for case factors	MOR	Proportion of variance in model explained by case factors
Tac+MPA/AZA	0.30	3.11	0.30	3.14	0.05
Tac alone, Tac+Pred	0.16	2.10	0.15	2.08	0.04
SRL-based	0.40	4.16	0.42	4.42	0.04
CsA-based	0.46	5.02	0.47	5.15	0.06
Other	0.14	2.03	0.15	2.06	0.02

AZA, azathioprine; CsA, cyclosporine; ISx, immunosuppression; MOR, median odds ratio; MPA, mycophenolate acid; Other, other regimens including CsA withdrawal or other trial medications; Pred, prednisone; SRL, sirolimus; Tac, tacrolimus.
Proportion of variance in hierarchical model is equal to the intraclass correlation coefficient.

high PRA, retransplant) were more likely to be maintained on triple therapy. In contrast, patients with lower eGFR at 6 mo were much more likely to be placed on a renal-sparing regimen containing SRL. CsA use appeared to be common in a selected group of centers, with average variation of fivefold in expected use across centers after accounting for case characteristics. Likelihood of use of CsA- and SRL-based regimens declined markedly over the study period.

These data provide the first rigorous assessment of ISx regimen with appropriate sample size to identify the effect of center practice on utilization after controlling for recipient, donor, and transplant characteristics. Examination of this unique database demonstrates marked variation in center practice, even after adjusting for factors including the use of induction agents, living donation, race, and ethnicity. In one prior examination of center-level variation in the use of corticosteroids, Fu et al examined utilization and outcomes from OPTN records. At the time of their publication (2008), approximately one-third of recipients were discharged on a steroid-sparing regimen. Interestingly, the selective use of a steroid-free regimen appeared more effective: Compared with centers from which 100% of patients were discharged on a steroid-free regimen, centers in which only 20–49% of patients were discharged steroid free had fewer deaths (odds ratio 0.73) and graft failures (odds ratio 0.71). Outcomes at these centers, however, were better than outcomes at centers that discharged all patients on triple therapy. This study suggests that tailored use of nonreference ISx regimens may improve patient outcomes (18,19).

In contrast with prior studies of ISx use reported to OPTN, the current study is based on pharmacy fill records, which are more comprehensive than center-reported transplant registry data at intermittent survey points. The use of pharmacy claims to assess ISx regimens has been validated previously based on comparisons to electronic medical records and the OPTN registry. Although the concordance among all three data sources was excellent at 1 year for CNIs (99–100%), the claims were somewhat more accurate in determining the use of MPA and AZA (20,21). Comparison of a large electronic pharmacy claims database with written prescriptions found negligible error rates of 0.02% for drug dispensed (22). Lau et al (23) and Boethius et al (24) independently found pharmacy records and claims to have near-perfect agreement with home inventories; however, physician-directed dose changes that are communicated without written prescriptions will be missed. Furthermore, although the absence of pharmacy claim for any drug is interpreted as no use in this design, alternative explanations may include noncompliance of use from an uncaptured "oversupply." Our study database also lacked drug levels as a measure of drug exposure. Although nothing is more accurate than an audit of patient households (25), such data collection is expensive, intrusive and difficult to accomplish on a large scale.

Our study was limited to the regimens used in the first 2 years after transplant. It is possible that ISx management may be changed after the second posttransplant anniversary; however, the majority of the early conversation trials (e.g. Spare the Nephron) recommend conversion within the first year, and late corticosteroid withdrawal has been associated with higher rates of rejection than early withdrawal (26). In the current study, regimen selection remained stable between years 1 and 2 in the majority of patients, especially those on triple-therapy, SRL-based and CsA-based regimens.

Some clinical conditions are not captured in OPTN data but affect the choice of ISx after kidney transplant. Patients with a history of, for example, CNI-induced thrombotic microangiopathy, severe CNI neurotoxicty or nephrotoxicity may be more likely to receive SRL-based therapy. As supported by our findings, early acute rejection episodes may result in increased intensity of ISx. Patients receiving ISx through trials rather than pharmacy fills also cannot be identified through our study data, although some of the patients in the Other category were likely managed under study protocols. Finally, the years of data collection in our study ended in 2010, and ongoing research is needed to evaluate the use and trends of recently approved agents including extended-dose Tac, everolimus and belatacept.

In conclusion, we found that despite an increasing body of literature that informs the tailoring of ISx therapy on the basis of patient characteristics, ISx choice remains largely driven by center practice. Clinically expected patient and donor characteristics were associated with ISx choice (e.g. highly sensitized patients were more commonly treated with triple therapy); however, case factors explained <6% of the national variation in practice in our study. Center choice explained up to nearly half of observed variation in regimen use. Further research including collaborative clinical trials and secondary data analyses of contemporary practice are needed to determine the relationship among center practice, posttransplant outcome and patient selection to advance from "one size fits all" to a personalized medicine approach to ISx.

Acknowledgments

This work was supported by a grant from the National Institutes of Health (NIH)/National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) R01DK102981.

Disclaimer

The data reported here have been supplied by the United Network for Organ Sharing as the contractor for the Organ Procurement and Transplantation Network (OPTN). The interpretation and reporting of these data

are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by OPTN or the U.S. Government.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

References

1. Lentine KL, Gheorghian A, Axelrod D, Kalsekar A, L'Italien G, Schnitzler MA. The implications of acute rejection for allograft survival in contemporary U.S. kidney transplantation. Transplantation 2012; 94: 369–376.
2. Alangaden GJ, Thyagarajan R, Gruber SA, et al. Infectious complications after kidney transplantation: Current epidemiology and associated risk factors. Clin Transplant 2006; 20: 401–409.
3. Pourmand G, Salem S, Mehrsai A, Taherimahmoudi M, Ebrahimi R, Pourmand M. Infectious complications after kidney transplantation: A single-center experience. Transpl Infect Dis 2007; 9: 302–309.
4. Lentine KL, Brennan DC, Schnitzler MA. Incidence and predictors of myocardial infarction after kidney transplantation. J Am Soc Nephrol 2005; 16: 496–506.
5. Lentine KL, Rocca Rey LA, Kolli S, et al. Variations in the risk for cerebrovascular events after kidney transplant compared with experience on the waiting list and after graft failure. Clin J Am Soc Nephrol 2008; 3: 1090–1101.
6. Lodhi SA, Lamb KE, Meier-Kriesche HU. Solid organ allograft survival improvement in the United States: The long-term does not mirror the dramatic short-term success. Am J Transplant 2011; 11: 1226–1235.
7. Stegall MD, Gaston RS, Cosio FG, Matas A. Through a glass darkly: Seeking clarity in preventing late kidney transplant failure. J Am Soc Nephrol 2015; 26: 20–29.
8. Vincenti F, Jensik SC, Filo RS, Miller J, Pirsch J. A long-term comparison of tacrolimus (FK506) and cyclosporine in kidney transplantation: Evidence for improved allograft survival at five years. Transplantation 2002; 73: 775–782.
9. Meier-Kriesche HU, Morris JA, Chu AH, et al. Mycophenolate mofetil vs azathioprine in a large population of elderly renal transplant patients. Nephrol Dial Transplant 2004; 19: 2864–2869.
10. Vanrenterghem Y, van Hooff JP, Squifflet JP, et al. Minimization of immunosuppressive therapy after renal transplantation: Results of a randomized controlled trial. Am J Transplant 2005; 5: 87–95.
11. Durrbach A, Rostaing L, Tricot L, et al. Prospective comparison of the use of sirolimus and cyclosporine in recipients of a kidney from an expanded criteria donor. Transplantation 2008; 85: 486–490.
12. Pascual J, Galeano C, Royuela A, Zamora J. A systematic review on steroid withdrawal between 3 and 6 months after kidney transplantation. Transplantation 2010; 90: 343–349.
13. Gill J, Sampaio M, Gill JS, et al. Induction immunosuppressive therapy in the elderly kidney transplant recipient in the United States. Clin J Am Soc Nephrol 2011; 6: 1168–1178.
14. Meier-Kriesche HU, Ojo A, Hanson J, et al. Increased immunosuppressive vulnerability in elderly renal transplant recipients. Transplantation 2000; 69: 885–889.
15. Department of Health and Human Services. Health Resources and Services Administration. 2004 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1994–2003.
16. Merlo J, Chaix B, Ohlsson H, et al. A brief conceptual tutorial of multilevel analysis in social epidemiology: Using measures of clustering in multilevel logistic regression to investigate contextual phenomena. J Epidemiol Community Health 2006; 60: 290–297.
17. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150: 604–612.
18. Luan FL, Steffick DE, Gadegbeku C, Norman SP, Wolfe R, Ojo AO. Graft and patient survival in kidney transplant recipients selected for *de novo* steroid-free maintenance immunosuppression. Am J Transplant 2009; 9: 160–168.
19. Luan FL, Steffick DE, Ojo AO. Steroid-free maintenance immunosuppression in kidney transplantation: Is it time to consider it as a standard therapy? Kidney Int 2009; 76: 825–830.
20. Buchanan PM, Schnitzler MA, Brennan DC, et al. Novel methods for tracking long-term maintenance immunosuppression regimens. Clin J Am Soc Nephrol 2008; 3: 117–124.
21. Stirnemann PM, Takemoto SK, Schnitzler MA, et al. Agreement of immunosuppression regimens described in Medicare pharmacy claims with the Organ Procurement and Transplantation Network survey. J Am Soc Nephrol 2006; 17: 2299–2306.
22. Levy AR, O'Brien BJ, Sellors C, Grootendorst P, Willison D. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. Can J Clin Pharmacol 2003; 10: 67–71.
23. Lau HS, de Boer A, Beuning KS, Porsius A. Validation of pharmacy records in drug exposure assessment. J Clin Epidemiol 1997; 50: 619–625.
24. Boethius G. Recording of drug prescriptions in the county of Jamtland, Sweden. II. Drug exposure of pregnant women in relation to course and outcome of pregnancy. Eur J Clin Pharmacol 1977; 12: 37–43.
25. Yang JC, Tomlinson G, Naglie G. Medication lists for elderly patients: Clinic-derived versus in-home inspection and interview. J Gen Intern Med 2001; 16: 112–115.
26. Weir MR, Mulgaonkar S, Chan L, et al. Mycophenolate mofetil-based immunosuppression with sirolimus in renal transplantation: A randomized, controlled Spare-the-Nephron trial. Kidney Int 2011; 79: 897–907.

Supporting Information

Additional Supporting Information may be found in the online version of this article.

Table S1: Comparison of immunosuppression regimens at 6–12 and 12–24 mo after transplant.

Table S2: Immunosuppression regimen selection in the second year compared with the regimen at 6–12 mo among patients with complete data (n = 18 298).