Influence of Early Posttransplantation Prednisone and Calcineurin Inhibitor Dosages on the Incidence of New-Onset Diabetes

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Risk for new-onset diabetes (NOD) after renal transplantation is higher with tacrolimus (Tac) than with cyclosporine (CsA), but the extent to which the diabetogenic effect of Tac is dosage dependent or steroid dependent remains uncertain. Patients who received a transplant between 1995 and 2002 were drawn from the United Network for Organ Sharing registry and prescription records and NOD diagnoses from Medicare claims, both provided by the United States Renal Data System. Patients were divided into six groups of steroid and Tac doses at 30 d after transplantation and referenced against CsA. Relative hazards of NOD with Cox proportional hazards regression were estimated incorporating propensity scores for Tac and nonimmunosuppressive factors related to NOD. A total of 8839 patients with valid immunosuppression records and without pretransplantation evidence of diabetes were included in the study. Unadjusted, cumulative, NOD incidence 1 yr after transplantation was 14.6% with CsA and 22.2% with Tac and at 3 yr after transplantation was 23.4% with CsA and 32.9% with Tac ($P < 0.0001$). Neither higher CsA nor higher steroid dosages were associated with NOD in CsA-treated patients. However, NOD hazard was significantly higher with Tac than with CsA in all six steroid/Tac dosing groups, including the cohort with the lowest dosages of Tac (dosage thresholds at 30 d after transplantation <0.12 mg/kg per d [mean 0.07 mg/kg per d] and steroids (<0.75 mg/kg per d; hazard ratio 1.28; 95% confidence interval 1.10 to 1.48; $P = 0.0012$). Whereas the incidence of NOD is greatest with high Tac dosages, the increased risk *versus* CsA is sustained with lower Tac dosages. Higher steroid dosages increase the early diabetogenic effect of Tac but not of CsA.

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Development of diabetes after transplantation is a well-documented complication of immunosuppression therapy (1). In addition to the macrovascular and microvascular complications of diabetes (*e.g.*, retinopathy, neuropathy, nephropathy, ulceration, increased cardiovascular risk) that occur in the general diabetes population, diabetes in the transplant population is associated with increases in graft loss and death (2). In economic terms, recent analyses showed that new-onset diabetes (NOD) increases health care costs for a transplant recipient by >$9000 during the first year after transplantation alone (3).

In the early days of transplantation, as many as half of all renal

transplant recipients developed NOD as a consequence of high dosages of steroids, and the term "steroid diabetes" was coined (4). Although reductions in steroid dosages, combined with azathioprine, reduced NOD incidence (5), approximately 25% of patients still developed NOD. The introduction of calcineurin inhibitors (CNI) facilitated further reductions in steroid dosages but were soon found to have diabetogenic effects of their own (6). National registry analyses suggest that 15 to 20% of renal transplant patients who do not have diabetes and receive a CNI currently develop NOD within 1 yr of transplantation (2,3). Among clinical trials, which tend to use more restrictive criteria for NOD, the incidence is estimated to be 10 to 15% (7).

Studies have examined the linkage between two CNI (cyclosporine [CsA] and tacrolimus [Tac]) and the development of NOD. Histologic research suggests that CsA and Tac may adversely affect pancreatic β islet cells in a similar manner to cause NOD but that these changes are more pronounced and frequent for patients who are treated with Tac (8). Consistent with this, clinical research has found that NOD occurs six times more frequently with Tac than with CsA (9–13), although one study failed to observe these differences (14). A recent meta-analysis of 35 trials that were published between 1992 and 2002

found that the incidence of NOD was approximately three-fold higher with Tac than with CsA (9.8 *versus* 2.7%; $P < 0.00001$) (7). Similarly, a recent registry analysis of data from >11,000 patients in the United States Renal Data System (USRDS) found that the risk for NOD increased by 53% when Tac was used as the initial maintenance immunosuppression (2). Another large registry study found that the difference in NOD between CsA and Tac occurs as soon as 3 mo after transplantation (3), a result confirmed by subsequent clinical trials (15–17).

Since the mid-1990s, concerted efforts have been made to lower the maintenance dosage of Tac from the high of 0.3 mg/kg per d in an attempt, in part, to reduce the incidence of NOD (9). Research that examined whether these relationships are dosage-dependent has yielded inconsistent results. Limited animal data and one trial suggested a dosage-dependent relationship (18,19), but in a meta-analysis of 35 trials, Heisel *et al.* (7) failed to find any evidence of dosage dependence between Tac and NOD. Newer research suggested that once a patient develops NOD, it can often be reversed or its severity decreased by reducing the dosage of Tac and steroids (20,21), but these studies were unable to separate the effect of steroids and CNI.

In this study, we report analysis of kidney recipients to assess the effect of CNI and steroid dosage, at today's lower levels, on development of NOD. Because of the recognized diabetogenic effect of steroid therapy (22), our models control for initial steroid dosage. This study is the first to use prescription data to assess the effect of CNI dosage on risk for development of NOD after kidney transplantation.

Materials and Methods

This study was approved by the Saint Louis University Institutional Review Board and adheres to the Declaration of Helsinki. Data came from the USRDS registry, which contains linked data from the Organ Procurement Transplant Network (OPTN) and Medicare billing records.

NOD

As validated in previous research (23,24), NOD diagnosis required a minimum of one inpatient or two outpatient claims separated by no more than 1 yr (*International Classification of Diseases, Ninth Revision, Clinical Modification* codes between 250.00 and 250.79). The date of onset of diabetes was set as the date of the first claim. It is important to note that this criterion is not the same as the "gold standards" established by the American Diabetes Association (ADA) and the World Health Organization (WHO), which require laboratory results and patient symptoms (25) that are unavailable in the USRDS. The definition used in this study has been validated in a number of studies that consistently found a high level of accuracy and concordance between cases that were identified by this definition and the ADA/WHO criteria (23,26,27).

Immunosuppression Dosages

As in previous studies (24,28), immunosuppression agents and dosages were identified using Healthcare Common Procedure Coding System billing codes (specific agent, pill size, total pill count) from Medicare Part B data. The prescription closest to 30 d after transplantation but no later than 30 d after transplantation was selected as the posttransplantation prescription for this analysis. Prescribed dosage (mg/kg per d) was estimated using prescription data and patient's weight (from the OPTN database) at the time of transplantation. It was

not possible with these data to identify intravenous steroids. Although the data presented is based on 30-d immunosuppressive agents, these analyses were repeated using CNI choice and dosage at 60, 90, 120, and 180 d after transplantation, with consistent results.

Patient Characteristics

All recipients with a first renal transplant between 1995 and 2001 and a Medicare immunosuppression claim within 30 d of transplantation were eligible for inclusion in this analysis. This time period was selected because widespread use of Tac outside clinical trials began in 1995 and because the OPTN expanded the quantity of data collected in that year. The year 2001 was the last year with available Medicare data. Patients were excluded when they had a multiorgan transplant or evidence of pretransplantation diabetes (primary or secondary code of 250.x for inpatient or outpatient care). Patients with prescribed dosages of Tac, CsA, or steroids above the 99th percentile of observed prescribed dosages were considered outliers and excluded from analysis. Patients without a prescription for CsA or Tac within 30 d after transplantation were also excluded.

Study End Point

The primary end point was diagnosis of NOD. Patients were censored at 3 yr of follow-up (the maximum Medicare benefit available to the majority of patients), 30 d after the last recorded immunosuppression prescription fill, graft failure, or death.

Statistical Analyses

The statistical analyses for this study involved seven primary steps: (*1*) Bivariate comparisons of patients on Tac and CsA; (*2*) bivariate comparisons of patients in the study sample with the entire renal transplant population; (*3*) calculation of propensity scores to identify and control for patient characteristics that were associated with CNI choice; (*4*) Kaplan-Meier analysis of NOD rates for patients who were on Tac and CsA, unadjusted for covariates; (*5*) Cox proportional hazard analyses to examine the impact of CNI on NOD, adjusting for covariates; (*6*) application of generalized additive models (GAM) of the Martingale residuals to examine the nonlinear relationships that were identified in the Cox proportional hazard analysis; and (*7*) final Cox proportional hazards analysis using the stratification points that were identified by the GAM analysis (29,30).

Bivariate analyses were conducted to compare the characteristics of patients who were on CsA and Tac with respect to age, gender, race, cause of ESRD, body mass index, hepatitis C antibody status, donor demographics, expanded criteria donor, HLA matching, primary immunosuppression, panel reactive antibody status, cold and warm ischemia time, and cytomegalovirus sero-pairing. Fisher exact test and *t* test (both two-sided) were used, as appropriate, to test for differences between CsA and Tac patients in each of these variables. All variables that were found to be significantly associated were included in subsequent analyses to examine their impact on the development of NOD. Identical analyses examined the extent to which patients in our sample differed from patients in the total renal transplant population for each of the characteristics described.

Multivariate propensity scores (propensity for Tac compared with CsA) were calculated with logistic regression (forward and backward entry) to adjust for any patient characteristic that was associated with choice of CNI (31) using the covariates described previously (32). The propensity score was categorized into deciles and used along the year of transplantation to stratify the final Cox analysis. All significant variables were included as covariates in the final Cox analyses.

Kaplan-Meier analyses tested for differences in the incidence of NOD

for patients who were on CsA compared with Tac. The unadjusted accumulated incidence of NOD was calculated for each day after transplantation using the product-limit (Kaplan-Meier) method (33). The incidence levels at each day reflected the accumulated incidence level of the previous day plus the new incidence (*e.g.*, number of new NOD diagnoses divided by the number of patients without an *International Classification of Diseases, Ninth Revision, Clinical Modification* report of diabetes on that day). This analysis was repeated using the CNI at 60, 90, 120, and 180 d after transplantation.

Cox regression analyses were conducted to examine the impact of CNI dosage, steroid dosage, and their interactions on the development of NOD, after controlling for CNI propensity, year of transplantation, and the other covariates described previously. These analyses revealed significant non-linear relationships, however. To understand these relationships better, we first used a series of power transformations, but none provided a good fit to the data. We next used GAM analysis of the Martingale residuals from the Cox regression (29), which provided an excellent fit. GAM analysis extends traditional linear modeling and allows for the estimation of non-linear relationships without requiring structural assumptions (30). The results of the GAM were used to identify stratification points for the combination of CNI and steroid dosages.

Results were considered statistically significant for $P < 0.05$. P values that involved multiple comparisons were adjusted with a Bonferroni correction. To ensure that our analytic techniques provided accurate results (34), we verified final results with two sets of 10,000 bootstrap cycles (35). All analyses were performed with SAS for Windows software (version 8.2; SAS Institute, Cary, NC).

Results

Population Characteristics

In total, 8839 patients were eligible for the study. In comparing the characteristics of these patients with those of the total renal transplant population (including those without Medicare coverage for immunosuppression), we found that our sample was slightly older (45.7 *versus* 45.0 yr), had significantly longer duration of dialysis (2.6 *versus* 1.8 yr; $P < 0.01$); and had a greater likelihood of being disabled (35.2 *versus* 31.7%).

At 30 d after transplantation, 5943 sample patients had prescriptions for CsA and 2895 for Tac. Median prescribed dosages were as follows: CsA 6.1 mg/kg per d (range 0.1 to 25.0); Tac 0.13 mg/kg per d (range 0.01 to 0.43), and oral steroids 0.39 mg/kg per d (range 0.0 to 1.61).

Factors Associated with Choice of CNI

As shown in Table 1, patients who were on Tac were more likely to be unemployed as a result of disability (odds ratio [OR] 1.30), have panel reactive antibody >80% (OR 1.60), have had a pretransplantation blood transfusion (OR 1.46), be on mycophenolate mofetil (OR 1.42) or sirolimus (OR 2.03), be a hypertensive donor (OR 1.28), and be black (OR 1.43) and were less likely to be on azathioprine (OR 0.27). These patient characteristics were used to calculate the propensity scores that controlled for predisposition toward a particular CNI in subsequent analyses.

Factors Associated with Incidence of NOD

Kaplan-Meier analysis identified differences in NOD incidence between Tac and CsA at both 1 and 3 yr after transplantation. The unadjusted cumulative incidence of NOD at 1 yr after transplantation was 14.6% with CsA and 22.2% with Tac; at 3 yr, the rates had risen to 23.4% with CsA and 32.9% with Tac ($P < 0.0001$). This analysis was repeated using CNI drug at 60, 90, 120, and 180 d after transplantation and yielded the same pattern of results (all $P < 0.001$).

Cox proportional hazards regression revealed a number of other factors that were associated with risk for NOD. As shown in Table 2, NOD was associated with increased recipient age, black ethnicity, body mass index >30, hepatitis C, ESRD caused by hypertension, cold ischemic time >24 h, donor death as a result of cerebrovascular accident, use of sirolimus, and no use of azathioprine. This analysis also served to confirm the higher rate of NOD with Tac, even after covariates were included in the model.

Relationship between Dosage of Immunosuppression and Risk for NOD

For patients who were receiving CsA, the continuously measured dosage of CsA, the dosage of steroids at 30 d, and their interaction were not significantly associated with NOD using

Table 1. Logistic regression analysis for variables that were significantly related to Tac *versus* CsA immunosuppression[a]

Covariate	Patients (n [%])		Logistic Regression, Tac *versus* CsA		
	CsA (n = 5943)	Tac (n = 2895)	OR	95% CI	P
Hypertensive donor	2243 (37.7)	1253 (43.3)	1.28	1.17 to 1.41	<0.0001
Recipient unemployed because of disability	1986 (33.4)	1124 (38.8)	1.30	1.18 to 1.43	<0.0001
Panel reactive antibody >80%	222 (3.7)	179 (5.9)	1.60	1.29 to 1.99	<0.0001
Pretransplantation blood transfusion	2076 (34.9)	911 (31.4)	1.46	1.29 to 1.66	<0.0001
MMF (*versus* no MMF)	3672 (61.8)	2288 (79.0)	1.42	1.26 to 1.63	<0.0001
Azathioprine (*versus* no azathioprine)	1916 (32.2)	257 (8.9)	0.27	0.23 to 0.32	<0.0001
Sirolimus therapy (*versus* no sirolimus)	261 (4.4)	253 (8.7)	2.03	1.65 to 2.49	<0.0001
Recipient race black	1628 (27.4)	1014 (35.0)	1.43	1.29 to 1.58	<0.0001

[a]CI, confidence interval; CsA, cyclosporine; MMF, mycophenolate mofetil; OR, odds ratio; Tac, tacrolimus.

Table 2. Covariate selection: Variables that were significantly associated with risk for NOD, excluding choice of CNI in multivariate Cox proportional hazards regression[a]

| Variable	Hazards Ratio	95% CI	P
Recipient age (yr)			
<45	1		Reference
45 to 59	1.89	1.69 to 2.11	<0.0001
>60	2.39	2.10 to 2.72	<0.0001
Recipient race			
white	1		Reference
black	1.82	1.58 to 2.09	<0.0001
Hispanic	1.41	1.22 to 1.64	<0.0001
other	1.42	1.15 to 1.76	0.0013
Recipient BMI >30	1.83	1.64 to 2.04	<0.0001
Recipient hepatitis C positive	1.38	1.16 to 1.65	0.0003
Cause of ESRD			
unknown	1		Reference
hypertension	1.2	1.06 to 1.34	0.0026
other	0.82	0.72 to 0.93	0.0015
Cold ischemia time >24 h	1.22	1.09 to 1.36	0.0003
Donor cause of death cerebrovascular accident	1.16	1.05 to 1.29	0.0036
Sirolimus (*versus* no sirolimus)	1.25	1.00 to 1.54[b]	0.050[b]

[a]BMI, body mass index; CNI, calcineurin inhibitor; NOD, new-onset diabetes.
[b]Sirolimus 95% CI and *P* value from maximum likelihood estimates were 1.03 to 1.55 and 0.047, respectively. The bootstrapping results shown in Table 2 could not confirm these to three digits.

Cox regression analysis or GAM analysis (with and without control variables and propensity scores). To examine these relationships in greater detail, we divided CsA and steroid dosages into six dosing categories and examined these relationships within each category. Higher dosages of CsA were associated with reduced risk for NOD across both the high and low steroid groups, with 3-yr cumulative incidence of NOD showing a reduction of 12% in the highest CsA dosage group (Figure 1). Although this result may suggest a protective benefit of CsA, it is possible that the result is due to a small sample size (303 patients in the two high-dosage CsA groups).

Using CsA as the reference group, we conducted Cox analysis to examine whether the incidence of NOD differed across the Tac dosing groups. Because this analysis revealed significant nonlinear relationships, which could not be corrected using traditional transformations, we applied GAM analysis to identify the most effective stratification points. This approach was used to divide Tac and steroid dosages into six distinct groups. Kaplan-Meier analysis of these groups found that the incidence of NOD rose significantly with increased dosages of Tac and steroids (Figure 2) for each of these six groups ($P < 0.0001$, adjusting for multiple comparisons).

We next conducted Cox proportional hazards analysis to examine these same dosing relationships with the propensity scores that were included to adjust for factors that were associated with physician choice of CNI (Tables 1 and 2). This analysis showed that the hazard ratio for NOD was significantly higher with Tac than with CsA in all six Tac groups, including the cohort with the lowest Tac and steroid dosages
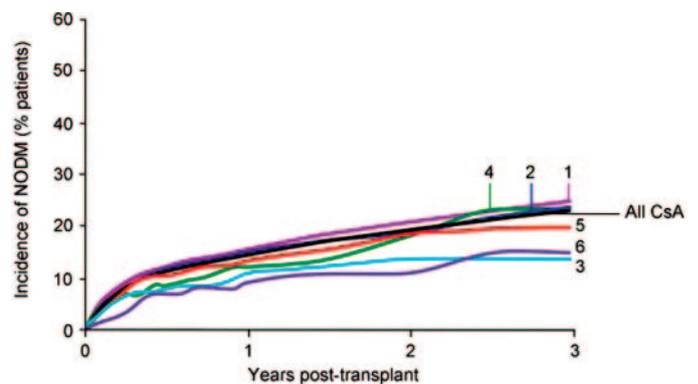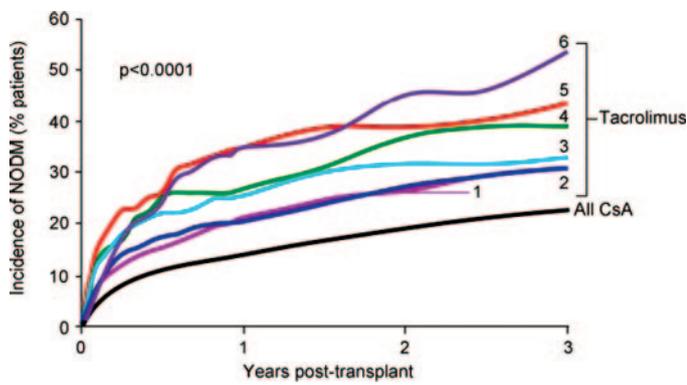

Group	Steroid dose (mg/kg/day)	CsA dose (mg/kg/day)	Incidence of NODM (%)
6 (n=102)	>0.75	>12.7	14%
5 (n=396)	>0.75	6.35-12.7	20%
4 (n=346)	>0.75	<12.7	23%
3 (n=201)	<0.75	>12.7	13%
2 (n=2,188)	<0.75	6.35-12.7	23%
1 (n=2,710)	<0.75	<6.35	24%
All CsA (n=5,943)	0.0-1.23	0.10-25.0 (CsA)	23%

Figure 1. Kaplan-Meier estimates of incidence of new-onset diabetes (NOD) in patients stratified according to cyclosporine (CsA) and steroid dosage at 30 d after transplantation, with overall CsA as a reference.

(hazard ratio 1.28; 95% confidence interval 1.10 to 1.48; $P = 0.0012$; Table 3).

The results described were based on data that were acquired from 1995 to 2005, during which time there were significant

Group	Steroid dose (mg/kg/day)	Tacrolimus dose (mg/kg/day)	Incidence of NODM (%)
6 (n=81)	>0.75	>0.23	54%
5 (n=219)	>0.75	0.12–0.23	43%
4 (n=159)	>0.75	<0.12	39%
3 (n=273)	<0.75	>0.23	33%
2 (n=966)	<0.75	0.12–0.23	31%
1 (n=1,197)	<0.75	<0.12	31%
All CsA (n=5,943)	0.0–1.23	0.10–25.0 (CsA)	23%

Figure 2. Kaplan-Meier estimates of incidence of NOD in patients stratified according to tacrolimus and steroid dosage at 30 d after transplantation, with CsA as a reference.

decreases in the prescribed dosages of both CNI and steroids in an attempt to reduce the frequency of NOD. To examine the impact of lower CNI dosing in greater detail, we further divided the lowest two dosing groups (groups 1 and 2) in the previous analysis into three subgroups (group 1: <0.04, 0.04 to 0.08, and 0.08 to 0.12 mg/kg per d Tac; group 2: 0.12 to 0.16, 0.16 to 0.20, and 0.20 to 0.23 mg/kg per d Tac). These new subgroups were then crossed with two levels of steroid dosage (split at 0.375 mg/kg per d), resulting in a total of 12 subgroups. Analyses of these lower dosage groups revealed the same basic relationship between choice of CNI and NOD, even for the lowest CNI dosage groups. That is, lowering patients' Tac dosing below 0.12 provided no additional protection against NOD. Furthermore, steroid dosing was unrelated to NOD whenever the Tac dosage dropped below 0.12 mg/kg per d (original group 1). For patients in original group 2 (Tac dosage of 0.12 to 0.23 mg/kg per d), however, reductions in steroid dosage below 0.375 were associated with a significant decline in the risk for NOD (hazard ratio 1.81; $P < 0.0001$), suggesting a potentially protective effect.

Discussion

Previous registry studies clearly demonstrated a strong association among steroid use, choice of CNI, and the development of NOD among renal transplant patients (2,3). This study furthers our understanding of these risk factors by examining whether the relationships with NOD depend on the dosage of CNI and steroids. Our results suggest that the increased risk for NOD for patients who were receiving Tac existed regardless of the dosing level of Tac or steroid. Even for the lowest dosage group for CNI and steroids, rates of NOD were significantly higher for Tac than for CsA. Although the diabetogenic effect of Tac may be reduced by lowering dosing to 0.12 mg/kg per d, no additional benefit is

gained by lowering the dosage below this level. These break points, however, were constructed for analytic purposes and should not be used to define exactly dosing targets.

In contrast, the dosage of CsA was unassociated with risk for NOD, and there was the suggestion that higher dosages were associated with less NOD. The absence of dosage-dependent effects of CsA on NOD were reported in two retrospective studies (16,36), as well as in one prospective study (22). The reason that our results suggest a potentially protective effect of higher CsA dosages remains unclear. There is some evidence that CsA but not Tac is associated with higher insulin-to-glucose ratios that may reflect increased insulin production in patients who are at particular risk for NOD (37). The effect of these CNI on both islet and β cells varies (8).

Our results suggest that higher steroid dosages potentiated the diabetogenic effect of Tac, such that patients who were on higher steroids dosages (>0.75 mg/kg per d) were at greater risk for NOD when given Tac than when given CsA. There was consistently less NOD with lower steroid dosages in patients who were receiving higher dosages of Tac; however, lower steroid dosages for the lowest dosages of Tac (<0.12 mg/kg per d) did not decrease the risk for NOD. It is interesting that there was no association between steroid dosage and NOD for any dosage of CsA. Again, the pathophysiologic basis for this result is unclear. Certain groups of patients can achieve therapeutic blood levels of Tac at low dosages. For example, those with hepatic dysfunction or hepatitis C infection have reduced capacity to metabolize the drug and can be effectively administered lower dosages (38). This hepatic dysfunction may contribute to NOD (39).

An unexpected result was the correlation between sirolimus and the development of NOD, which just reached the edge of statistical significance. A number of subanalyses were conducted to examine this relationship more fully. We repeated the analyses with and without the inclusion of sirolimus by excluding sirolimus-treated patients, by examining sirolimus dosages, and by examining the interactions with other medications. Across all of these analyses, no significant results that shed insight on the association between sirolimus and NOD were obtained. A diabetogenic effect of sirolimus has not been reported in clinical studies (40,41) and may be a spurious finding as a result of the small number of sirolimus-treated patients reported here.

It is important to note that although the primary analyses focused on steroid and CNI dosages at 30 d after transplantation, these analyses were repeated using dosing at 60, 90, 120, and 180 d. In each case, the same patterns of results were obtained.

Registry analyses, with relatively large national samples, can serve as a vehicle for examining complicated relationships among treatments and outcomes, which may not be ethical or practical to examine in a randomized, controlled trial design. For example, to test prospectively for 3-yr differences in NOD between Tac and CsA (80% power, $\alpha = 0.05$), >1000 patients per dosage per CNI category would be required. Studies of this scope could not feasibly be conducted with transplant patients.

Despite the benefits of registry analysis, there are several limitations that must be recognized. First, the absence of laboratory results and patient symptoms in the USRDS made it impossible to use the gold standard definitions for diabetes that were estab-

Table 3. Multivariate analysis of NOD hazard in Tac-treated patient groups identified by GAM analysis stratified by propensity score for choice of Tac *versus* CsA and year of transplantation[a]

Group	Steroid Dosage (mg/kg per d)	Tac Dosage (Median Dosage; mg/kg per d)	Patients (n [%])	Hazards Ratio for NOD *versus* CsA	95% CI	P
1	<0.75	<0.12 (0.08)	1197 (41.4%)	1.28	1.10 to 1.48	0.0012
2	<0.75	0.12 to 0.23 (0.16)	966 (33.4%)	1.44	1.24 to 1.68	<0.0001
3	<0.75	>0.23 (0.27)	273 (9.4%)	1.81	1.42 to 2.32	<0.0001
4	>0.75	<0.12 (0.09)	159 (5.5%)	1.99	1.47 to 2.69	<0.0001
5	>0.75	0.12 to 0.23 (0.16)	219 (7.6%)	2.45	1.92 to 3.11	<0.0001
6	>0.75	>0.23 (0.29)	81 (2.8%)	2.44	1.69 to 3.52	<0.0001

[a]All Tac and steroid dosage groupings are relative to CsA-treated patients. GAM, generalized additive model.

lished by the ADA and the WHO. The definition that was used in this study had been developed and tested in a number of validation studies that found strong accuracy when compared with the gold standard definitions (23,26,27), but this definition still does not provide the much more definitive diagnosis that is possible with laboratory results. It is important to recognize that definitional issues may have yielded different results than would have been observed using the ADA and WHO criteria.

Second, the use of Medicare billing data to obtain key patient information (*e.g.*, dosing, weight), although shown to be highly reliable (42–44), deserves further investigation to establish its accuracy. Patient body weight, assessed in our study at 30 d, may have undergone change in the months after transplantation, and these weights were not included in these analyses. Medicare billing records are also unable to identify separately the timing of any episode of acute rejection or intravenous dosages of steroids, either for rejection treatment or as part of the transplantation protocol. Last, the registry contains CNI dosages rather than actual blood levels, because these data are unavailable in our data. Although we expect that our results are driven by differences in blood levels related to dosing, we cannot prove this expectation with these data. Also, any actual differences should be equally distributed across patients who are on Tac and on CsA.

Conclusion

This study of >8000 renal transplant patients confirms findings of previous research that the incidence of NOD is significantly higher with Tac than with CsA. At the highest dosages of Tac, the risk for NOD compared with CsA is increased more than two-fold, but even at the lowest Tac dosages, there is still a significant increase in risk that did not fall below 28%. Increasing steroid dosages potentiated the diabetogenic effect of Tac, and patients who receive >0.75 mg/kg per d steroids seem to be at particular risk for NOD when given Tac. Steroid dosage does not seem to affect the risk for NOD in patients who receive CsA.

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Disclosures
None.

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