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The Privilege of Induction Avoidance and Calcineurin Inhibitors Withdrawal in 2 Haplotype HLA Matched White Kidney Transplantation

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Background. White recipients of 2-haplotype HLA-matched living kidney transplants are perceived to be of low immunologic risk. Little is known about the safety of induction avoidance and calcineurin inhibitor withdrawal in these patients. **Methods.** We reviewed our experience at a single center and compared it to Organ Procurement and Transplantation Network (OPTN) registry data and only included 2-haplotype HLA-matched white living kidney transplants recipients between 2000 and 2013. **Results.** There were 56 recipients in a single center (where no induction was given) and 2976 recipients in the OPTN. Among the OPTN recipients, 1285 received no induction, 903 basiliximab, 608 thymoglobulin, and 180 alemtuzumab. First-year acute rejection rates were similar after induction-free transplantation among the center and induced groups nationally. Compared with induction-free transplantation in the national data, there was no decrease in graft failure risk over 13 years with use of basiliximab (adjusted hazard ratio [aHR], 0.86; confidence interval [CI], 0.68-1.08), Thymoglobulin (aHR, 0.92; CI, 0.7-1.21) or alemtuzumab (aHR, 1.18; CI, 0.72-1.93). Among induction-free recipients at the center, calcineurin inhibitor withdrawal at 1 year (n = 27) did not significantly impact graft failure risk (HR,1.62; CI, 0.38-6.89). **Conclusions.** This study may serve as a foundation for further studies to provide personalized, tailored, immunosuppression for this very low-risk population of kidney transplant patients.

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High-risk versus low-risk kidney transplantation has been defined epidemiologically and immunologically. Epidemiologic high risks include African Americans and adolescents.[1,2] Immunologic risks include high panel-reactive antibody (PRA) levels, ABO incompatibility, as well as HLA incompatibility.[3-7] The few scenarios with very low immunologic risk include transplantation between identical twins and between 2 haplotype HLA-matched siblings.[8] The outcome advantages of 2-haplotype HLA-matched living transplantation include lower rejection rates and better overall patient and graft survival compared with transplantation with greater degrees of HLA mismatches.[9-12]

Currently, most immunosuppression protocols include antibody induction with calcineurin inhibitor (CNI) maintenance regimens.[13] The immunologic privilege of the 2-haplotype living related transplant would seemingly allow for less overall immunosuppression. There are, however, few published studies investigating the use and the type of induction, and the intensity of maintenance therapy including withdrawal of the CNI in 2-haplotype-matched living related transplants.

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Historically, African American recipients of 2-haplotype living related transplants have higher rates and earlier onset of rejections compared to their white counterparts. An analysis of Organ Procurement and Transplantation Network (OPTN) data of 2-haplotype HLA matched living related kidney transplants between 1984 and 1992 reported higher incidences of acute rejection and poorer long-term graft survival in black compared with white recipients.[14] Because of the immunologic privilege afforded by a high-degree HLA-matching, it has been our center's policy that white, 2-haplotype matched living related kidney transplant recipients do not receive induction and undergo CNI withdrawal within 6 to 12 months after transplantation. The aim of this study was to examine center-specific and OPTN data to assess the safety and efficacy of such practice in local and national experience.

METHODS

This study was approved by the institutional review board of Washington University in St. Louis. Two-haplotype HLA matched white kidney transplantation was defined as white living donors matched with HLA A, B, C, DR, DQ, and DP antigens by intermediate resolution DNA typing by a Luminex Flow Analyzer with white sibling recipients. None of these patients were from identical twins. In the OPTN database, 2 haplotype was captured using "HAPLO_TY_MATCH_DON" variable. These patients were identified from January 2000 and December 2013 in our center, "the center," as well as those documented in the OPTN database. The center patients who fell in this category underwent transplantation without induction (center-no-induction). In the OPTN data, white 2-haplotype matched siblings were analyzed according to induction: basiliximab, thymoglobulin, alemtuzumab, or no induction (OPTN-no-induction). Donor and recipient demographic and clinical factors are summarized in Table 1. Peak PRA was the highest reported value before transplantation.

The center protocol calls for CNI withdrawal within the first year; however, not all were withdrawn from the CNI by 1 year. Thus, the center patients (n = 56) were divided according to CNI status at 1 year into CNI continuation and CNI withdrawal (Figure 1). All patients were on prednisone 5 mg daily as maintenance. None was in a prednisone avoidance protocol. Twenty-seven patients achieved CNI withdrawal by 1 year and were compared with 29 patients who continued to be on CNI by year 1. Underlying reasons for CNI continuation were: 4 with previous transplants, 3 with antimetabolite discontinuation due to infections and malignancies, 3 with high risk of primary glomerulonephritis recurrence, 1 with known history of poor medication adherence, 1 with rejection within the first year, and 17 with protocol deviation or preference of an outside provider for CNI continuation. Of these 17 patients, 11 subsequently had CNI withdrawal within the second and third year after transplantation. Because of the small sample size and similar characteristics, patients who continued CNI after the first year were categorized in 1 group. Because of the limitations of the data registry, patients could not be accurately categorized according to CNI continuation in the national OPTN sample.

Graft Failure and Death

Graft and patient survival in the center-no-induction group were compared with survival outcomes in the induction groups in the OPTN. We also compared survival outcomes between the OPTN-no-induction and the induction groups. Kidney allograft survival was defined as time from initial transplant to retransplantation, initiation of dialysis or recipient death. Thus, patient death was included as allograft loss regardless of the functional status of the kidney allograft at the time of death. Patient survival was considered from time of transplant to patient death. Survival times were censored at the study end on October 31, 2014.

Secondary Outcomes

Acute rejection within the first year of transplant was examined in the center group and compared with the OPTN induction groups. Other secondary outcomes were assessed in the form of infections and malignancies. Infections included cytomegalovirus (CMV) and BK, whereas malignancies included melanoma and posttransplant lymphoproliferative disorder (PTLD).

Because OPTN data do not record CMV or BK viral infections unless reported as a cause of graft loss, we compared the rates of CMV and BK infections between the center-no-induction patients to all live donor kidney transplant recipients at the center who received induction, mostly thymoglobulin, during the same period as an internal control. CMV viremia was documented from quantitative DNA analysis using the polymerase chain reaction assays. BK was reported as either BK viremia or from evidence of BK nephropathy on kidney allograft biopsy.

For malignancies, we extracted rates of melanoma and PTLD in the center-no-induction group and compared the results to national recipients managed with and without induction.

Statistical Analysis

Recipient characteristics were described using proportions for categorical variables, and means with standard deviations for continuous variables. Recipient and donor factors were compared among the groups using a χ^2 or Fisher test for categorical variables and analysis of variance test or Kruskal Wallis tests for continuous variables, depending on the distribution of the variable.

Allograft and recipient survival were assessed using the Kaplan-Meier survival analysis, and *P* values were calculated using the log-rank test. Multivariate analysis using the Cox model was used to calculate the hazard ratio during the follow up period for allograft failure and recipient death. In the OPTN, the associations between the use and the type of induction and kidney allograft and recipient survival were assessed after adjusting for donor and recipient age, sex, body mass index (BMI), hypertension (HTN), and other recipient-specific variables, such as causes of ESRD, dialysis before transplantation, PRA, and delayed graft function (DGF) as listed in Table 1. Given the small available sample for the center comparison, the multivariate model of center-no-induction versus OPTN induction groups was adjusted for a more limited set of baseline factors as follows: recipient and donor age and recipient sex. Statistical analyses were performed using SAS statistical software (version 9.4, Cary, NC).

RESULTS

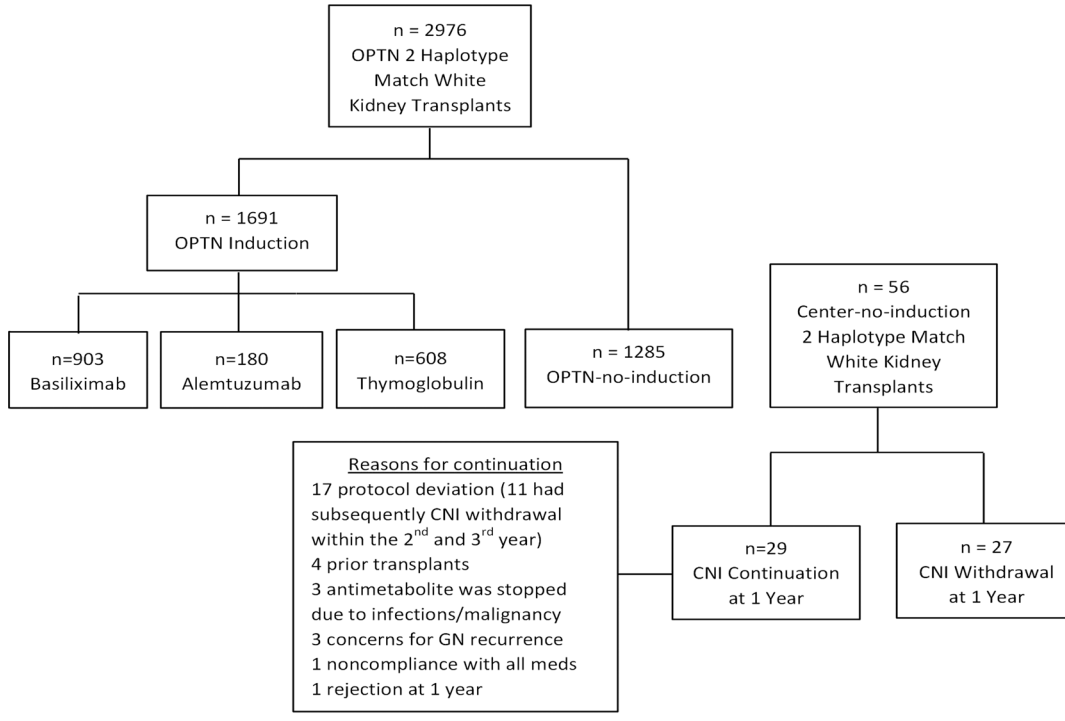
Between January 2000 and December 2013, a total of 531 living-related kidney transplants were performed at the center. Of these, 56 were performed between white 2-haplotype

TABLE 1.

Recipient and donor characteristics among the OPTN patients (stratified by induction) and the center-no-induction group

	Comparison: OPTN-no-induction vs OPTN induction groups					Comparison: center-no-induction to OPTN Induction Groups	
	OPTN-no-induction (N = 1285)	OPTN Basiliximab (N = 903)	OPTN Thymoglobulin (N = 608)	OPTN Alemtuzumab (N = 180)	*P*	Center no induction (N = 56	*P*
Recipient							
Age: mean, ± SD, y	44 (12)	46 (12)	45 (11)	45 (12)	0.06	41 (10)	0.05
Sex Female, %	40	40	45	41	0.21	41	0.34
BMI: mean ± SD	27 (5)	27 (5)	27 (5)	27 (6)	0.70	26 (5)	0.94
HTN, %	57	45	42	25	<0.01	84	<0.01
Diabetes, %	28	25	30	26	0.16	21	0.24
PVD, %	3	4	4	2	0.19	0	0.09
COPD, %	0.5	0.3	1.1	1.2	0.15	0	0.14
CVD, %	1.6	1.2	1.8	1.1	0.78	9	<0.01
CAD, %	3.4	2.9	10.6	2.4	<0.01	9	0.02
Cause of ESRD, %					0.09		<0.01
DM	15	15	21	16	20		
HTN	11	11	12	13	11		
GN	32	31	32	32	37		
PKD	11	12	10	13	14		
Other/missing	31	31	25	26	18		
PRA, %							
0	64	61	61	55	<0.01	64	0.03
$0 < PRA \leq 20$	21	19	16	30	16		
$20 < PRA \leq 80$	8	12	13	8	14		
$PRA > 80$	4	4	6	5	5		
Missing	2	3	4	2	2		
Time on Dialysis, %					0.01		<0.01
Preemptive	42	39	43	50	36		
≤24 months	20	26	22	21	55		
>24 months	7	7	6	8	9		
Missing	31	28	29	21	0		
DGF, %	2	3	3	3	0.68	0	0.61
Donor							
Age: mean ± SD, y	42 (11)	44 (11)	43 (11)	44 (12)	0.03	40 (10)	0.09
Sex: Female, %	59	57	57	57	0.90	50	0.76
BMI, Mean ± SD,	27 (5)	27 (4)	27 (4)	27 (6)	0.24	26 (4)	0.77
HTN, %	1	2	2	4	0.07	2	0.63

PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus.



Abbreviations: CNI; calcineurin inhibitor, GN; glomerulonephritis, OPTN; organ procurement and transplant network

FIGURE 1. Patient distribution stratified in OPTN by induction and in the center by CNI withdrawal.

matched siblings without induction (center-no-induction). During the same period, 2976 patients were captured in the OPTN that matched the criteria of white recipients of 2-haplotype matched live donor transplants. Of these, 1285 (43%) received no induction (OPTN-no-induction), 903 (30 %) basiliximab, 608 (20 %) thymoglobulin, and 180 (6 %) alemtuzumab (Figure 1).

Demographics

Baseline demographic comparisons are shown in Table 1. Donor and recipient characteristics of gender, age, and BMI were similar between transplants at the center and national experience in the OPTN. Baseline characteristics were also similar across OPTN groups classified by induction, with the exception that donors for the OPTN-no-induction transplants were slightly younger than donors in the 3 OPTN induction groups ($P = 0.03$). Recipient comorbidities, such as peripheral vascular disease, chronic obstructive pulmonary disease, and diabetes mellitus were similar between the center-no-induction group and the OPTN induction groups ($P = 0.25$, $P = 0.14$, and $P = 0.24$, respectively) and between the OPTN-no-induction groups and the OPTN induction groups ($P = 0.19$, $P = 0.16$, and $P = 0.16$, respectively). The patients in the center-no-induction group were more likely to have HTN ($P < 0.01$), cerebrovascular disease (CVD), ($P < 0.01$), and be on dialysis before transplantation ($P = 0.03$) than recipients in the OPTN induction groups. Thirty-six percent of patients in the center-no-induction group underwent preemptive transplants, which was lower compared with the OPTN-no-induction (42%), OPTN-basiliximab (39%), OPTN-thymoglobulin (43%), and OPTN-alemtuzumab (50%) groups. There were no episodes of DGF in the center-no-induction group, which was not significantly different compared with the OPTN induction groups (3% basiliximab, 3% thymoglobulin, and 3% alemtuzumab; $P = 0.61$). A similar rate of DGF was noted in the OPTN-no-induction group (2%, $P = 0.68$). Other descriptive analyses are reported in Table 1.

Graft and Patient Survival: OPTN-No-Induction vs OPTN Induction Groups

Graft and patient survival in the OPTN groups were similar regardless of induction use or type. The 1-, 5-, and 10-year graft survival were as follows: no-induction (97%, 89%, 73%), basiliximab (98%, 90%, 77%), thymoglobulin (98%, 91%, 73%), and alemtuzumab (97%, 91%, 56%) ($P = 0.49$) (Figure 2A). The 1-, 5-, and 10-year patient survival were: no-induction (99%, 93%, 82%), basiliximab (99%, 94%, 86%), thymoglobulin (99%, 95%, 78%), and alemtuzumab (99%, 95%, 86%) ($P = 0.49$) (Figure 2B).

After multivariate adjustment for recipient, donor and transplant factors, graft failure risk was not significantly reduced with the use of induction with basiliximab (adjusted hazard ratio [aHR], 0.86; confidence interval [CI], 0.68-1.08; $P = 0.19$), thymoglobulin (aHR, 0.92; CI, 0.70-1.21; $P = 0.55$), or alemtuzumab (aHR, 1.18; CI, 0.72-1.93; $P = 0.51$) compared with OPTN-no-induction. There was also no added patient benefit on mortality risk with basiliximab (aHR, 0.88; CI, 0.65-1.18; $P = 0.38$), thymoglobulin (aHR, 1.04; CI, 0.74-1.47; $P = 0.82$), alemtuzumab (aHR, 1.02; CI, 0.53-1.98; $P = 0.95$) (Table 2). Other correlates of graft failure and death are as listed in **Table S1, SDC** (http://links.lww.com/PRSGO/A374).

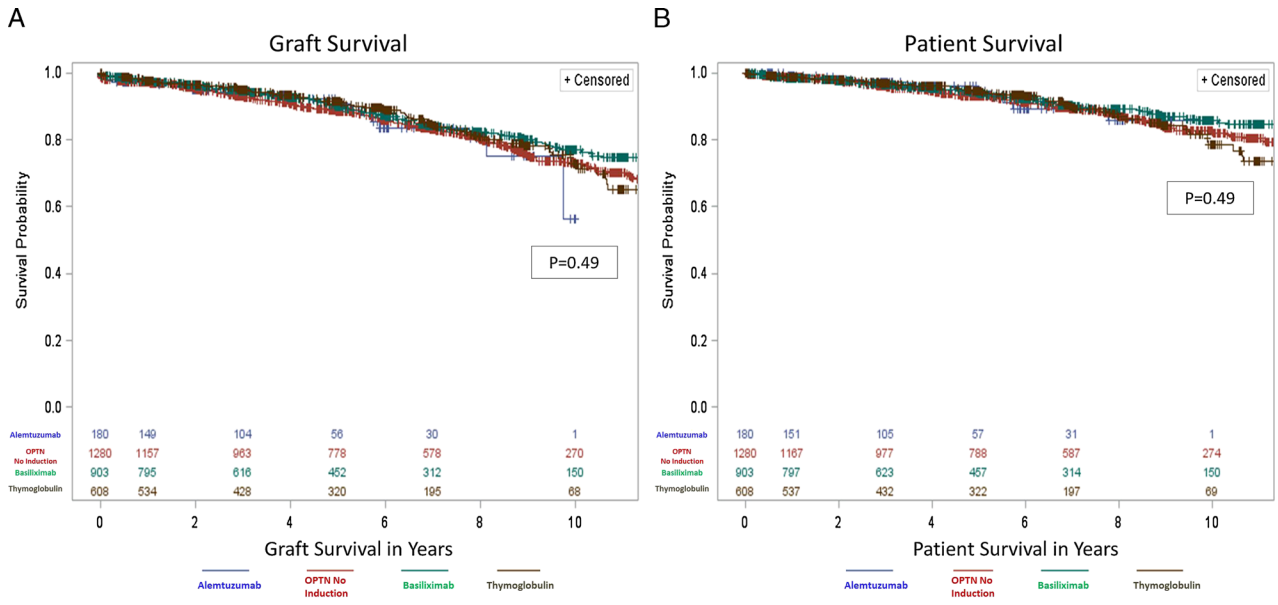


FIGURE 2. Graft and patient survival in the OPTN-no-induction group compared to OPTN induction groups. A, Graft survival. B, Patient survival.

Graft and Patient Survival: Center-no-induction vs OPTN Induction Groups

Kaplan-Meier estimates of graft and patient survival were equivalent between the center-no-induction and the OPTN induction groups. The 1-, 5-, and 10-year allograft survival were as follows: OPTN-basiliximab (98%, 90%, 77%), OPTN-thymoglobulin (98%, 91%, 73%), OPTN-alemtuzumab (97%, 91%, 56%), and center-no-induction (100%, 90%, 90%) ($P = 0.22$) (Figure 3A). Patient survival at 1-, 5-, and 10-year was also similar between the groups ($P = 0.13$) (Figure 3B).

Compared with the center-no-induction group, no improvement in graft survival was noted with basiliximab (HR, 1.63; CI, 0.78-3.4; $P = 0.19$), thymoglobulin (HR, 1.78; CI, 0.85-3.77; $P = 0.13$), or alemtuzumab (HR, 2.03; CI, 0.87-4.77; $P = 0.1$) induction after adjustment including recipient age and sex and donor age. In addition, there was no improvement in patient survival with the use of basiliximab (HR, 2.13; CI, 0.65-6.97; $P = 0.19$), thymoglobulin (HR, 2.8; CI, 0.85-9.25; $P = 0.09$), or alemtuzumab (HR, 2.44; CI, 0.65-9.22; $P = 0.21$) in the national experience compared with center-non-induction (Table 2).

CNI Withdrawal

The kidney graft survival in the center-CNI-withdrawal group at 1, 5, and 10 years was 100%, 89%, and 89%, respectively, and similar to graft survival in the CNI continuation group (100%, 92%, and 92%, respectively, $P = 0.51$) (Figure 4A).

Patient survival in the CNI withdrawal group was 100% at 1, 5, and 10 years and was statistically similar to survival in the CNI continuation group (100%, 96%, and 96%, respectively, $P = 0.64$) (Figure 4B).

TABLE 2.

Adjusted association of induction use and graft failure and patient death

OPTN-no-induction vs OPTN induction groups: adjusted association of induction use

	Graft failure		Patient death	
Induction	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
OPTN no-induction	Reference		Reference	
OPTN basiliximab	0.86 (0.68-1.08)	0.19	0.88 (0.65-1.18)	0.38
OPTN thymoglobulin	0.92 (0.70-1.21)	0.55	1.04 (0.74-1.47)	0.82
OPTN alemtuzumab	1.18 (0.72-1.93)	0.51	1.02 (0.53-1.98)	0.95

Center-no-induction vs OPTN Induction Groups: Adjusted Association of Induction Use

	Graft failure		Patient death	
Induction	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
Center-no-induction	Reference		Reference	
OPTN basiliximab	1.63 (0.78-3.4)	0.19	2.13 (0.65-6.97)	0.19
OPTN thymoglobulin	1.78 (0.85-3.77)	0.13	2.8 (0.85-9.25)	0.09
OPNT alemtuzumab	2.03 (0.87-4.77)	0.1	2.44 (0.65-9.22)	0.21

CVD, cardiovascular disease; GN, glomerulonephritis.

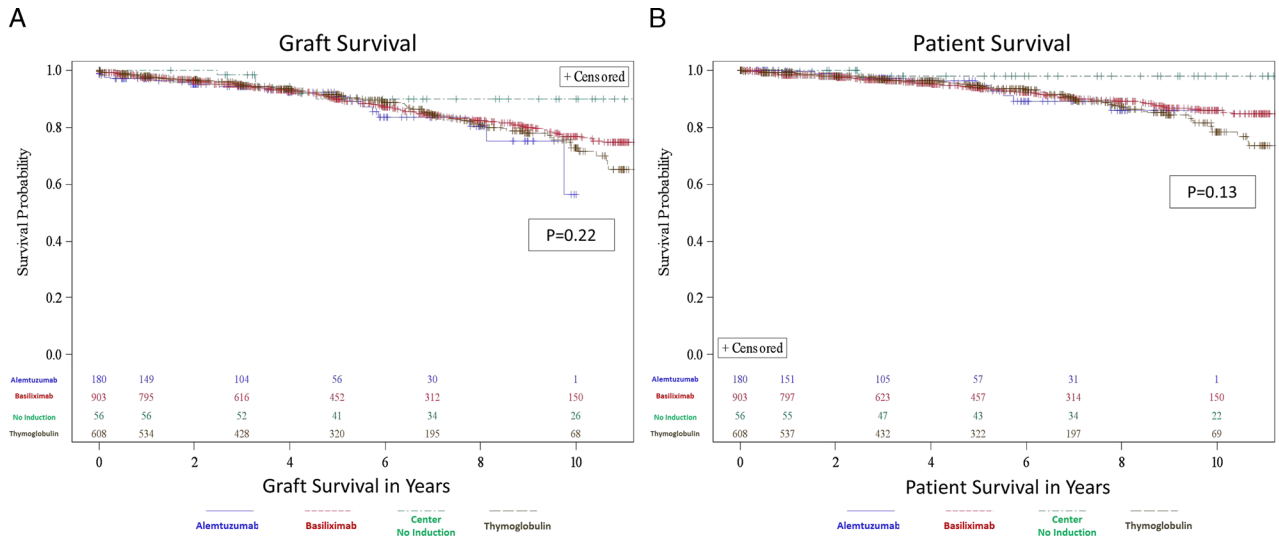


FIGURE 3. Graft and patient survival in the center-no-induction group compared to the OPTN Induction groups. A, Graft survival. B, Patient survival.

Unadjusted Cox analysis showed that CNI withdrawal at 1 year was not associated with increased risk for graft failure (HR, 1.62; CI, 0.38-6.89; P = 0.52) or patient death (HR, 0.56; CI, 0.05-6.31; P = 0.64) compared with CNI continuation.

Secondary Outcomes: Rejection, Malignancy, and Infection

Within 1 year of transplantation, there were 2 patients affected by acute rejection in the center-no-induction group (4%), similar to the rejection rate in the OPTN induction groups (4% basiliximab, 3% thymoglobulin, and 1% alemtuzumab; P = 0.19). Similarly, there was no difference in the rejection rate between the OPTN-no-induction group (3%) and the OPTN induction groups (P = 0.19).

There were no episodes of PTLD in the center-no-induction group, which was not significantly different compared with the OPTN induction groups (1% in each of basiliximab, thymoglobulin, and alemtuzumab groups, P = 0.85). The OPTN-no-induction group had a similar rate of PTLD (1%, P = 0.89).

Similarly, there were no melanoma cases in the center-no-induction group, and no difference in the melanoma rate compared with the OPTN induction groups (1% for basiliximab and thymoglobulin, and 0% alemtuzumab, P = 0.65). The OPTN-no-induction group had a similar rate of melanoma (1%, P = 0.74).

The center-no-induction recipients had lower rates of BK viremia compared to all live donor kidney transplant recipients who received induction at the center (7% vs 17%, P = 0.046). However, the rates of CMV viremia were not different (8% vs 5%, P 0.62).

GN Recurrence

OPTN queries information on recurrent disease only as cause of graft failure. We examined the subjects with ESRD secondary to GN (n = 944) and identified 66 cases with allograft failure. Of these, 35% (n = 23) had graft failure

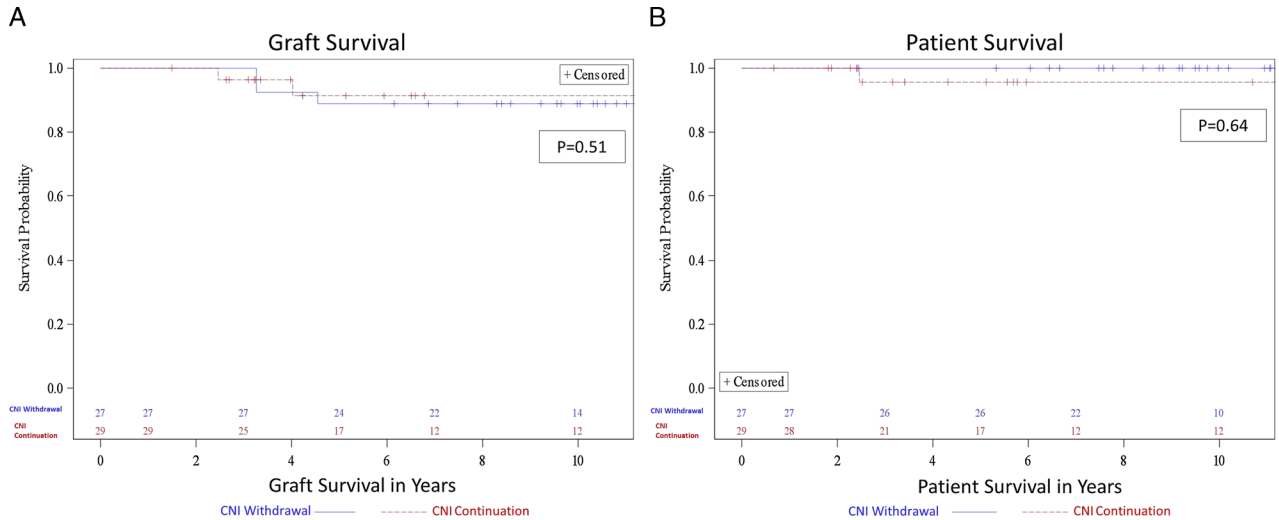


FIGURE 4. Graft and patient survival in the Center-no-induction group stratified by CNI withdrawal at 1 year post-kidney transplantation. A, Graft survival. B, Patient survival.

attributed as due to recurrent disease. Considered by regimen, the proportion of graft losses in patients with primary GN attributed to recurrent disease was as follows, no-induction, 26% (10 of 38); basiliximab, 50% (6 of 12); thymoglobulin 54% (6 of 11); and alemtuzumab 20% (1 of 5) ($P = 0.4$). In our center, no graft failure was attributed to recurrent GN. We do not do protocol biopsies, but among the 21 patients with ESRD secondary to GN, 5 had a kidney biopsy for a cause and only 1 had recurrent GN "FSGS 10 years after transplant," but did not have a graft failure.

DISCUSSION

Overall, acute rejection rates have fallen and renal graft outcomes have significantly improved over the past 15 years with the introduction of antibody induction therapy and CNIs.[15-17] However, such potent immunosuppression may increase the risk of malignancies, infections, and nephrotoxicity.[18-21]

Tailored reduction of immunosuppression in low immunologic risk patients may provide adequate protection against acute rejection while reducing the risks of immunosuppression-related toxicities. However, in the transplant community, there is still no consensus regarding the use or the type of induction therapy that is needed in 2-haplotype HLA matched white kidney transplant recipients. We found wide variation in the use and type of induction among these patients at a national level, with 30% receiving basiliximab, 20% thymoglobulin, 6 % alemtuzumab, and 43% no induction.

The published literature on induction avoidance in these patients is limited. One case series of 6 recipients of 2 haplotype matched living kidney transplants in Spain managed with induction avoidance and CNI withdrawal within 3 to 12 months followed by mycophenolate maintenance showed excellent outcomes, with only 1 episode of rejection over 10 years of follow up.[22] The single rejection event was attributed to medication nonadherence.[22] Glomerular filtration rates were 54, 60, and 62 mL/min per 1.73 m^2 at 3 months, 12 months, and last follow-up, respectively, in that study.[22] Our study reports the largest experience of induction avoidance in a single center, with equivalent outcomes of graft survival observed compared with different induction groups in national experience and no increase in the rate of rejection within the first year (2 patients of 56).

A prospective study of twenty 2-haplotype matched living kidney transplant recipients assessed the 1-year outcomes with antibody induction, steroid avoidance, and subsequent withdrawal of tacrolimus and (or) sirolimus. There were no significant acute rejection episodes observed over the follow-up period and no statistically significant changes in creatinine at 6, 12, and 24 months.[23] A smaller study evaluated 7 patients managed with mycophenolate maintenance monotherapy after antibody induction and subsequent withdrawal of CNIs.[24] There were no episodes of rejection and serum creatinine levels remained relatively unchanged during the follow up period of 5 to 50 months.[24] Another study from the University of Minnesota reported experience with 2-haplotype HLA matched white living kidney transplant recipients before 1984 (antilymphocyte globulin induction and azathioprine-prednisone maintenance), 1984 to 1999 (Minnesota antilymphocyte globulin induction and CNI-mycophenolate-prednisone maintenance), and 1999 to 2011 (thymoglobulin induction and CNI mycophenolate maintenance) with n = 114, 262, and 77, respectively. There was no difference in patient and graft survival between those who did receive CNIs, with a trend toward higher rates of chronic allograft nephropathy in CNI-exposed patients, leading to the conclusion that CNI maintenance was not warranted in this patient population.[25] Our study confirms these earlier findings by showing that CNIs can be withdrawn in white recipients of 2-haplotype matched living related kidneys, but extends these findings by further showing that this privileged group of patients do not require induction therapy. This is an important observation with implications for the immunosuppressive management and overall costs of care for these patients.

Despite the relatively small numbers of CNI withdrawal and CNI continuation groups, the 100% patient survival at 10 years in the CNI withdrawal arm supports the safety of induction avoidance combined with CNI withdrawal at 1 year for long-term survival in 2-haplotype HLA matched recipients. Notably, graft and patient survival with induction avoidance were excellent in patients managed with either CNI withdrawal or continuation, and further study in larger samples is needed to determine if avoiding nephrotoxic agents may provide additional benefits in these low immunologic risk patients.

Our study has several limitations. First, it was not a controlled prospective study, with all the limitations that come with a retrospective study. Second, patients could not be accurately categorized according to CNI continuation at the OPTN level. Therefore, CNI withdrawal was examined only at the single-center level. For secondary outcomes, there were no detailed data on BK or CMV infection available at OPTN; therefore, we used a different control group of living donors to study the effects of induction on these outcomes. Another limitation, melanoma and PTLD might be underreported to the OPTN, and the small number of events limits the power for this comparison.

Our study also has unique strengths. We describe the largest single-center experience of induction avoidance in white recipients of 2-haplotype HLA-matched living related kidney transplants. Furthermore, we compared our experience to a large pool of patients with induction captured in the national OPTN registry and also compared the OPTN-no-induction group to the OPTN induction groups, which adds more strength to the conclusions of the study than if the comparison was done within the center only. Another strength is the 13-year duration of follow-up, which was adequate to see meaningful changes in graft and patient survival.

In summary, long-term single center and national data indicate excellent graft and patient outcomes in 2 haplotype-matched white kidney transplant recipients managed with induction avoidance and CNI withdrawal within the first year of transplantation. This study can serve as a foundation to provide personalized, tailored, immunosuppression for this very low-risk population of kidney transplant patients.

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