Induction Type and Outcomes in HLA-DR Mismatch Kidney Transplantation

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ABSTRACT

Background. In kidney transplantation, donor recipient human leukocyte antigen (HLA)-DR mismatch signals high immunologic risk and portends inferior outcomes. We compared the impacts of depleting vs non-depleting antibody induction on the outcomes in kidney transplant recipients (KTRs) at different levels of HLA-DR mismatches.

Methods. Using the Organ Procurement and Transplantation Network/United Network for Organ Sharing database, we identified adult KTRs from 2001 to 2015 who received induction therapy with either depleting (thymoglobulin/alemtuzumab) or non-depleting (basiliximab/daclizumab) antibody and were discharged on calcineurin inhibitor/mycophenolic acid maintenance. Patients were then stratified by the number of donor-recipient HLA-DR mismatches (0, 1, 2) in both living donor (LD) and deceased donor (DD) KTRs. Under each HLA-DR mismatch category, long-term outcomes were compared for depleting vs non-depleting induction using a Cox model.

Results. A total of 63,821 LD (HLA-DR mismatches: 0, n = 6945 [depleting = 4409, non-depleting = 2536]; 1, n = 19,557 [depleting = 13,558, non-depleting = 6019]; and 2, n = 10,727 [depleting = 7694, non-depleting = 3033]) and 64,922 DD (HLA-DR mismatches: 0, n = 13,915 [depleting = 10,124, non-depleting = 3791]; 1, n = 27,994 [depleting = 20,454, non-depleting = 7540]; and 2, n = 23,013 [depleting = 16,908, non-depleting = 6105]) KTRs were included in the analysis. Adjusted patient death risk was significantly lower in the depleting vs non-depleting antibody induction group among DD kidney recipients (hazard ratio 0.90, 95% CI 0.85–0.96, $P = .001$) and trended lower among LD kidney recipients (HR 0.88, 95% 0.79–1.01, $P = .05$) with 2 HLA-DR mismatches.

Discussion. Our study found a patient survival benefit associated with the use of peri-operative induction with depleting when compared to non-depleting antibody in KTRs with 2 HLA-DR mismatches and maintained on a calcineurin inhibitor/mycophenolic acid regimen.

IN KIDNEY transplantation, donor recipient human leukocyte antigen (HLA)-DR mismatch signals high immunologic risk and portends inferior outcomes. HLA-DR mismatch increases the risk for development of donor-specific antibodies (DSA) and subsequent antibody-mediated rejection [1,2]. Studies have shown associations between HLA-DR mismatches and rejection, transplant glomerulopathy, graft failure, and death with functioning graft following kidney transplantation [3–5]. HLA-DR mismatch was found to be an independent risk factor for the development of de novo DSA and T-cell–mediated rejection among elderly kidney transplant recipients (KTRs) in the Eurotransplant Senior Program, which generally neglects HLA matching in older patients [6]. A meta-analysis

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involving 23 cohort studies and 486,608 patients showed an association between HLA mismatch and an increased risk for overall graft failure, death-censored graft failure, and all-cause mortality [7]. HLA-DR mismatches in particular were significantly associated with worse overall graft survival.

One potential way to overcome the immunologic barrier posed by HLA-DR mismatch is to enhance the intensity of immunosuppression, such as via use of depleting antibody induction in the perioperative period. We aimed to compare the impact of depleting vs non-depleting antibody induction on the outcomes of KTRs at different levels of HLA-DR mismatches.

MATERIALS AND METHODS

The study protocol was approved by the institutional review board. Using the Organ Procurement and Transplantation Network/United Network for Organ Sharing database, we identified adult kidney-only transplant recipients who, from January 2001 to December 2015, received induction therapy with either depleting (thymoglobulin/alemtuzumab) or non-depleting (basiliximab/daclizumab) antibody and were discharged on calcineurin inhibitor/mycophenolic acid (CNI/MMF)-based maintenance immunosuppression. Patients were then stratified by the number of donor-recipient HLA-DR mismatches (0, 1, 2) in both living donor (LD) and deceased donor (DD) KTRs. Under each HLA-DR mismatch group, patients were divided based on whether they received depleting or non-depleting antibody induction. Multiorgan transplant recipients were excluded from the analysis. Similarly, patients who received no induction or different maintenance immunosuppression were excluded.

Using a Cox model adjusting for donor-, recipient-, and transplant-related factors, overall and death-censored graft failure risks along with patient death risk were compared for depleting vs non-depleting antibody induction under each HLA-DR mismatch category in both the LD and DD kidney transplant groups. A subset analysis evaluating graft and patient outcomes was performed for KTRs $\geq$65 years of age. A graft was considered to have failed if the patient went back on maintenance dialysis, underwent re-transplantation, or died. Values are expressed as hazard ratio (HR) with 95% confidence interval (CI). Variables included in the multivariate analysis were as follows: donor-related—age, sex, expanded criteria donor kidney, donation after cardiac death kidney, Kidney Donor Profile Index, and cause of donor death; recipient-related—age, African-American race, diabetes mellitus, body mass index, cause of end-stage kidney disease, dialysis duration, calculated panel reactive antibody, HLA mismatch, and hepatitis B/C sero-status; and transplant related—cold ischemia time, delayed graft function (defined as a need for dialysis within the first week of transplant), previous transplant, kidney on pump, steroid maintenance, and transplant year. Values are expressed as either mean $\pm$ standard deviation or as percentages. A P value of $< .05$ was considered statistically significant. Statistical analysis was performed using SPSS software version 18 (IBM, Armonk, NY, United States).

RESULTS

Median follow-up of the whole study group was 49 $\pm$ 62 months. A total of 63,821 LD and 64,922 DD KTRs were included in the analysis. LD KTRs were further divided into groups based on HLA-DR mismatches and type of induction received, as follows: HLA-DR mismatches, 0 (n = 6945 [depleting = 4409, non-depleting = 2536]; 1 (n = 19,557 [depleting = 13,558, non-depleting = 6019]); and 2 (n = 10,727 [depleting = 7,694, non-depleting = 3033]). DD KTRs were divided as follows: HLA-DR mismatches, 0 (n = 13,915 [depleting = 10,124, non-depleting = 3791]); 1 (n = 27,994 [depleting = 20,454, non-depleting = 7540]); and 2 (n = 23,013 [depleting = 16,908, non-depleting = 6105]). Demographic features of the different HLA-DR mismatch groups are shown in Table 1. Among depleting antibody–induced groups in both LD and DD KTRs across all HLA-DR mismatches, recipients were younger, were more likely to be women and African-American, had higher panel reactive antibodies, and were more likely to have had previous transplants; fewer were on steroid maintenance and were transplanted more recently. Donors were younger and HLA mismatch higher in the depleting antibody–induced group among LD kidney recipients across all HLA-DR mismatches. Among DD kidney recipients, the depleting antibody–induced group had longer dialysis vintage, had a lower incidence of diabetes, received kidneys with a higher Kidney Donor Profile Index, and had a higher proportion of donation after cardiac death kidneys across all HLA-DR mismatch groups.

Adjusted graft and patient outcomes are shown in Table 2. Adjusted graft and patient outcomes were similar for depleting vs non-depleting induction groups under HLA-DR 0 and 1 mismatch categories for both LD and DD kidney recipients (Table 2). For patients with 2 HLA-DR mismatches, adjusted overall graft failure risk was significantly lower in the depleting vs non-depleting induction group in DD kidney recipients (HR 0.93, 95% CI 0.89–0.99, $P = .02$) but similar in LD kidney recipients (HR 0.93, 95% CI 0.84–1.03, $P = .16$), as shown in Table 2. There were no differences in adjusted death-censored graft failure risks. Adjusted patient death risk was significantly lower in depleting vs non-depleting antibody induction group among DD kidney recipients (HR 0.90, 95% CI 0.85–0.96, $P = .001$) and trended inferior among LD kidney recipients with 2 HLA-DR mismatches (HR 0.88, 95% CI 0.78–1.00, $P = .05$) (Table 2).

Among the subset of KTRs $\geq$65 years of age, adjusted overall and death-censored graft failure risks were similar between the induction types under each HLA-DR mismatch category among LD and DD KTRs. However, adjusted patient death risk was significantly lower in the depleting induction group among LD kidney recipients (HR 0.71, 95% 0.50–0.92, $P = .02$) and trended lower in DD kidney recipients with 2 HLA-DR mismatches (HR 0.88, 95% 0.79–1.01, $P = .05$).

DISCUSSION

In KTRs with 2 HLA-DR mismatches maintained on CNI/MMF-based immunosuppression, our analysis showed an association between depleting antibody induction and improved patient survival. This benefit was significant among DD kidney recipients and trended significant in LD recipients. Among the subgroup of KTRs $\geq$65 years of age,

Table 1. Demographic Features

	Living Donor Transplants						Deceased Donor Transplants					
No. of HLA Mismatches	0		1		2		0		1		2	
Induction Type	Depl.	Non-depl.	Depl.	Non-depl.	Depl.	Non-depl.	Depl.	Non-depl.	Depl.	Non-depl.	Dep	Non-depl.
Donor Age (Mean ± SD), y	40 ± 11	41 ± 11†	41 ± 12	41 ± 11*	42 ± 11	43 ± 11*	36 ± 15	35 ± 16	38 ± 16	38 ± 16	40 ± 18	40 ± 17
Donor Sex (M)%	42	41	40	39	37	36	61	61	59	60	59	59
Average KDPI (%)	-	-	-	-	-	-	40 ± 26	39 ± 26*	47 ± 27	46 ± 28†	52 ± 28	50 ± 28†
ECD Kidney (%)	-	-	-	-	-	-	8	9	15	15	24	22*
DCD Kidney (%)	-	-	-	-	-	-	10	7†	14	10†	13	8†
HLA Mismatch	1.4 ± 1.2	1 ± 1.1†	3.2 ± 1	3.1 ± 1*	5.1 ± .8	5.1 ± .8	1.5 ± 1.6	1.5 ± 1.6	4 ± 1	3.9 ± 1*	5.2 ± .8	5.2 ± .8
Recipient Age (Mean y ± SD)	46 ± 14	47 ± 14†	48 ± 14	49 ± 15†	47 ± 13	49 ± 14†	51 ± 13	52 ± 14†	52 ± 13	53 ± 14†	52 ± 13	54 ± 14†
Recipient Sex (M)%	55	60†	59	64†	62	68†	54	61†	59	66†	60	64†
Recipient African American (%)	13	9.3†	15	12†	15	13*	21	17†	35	16†	39	31†
Recipient Diabetes (%)	26	26	29	29	28	27	32	35†	32	34*	33	35*
Dialysis Duration (Mean ± SD), mo	16 ± 28	14 ± 21*	16 ± 27	15 ± 25†	16 ± 25	16 ± 23	41 ± 39	37 ± 37†	52 ± 41	47 ± 40†	55 ± 42	51 ± 42†
Calculated PRA	14 ± 29	7 ± 20†	9.5 ± 23	4 ± 14†	8 ± 21	3 ± 12†	32 ± 40	12 ± 27†	19.8 ± 33	7.4 ± 20†	16.6 ± 30	6.4 ± 19†
Cold Ischemia Time, h	4.7 ± 6	4.7 ± 6	4.7 ± 6	4.7 ± 6	4.7 ± 6	4.7 ± 7	18 ± 8	18 ± 9	17.6 ± 9	17.9 ± 10*	17.6 ± 9	17.2 ± 9*
Delayed Graft Function (%)	3	3	3	4	3	5*	22	20	26	25*	29	28
Steroid Maintenance (%)	55	79†	54	85†	55	86†	67	87†	67	89†	69	89†
Previous Transplant History	16	8†	12	6†	11	6†	22	10†	14	6†	11	6†
Transplant Year	2008 ± 4	2007 ± 4†	2008 ± 4	2007 ± 4†	2008 ± 4	2007 ± 4†	2009 ± 4	2006 ± 4†	2009 ± 4	2007 ± 4†	2008 ± 4	2007 ± 4†

Abbreveation: DCD, donation after cardiac death; depl, Depleting; ECD, expanded criteria kidney; HLA, human leukocyte antigen; KDPI, kidney donor profile index; non-depl, non-depleting; M, men; PRA, panel reactive antibodies.

*$P < .05$.

†$P < .001$.

Table 2. Adjusted Graft and Patient Outcomes for Depleting vs Non-depleting Induction Type Under Different HLA-DR Mismatch Groups

	Living Donor Transplant			Deceased Donor Transplant		
No. of HLA-DR Mismatch	0	1	2	0	1	2
Depleting (n)	4409	13,558	7694	10,124	20,454	16,908
Non-depleting (n)	2536	6019	3033	3791	7540	6105
Outcomes (Hazard Ratio [95% Confidence Interval])						
Overall Graft Failure Risk	1.06 (0.93–1.20) $P = .39$	1.02 (0.95–1.10) $P = .54$	0.93 (0.84–1.03) $P = .16$	0.97 (0.89–1.04) $P = .39$	0.96 (0.92–1.014) $P = .151$	0.93 (0.89–0.99) $P = .02$
Death-censored Graft Failure Risk	1.05 (0.88–1.26) $P = .60$	0.995 (0.90–1.09) $P = .90$	0.97 (0.85–1.10) $P = .6$	0.97 (0.87–1.09) $P = .60$	0.99 (0.92–1.06) $P = .77$	0.97 (0.90–1.05) $P = .4$
Patient Death Risk	1.08 (0.92–1.25) $P = .34$	1.04 (0.95–1.13) $P = .40$	0.88 (0.78–1.0) $P = .05$	0.95 (0.88–1.04) $P = .26$	0.97 (0.91–1.03) $P = .29$	0.90 (0.85–0.96) $P = .001$

patient survival benefit associated with depleting antibody induction was significant among LD kidney recipients and trended superior among DD kidney recipients. There were no differences in death-censored graft survival among any of the groups.

Two mismatches at the HLA DR locus is considered to indicate high immunologic risk in kidney transplantation. Kidney Disease Improving Global Outcomes clinical practice guidelines for the care of kidney transplant recipients recommend using induction with a lymphocyte-depleting agent in high-immunologic-risk recipients [8]. In a prospective study involving DD KTRs at high risk for rejection, depleting induction with anti-thymocyte globulin resulted in significant reduction in the incidence and severity of acute rejection when compared to non-depleting induction with basiliximab [9]. In a single-center study involving predominantly African-American KTRs, 2 mismatches at HLA-DR significantly lowered actuarial graft survival, an effect that was diminished in patients who received anti-thymocyte globulin induction [10]. Patient survival was not reported in that study. Our study showed a patient- but not death-censored graft survival benefit associated with depleting induction in HLA-2DR mismatch KTRs. One could speculate that better allograft function from reduced ongoing inflammation as a result of more robust immunosuppression with depleting antibody induction is a potential explanation for the survival benefit in these patients. A previous large study demonstrated a strong graded association between reduced estimated glomerular filtration rate and increased risk of death [11].

Older KTRs are generally considered at increased risk for adverse consequences of enhanced immunosuppression. However, the patient survival benefit of depleting antibody induction in our analysis was extended to elderly KTRs with 2 HLA-DR mismatches. As mentioned, HLA-DR mismatch was found to be associated with adverse immunologic outcomes among elderly KTRs in the Eurotransplant Senior Program [6]. Recent studies have shown that HLA-DR/DQ molecule eplet mismatch in particular had a significant association with increased risk for developing de novo DSA, antibody/T-cell mediated rejection, and worse overall graft survival and may be a precise prognostic biomarker that can be used to tailor immunosuppression [12].

CONCLUSION

Our study found that a patient survival benefit was associated with the use of perioperative induction with depleting antibody in KTRs with 2 HLA-DR mismatches and maintained on a CNI/MMF regimen. The study's limitations include the retrospective study design, lack of granularity on variables such as immunosuppressive medication dosages and therapeutic drug levels, and the possible influence of residual confounding.

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