ORIGINAL ARTICLE

Outcomes of induction antibody therapies in the nonbroadly sensitized adult deceased donor kidney transplant recipients: a retrospective cohort registry analysis

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SUMMARY

The outcomes of lymphocyte-depleting antibody induction therapy (LDAIT), [thymoglobulin (ATG) or alemtuzumab (ALM)] versus interleukin-2 receptor antagonist (IL-2RA) in the nonbroadly-sensitized [pretransplant calculated panel reactive antibody (cPRA), <80%] adult deceased donor kidney transplant recipients (adult-DDKTRs) are understudied. In this registry, study of 55 593 adult-DD-KTRs, outcomes of LDAIT [(ATG, N = 32 985) and (ALM, N = 9429)], and IL-2RA (N = 13 179) in <10% and 10–79% cPRA groups was analyzed. Adjusted odds ratio (aOR) of one-year biopsy-proven acute rejection (BPAR) was lower; while, aOR of 1-year composite of re-hospitalization, graft loss, or death was higher with LDAIT than IL2-RA in both cPRA groups. Adjusted odds ratio (aOR) of delayed graft function was higher with LDAIT than IL-2RA in the <10% cPRA group. Adjusted hazard ratio (aHR) of 5-year death-censored graft loss (DCGL) in both <80% cPRA groups seemed higher with ALM than other inductions [(<10% cPRA: ALM versus IL2RA, aHR = 1.11, 95% CI = 1.00–1.23 and ATG versus ALM: aHR = 0.84, 95% CI = 0.77–0.91; 10–79% cPRA: ALM versus IL2RA, aHR = 1.29, 95% CI = 1.02–1.64; and ATG versus ALM, aHR = 0.83, 95% CI = 0.70–0.98)]. Five-year aHR of death did not differ among induction therapies in both cPRA groups. In nonbroadly sensitized adult-DDKTRs, LDAIT is more protective against 1-year BPAR (not 5-year mortality) than IL-2RA; the trend of a higher 5-year DCGL risk with ALM than ATG or IL-2RA needs further investigation.

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Key words
anti-IL-2R, histocompatibility and immunogenetics, immunosuppression clinical, kidney clinical, other, other monoclonals, outcome, pre-sensitisation, rejection

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Introduction

The main aim of induction immunosuppressive therapy at kidney transplantation is to avoid early acute rejection which increases the risk of allograft loss [1,2]. Studies have established the differences in the impact of induction regimens based on risk factors such as age, recipient race, primary diagnosis, transplantation period, and

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sensitization [2–6]. In clinical trials, panel reactive antibody (PRA) had been the most frequently used parameter to identify the sensitized KTRs who are more likely to suffer rejections, graft losses, cancers, and deaths than the unsensitized kidney transplant recipients (KTRs) [7–10]. In 2007, the calculated PRA (cPRA) has been introduced and eventually replaced PRA in the US kidney transplant allocation system [11]. Since PRA and cPRA differ in derivation and clinical interpretation, the applicability of induction therapy selection recommendations anchored on the "old" PRA allocation system to the "newer" cPRA allocation system is unknown [12,13].

Immunosuppression induction agents commonly used in kidney transplantation include the lymphocyte-depleting agents: rabbit anti-thymocyte globulin (ATG) and alemtuzumab (ALM), and the nonlymphocyte-depleting agents, interleukin-2 receptor antagonist (IL-2RA; currently basiliximab only, but previously also included daclizumab) [4,15]. Randomized clinical trials have shown that lymphocyte-depleting antibody induction therapies (LDAITs) lower acute rejection rates better than IL-2RA [15,16]. A pre-2007 meta-analysis of patient-level data had shown that among the various risk factors for graft loss [including human leukocyte antigen (HLA)-DR mismatch, delayed graft function (DGF), African American ethnicity, and diabetes mellitus] only presensitization as determined by PRA level is benefited by LDAIT [17]. Consistent with this and similar studies, guidelines and experts' opinions favor LDAIT in the sensitized, and IL-2RA induction in the unsensitized KTRs [12,14,18,19]. However; in US transplant centers, LDAs appear to be the preferred induction agents regardless of the KTRs' sensitization status based on their risk factors [1,20,21]. As we observed in the 2016 Scientific Registry of Transplant Recipients' (SRTRs) annual data report, a majority (>70%) of deceased donor KTRs received LDAITs; although only 18% had cPRAs >80% and 13% were re-transplants recipients [22].

Although transplant practitioners may be confident in choosing a LDAIT for the broadly sensitized (≥80% cPRA) KTRs [11], the disparity between expert recommendations and prevailing practice may create a dilemma for clinicians when planning induction immunosuppression in the average-risk nonbroadly sensitized KTR. Therefore, using SRTR data from 2007 to 2017, we studied the adjusted risks of LDAIT versus IL-2RA induction for graft loss, patient death, acute rejection, re-hospitalization, and delayed graft function (DGF)] in nonbroadly sensitized adult-DDKTRs [11], stratified into <10% and 10–79% cPRA groups [21,22]. Our findings would be informative to transplant clinicians on the risks and outcomes of LDAIT and IL-2RA induction in nonbroadly sensitized adult-DDKTRs in the context of the cPRA allocation system.

Patients and methods

Data source

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR system includes data on all donor, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere [21]. The Health Resources and Services Administration provides oversight to the activities of the OPTN and SRTR contractors. This study was approved by the University of Rhode Island Institutional review board.

Study design and population

This is an observational cohort study based on pre-existing data from the SRTR that included patients age 18 years and older who received a deceased donor (DD) kidney transplant (KT) between 1 January 2007 and 31 December 2017 and had a recorded pretransplant calculated panel reactive antibody (cPRA). Only adult-DDKTRs who received immunosuppression induction therapy with LDAIT [anti-thymocyte globulin (ATG) or alemtuzumab (ALM)] or an interleukin-2 receptor antagonist (IL-2RA), basiliximab or daclizumab; discharged on a maintenance immunosuppression regimen consisting of a calcineurin inhibitor (CNI), (cyclosporine or tacrolimus), and mycophenolic acid (MPA) with or without steroids; and had a pretransplant cPRA <80% were included in this study. KTRs were excluded from analysis if they had not received one or had received an induction agent other than ATG, ALM, or IL-2RA; had received living donor or combined organ transplants; had missing record/s of induction therapy or cPRA; or had experienced graft loss or died within the first 7 days after receiving a kidney transplant. Consistent with the cPRA categorization in the SRTR program-specific technical report, adult-DDKTRs were categorized into the <10% and 10–79% groups based on their cPRA prior to kidney transplant [22].

Outcomes and measurements

Primary outcomes were overall graft survival, death-censored graft survival, and patient survival in the 5 years

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following kidney transplant. Overall graft survival was defined as the time from transplantation to return to dialysis, re-transplantation, death, or last follow-up with a functioning graft censored for 5 year post-transplantation. Death-censored graft survival was defined as the time from transplantation to return to dialysis, re-transplantation, or last follow-up with a functioning graft censored for the first of either death or 5-year post-transplantation. Patient survival was defined as the time from transplantation to death or last follow-up, censored for 5-year post-transplantation. Secondary outcomes were delayed graft function (DGF) defined as the need for dialysis in the first week of transplant; re-hospitalization within the year following transplant surgery; composite of re-hospitalization, graft loss, and death within the year following transplant surgery; biopsy-proven acute rejection (BPAR) within the year following transplant surgery; composite of BPAR, graft loss, and death within the year following transplant surgery; and de novo solid malignancy and lymphoma (referred to as malignancy) within 5 years following transplant surgery.

Statistical analysis

Baseline categorical data were presented as frequencies and percentages. Unadjusted Kaplan–Meier (KM) curves were used to analyze time-to-event survival functions for overall and death-censored graft survival, and patient survival in the 5 years following KT comparing induction subgroups using univariate log-rank tests within the <10% and 10–79% cPRA groups. Multivariable Cox regression hazards models (Cox models) were used to analyze the associations of induction with overall and death-censored allograft loss (OAGL and DCGL, respectively), and patient death in the five years following kidney transplant. Results were reported as hazard ratio (HR) with a 95% confidence interval (CI). Unadjusted DGF, BPAR, re-hospitalization, or malignancy incidence rates were compared between induction subgroups using chi-square test and Marascuilo's procedure for comparing multiple proportions. The likelihood of DGF; one-year BPAR; one-year composite of BPAR, graft loss, and death; one-year re-hospitalization; and one-year composite of re-hospitalization, graft loss, and death associated with induction agents were analyzed using multivariable logistic regression models. Results were reported as odds ratio (OR) with 95% CI. The likelihood of malignancy was not analyzable by multivariable logistic regression due to low incidence rates in most induction subgroups. All covariates in the multivariable Cox and logistic regression models (as enumerated in Table 1) were selected a priori based on their clinical relevance.

For sensitivity analyses, propensity score (PS) method was used to control for confounding bias in the ascertainment of induction therapies. PS is the multinomial logistic regression-derived conditional probability of a KTR being given an induction therapy based on pre-existing or predetermined potentially confounding variables [23]. In this study, the inverse probability of treatment weight (IPTW), derived from the inverse of the computed PS, was used to generate a pseudo-population, in which the exposure variable became independent of all adjusted covariates [23]. To remove confounding due to residual imbalance, PS-weighted logistic and Cox regression models were fitted to analyze causal associations of induction therapies with outcomes.

In all analyses, statistical significance was based on a 2-sided P-value of ≤ 0.05 adjusted whenever appropriate for multiple comparisons using Benjamini and Hochberg's false discovery rate (FDR) method denoted as P_{adj} [24]. Analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Study population

There were 55 593 adult-DDKTRs included in the analysis. Induction immunosuppression was ATG in 32 985 (59.33%), alemtuzumab in 9429 (16.96%), and IL-2RA in 13 179 (23.71%) of KTRs. IL2-RA agent utilization was higher in the cPRA < 10% than 10–79% cohort (25.9% vs. 14.8%). ATG, ALM induction and steroid maintenance immunosuppression utilization rates increased with the cPRA strata (Table 1). The baseline demographic and transplant-related clinical characteristics for adult-DDKTRs categorized by induction agent in the cPRA subgroups are presented in Tables S1 and S2.

Induction agents and primary outcomes in cPRA groups

Overall graft survival

In the <10% cPRA group, the unadjusted Kaplan–Meier (KM) 5-year overall graft survival (OAGS) probabilities were 81.6% for ATG, 80.9% for ALM, and 80.3% for IL-2RA ($P = 0.012$). Differences between induction subgroups were very small, ranging from 0.64% to 1.32%,

Table 1. Baseline patient and transplant characteristics.

Risk factor	Calculated panel reactive antibody (cPRA) cohort	
	cPRA 0–9% *N* = 44 653 *N* (%)	cPRA 10–79% *N* = 10 940 *N* (%)
Induction antibody		
Anti-thymocyte globulin	25 552 (57.22)	7433 (67.94)
Alemtuzumab	7541 (16.89)	1888 (17.26)
IL-2RA	11 560 (25.89)	1619 (14.80)
KDRI (Rao)		
<0.96	12 346 (27.65)	3108 (28.41)
0.96–1.14	10 872 (24.35)	2921 (26.70)
1.15–1.44	14 026 (31.41)	3310 (30.26)
≥1.45	7409 (16.59)	1601 (14.63)
Recipient age		
18–49 years	15 432 (34.56)	4196 (38.35)
50–64 years	19 267 (43.15)	4653 (42.53)
≥65 years	9954 (22.29)	2091 (19.11)
Recipient sex		
Female	14 369 (32.18)	5703 (52.13)
Male	30 284 (67.82)	5237 (47.87)
Recipient BMI (kg/m^2)		
<30	28 793 (64.48)	6966 (63.67)
≥30	15 860 (35.52)	3974 (36.33)
Recipient ethnicity		
White	18 746 (41.98)	4326 (39.54)
African American	14 720 (32.97)	3947 (36.08)
Hispanic	7153 (16.02)	1652 (15.10)
Other	4034 (9.03)	1015 (9.28)
Primary diagnosis		
Hypertension	12 505 (28.00)	3035 (27.74)
Glomerulonephritis	9330 (20.89)	2709 (24.76)
Diabetes mellitus	13 479 (30.19)	2761 (25.24)
Polycystic kidney dis.	3851 (8.62)	901 (8.24)
Other	5396 (12.08)	1469 (13.43)
Missing	92 (0.21)	65 (0.59)
Dialysis history		
None	3839 (8.60)	912 (8.34)
1–730 days	9094 (20.37)	1993 (18.22)
>730 days	31 720 (71.04)	8035 (73.45)
HLA mismatch/es		
0	2274 (5.09)	1450 (13.25)
1–3	7589 (17.00)	1842 (16.84)
4–6	34 790 (77.91)	7648 (69.91)
Transplant year		
2007–2011	23 167 (51.88)	4524 (41.35)
2012–2017	21 486 (48.12)	6416 (58.65)
Kidney re-transplant		
No	42 525 (95.23)	9127 (83.43)
Yes	2128 (4.77)	1813 (16.57)
Steroids, maintenance immunosuppression		
No	14 556 (32.60)	2667 (24.38)
Yes	30 097 (67.40)	8273 (75.62)
Maintenance regimen		
CSA + MPA	1504 (3.47)	243 (2.22)
Tac + MPA	43 149 (96.63)	10 697 (97.78)
Primary insurance		
Private	11 036 (24.72)	2477 (22.64)
Public	33 556 (75.15)	8443 (77.18)
Other	61 (0.14)	20 (0.18)
Cold ischemia time		
<20 h	28 973 (64.88)	7329 (66.99)
≥20 h	15 038 (33.68)	3499 (31.98)

BMI, body mass index; cPRA, calculated panel reactive antibody; CSA, cyclosporine; HLA, human leukocyte antigen; IL-2RA, interleukin-2 receptor antagonist; KDI, kidney donor risk index; MPA, mycophenolate; Tac., tacrolimus.

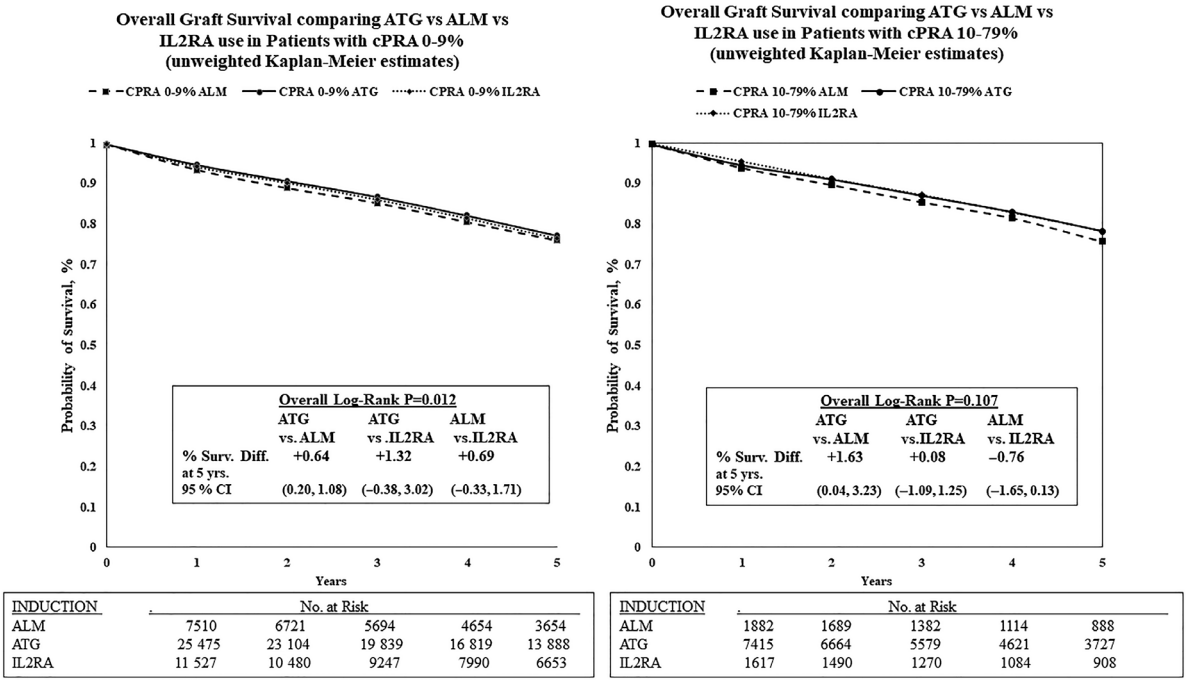
Test of significant difference between cPRA 0–9% and 10 = 79% cPRA groups are all significant ($P < 0.001$), except for BMI, $P = 0.114$.

and there was a negligible difference between ATG versus ALM (diff. = 0.64%, 95% CI = 0.20–1.08; Fig. 1). However, on multivariable analyses, the risk of overall graft loss (OAGL) with ATG was lower than ALM induction by 10% and 14% in the unweighted and IPTW-weighted Cox analyses, respectively, [(HR = 0.90, 95% CI = 0.84–0.96) and (HR = 0.86, 95% CI = 0.81–0.92), respectively] while the OAGL risk with ALM was either suggestively or significantly higher than IL-2RA induction in the unweighted and IPTW-weighted Cox analyses, respectively [(HR = 1.06, 95% CI = 0.99–1.14, $P_{adj} = 0.182$) and (HR = 1.14, 95% CI = 1.07–1.22; $P_{adj} < 0.001$), respectively] (Table 2).

In the 10–79% cPRA group, the unadjusted KM 5-year OAGS probabilities were 83.2% for ATG, 81.6% for ALM, and 82.3% for IL-2RA ($P = 0.107$). Differences between induction subgroups were small (ranging from −0.76% to 1.63%), and none of the comparisons between induction subgroups was significant (Fig. 1). On multivariable analysis, the risk of OAGL did not differ between induction agents, although ATG trended toward a lower risk of OAGL than ALM on the IPTW-weighted Cox analysis (HR = 0.88, 95% CI = 0.78–0.98; $P_{adj} = 0.051$; Table 2).

Death-censored graft survival

In the <10% cPRA group, the unadjusted KM 5-year death-censored graft survival (DCGS) probabilities were 90.4% for ATG, 88.9% for ALM and 90.2% for IL-2RA



INDUCTION	No. at Risk				
ALM	7510	6721	5694	4654	3654
ATG	25 475	23 104	19 839	16 819	13 888
IL2RA	11 527	10 480	9247	7990	6653

INDUCTION	No. at Risk				
ALM	1882	1689	1382	1114	888
ATG	7415	6664	5579	4621	3727
IL2RA	1617	1490	1270	1084	908

Figure 1 Overall graft survival comparing ATG versus ALM, versus IL2RA in patients with cPRA 0–9% (left panel). Overall graft survival comparing ATG versus ALM, versus IL2RA in patients with cPRA 10–79% (right panel). ALM, alemtuzumab; ATG, anti-thymocyte globulin; cPRA, calculated panel reactive antibody; IL2RA, interleukin-2 receptor antagonist.

($P < .001$; Fig. 2). On induction subgroup comparisons, ALM had a minimally lower DCGS probability than ATG or IL-2RA [(diff. = −1.4%, 95% CI = −0.70 to −0.21) and (diff. = −1.3%, 95% CI = −1.96 to −0.64)]; respectively; Fig. 2). On multivariable analyses, ALM had a suggestively or significantly higher risk of death-censored graft loss (DCGL) than IL-2RA or ATG in the unweighted and IPTW-weighted Cox models (Table 2). The DCGL risks were similar between ATG and IL-2RA in the unweighted Cox model (HR = 0.94, 95% CI = 0.87–1.01; $P_{adj} = 0.182$), but lower for ATG in the IPTW-weighted Cox model [(HR = 0.92, 95% CI = 0.86–0.99; $P_{adj} = 0.050$)], (Table 2).

In the 10–79% cPRA group, the unadjusted KM 5-year DCGL probabilities were 91.0% for ATG, 89.4% for ALM, and 92.2% for IL-2RA ($P = 0.002$), as in above, ALM had a minimally lower DCGS probability than ATG or IL-2RA [(diff. = −1.66%, 95% CI = −0.35 to −0.30) and (diff. = −2.81%, 95% CI = −4.42 to −1.20)]; respectively; Fig. 2). On multivariable analyses, ATG and IL-2RA had similar DCGL risks (Table 2). Compared with IL-2RA; ALM had a trend of a higher DCGL risk (HR = 1.29, 95% CI = 1.02–1.64; $P_{adj} = 0.094$) on the unweighted Cox model, not supported by the IPTW-weighted Cox model (HR = 1.02, 95% CI = 0.84–1.25; $P_{adj} = 0.900$). ALM had a suggestively higher risk of DCGL than ATG in both the unweighted and IPTW-weighted Cox models, respectively [(ATG versus ALM (ref): HR = 0.83, 95% CI = 0.70–0.98; $P_{adj} = 0.084$) and (ATG versus ALM (ref.): HR = 0.84, 95% CI = 0.72–0.97; $P_{adj} = 0.050$)], (Table 2).

Patient survival

In the <10% CPRA group, the unadjusted KM 5-year patient survival probabilities were slightly higher with ATG (89.8%) and ALM (90.6%) than IL-2RA (88.2%); [(diff. = 1.61%, 95% CI = 0.7–2.52) and (diff. = 2.41%, 95% CI = 0.97–3.85); respectively] and similar between ATG and ALM (diff. = 0.8%, 95% CI = −2.99 to 1.39; Fig. 3). In the 10–79% CPRA group, the unadjusted KM 5-year patient survival probabilities ranging from 89.4% to 90.9% did not differ among and between induction subgroups (Fig. 3). On multivariable analyses, the risk of patient death did not differ between induction agents in both the <10% and 10–79% CPRA groups (Tables 3).

Induction agents and secondary outcomes in cPRA groups

Re-hospitalization in the first post-transplant year

The rate of re-hospitalization within 1 year of kidney transplant among adult-DDKTRs with <10% cPRA were

Table 2. Induction outcomes based on multivariable Cox regression models in non-broadly sensitized adult deceased-donor kidney transplant recipients.

	ATG versus IL-2RA (ref.)			ALM versus IL-2RA (ref.)			ATG versus ALM (ref.)		
Outcome	HR	95% CI	P_{adj}	HR	95% CI	P_{adj}	HR	95% CI	P_{adj}
cPRA < 10%									
Graft loss, overall									
Uwtd	0.98	0.92–1.02	0.260	1.06	0.99–1.14	0.182	0.90	0.84–0.96	0.004
IPTW-PS	0.95	0.90–1.00	0.076	1.14	1.07–1.22	<0.001	0.86	0.81–0.92	<0.001
Graft loss, DC									
Uwtd	0.94	0.87–1.01	0.182	1.11	1.00–1.23	0.108	0.84	0.77–0.91	0.004
IPTW-PS	0.92	0.86–0.99	0.050	1.26	1.16–1.38	<0.001	0.79	0.73–0.86	<0.001
Patient death									
Uwtd	0.99	0.90–1.10	0.600	0.97	0.91–1.04	0.906	0.97	0.89–1.06	0.689
IPTW-PS	0.96	0.90–1.02	0.300	1.06	0.97–1.16	0.298	0.93	0.86–1.01	0.164
Outcome	HR	95% CI	P_{adj}	HR	95% CI	P_{adj}	HR	95% CI	P_{adj}
cPRA 10–79%									
Graft loss, overall									
Uwtd	1.02	0.90–1.17	0.811	1.15	0.97–1.36	0.182	0.88	0.78–1.00	0.116
IPTW-PS	0.97	0.86–1.10	0.736	0.97	0.84–1.12	0.749	0.88	0.78–0.98	0.051
Graft loss, DC									
Uwtd	1.09	0.90–1.32	0.552	1.29	1.02–1.64	0.094	0.83	0.70–0.98	0.084
IPTW-PS	0.94	0.79–1.11	0.644	1.02	0.84–1.25	0.900	0.84	0.72–0.97	0.050
Patient death									
Uwtd	1.04	0.87–1.23	0.755	1.09	0.87–1.37	0.600	0.95	0.80–1.13	0.689
IPTW-PS	1.06	0.89–1.25	0.679	1.04	0.85–1.27	0.813	0.92	0.79–1.08	0.476

ATG, anti-thymocyte globulin; cPRA, calculated panel reactive antibody; DC, death-censored; DGF, delayed graft function; IL2-RA, interleukin-2 receptor antagonist; IPTW-PS, inverse probability of treatment weighted, propensity score model; Pt. Est.: Hazard ratio for overall graft loss, death-censored graft loss, and death and Odds ratio for hospitalization, delayed graft function, and acute rejection; Test of statistical significance 2-tailed alpha = 0.05: P_{adj}, *P*-value adjusted for multiple comparisons based on False Discovery Rate method, Benjamini, Y. & Hochberg, Y; uwtd., unweighted model.

Models were adjusted for the following covariates: kidney donor risk index (KDRI), (Rao) <0.96, 0.96 to <1.15, 1.15 to <1.45, ≥1.45; Recipient Age, years: 18–49, 50–64, ≥65; Recipient BMI in kg/sq.m.: <30, ≥30; recipient race: white, African American, Hispanic, other; primary diagnosis: diabetes mellitus, hypertension, glomerulonephritis, polycystic kidney disease and other; pre-transplant dialysis duration: 1 day–2 years, >2 years, no dialysis; number of HLA mismatches: 0–, 1–3, 4–6; transplant year: 2007–2010 or 2011–2015; re-transplant versus first transplant; steroids or none in maintenance immunosuppression; maintenance regimen: calcineurin inhibitor + mycophenolate, mammalian target of rapamycin-containing, other, none; Primary insurance: private, medicare or medicaid, and other; cold ischemia time: 0 to <20 h, ≥20 h.

42.1% for ATG (10 760/25 552), 40.5% for ALM (3056/7541), and 39.5% for IL-2RA (4561/11 560) induction subgroups, ($P < .001$; Table 3). In the <10% cPRA group, odds for 1-year re-hospitalization with ATG was higher than IL-2RA in both the unweighted and IPTW-weighted logistic regression models (LRM), and ALM in the unweighted LRM only (Table 4).

In the 10–79% cPRA group, re-hospitalization rates within 1 year of kidney transplantation were 41.7% for ATG (3101/7433), 42.5% for ALM (803/1888), and 37.9% for IL-2RA (614/1619) induction subgroups, ($P = 0.009$; Table 3). On multivariable analysis in the 10–79% cPRA group, the odds of re-hospitalization within one year of deceased donor kidney transplant were higher for ALM than IL-2RA induction in the IPTW-weighted LRM (Table 5).

In both the <10% and 10–79% cPRA groups, odds of 1-year composite of re-hospitalization, graft loss, and death were higher with ATG or ALM than IL-2RA and similar between ATG and ALM (Tables 4 and 5, respectively).

Delayed graft function

DGF rates in the <10% CPRA and 10–79% CPRA groups are shown in Table 3. On multivariable analyses, the odds of DGF in KTRs with <10% cPRA were lower with ATG than ALM induction (Table 4) and higher

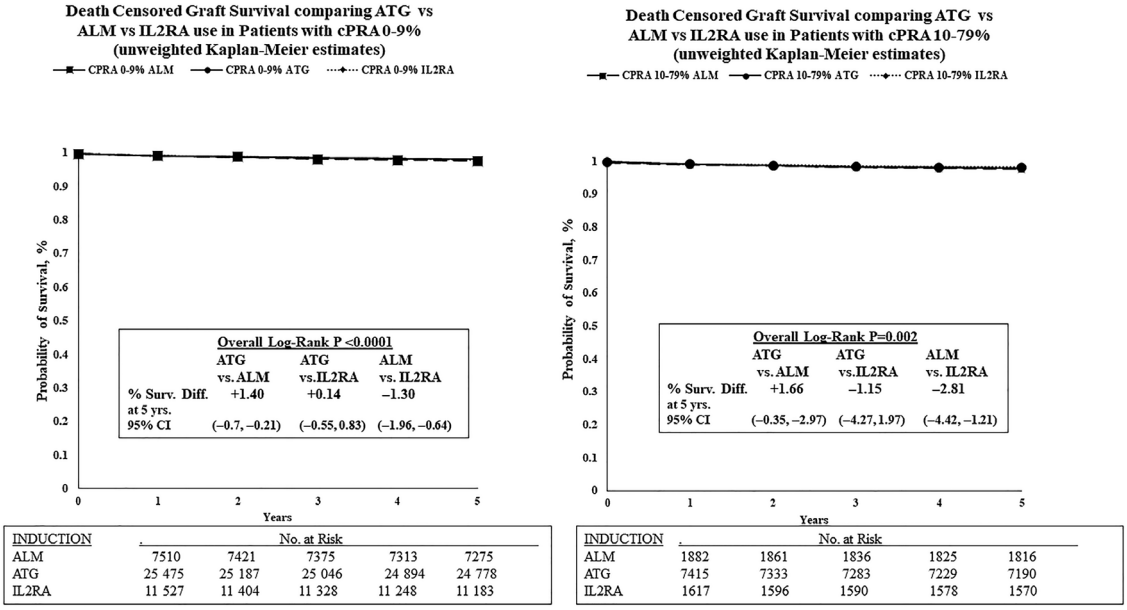


Figure 2 Death-censored graft survival comparing ATG versus ALM, versus IL2RA in patients with cPRA 0–9% (left panel). Death-censored graft survival comparing ATG versus ALM, versus IL2RA in patients with cPRA 10–79% (right panel). ALM, alemtuzumab; ATG, anti-thymocyte globulin; cPRA, calculated panel reactive antibody; IL2RA, interleukin-2 receptor antagonist.

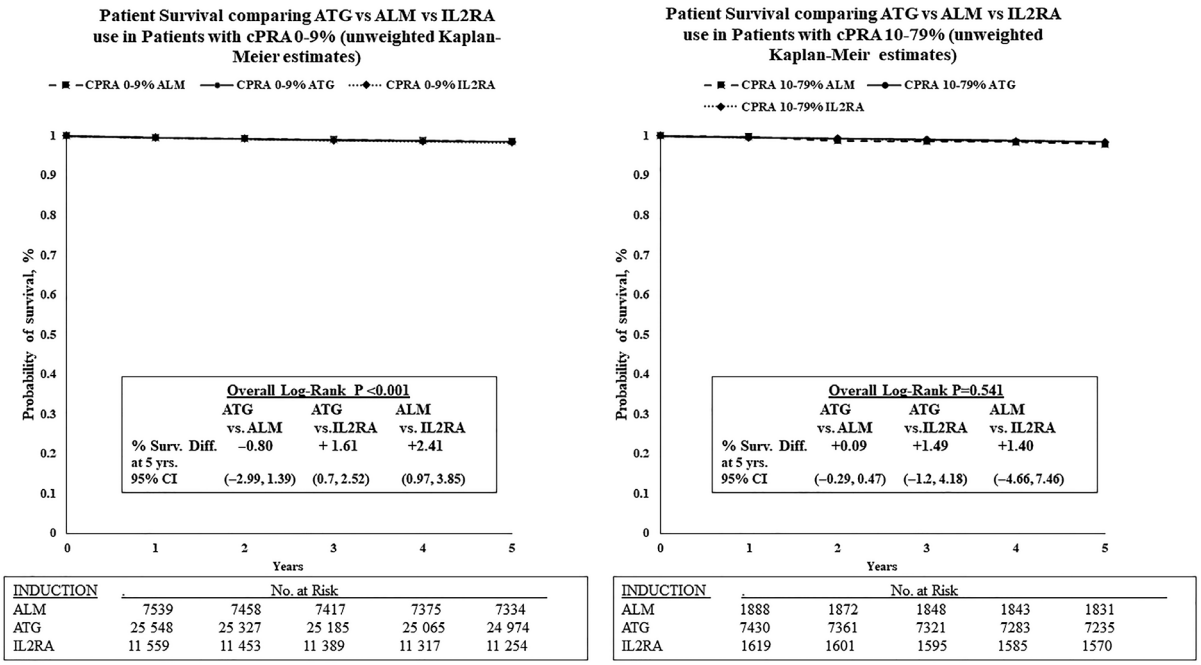


Figure 3 Patient survival comparing ATG versus ALM, versus IL2RA in patients with cPRA 0–9% (left panel). Patient survival comparing ATG versus ALM, versus IL2RA in Patients with cPRA10–79% (right panel). ALM, alemtuzumab; ATG, anti-thymocyte globulin; cPRA, calculated panel reactive antibody; IL2RA, interleukin-2 receptor antagonist.

with any LDAIT than IL-2RA induction in the unweighted and IPTW-weighted LRMs (Table 4). In KTRs with 10–79% cPRA, the odds for DGF did not differ among induction agents (Table 5).

Biopsy-proven acute rejection in the first post-transplant year

The biopsy-proven acute rejection rates (BPAR) in the first year of transplant among adult-DDKTRs with

Table 3. Unadjusted complications rates in induction therapy subgroups, <10% and 10–79% calculated panel reactive antibody (cPRA) transplant groups.

	<10% cPRA				Subgroup comparisons *P* adjusted (FDR)		
Event	ATG *N* = 25 552	ALM *N* = 7541	IL-2RA *N* = 11 560	Overall *P*	ATG versus ALM	ATG versus IL2RA	ALM versus IL2RA
Delayed graft function	6912* (27.24)	1973† (26.41)	2646‡ (23.04)	<0.001	0.563	<0.017	<0.001
Biopsy-proven acute rejection, first transplant year	2141 (8.38)	548 (7.27)	1260 (10.90)	<0.001	0.017	<0.001	<0.001
Re-hospitalization, first transplant year	10 760 (42.11)	3056 (40.53)	4561 (39.46)	<0.001	0.106	<0.001	0.563
Malignancy, 5 year	707 (2.77)	194 (2.57)	335 (2.90)	0.408	0.786	0.853	0.563
	10–79% cPRA				Subgroup comparisons *P* adjusted (FDR)		
Event	ATG *N* = 7433	ALM *N* = 1888	IL-2RA *N* = 1619	Overall *P*	ATG versus ALM	ATG versus IL2RA	ALM versus IL2RA
Delayed graft function	1760§ (23.83)	464¶ (24.74)	366** (22.76)	0.391	0.812	0.786	0.563
Biopsy-proven acute rejection, first transplant year	567 (7.63)	132 (6.99)	182 (11.24)	<0.001	0.786	<0.001	<0.001
Re-hospitalization, first transplant year	3101 (41.72)	803 (42.53)	614 (37.92)	0.009	0.863	0.044	0.050
Malignancy, 5 year	197 (2.65)	36 (1.91)	46 (2.84)	0.136	0.253	0.915	0.366

ALM, alemtuzumab; ATG, anti-thymocyte globulin; FDR, false discovery rate; IL-2RA, interleukin-2 receptor antagonist.

*N = 25 370.

†N = 7472.

‡N = 11 484

§N = 7387

¶N = 1875.

**N = 1608.

Table 4. Induction secondary outcomes in adult deceased-donor kidney transplant recipients with calculated panel reactive antibody <10%.

	Lymphocyte-depleting versus IL-2RA induction regimens						Lymphocyte-depleting induction regimens		
	ATG versus IL-2RA (ref.)			ALM versus IL-2RA (ref.)			ATG versus ALM (ref.)		
Outcome	OR	95% CI	P_{adj}	OR	95% CI	P_{adj}	OR	95% CI	P_{adj}
Re-Hosp									
Uwtd	1.10	1.05–1.15	0.001	1.02	0.95–1.09	0.124	1.08	1.02–1.14	0.025
IPTW-PS	1.09	1.04–1.14	0.001	1.03	0.97–1.09	0.536	1.04	0.99–1.10	0.221
Composite: Re-Hosp, GL, death									
Uwtd	1.0.08	1.03–1.01	0.007	1.04	0.97–1.11	0.341	1.03	0.98–1.09	0.341
IPTW-PS	1.0.06	1.01–1.11	0.035	1.10	1.03–1.17	0.007	0.98	0.93–1.04	0.541
BPAR									
Uwtd	0.63	0.56–1.13	0.001	0.71	0.66–0.77	0.001	1.12	1.00–1.24	0.108
IPTW-PS	0.71	0.66–0.76	<0.001	0.75	0.68–0.83	<0.001	1.00	0.80–1.21	0.679
Composite: BPAR, GL, death									
Uwtd	0.79	0.75–0.85	<0.001	0.82	0.74–0.90	<0.001	0.96	0.88–1.05	0.442
IPTW-PS	0.78	0.73–0.83	<0.001	0.93	0.85–1.00	0.657	0.90	0.84–0.98	0.029
DGF									
Uwtd	1.24	1.17–1.31	0.001	1.32	1.22–1.43	0.001	0.92	0.86–0.98	0.026
IPTW-PS	1.20	1.14–1.26	<0.001	1.24	1.15–1.32	<0.001	0.89	0.84–0.95	0.002

ATG, anti-thymocyte globulin; ATG, anti-thymocyte globulin; cPRA, calculated panel reactive antibody; Death, patient death within 1-year post-transplant; DGF, delayed graft function, defined as dialysis within first seven days of kidney transplant; GL, graft loss within 1-year post-transplant; IL2-RA, interleukin-2 receptor antagonist; IPTW, inverse probability of treatment weighted model; Log. Reg., multivariable logistic regression; OR, odds ratio; PS, propensity score; Re-Hosp., re-hospitalization within 1-year post-transplant; Test of statistical significance 2-tailed alpha = 0.05: P_{adj}, *P*-value adjusted for multiple comparisons based on False Discovery Rate method, Benjamini, Y. & Hochberg, Y; uwtd., unweighted model.

Based on multivariable logistic regression models. Models were adjusted for the following covariates: kidney donor risk index (KDRI), (Rao) <0.96, 0.96 to <1.15, 1.15 to <1.45, ≥1.45; recipient age, years: 18–49, 50–64, ≥65; Recipient BMI in kg/sq.m.: <30, ≥30; recipient race: white, African American, Hispanic, other; primary diagnosis: diabetes mellitus, hypertension, glomerulonephritis, polycystic kidney disease and other; pretransplant dialysis duration: 1 day–2 years, >2 years, no dialysis; number of HLA mismatches: 0–, 1–3, 4–6; transplant year: 2007–2010 or 2011–2015; Re-transplant versus first transplant; steroids or none in maintenance immunosuppression; maintenance regimen: calcineurin inhibitor + mycophenolate, mammalian target of rapamycin-containing, other, none; primary insurance: private, medicare or medicaid, and other; cold ischemia time: 0 to <20 h, ≥20 h.

<10% cPRA were 8.4% for ATG (2141/25 552), 7.3% for ALM (548/7541), and 10.9% for IL-2RA (1260/11 560); ($P < .001$; Table 3). On multivariable analyses, 1-year BPAR odds for adult-DDKTRs with <10% cPRA were similar between ATG and ALM inductions (Table 4); however, on unweighted and IPTW-weighted LRMs, BPAR odds were lower for ATG (by 37% or 29%, respectively) or ALM (by 29% or 25%, respectively) than IL-2RA induction (Table 4).

The BPAR rates in the first transplant year among adult-DDKTRs with 10–79% cPRA were 7.6% for ATG (567/7433), 7.0% for ALM (132/1888), and 11.2% for IL-2RA (182/1619); ($P < .001$; Table 3). On multivariable analyses, 1-year BPAR odds for adult-DDKTRs with 10–79% cPRA were similar between ATG and ALM inductions (Table 5); however, on unweighted and IPTW-weighted LRM, they were lower for ATG (by 43% or 48%, respectively) or ALM (by 46% or 54%, respectively) than IL-2RA induction (Table 5).

In both the <10% and 10–79% cPRA groups, odds for 1-year composite of BPAR, graft loss, and death were lower for ATG or ALM than IL-2RA (Tables 4 and 5, respectively). In the <10% cPRA group ATG had lower odds; while in the 10–79% cPRA group ATG had similar odds of BPAR, graft loss, or death as ALM (Tables 4 and 5, respectively).

Malignancy

The 5-year incidence of de novo solid malignancy or lymphoma varied by 2.57–2.90% ($P = 0.408$) in induction subgroups among <10% cPRA adult-DDKTRs and

Table 5. Induction secondary outcomes in adult deceased-donor kidney transplant recipients with calculated panel reactive antibody 10–79%.

	Lymphocyte-depleting versus IL-2RA induction regimens						Lymphocyte-depleting induction regimens		
	ATG versus IL-2RA (ref.)			ALM versus IL-2RA (ref.)			ATG versus ALM (ref.)		
Outcome	OR	95% CI	P_{adj}	OR	95% CI	P_{adj}	OR	95% CI	P_{adj}
Re-Hosp									
Uwtd	1.12	1.00–1.26	0.108	1.13	0.98–1.31	0.171	0.97	0.89–1.10	0.822
IPTW-PS	1.11	1.00–1.24	0.112	1.19	1.04–1.36	0.026	1.04	0.99–1.10	0.182
Composite: Re-Hosp, GL, death									
Uwtd	1.15	1.03–1.37	0.035	1.19	1.03–1.37	0.036	0.96	0.86–1.07	0.487
IPTW-PS	1.09	0.98–1.21	0.182	1.15	1.01–1.32	0.062	0.90	0.82–1.00	0.066
BPAR									
Uwtd	0.57	0.48–0.68	0.001	0.54	0.42–0.69	0.001	1.09	0.88–1.35	0.815
IPTW-PS	0.52	0.43–0.61	0.001	0.46	0.37–0.59	0.001	1.00	0.83–1.21	0.998
Composite: BPAR, GL, death									
Uwtd	0.77	0.65–0.90	0.006	0.79	0.64–0.97	0.049	0.97	0.82–1.15	0.719
IPTW-PS	0.67	0.58–0.77	<0.001	0.69	0.58–0.83	<0.001	0.93	0.80–1.08	0.418
DGF									
Uwtd	0.96	0.84–1.10	0.689	1.04	0.88–1.23	0.755	0.93	0.82–1.06	0.383
IPTW-PS	1.00	0.88–1.14	0.998	0.99	0.85–1.17	0.983	0.97	0.86–1.09	0.695

ATG, anti-thymocyte globulin; ATG, anti-thymocyte globulin; cPRA, calculated panel reactive antibody; Death, patient death within 1-year post-transplant; DGF, delayed graft function, defined as dialysis within first seven days of kidney transplant; GL, graft loss within 1-year post-transplant; IL2-RA, interleukin-2 receptor antagonist; IPTW, inverse probability of treatment weighted model; Log. Reg., multivariable logistic regression; OR, odds ratio; PS, propensity score; Re-Hosp., re-hospitalization within 1-year post-transplant; Test of statistical significance 2-tailed alpha = 0.05: P_{adj}, *P*-value adjusted for multiple comparisons based on False Discovery Rate method, Benjamini, Y. & Hochberg, Y; uwtd., unweighted model.

Based on multivariable logistic regression models. Models were adjusted for the following covariates: kidney donor risk index (KDRI), (Rao) <0.96, 0.96 to <1.15, 1.15 to <1.45, ≥1.45; recipient age, years: 18–49, 50–64, ≥65; recipient BMI in kg/sq.m.: <30, ≥30; recipient race: white, African American, Hispanic, other; primary diagnosis: diabetes mellitus, hypertension, glomerulonephritis, polycystic kidney disease and other; pretransplant dialysis duration: 1 day–2 years, >2 years, no dialysis; number of HLA mismatches: 0–, 1–3, 4–6; transplant year: 2007–2010 or 2011–2015; re-transplant versus first transplant; steroids or none in maintenance immunosuppression; maintenance regimen: calcineurin inhibitor + mycophenolate, mammalian target of rapamycin-containing, other, none; primary insurance: private, medicare or medicaid, and other; cold ischemia time: 0 to <20 h, ≥20 h.

1.91–2.84% ($P = 0.136$) in induction subgroups in 10–79% cPRA adult-DDKTRs. Univariate comparisons did not show significant differences between induction subgroups in <80% cPRA groups. Multivariable analysis was not performed due to low event rates in most induction subgroups (Table 3).

DISCUSSION

We studied the SRTR database of adult deceased donor kidney transplants between January 1, 2007, and December 31, 2017, to determine differences in outcomes associated with 3 common induction agents in the nonbroadly sensitized (<10% and 10–79%) cPRA strata. The underlying aim of this study is to investigate mainly the clinical impact of using lymphocyte-depleting versus IL-2RA induction therapies in adult-DDKTRs with low and intermediate degrees of sensitization based on pretransplant cPRA. To clarify the independent associations of induction agents with outcomes in each cPRA stratum, the statistical models were adjusted for potentially confounding factors including a composite of donor factors, the kidney donor risk index; recipient characteristics and; transplant-related factors; and only adult-DDKTRs sharing similar maintenance immunosuppression regimens consisting of CNI and MPA ± steroids were included in the study. Additionally, sensitivity analyses with PS-weighted logistic and Cox regression models were conducted to validate results. Our most salient findings were: in the <10% and 10–79% cPRA strata, LDAITs (ATG and ALM) are associated with lower likelihood of BPAR than IL-2RA induction; however, in the <10% cPRA stratum,

both LDAITs are associated with higher odds of DGF than IL-2RA induction. Induction with ATG or ALM is associated with a higher likelihood of re-hospitalization than IL-2RA in the <10% and 10–79% cPRA strata, respectively. Between the LDAITs, ATG is associated with a lower likelihood of DGF, but has a trend of higher odds for re-hospitalization than ALM in the <10% cPRA stratum. On the primary outcomes, the LDAITs and IL-2RA induction are associated with similar 5-year patient mortality risks, but ALM is associated with a trend of higher death-censored graft loss (DCGL) risk than ATG or IL-2RA induction in the <10% and 10–79% CPRA strata.

Studies have shown that in clinical practice, immunologic risk factors are not the main determinants of induction selection [1,14,25]. In the United States, center effects rather than clinical risk factors account for the variations in induction immunosuppression selection for kidney transplantation [25]. Clinical guidelines based on studies using the "old" (pre-2007) PRA allocation system recommended IL-2RA induction for the low immunologic risk and LDAIT for the high-immunologic risk KTRs [2,14,17]. These recommendations were based on the theory that in KTRs at low risk for rejection, the risk of over-immunosuppression from LDAITs would outweigh their putatively greater anti-rejection benefit [12,14]. After the cPRA allocation system changes began in 2007, the applicability of the above traditional recommendation has been unknown [11].

The results of our study support the clinical recommendations above since despite their superior anti-rejection benefit over IL-2RA in the nonbroadly sensitized adult-DDKTRs on standard CNI-MPA regimen; the LDAITs (as a class) did not provide a superior 5-year patient or allograft survival benefit over IL-2RA induction and one or both is associated with a higher likelihood of DGF, 1-year re-hospitalization (and its composite with graft loss, and death), or 5-year DCGL depending on cPRA stratum.

Our findings partially concur with previous studies of KTRs showing that ALM is associated with an inferior allograft survival than other induction agents, although we did not confirm ALM's association with a higher risk of mortality [26–28]. Schold et al. [26] demonstrated that ALM is associated with a higher risk of graft loss than ATG induction in re-transplant recipients. Hurst et al. [27] have shown that ALM is associated with higher death and graft loss risks than basiliximab in elderly KTRs. And, while ALM is a risk factor for living donor kidney allograft loss [28], ATG has been associated with improved deceased donor allograft survival [29]. Our study differed from the referenced studies since it investigated the outcomes associated with induction therapies using cPRA (instead of PRA in the old allocation system) to categorize pretransplant sensitization in nonbroadly sensitized adult-DDKTRs. Therefore, we hypothesize that ALM may not be a beneficial induction agent in the nonbroadly sensitized adult-DDKTRs to be maintained on CNI-MPA ± steroids.

Our analyses showed that across the <10% and 10–79% cPRA strata, ATG and ALM are both associated with lower adjusted risks of 1-year BPAR (and its composite with graft loss, and death) than IL-2RA induction that does not redound into an improved 5-year allograft or patient survival. Our findings are consonant with results of multiple randomized-controlled trials showing the LDAIT's superior rejection prophylaxis effect over IL-2RA induction [15,16]. However, in a study using a mate-kidney model, LDAIT tended to reduce the risk of death despite similar acute rejection and DGF effects as IL-2RA in low immunologic risk patients [30]. In a cohort study of sensitized adult KTRs without donor-specific antibody, Goumard et al. [31] found that the risks of acute rejection and the composite outcomes of AR, graft loss, and death at 5 years were higher with IL-2RA (basiliximab) than ATG. Compared with the immediately cited analysis, our study showed similar outcomes using a different (1-year) follow-up time frame in nonbroadly sensitized adult-DD-KTRs.

The likelihood of first transplant year composite of re-hospitalization, graft loss, or death is higher with ATG or ALM than IL-2RA induction in both <80% cPRA groups indicating that the higher BPAR risk of IL-2RA did not translate into a higher re-hospitalization risk. The result may be reflective that immunosuppression-related infections have surpassed BPAR as the primary cause of early post-transplant re-hospitalizations and complications [28,32,34]. The likelihood of DGF is higher with the LDAITs than IL-2RA but lower for ATG than ALM induction in the lowest cPRA stratum (Tables 4 and 5). Instead of causality, we suspect that residual confounding may underlie the findings [35,36].

Limitations of the study

Limitations of this study include a lack of information on the dose and appropriate drug levels of maintenance immunosuppressant drugs [37]. Likewise, the association of induction with pretransplant and de novo post-transplant DSAs and complications of infection as previously reported [31] are not included in this report.

Multivariable analysis of post-transplant de novo solid tumor or lymphoma was precluded due to low event rates in induction subgroups.

Conclusion

LDAIT (ATG or ALM) provides better protection than IL-2RA induction against BPAR (in the first transplant year) but one or another is associated with an increased risk of DGF or first transplant year composite of re-hospitalization, graft loss, or death in adult-DDKTRs with <10% or 10–79% pretransplant cPRA. There is no 5-year post-transplant patient and graft survival class advantage of LDAIT over IL-2RA induction in the non-broadly sensitized adult-DDKTRs and the trend of a higher 5-year DCGL risk with ALM than ATG or IL-2RA induction needs further investigation.

Authorship

AS, UA and KA: researched the design. XW, YL and AS: performed the research. AS, HI, KW and ML: wrote the manuscript. AS, XW and YL: analyzed the data.

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Conflict of interest

None declared. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics: CPRA <10% cohort.

Table S2. Baseline characteristics: CPRA 10–79% cohort.

REFERENCES

1. Hardinger KL, Brennan DC, Klein CL. Selection of induction therapy in kidney transplantation. *Transpl Int* 2013; **26**: 662.
2. 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.
3. Hussain SM, Sureshkumar KK, Ko TY, *et al.* Effect of induction agent on posttransplant outcomes in deceased donor kidney transplant recipients: influence of race. *Transplant Proc* 2013; **45**: 119.
4. Koyawala N, Silber JH, Rosenbaum PR, *et al.* Comparing outcomes between antibody induction therapies in kidney transplantation. *J Am Soc Nephrol* 2017; **28**: 2188.
5. Pascual J, Mezrich JD, Djamali A, *et al.* Alemtuzumab induction and recurrence of glomerular disease after kidney transplantation. *Transplantation* 2007; **83**: 1429.
6. Santos AH, Casey MJ, Womer KL. Analysis of risk factors for kidney retransplant outcomes associated with common induction regimens: a study of over twelve-thousand cases in the United States. *J Transplant* 2017; **8132672**: 1.
7. Pratschke J, Dragun D, Hauser I, *et al.* Immunological risk assessment: the key to individualized immunosuppression after kidney transplantation. *Transplant Rev (Orlando)* 2016; **30**: 77.
8. Pereira M, Guerra J, Neves M, *et al.* Predictive factors of acute rejection in low immunologic risk kidney transplant recipients receiving basiliximab. *Transplant Proc* 2016; **48**: 2280.
9. Cai J, Terasaki PI. Current trend of induction and maintenance treatment in positive panel-reactive antibody patients: a report on OPTN/UNOS kidney transplant registry data. *Chin Med J (Engl)* 2011; **124**: 649.
10. Lim WH, Chapman JR, Wong G. Peak panel reactive antibody, cancer, graft, and patient outcomes in kidney transplant recipients. *Transplantation* 2015; **99**: 1043.
11. Cecka JM, Calculated PRA. (CPRA): the new measure of sensitization for transplant candidates. *Am J Transplant* 2010; **10**: 26.
12. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant* 2009; **9**(Suppl. 3): S1.
13. Heemann U, Abramowicz D, Spasovski G, Vanholder R, European Renal Best Practice (ERBP) Work Group on Kidney Transplantation. Endorsement of the Kidney Disease Improving Global Outcomes (KDIGO) guidelines on kidney transplantation: a European Renal Best Practice (ERBP) position statement. *Nephrol Dial Transplant* 2011; **26**: 2099.

14. Wagner SJ, Brennan DC. Induction therapy in renal transplant recipients: how convincing is the current evidence? *Drugs* 2012; **72**: 671.
15. Morgan RD, O'Callaghan JM, Knight SR, Morris PJ. Alemtuzumab induction therapy in kidney transplantation: a systematic review and meta-analysis. *Transplantation* 2012; **93**: 1179.
16. Andress L, Gupta A, Siddiqi N, Marfo K. Rabbit anti-thymocyte globulin induction in renal transplantation: review of the literature. *Transplant Res Risk Manage* 2014; **6**: 9.
17. Szczech LA, Berlin JA, Feldman HI, Anti-Lymphocyte Antibody Induction Therapy Study Group. The effect of antilymphocyte induction therapy on renal allograft survival. A meta-analysis of individual patient-level data. *Ann Intern Med* 1998; **128**: 817.
18. Brennan DC, Daller JA, Lake KD, *et al*. Rabbit antithymocyte globulin versus basiliximab in renal transplantation. *N Engl J Med* 2006; **355**: 1967.
19. Webster AC, Ruster LP, McGee R, *et al*. Interleukin 2 receptor antagonists for kidney transplant recipients. *Cochrane Database Syst Rev* 2010: CD003897.
20. Laftavi MR, Sharma R, Feng L, Said M, Pankewycz O. Induction therapy in renal transplant recipients: a review. *Immunol Invest* 2014; **43**: 790.
21. Leppke S, Leighton T, Zaun D, *et al*. Scientific Registry of Transplant Recipients: collecting, analyzing, and reporting data on transplantation in the United States. *Transplant Rev (Orlando)* 2013; **27**: 50.
22. Scientific Registry of Transplant Recipients. Technical Methods for the Program-Specific Reports 2016. https://www.srtr.org/about-the-data/technical-methods-for-the-program-specific-reports#tablec4. Accessed 11/3/2018.
23. Stuart EA. Matching methods for causal inference: a review and a look forward. *Stat Sci* 2010; **25**: 1.
24. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J Roy Stat Soc Ser B (Methodol)* 1995; **57**: 289.
25. Dharnidharka VR, Naik AS, Axelrod DA, *et al*. Center practice drives variation in choice of US kidney transplant induction therapy: a retrospective analysis of contemporary practice. *Transpl Int* 2018; **31**: 198.
26. Schold J, Poggio E, Goldfarb D, Kayler L, Flechner S. Clinical outcomes associated with induction regimens among retransplant kidney recipients in the United States. *Transplantation* 2015; **99**: 1165.
27. Hurst FP, Altieri M, Nee R, Agodoa LY, Abbott KC, Jindal RM. Poor outcomes in elderly kidney transplant recipients receiving alemtuzumab induction. *Am J Nephrol* 2011; **34**: 534.
28. LaMattina JC, Mezrich JD, Foley DP, D'Alessandro AM, Sollinger HW, Pirsch JD. Alemtuzumab as compared to alternative contemporary induction. *Transpl Int* 2012; **25**: 518.
29. Gharibi Z, Ayvaci MUS, Hahsler M, Giacoma T, Gaston RS, Tanriover B. Cost-effectiveness of antibody-based induction therapy in deceased donor kidney transplantation in the United States. *Transplantation.* 2017; **101**: 1234.
30. Sureshkumar KK, Katragadda V, Chopra B, Sampaio M. Role of induction therapy in low immune risk kidney transplant recipients: a mate kidney analysis. *Clin Transplant* 2019; e13442.
31. Goumard A, Sautenet B, Bailly E, *et al*. Increased risk of rejection after basiliximab induction in sensitized kidney transplant recipients without pre-existing donor-specific antibodies – a retrospective study. *Transpl Int* 2019; **32**: 820.
32. Opelz G, Unterrainer C, Süsal C, Döhler B. Efficacy and safety of antibody induction therapy in the current era of kidney transplantation. *Nephrol Dial Transplant* 2016; **31**: 1730.
33. Lee H, Lee S, Leon JS, *et al*. Thymoglobulin versus basiliximab induction therapy in low-risk kidney transplant recipients: a single-center experience. *Transplant Proc* 2018; **50**: 1285.
34. Daratha KB, Short RA, Corbett CF, *et al*. Risks of subsequent hospitalization and death in patients with kidney disease. *Clin J Am Soc Nephrol* 2012; **7**: 409.
35. Irish WD, McCollum DA, Tesi RJ, *et al*. Nomogram for predicting the likelihood of delayed graft function in adult cadaveric renal transplant recipients. *J Am Soc Nephrol* 2003; **14**: 2967.
36. Siedlecki A, Irish W, Brennan DC. Delayed graft function in the kidney transplant. *Am J Transplant* 2011; **11**: 2279.
37. Kaplan B, Schold J, Meier-Kriesche H. Overview of large database analysis in renal transplantation. *Am J Transplant* 2003; **3**: 1052.