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ORIGINAL ARTICLE

Outcomes of kidney transplantation in patients with IgA nephropathy based on induction: A UNOS data analysis

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Abstract

Introduction: IgA nephropathy (IgAN) can cause end-stage kidney disease (ESKD). This study assesses the impact of induction and maintenance immunosuppression on IgAN recurrence, graft survival, and mortality in living and deceased donor kidney transplants (LDKT and DDKT).

Methods: Retrospective analysis of the UNOS database in adults with ESKD secondary to IgAN who received kidney transplants between January 2000 and June 30, 2022. Patients with thymoglobulin (ATG), alemtuzumab, or basiliximab/daclizumab induction with calcineurin inhibitor (CNI) and mycophenolate mofetil (MMF) with or without prednisone maintenance were analyzed. Multivariate logistic regression was performed to identify factors correlated with IgA recurrence. Multivariable Cox regression analyses were performed for clinically suspected risk factors. Kaplan Meir Analysis was utilized for overall graft survival.

Results: Compared to ATG with steroid maintenance, alemtuzumab with steroid increased the odds of IgAN recurrence in DDKTs (OR 1.90, $p < .010$, 95% CI [1.169–3.101]). Alemtuzumab with and without steroid increased the odds of recurrence by 52% ($p = .036$) and 56% ($p = .005$), respectively, in LDKTs. ATG without steroids was associated with less risk of IgAN recurrence (HR .665, $p = .044$, 95% CI [.447–.989]), graft failure (HR .758, $p = .002$, 95% CI [.633–.907]), and death (HR .619, $p < .001$, 95% CI [.490–.783]) in DDKTs. Recurrence was strongly associated with risks of graft failure in DDKTs and LDKTs and death in LDKTs.

Conclusion: In patients with IgAN requiring a kidney transplant, Alemtuzumab induction correlates with increased IgAN recurrence. Relapse significantly affects graft survival and mortality. ATG without steroids is associated with the least graft loss and mortality.

KEYWORDS
alemtuzumab, basiliximab, daclizumab, IgA, kidney, nephropathy, outcome, thymoglobulin, transplant

1 | INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is a disease characterized by IgA deposition in the glomerular mesangium. It is the most common type of primary glomerular disease globally. The incidence of IgAN is at least 2.5/100,000 in adults.[1] Clinical symptoms range from mild hematuria and proteinuria with mesangial expansion to fulminant, rapidly progressive crescentic glomerulonephritis (GN).[2] The disease is one of the leading causes of end-stage kidney disease (ESKD). Up to 40% of sufferers progress to ESKD within 20 years of diagnosis.[3] It is currently the subject of ongoing clinical trials with repurposed agents and novel molecules.[4,5]

ESKD, including when due to glomerulonephritis, is best treated with renal transplantation. IgAN is one of the most commonly recurring GNs in the allograft with reported rates ranging between 9% and 61%. Graft loss rates attributed to recurrence vary between .9% and 17.2%.[6,7] There are multiple risk factors for IgAN recurrence such as a recipient's HLA haplotypes and age which cannot be controlled. Two factors that can be managed are the recipient's induction regimen as well as the immunosuppressive maintenance regimen.[7]

Maintenance therapy relies on mycophenolate mofetil (MMF), a calcineurin inhibitor (CNI) and steroids in most centers. A steroid-free regimen does not seem to have a benefit vis-à-vis recurrence.[8] Von Visger recounted that steroid-free regimens have an 8 times higher risk of IgAN recurrence.[9] Although there is more tendency to use steroids for treatment in native kidneys with high-risk IgA nephropathy,[10] no clear consensus exists with regards to the ability of steroids in preventing the recurrence of IgAN in the kidney transplant recipient.

The standard of care for induction immunosuppression to prevent rejection includes Thymoglobulin (ATG), Basiliximab and, Alemtuzumab (Campath®—Sanofi, France). ATG is a polyclonal antilymphocyte preparation containing antibodies against a variety of T-cell surface antigens. It is generated in rabbits. It does not deplete B-cells. Alemtuzumab, however, is a monoclonal antibody directed against CD52 antigen present on both B and T cells and leads to depletion of both populations.[11,12] Alemtuzumab is currently only available through a special restricted program in the United States. Basiliximab and Daclizumab are both murine/human chimeric monoclonal antibodies directed against the interleukin-2 receptor alpha chain (CD25 antigen) expressed on the surface of T-lymphocytes. Activation of CD25 leads to differentiation of T-cells and proinflammatory transcription.[13–15]

This study aims to assess outcomes related to induction, notably ATG, basiliximab/daclizumab (IL2Ra) and alemtuzumab, as well as maintenance therapy's impact on IgAN recurrence and graft loss through assessment of the most prevalent regimen (Tacrolimus + MMF) with and without steroid.

2 | MATERIALS AND METHODS

2.1 | Data, data sources and population

A retrospective analysis was performed using the UNOS database between January 1, 2000, and June 30, 2022, to identify risk factors for a recurrence of IgA nephropathy (IgAN) in kidney transplant recipients. There were 264,493 transplant recipients whose immunosuppressive drug regimen or the follow-up data were not missing. Of those, 12,614 (4.8%) recipients had a diagnosis of IgAN at the time of transplant. Of those, we kept 11,679 (93%) recipients who received the combination of CNI and MMF with or without prednisone as the maintenance regimen. Further, we screened down the recipients to keep 11,341 (97.1%) recipients who received either antithymocyte globulin (Thymoglobulin®), alemtuzumab (Campath®), basiliximab (Simulect®) or daclizumab (Zenapax®) for induction. The recipients of other induction regimens as well as the patients receiving a combination of the aforementioned induction drugs were excluded from the final data. We also excluded pediatric patients and recipients of multiple organs as well as pediatric donor recipients. In the final data, the composition of the recipients receiving different induction drugs was as follows: ATG shared 56.35% ($N = 6,391$); the alemtuzumab recipients shared 16.84% ($N = 1,910$); the basiliximab recipients shared 22.75% ($N = 2,580$); and the daclizumab recipients shared 4.06% ($N = 460$). The recipients of CNI and MMF with or without prednisone as the maintenance regimen shared 70.05% ($N = 7,944$) and 29.95% ($N = 3,397$) respectively. The recurrence of IgAN was identified by first querying the transplant recipients whose primary diagnosis at the time of transplant was IgAN. These recipients were then assessed by the recurrence status (yes/no) of the primary diagnosis recorded in the follow-up data. The final data had 10,731 (95%) transplant recipients who did not experience the recurrence and 610 (5%) recipients who did.

2.2 | Population and variables

The presence of the IgA nephropathy recurrence as well as two standard transplant outcomes, that is, graft failure and patient mortality, were compared by induction and immunosuppressive maintenance therapy. Other recipient characteristics included age, days on waitlist, retransplant recipient, diabetes status, dialysis status, glomerular filtration rate (GFR), BMI, and calculated panel reactive antibody (cPRA) at the time of transplant. For donor characteristics, we queried age, sex, ethnicity, BMI, creatinine level, history of hypertension, and measures for organ quality including Kidney Donor Profile Index (KDPI), kidneys from the donors with cardiac death (DCD) and expanded criteria donors (ECD). Additional transplant-related variables, such as HLA mismatch level as well as cold ischemic time (CIT) and organ sharing status were also included.

2.3 | Statistical analysis

The recipient, donor and transplant characteristics were compared between the two cohorts (recurrence vs. no recurrence) using t-/Wilcoxon–Mann–Whitney and Chi-sq/Fishers exact tests, depending on the sample size and the distribution of the variables included. The factors influencing the likelihood of IgAN recurrence were investigated using the multivariable logistic regression with the recurrence (yes/no) as the dependent variable and the induction and maintenance immunosuppressive regimens, and aforementioned recipient, donor and transplant characteristics as the independent variables. Patient and graft survival rates as well as recurrence-free rate (at 3-, 6-month, and 1-, 3- and 5-years post-transplant) were analyzed. Survival curves and the estimates for these outcomes were obtained using the Kaplan–Meier (KM) Product Limit method. In the survival analysis, days to graft failure, patient death as well as time to IgAN recurrence were the endpoints. Recipients who did not experience any of these endpoints, including death, or whose health or graft status was unknown were censored on the last follow-up or the last day of the study. Median follow-up was 1748 days. Both graft and patient survival rates were estimated in two ways: I) including all transplant recipients who had a primary diagnosis of IgAN at the time of transplant; and II) including only those transplant recipients who experienced the IgAN recurrence. Multivariable Cox regression analyses were performed for clinically suspected risk factors. The potential risk factors explored are the induction and maintenance immunosuppressive regimens, recipient and donor characteristics potentially linked for transplant outcomes. Separate analyses were performed for living and deceased donor transplants as KDPI is only available for deceased donors. For the deceased donor analyses, KPDI and additional donor characteristics that are not part of the KPDI calculation were included to reflect the quality of kidneys transplanted. Statistical significance was defined by $p < .05$ in the analysis.

3 | RESULTS

3.1 | Characteristics of the population

IgAN recurred in 5.38% of transplanted patients. Time to recurrence ranged from 70 to 4379 days, with a mean of 794 days and standard deviation of 561.4 days (data not shown). Recipients experiencing recurrence were more frequently younger at the time of transplant (40.53 vs. 45.43 years, $p < .001$), male (71.97% vs. 64.19%, $p < .001$), white (68.69% vs. 59.26%, $p < .001$), and had fewer days on the waitlist (258 vs. 371 days, $p < .001$) compared to those who did not recur. Mean cPRA scores were lower in the recurrence group (12.75 vs. 15.46, $p = .046$). Allografts from living donors and from female donors were associated with more frequent IgAN recurrence. HLA mismatch did not correlate with any of the outcomes measured. Recurrence correlated with shorter cold ischemia time (Table 1). Of the 11,341 patients analyzed, 56.35% received induction with ATG while 16.84% received alemtuzumab and 26.82% received IL2-RA. 29.97% received steroid-free maintenance therapy (Table S1).

3.2 | Immunosuppression and IgAN recurrence

In logistic regression modelling, alemtuzumab induction with a steroid-containing maintenance regimen increased the odds of recurrence by 90% when compared to ATG with steroid-containing maintenance therapy in DDKT recipients (OR 1.90, $p < .010$, 95% CI [1.169–3.101]). No significant difference was seen with alemtuzumab with steroid-free maintenance. In a parallel comparison with LDKT recipients, alemtuzumab induction both with and without a steroid-containing maintenance regimen significantly increased the odds of recurrence by 52% ($p = .036$) and 56% ($p = .005$), respectively, when compared to ATG induction with steroid maintenance. There were no differences in odds of recurrence when comparing ATG without steroids or IL2-RA with or without steroid maintenance to ATG with steroids (Tables S2a and S2b).

In Cox regression modelling, ATG induction without steroid maintenance was associated with 43% less risk of IgAN recurrence over time compared to ATG with steroid in DDKT recipients (HR .665, $p = .044$, 95% CI [.447–.989]). This finding was not seen in LDKT recipients, although in this cohort there was a trend toward increased likelihood of recurrence in those treated with alemtuzumab with steroid maintenance. This approached but did not reach statistical significance. No other associations between induction or maintenance regimens were seen by Cox regression (Tables 2 and 3 and Figures S1a and S1b).

3.3 | Immunosuppression and graft survival

In analysis of death-censored graft failure, ATG without steroid maintenance was associated with 34% less risk of graft failure compared to ATG with a steroid-containing regimen in DDKT recipients (HR .758, $p = .002$, 95% CI [.633–.907]). This trend was also seen in death-uncensored graft failure in those receiving allografts from DDKTs (data not shown), though was not observed in death-censored or -uncensored LDKT recipients. No other treatment regimens were associated with significant differences in death-censored or -uncensored graft failure when compared to the referent. IgAN recurrence was strongly associated with the risk of graft failure in both DDKT and LDKT recipients (Tables 4 and 5 and Figures 1A,B, 2A,B).

3.4 | Immunosuppression and graft survival after IgAN recurrence

When analyzing the subset of patients who experienced IgAN recurrence separately, no significant differences in risk of graft failure were observed among induction or maintenance regimens. This finding was consistent in both death-censored and death-uncensored analyses (Tables S3a and S3b).

TABLE 1 Recipient and donor characteristics by IgA recurrence status.

Recipient characteristics	No IgA recurrence ($n = 10,731$)	IgA recurrence ($n = 610$)	*P*-value
Demographics			
Age, mean (sd)	45.43 (12.78)	40.53 (12.90)	<.001
Male, n (%)	6,888 (64.19%)	439 (71.97%)	<.001
Ethnicity/Race, n (%)			
White	6,359 (59.26%)	419 (68.69%)	<.001
African American	581 (5.41%)	29 (4.75%)	.482
Hispanic	1,475 (13.75%)	51 (8.36%)	<.001
Asian	2,035 (18.96%)	94 (15.41%)	.029
Other	281 (2.62%)	17 (2.79%)	.800
Days on waitlist, median (IQR)	371 (137, 945)	258 (96, 682)	<.001
Clinical factors			
Prior transplant, n (%)	695 (6.48%)	32 (5.25%)	.227
BMI at the time of transplant, mean (sd)	27.65 (5.44)	27.52 (5.48)	.523
Dialysis at the time of transplant, n (%)	6,793 (63.33%)	363 (59.51%)	.057
Diabetes at the time of transplant, n (%)	597 (5.59%)	20 (3.29%)	.015
GFR at the time of transplant, mean (sd)	13.78 (4.49)	13.84 (4.53)	.820
cPRA at the time of transplant, mean (sd)	15.46 (29.88)	12.75 (27.16)	.046
Immunosuppressive regimen, n (%)			
Induction using Antithymocyte globulin	6,081 (56.67%)	310 (50.82%)	.005
Induction using Alemtuzumab	1,765 (16.45%)	145 (23.77%)	<.001
Induction using Basiliximab or Daclizumab	2,855 (26.88%)	155 (25.41%)	.424
Maintenance using CNI and MMF	3,187 (29.70%)	210 (34.43%)	.013
Maintenance using CNI, MMF, and prednisone	7,544 (70.30%)	400 (65.57%)	.013
Antithymocyte induction + steroid maintenance	4,221 (39.33%)	202 (33.11%)	.002
Antithymocyte induction + no steroid maintenance	1,860 (17.33%)	108 (17.70%)	.813
Alemtuzumab induction + steroid maintenance	717 (6.68%)	58 (9.51%)	.007
Alemtuzumab induction + no steroid maintenance	1,048 (9.77%)	87 (14.26%)	<.001
IL2Ra induction + steroid maintenance	2,606 (24.28%)	140 (22.95%)	.454
IL2Ra induction + no steroid maintenance	279 (2.60%)	15 (2.46%)	.831
Donor/organ/transplant characteristics	**No IgA recurrence ($n = 10,731$)**	**IgA recurrence ($n = 610$)**	***P*-value**
Demographics			
Age, mean (sd)	40.21 (12.55)	40.66 (12.09)	.386
Male, n (%)	5,508 (51.33%)	250 (40.98%)	<.001
Ethnicity/Race, n (%)			
White	7,657 (71.35%)	461 (75.57%)	.025
African American	653 (6.09%)	30 (4.92%)	.239
Hispanic	1,509 (14.06%)	64 (10.49%)	.013
Asian	700 (6.52%)	39 (6.39%)	.900
Other	281 (2.62%)	17 (2.79%)	.800
BMI at the time of transplant, mean (sd)	27.37 (5.52)	26.81 (5.19)	.073

(Continues)

TABLE 1 (Continued)

Donor/organ/transplant characteristics	No IgA recurrence ($n = 10,731$)	IgA recurrence ($n = 610$)	*P*-value
Diabetes n (%)	5,700 (53.29%)	413 (67.82%)	<.001
Hypertension, n (%)	1,442 (13.92%)	55 (9.26%)	.001
Living Donor, n (%)	5,355 (49.90%)	405 (66.39%)	<.001
ECD, n (%)	596 (11.09%)	17 (8.29%)	.209
DCD, n (%)	1,093 (10.19%)	38 (6.23%)	.002
Organ/Transplant factors			
HLA mismatch level (0-6), mean (sd)	3.76 (1.65)	3.69 (1.60)	.368
KDPI, mean (sd)	.37 (.25)	.36 (.24)	.543
Cold ischemic time in hrs, mean (sd)	10.36 (10.25)	7.65 (9.69)	<.001
Locally shared, n (%)	9,289 (86.56%)	548 (89.84%)	.020
Regionally shared, n (%)	559 (5.21%)	20 (3.28%)	.035
Nationally shared, n (%)	883 (8.23%)	42 (6.89%)	.238

TABLE 2 Cox regression for IgAN recurrence in deceased-donor kidney transplant.

Cox regression: IgAN recurrence	HR	*P*-value	[95%	C.I.]
Recipient age	1.004	.523	.992	1.015
Male recipient[a]	.964	.812	.711	1.307
White recipient[b]	1.308	.076	.973	1.758
KDPI at the time of TX	.765	.383	.419	1.397
Immunosuppressive regimen[c]				
ATG induction w/o prednisone maintenance	.665	.044	.447	.989
Alemtuzumab induction w prednisone maintenance	.989	.963	.613	1.595
Alemtuzumab induction w/o prednisone maintenance	.951	.845	.573	1.577
IL2Ra induction w prednisone	.755	.164	.508	1.122
IL2Ra induction w/o prednisone	.520	.208	.188	1.440

[a]Female is the reference.
[b]All other race groups are the reference.
[c]ATG induction with prednisone maintenance is the reference.

TABLE 3 Cox regression for IgAN recurrence in living-donor kidney transplant.

Cox regression: IgAN recurrence	HR	*P*-value	[95%	C.I.]
Recipient age	1.000	.959	.992	1.008
Male recipient[a]	1.271	.048	1.002	1.613
White recipient[b]	.984	.891	.777	1.245
Immunosuppressive regimen[c]				
ATG induction w/o prednisone maintenance	1.081	.608	.802	1.457
Alemtuzumab induction w prednisone maintenance	1.434	.060	.984	2.089
Alemtuzumab induction w/o prednisone maintenance	1.044	.779	.775	1.406
IL2Ra induction w prednisone	.826	.162	.632	1.080
IL2Ra induction w/o prednisone	.892	.717	.480	1.657

[a]Female is the reference.
[b]All other race groups are the reference.
[c]ATG induction with prednisone maintenance is the reference.

TABLE 4 Cox regression for death-censored graft failure in deceased-donor kidney transplant.

Cox regression: Graft failure	HR	*P*-value	[95%	C.I.]
Recipient age	1.002	.358	.997	1.007
Male recipient[a]	1.137	.048	1.001	1.291
White recipient[b]	1.191	.006	1.052	1.348
KDPI at the time of TX	2.840	<.001	2.229	3.619
IgA recurrence	2.463	<.001	1.983	3.059
Immunosuppressive regimen[c]				
ATG induction w/o prednisone maintenance	.758	.002	.633	.907
Alemtuzumab induction w prednisone maintenance	.957	.748	.732	1.252
Alemtuzumab induction w/o prednisone maintenance	1.045	.701	.836	1.304
IL2Ra induction w prednisone	.947	.467	.817	1.097
IL2Ra induction w/o prednisone	.619	.053	.380	1.007

[a]Female is the reference.
[b]All other race groups are the reference.
[c]ATG induction with prednisone maintenance is the reference.

TABLE 5 Cox regression for death-censored graft failure in living-donor kidney transplant.

Cox regression: Graft failure	HR	*P*-value	[95%	C.I.]
Recipient age	.993	.029	.988	.999
Male recipient[a]	1.079	.345	.922	1.264
White recipient[b]	1.188	.037	1.011	1.396
IgA recurrence	3.016	<.001	2.491	3.651
Immunosuppressive regimen[c]				
ATG induction w/o prednisone maintenance	1.056	.616	.854	1.305
Alemtuzumab induction w prednisone maintenance	1.160	.428	.803	1.676
Alemtuzumab induction w/o prednisone maintenance	1.246	.061	.990	1.569
IL2Ra induction w prednisone	1.048	.611	.875	1.256
IL2Ra induction w/o prednisone	.779	.209	.529	1.150

[a]Female is the reference.
[b]All other race groups are the reference.
[c]ATG induction with prednisone maintenance is the reference.

3.5 | Immunosuppression and recipient mortality

In DDKT recipients, ATG induction without steroid-containing maintenance therapy was associated with 38% less likelihood of death compared to ATG with steroid maintenance (HR .619, $p < .001$, 95% CI [.490–.783]). This was not observed in LDKT recipients. IgAN recurrence itself, however, was associated with increased risk of death in the LDKT recipient cohort (Tables 6 and 7 and Figures 3 and S2).

3.6 | Outcomes and steroid maintenance

We specifically analyzed the effects of steroid maintenance versus rapid withdrawal on IgAN recurrence, graft survival, and patient survival. There were no significant differences in IgAN recurrence or death censored graft survival when comparing patients who received steroid maintenance versus rapid steroid taper by log-rank test in DDKT or LDKT recipients (Figures S3a, S3b, and S4a, S4b). There was also no significant difference in death censored graft failure for the subgroups of DDKT and LDKT recipients who experienced IgAN recurrence (data not shown). We did observe significantly worse patient survival in DDKT recipients treated with steroid maintenance compared to those on steroid-free regimens (Figure S5a). This was not observed in LDKT recipients (Figure S5b).

4 | DISCUSSION

IgAN is the most common primary glomerular disease globally. Our data shows an optimistic recurrence rate of 5.3% with graft loss proportions of 16.8% in the main cohort and 36.3% among the subgroup of recurring IgAN, respectively. Graft loss occurrence in the IgAN

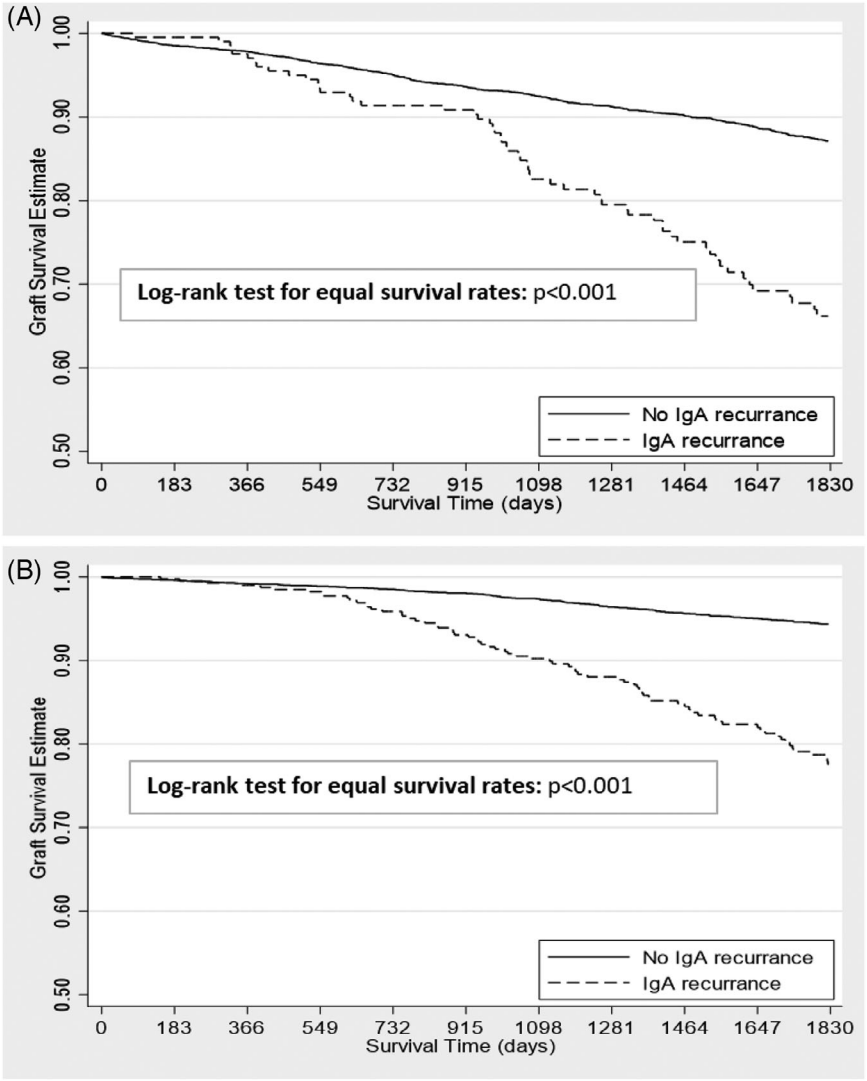

FIGURE 1 (A) Effect of IgAN recurrence on deceased-donor kidney transplants death-censored graft survival. (B) Effect of IgAN recurrence on living-donor kidney transplants death-censored graft survival.

TABLE 6 Cox regression for patient death in deceased-donor kidney transplant.

Cox regression: Patient mortality	HR	*P*-value	[95%	C.I.]
Recipient age	1.053	<.001	1.046	1.060
Male recipient[a]	1.326	.001	1.125	1.563
White recipient[b]	1.405	<.001	1.201	1.643
KDPI at the time of TX	2.266	<.001	1.707	3.008
IgA recurrence	1.136	.486	.794	1.624
Immunosuppressive regimen[c]				
ATG induction w/o prednisone maintenance	.619	<.001	.490	.783
Alemtuzumab induction w prednisone maintenance	1.228	.196	.900	1.677
Alemtuzumab induction w/o prednisone maintenance	1.016	.911	.767	1.347
ILR2a induction w prednisone	.896	.224	.751	1.069
ILR2a induction w/o prednisone	.710	.172	.435	1.160

[a]Female is the reference.
[b]All other race groups are the reference.
[c]ATG induction with prednisone maintenance is the reference.

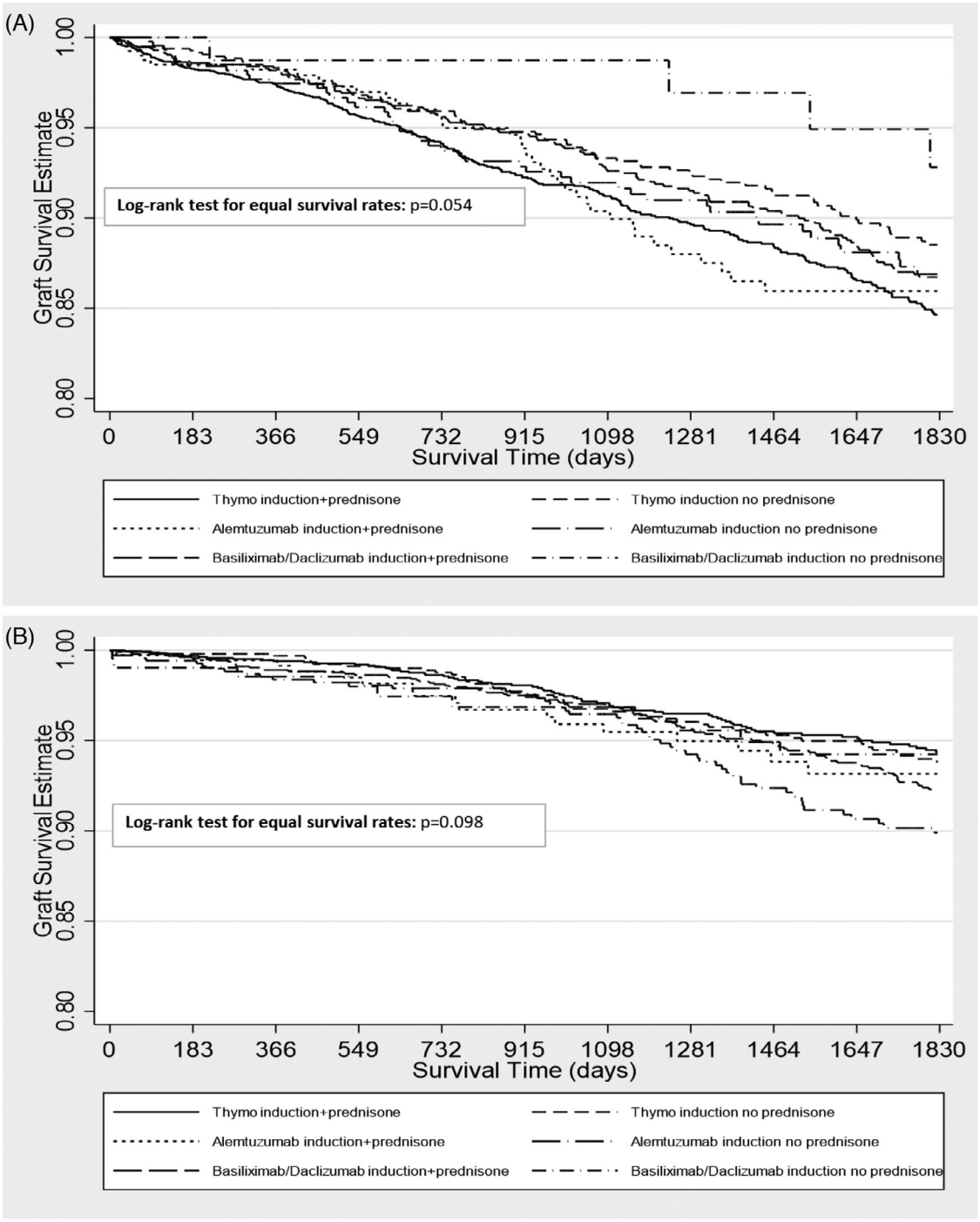

FIGURE 2 (A) Induction regimen and deceased-donor kidney transplants death-censored graft survival. (B) Induction regimen and living-donor kidney transplants death-censored graft survival.

recurrence subgroup accounted for 11.6% of all graft losses. These rates for graft loss are in line with those previously reported in the literature.[16,17]

In 2021, 93.1% of kidney transplant recipients received induction immunosuppression.[18] We sought to determine whether various induction agents or the use of a steroid-containing maintenance regimen are associated with differential risks of recurrent IgAN, allograft loss, and recipient mortality. To our knowledge, this study represents one of the longest analyses of outcomes after kidney transplantation in patients with ESKD due to IgAN (Chart 1).

We report that alemtuzumab induction with steroid maintenance is associated with 90% increased odds of IgAN recurrence in DDKT recipients when compared to ATG with steroid maintenance. In LDKT recipients, alemtuzumab is associated with increased odds of recurrent disease both with and without the use of steroids (52% and 56% increased odds, respectively). To our knowledge this association has

TABLE 7 Cox regression for patient death in living-donor kidney transplant.

Cox regression: Patient mortality	HR	*P*-value	[95%	C.I.]
Recipient age	1.057	<.001	1.048	1.067
Male recipient[a]	1.370	.015	1.063	1.767
White recipient[b]	1.342	.025	1.038	1.736
IgA recurrence	1.697	.006	1.162	2.480
Immunosuppressive regimen[c]				
ATG induction w/o prednisone maintenance	1.003	.985	.730	1.378
Alemtuzumab induction w prednisone maintenance	1.307	.309	.780	2.191
Alemtuzumab induction w/o prednisone maintenance	.997	.988	.679	1.463
IL2Ra induction w prednisone	.938	.636	.721	1.222
IL2Ra induction w/o prednisone	.697	.221	.390	1.243

[a]Female is the reference.
[b]All other race groups are the reference.
[c]ATG induction with prednisone maintenance is the reference.

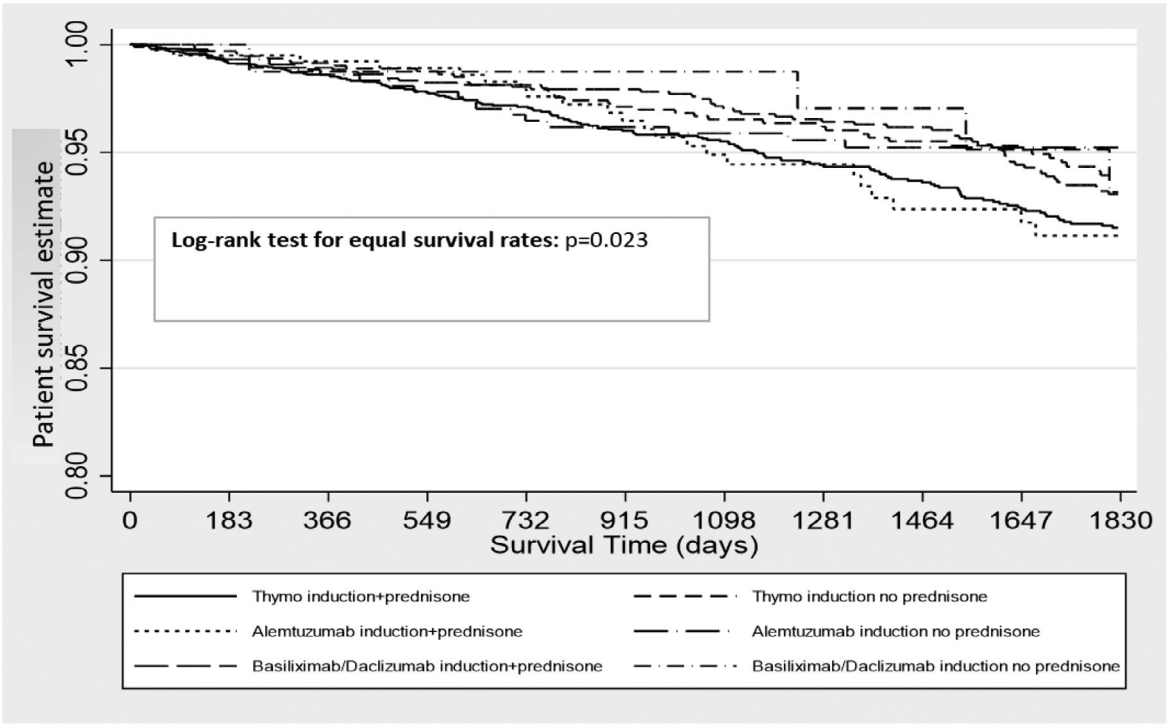

FIGURE 3 Induction regimen impact on patient survival among deceased-donor kidney transplants.

not been reported previously and suggests alemtuzumab may be a less favorable agent for induction when transplant is undertaken for IgAN. There is prior evidence that ATG induction is protective in preventing IgAN recurrence when compared to basiliximab, but this was not observed in our analysis.[19]

Asderakis et al. found that ATG provided an advantage over alemtuzumab and basiliximab in terms of overall graft survival after two years, though without IgAN as a specific reason for transplant.[20] In our analysis, ATG induction without steroid maintenance decreased risk of IgAN recurrence by 43%, decreased risk of graft failure by 34%, and decreased risk of death by 38% in DDKT recipients compared to ATG with steroid maintenance, suggesting a deleterious effect of long-term steroid therapy. When we analyzed steroid maintenance versus steroid-sparing regimens alone without consideration of induction agent, we observed no difference in the rate of IgAN recurrence or graft failure but did note an increased rate of mortality in the steroid maintenance group in DDKT recipients.

In a prior report by Leeaphorn et al. utilizing the UNOS database to analyze 9690 patients with IgAN transplanted between 2000-2014, no differences in death-censored graft failure or patient survival were

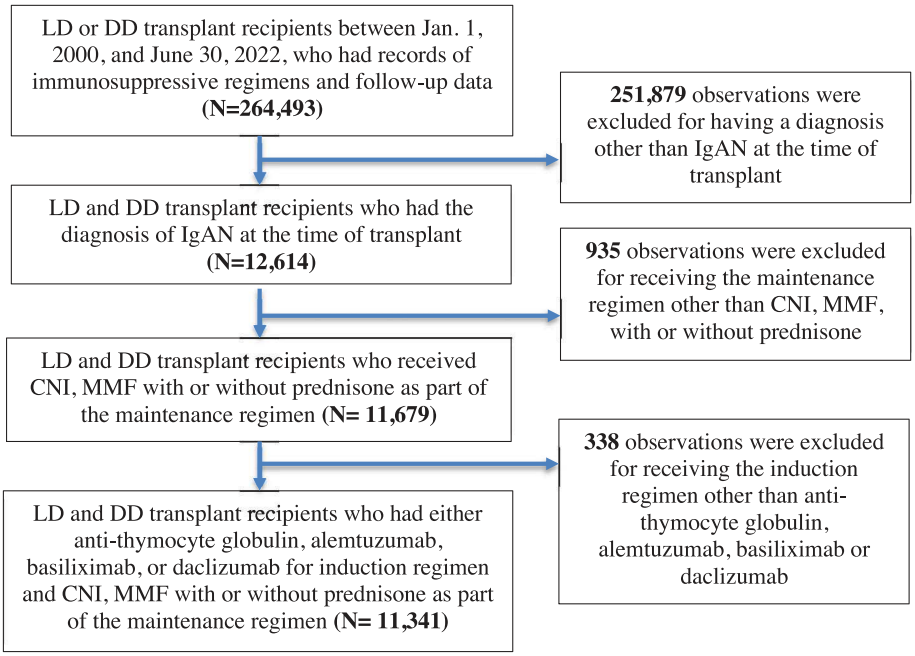

CHART 1 Flow chart for population selection. LD: Living donor; DD: Deceased donor; IgAN: IgA Nephropathy; CNI: calcineurin inhibitor; MMF: Mycophenolate Mofetil.

observed, but they did note a decreased risk of recurrence with steroid maintenance versus early steroid withdrawal.[21] In a large analysis of 1521 patients in the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) transplanted for ESKD due to IgAN between 1988 and 2007, Clayton et al also reported a strong association between steroid use and reduced risk of recurrence.[22] The contrast between our findings and those of Leeaphorn and colleagues (who used the same database) may be explained by differences in population size as well as methodology. We used multivariable Cox regression (as opposed to competing risk regression) as our primary objective was to identify the factors associated with the recurrence, graft failure and patient death with no specific risk comparators. The difference between our findings and those of Clayton et al may be related to the significant difference in population size. Our cohort was treated with steroid-free maintenance at rates similar to those described in the most recent SRTR reports (65% of regimens using steroid maintenance and the remaining protocols using rapid steroid withdrawal). We surmise that steroids likely do not play a major role in prevention of IgAN recurrence, but rather that the induction agent utilized has the greater impact on recurrence rates. Indeed, patients using alemtuzumab induction had a higher risk of recurrence both in deceased and living donor transplants (irrespective of steroid use in the LDKT population). The combination of CNI and MMF may have an adequate protection potential without the need for prolonged steroid exposure. The decreased recipient survival we observed in DDKT recipients on steroid maintenance likely relates to the known complications of long-term steroid therapy, namely increased infection risk.

When IgAN did recur, it had a large bearing on graft failure and recipient mortality in our population. Recurrence increased the risk of death-censored graft failure by 146% in DDKT recipients and by 200% in LDKT recipients. The risk of mortality increased by 70% in recipients of LDKTs who experienced IgAN recurrence. These findings contradict the previous report by Di Vico et al which observed that graft loss and patient survival were not affected by IgAN recurrence.[23] The differences in our analysis may relate to the significant difference in population sizes between the two studies.

Recipients with average waitlisting of more than 1 year experienced less recurrence than those with average waitlisting of less than a year (Table 1). It is unclear if there is an impact of a lead time bias versus changes in the immune system while on dialysis. The same outcome was observed in the ANZDATA registry.[24] Older recipient age reduced the risk of recurrence, which could reflect changes in the aging host immune system or the progressive development of tolerance (Tables 1, 4, and 5). However, a time bias cannot be excluded as younger recipients live longer, hence the increase in the detection rate of recurring cases. Male gender and white recipients had higher rates of recurrence, and the reason for this is unclear. A genetic component is a possibility.

There are multiple limitations to this retrospective analysis. The rate of biopsies to confirm IgAN recurrence remains undetermined. A lack of systematic biopsies also limits an exact assessment of the occurrence of IgAN post-transplant that otherwise can be clinically undetected. Another limitation is the lack of data on the use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers as well as information on the initiation of prednisone or increase in dose when already part of the maintenance immunosuppression. While these approaches are presumed to have been employed, we do not have the full clinical picture and illness narrative for each patient.

In general, we notice that induction with ATG has better odds of avoiding recurrence when compared to alemtuzumab, and in combination with steroid-free maintenance has lower recurrence risk as well

as better graft and patient survival in DDKT but not in LDKT recipients when compared to ATG with steroid. Across all induction groups, steroid maintenance seems to increase the rate of recipient mortality. Our results provide reassurance and an invitation to steer away from prednisone use, which contradicts previous studies. However, renal failure from IgAN recurrence in kidney transplant recipients is not uncommon, and a stratified risk approach still applies to determine who can benefit from a more aggressive induction and maintenance regimen. In the future, a randomized controlled study of ATG induction with a steroid free approach should be undertaken.

5 | CONCLUSION

IgAN recurrence has a strong effect on graft failure and patient survival. Alemtuzumab induction carries a higher risk of recurrence compared to ATG. Risks of recurrent disease, graft failure, and mortality were lower when ATG was utilized with a steroid-sparing approach. Steroid maintenance across our entire cohort was associated with increased recipient mortality. In general, ATG with MMF/CNI maintenance without prednisone seems to correlate with the best outcome overall. However, IgAN remains a pathology that needs to be assessed on an individual basis and therapy considered given the increasing lifespan of kidney grafts and the influx of novel therapies.

AUTHOR CONTRIBUTIONS

Emmanuel Albert Aydin-Ghormoz: reviewed and checked data, interpreted data, wrote manuscript. Jason Perlmutter: discussed data, literature review. Naoru Koizumi: collected/analyzed data, explained data, wrote manuscript. Jorge Ortiz: designed study, reviewed manuscript, critical revision, and approval of manuscript. Geovani Faddoul: reviewed and checked data, interpreted data, wrote manuscript, approval of manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

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