ORIGINAL ARTICLE

Recurrence of IgA nephropathy after kidney transplantation in steroid continuation versus early steroid-withdrawal regimens: a retrospective analysis of the UNOS/OPTN database

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SUMMARY

In the past 20 years, there has been an increase in use of steroid-withdrawal regimens in kidney transplantation. However, steroid withdrawal may be associated with an increased risk of recurrent IgA nephropathy (IgAN). Using United Network of (Organ Sharing/Organ Procurement and Transplantation Network) UNOS/OPTN data, we analyzed adult patients with end-stage renal disease (ESRD) due to IgAN who received their first kidney transplant between 2000 and 2014. For the primary outcome, we used a competing risk analysis to compare the cumulative incidence of graft loss due to IgAN recurrence between early steroid-withdrawal (ESW) and steroid continuation groups. The secondary outcomes were patient survival and death-censored graft survival (DCGS). A total of 9690 recipients were included (2831 in ESW group and 6859 in steroid continuation group). In total, 1238 recipients experienced graft loss, of which 191 (15.43%) were due to IgAN recurrence. In multivariable analysis, steroid use was associated with a decreased risk of recurrence (subdistribution hazard ratio 0.666, 95% CI 0.482–0.921; $P = 0.014$). Patient survival and DCGS were not different between the two groups. In the USA, ESW in transplant for ESRD due to IgAN is associated with a higher risk of graft loss due to disease recurrence. Future prospective studies are warranted to further address which patients with IgAN would benefit from steroid continuation.

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Introduction

IgA nephropathy (IgAN) is the most prevalent glomerular disease worldwide [1]. Recurrent IgA deposition in the kidney allograft is common and may lead to allograft loss. In retrospective studies, 10%–58% of all IgAN patients who underwent kidney transplantation had histological recurrence of IgAN with 2.25%–9.84% eventually experiencing graft loss due to the same [2–8].

Steroid therapy is an important part of the treatment of IgAN in native kidneys and provides renal protection in proteinuric patients with preserved renal function [9–11]. Given the reduced metabolic side effects with steroid minimization, early steroid-withdrawal (ESW) protocols have become more popular over the last two decades [12–15]. The use of ESW increased from 5% in 1998 to 34% in 2006 [16]. However, existing literature suggests that recurrent

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IgAN may be more common with these regimens [17–19].

Kukla *et al.* [17] and Visger *et al.* [19] observed a lower risk of recurrent IgAN with steroid maintenance. Both studies were from single centers; therefore, small sample sizes were their major limitations. Using large national databases from Australia and New Zealand, Clayton *et al.* [18] also documented strong negative correlation between steroid use and IgAN recurrence. However, the finding might not be applicable universally as induction therapy and ESW protocols were less commonly used in Australia and New Zealand than in the United States. In addition, overall patient survival and graft survival between ESW and steroid continuation groups were not addressed in their cohort.

Using United Network for Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) data, we conducted the largest study to date examining the impact of steroid withdrawal on recurrent IgAN.

Materials and methods

Data source and study population

We used the OPTN/UNOS database (as of June 30, 2016) to select adult patients with end-stage renal disease (ESRD) due to IgAN (identified by diagnosis code 3004) who received a kidney-only transplant between January 1, 2000, and December 31, 2014. The last follow-up date of this study was March 31, 2016. Patients with a history of prior organ transplantation were excluded. Patients with missing values for steroids upon discharge and patients who had graft failure before or on the date of discharge were also excluded.

Outcome measures

The primary outcome of this study was graft loss due to recurrent IgAN. Analysis of the primary outcome was stratified by steroids upon discharge (nonsteroid vs. steroid). UNOS/OPTN does not require information on biopsy, and the diagnosis of graft loss due to IgAN recurrence was based on codes with no place to document how diagnosis was made (clinical judgment versus biopsy). The secondary outcomes were patient survival and death-censored graft survival (DCGS). For patient survival analyses, patients were censored at their last follow-up data to UNOS/OPTN. For kidney graft survival analyses, patients were censored for patient death or at the last follow-up visits. The secondary outcomes were stratified by steroids upon discharge (nonsteroid vs. steroid) and donor type (deceased vs. living donor). The starting date of all outcome analyses was at the time of discharge; therefore, patients who had graft failure prior to or on the date of discharge were excluded.

A new variable was created alongside the existing cause of graft loss variable to better categorize the recipients for whom the original causes of graft loss were coded as "other specified." Free-text narratives were examined manually to determine which causes of graft failure they contained. For example, if the original cause of graft loss due to "other specified" was specified as a "IgA nephropathy," the new variable would be coded as "IgA recurrence." Observations that were originally coded as "other specified" that do not provide any useful information about the cause of graft loss were coded as "other or uninformative." It is of note that the variable for steroids at the time of discharge was blinded during the manual recoding. The competing risk model for graft loss due to IgA recurrence was reanalyzed based on the newly created variable for causes of graft loss.

Statistical analysis

Donor, recipient, and transplant characteristics were described using medians with interquartile ranges, or frequencies, where appropriate. To compare categorical and continuous variables, the chi-square and Kruskal–Wallis tests were used, respectively.

Competing risks regression by the method of Fine and Gray was used to analyze associations between the primary outcome and covariates. Graft loss due to acute rejection and chronic allograft nephropathy (CAN) were considered competing events. Factors potentially associated with the outcomes on univariate analysis ($P < 0.10$) were included in a multivariable model. Recipient age, sex, race as well as donor age, sex, race, transplant type (deceased vs. living), and transplant eras were included in the final model empirically. The exact methodology was used to identify the associations between steroid use and graft loss due to other causes, shown in the supplement.

Patient survival and DCGS outcomes were analyzed using the Kaplan–Meier product limit method with significance tested using the log-rank test. Hazard ratios [HR] and 95% confidence interval [CI] of death, and death-censored kidney graft failure were calculated using Cox proportional hazards. Similar to competing risk analysis, factors potentially associated with the survival outcomes on univariate analysis ($P < 0.10$) were included in the multivariable model. Recipient age, sex, race as well as donor age, sex, race, and transplant eras

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were included in the final model empirically. All *P*-values were two-tailed, and *P*-values of <0.05 were considered significant. Stata version 13 (StataCorp, College Station, TX, USA) was used for all statistical analyses.

Results

Patients

After excluding 113 patients with missing values for steroid upon discharge and 81 patients who had graft failure before or on the date of discharge, there were 9690 patients in this analysis, with a median follow-up time of 5.64 years (interquartile range (IQR): 2.97–8.98 years). Of these, 2831 recipients (29.22%) did not receive steroids at time of discharge after kidney transplantation; median follow-up time for this group was 4.99 years (IQR: 2.90–7.88 years). In total, 6859 recipients (70.78%) were discharged on steroids; median follow-up time for this group was 5.88 years (IQR: 3.00–9.65 years).

Variables for steroid use and steroid use over time

For our analyses, we identified whether the patient received steroids at the time of discharge after transplantation and at the time of their one-year follow-up; these groups were then stratified based on the arbitrarily defined transplant eras. As would be expected, kidney transplant recipients from earlier eras were more likely to be continued on steroids. In the years, 2000–2004, 2005–2009, and 2010–2014, 13.74%, 35.26%, and 35.69% of the recipients did not receive steroids at the time of discharge (Fig. 1a), and 15.44%, 34.86%, and 32.37% did not receive steroids at one-year follow-up, respectively (Fig. 1b).

In total, 2149 of 2766 recipients (77.69%), who were steroid-free upon discharge and had functioning grafts at the time of one-year follow-up, remained steroid-free at one-year follow-up, 458 recipients (16.56%) switched to steroid use, and 159 recipients (5.75%) had missing values at a year follow-up. Of 6620 recipients who received steroids upon discharge and had functioning grafts at a year follow-up, 5678 recipients (85.63%) remained on steroids, 513 recipients (7.75%) switched to a steroid-free regimen, and 429 recipients (6.45%) had missing values at a year follow-up.

Baseline characteristics

Baseline characteristics of the two groups are described in Table 1. Recipients in the early steroid-withdrawal group were more likely to be Caucasian, have received living donor transplants, and have received preemptive transplants. Thymoglobulin induction and tacrolimus maintenance immunosuppression were used more in the ESW group than the steroid continuation group. Notably, there was no difference in the distribution of peak panel reactive antibody (PRA), proportion of zero-human leukocyte antigen (HLA) mismatches, HLA-DR mismatches, and expanded criteria donor (ECD) kidneys between the two groups.

Causes of graft loss

In total, 1238 (12.78%) recipients had graft loss during follow-up. In total, 191(15.43%) of these were attributed to IgA recurrence. As shown in Table 2, the most common cause of graft loss responsible for this outcome in 440 (35.54%) of the cases was CAN. Other notable causes of graft loss included acute rejection (197; 15.91%), primary failure (55; 4.44%), graft thrombosis (14; 1.13%), and BK virus nephropathy (33; 2.67%). It is of note that there were 291 graft losses (23.51%) that were categorized as "other specified."

When the causes of graft loss were stratified by steroid use upon discharge, there was a higher rate of graft loss due to IgA recurrence in the ESW group when compared to the steroid continuation group (20.54% vs. 13.82%). The steroid continuation group had a higher rate of graft loss due to acute rejection (16.79% vs. 13.13%) and CAN (37.83% vs. 28.28%) when compared to the ESW group (Table 2).

Differences in causes of graft loss between ESW and steroid continuation regimens

The 10-year unadjusted cumulative incidence of graft loss due to recurrent IgAN is shown in Fig. 2. Recipients who were continued on steroids had a lower incidence of graft loss due to recurrent IgAN. In univariate analysis, the use of steroids was associated with a reduction in graft loss due to IgAN recurrence with a subdistribution hazard ratio (SHR) of 0.695 (95% CI, 0.511–0.945; $P = 0.020$). This difference persisted in the multivariable model after adjusting for recipient age, sex, race, dialysis duration, donor age, sex, race, transplant type (deceased vs. living), and transplant eras, and steroid continuation was also significantly associated with a reduction in graft loss with a SHR of 0.666 (95% CI, 0.482–0.921; $P = 0.014$) (Table 3). Interestingly, induction and maintenance immunosuppressive medications

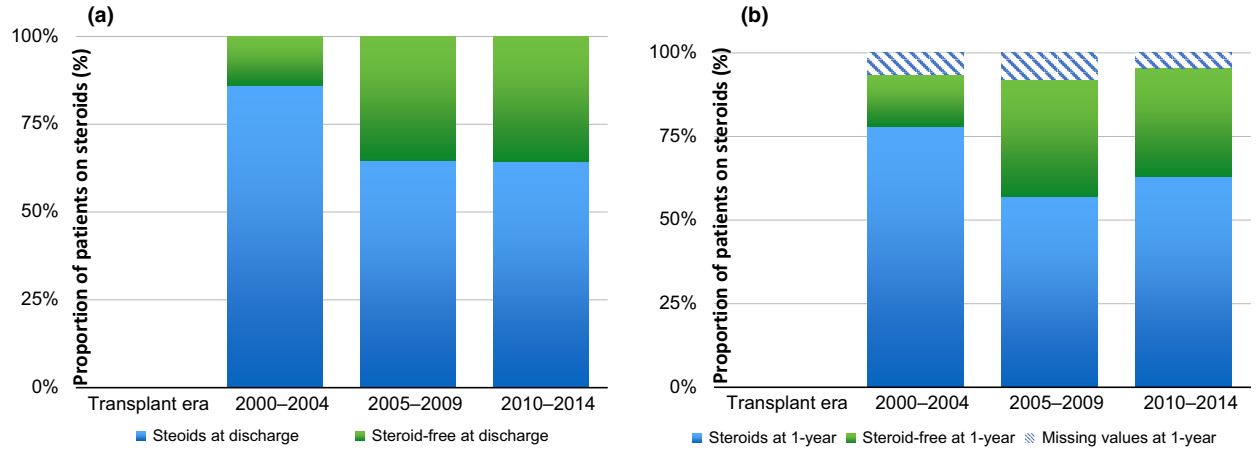

Figure 1 (a) Steroid use upon discharge categorized by transplant eras; 13.74%, 35.26%, and 35.69% of the recipients were steroid-free upon discharge in 2000–2004, 2005–2009, and 2010–2014 eras, respectively. (b) Steroid use at a year follow-up categorized by transplant eras excluding those who had failed allograft at a year; 15.44%, 34.86%, and 32.37% of the recipients were steroid-free upon discharge in 2000–2004, 2005–2009, and 2010–2014 eras, respectively, with 6.50%, 7.97%, and 4.51% of recipients that had missing value, respectively.

other than steroids did not have any impact on graft loss due to IgAN recurrence.

We then examined the cumulative incidence of graft loss due to other causes. In univariate analysis, recipients who continued on steroids had a higher incidence of graft loss due to acute rejection and CAN; however, the statistical significance was lost in the multivariable model. Additionally, steroid therapy did not have any effect on graft loss due to BK virus nephropathy in both univariate and multivariable models (see Table S3).

Patient survival

Figure 3a shows unadjusted Kaplan–Meier curves for patient survival for both living and deceased kidney donor recipients. The patient survival of the deceased donor recipients who received steroids upon discharge was not different from ESW group (log-rank $P = 0.354$). Similarly, the unadjusted patient survival in the living donor recipients who continued on steroids was not different from ESW group (log-rank $P = 0.444$).

Cox proportional hazard models were fitted to adjust for risk factors associated with patient survival. In univariate analyses, steroid maintenance therapy did not have statistically significant effects on mortality in either deceased donor or living donor cohorts (HR 1.113, 95% CI 0.888–1.395 in deceased donor cohort and HR 1.111, 95% CI 0.849–1.454 in living donor cohort). In multivariable analyses adjusted for potential risk factors (see Table S1A and Table S1B), steroid maintenance therapy did not have any statistically significant effect on risk of death in either deceased donor or living donor cohort (HR 1.169, 95% CI 0.909–1.504; $P = 0.224$ in deceased donor cohort and HR 1.027, 95% CI 0.774–1.363; $P = 0.855$ in living donor cohort).

Death-censored graft survival

Unadjusted DCGS is shown in Fig. 3b. There was no difference in kidney graft survival between ESW groups and steroid continuation groups in either deceased donor ($P = 0.732$) or living donor cohort ($P = 0.657$).

Cox proportional hazard models were used to assess the outcome of graft survival. In univariate analyses, steroid maintenance therapy did not have statistically significant effects on death-censored graft failure in either deceased donor or living donor cohorts (HR 1.034, 95%CI 0.854–1.251 in deceased donor cohort and HR 1.040, 95% CI 0.875–1.237 in living donor cohort). In multivariable analyses adjusted for potential risk factors (see Table S2A and Table S2B), steroid maintenance therapy did not have any statistical significant effect on graft failure in either deceased donor or living donor cohort (HR 1.021, 95% CI 0.821–1.271; $P = 0.849$ in deceased donor cohort and HR 1.030, 95% CI 0.840–1.264; $P = 0.774$ in living donor cohort).

Further analysis after manually examining free-text narratives of "other specified" as causes of graft loss

Because of substantial numbers of recipients had "other specified" as the cause of graft loss, we manually reviewed free-text narratives to better categorize their actual causes of graft loss by creating a new variable for

Table 1. Baseline characteristics stratified by steroids upon discharge.

Characteristics	ESW (n = 2831)	Steroid continuation (n = 6859)	P-value
Male, %	67.01	65.74	$P = 0.23$
Age, median (25th, 75th)	42 (33, 52)	42 (33, 52)	$P = 0.81$
Race, %			$P < 0.001$
White	66.30	62.08	
Black	4.49	5.58	
Hispanic	11.62	12.01	
Asian	15.40	17.13	
Other	2.19	3.19	
Peak PRA, %			$P = 0.02$
Missing	22.75	21.94	
≤10	63.97	63.86	
11–30	5.86	5.32	
>30	7.42	8.88	
HLA zero mismatch, %	11.16	10.31	$P = 0.21$
HLA-DR mismatch, %			$P = 0.47$
0	22.52	22.08	
1	48.23	47.41	
2	29.26	30.52	
Recipient BMI, median (25th, 75th)	26.6 (23.4, 30.7)	26.2 (22.9, 30.2)	$P < 0.001$
Diabetes, %	4.59	4.43	$P = 0.73$
Preemptive, %	29.53	23.17	$P < 0.001$
Dialysis duration in days, median (25th, 75th)	569 (241, 1211)	652 (272, 1317)	$P < 0.001$
Follow-up time in days, median (25th, 75th)	1823 (1057, 2877)	2148 (1094, 3524)	$P < 0.001$
Donor age, median (25th, 75th)	39 (29, 49)	39 (28, 48)	$P = 0.21$
Male donors, %	50.48	48.65	$P = 0.10$
Donor race, %			$P = 0.13$
White	72.80	71.40	
Black	6.00	6.58	
Hispanic	13.35	13.06	
Asian	6.25	6.91	
Other	1.59	2.06	
Donor type, %			$P < 0.001$
Deceased	38.90	44.57	
Living	61.10	55.43	
Donor hypertension, %	10.84	9.30	$P = 0.02$
ECD, % (only for deceased donor kidney transplant)	9.26	10.24	$P = 0.36$
Cold ischemic time in hours, median (25th, 75th) (only for deceased donor kidney transplant)	17 (11.8, 24)	16 (11, 22)	$P < 0.001$
KDPI percentile (25 th, 75 th) (only for deceased donor kidney transplant)	44 (23, 66)	41 (21, 63)	$P = 0.01$
Transplant year, %			$P < 0.001$
2000–2004	13.56	35.14	
2005–2009	41.22	31.24	
2010–2014	45.21	33.62	

Table 1. Continued.

Characteristics	ESW (n = 2831)	Steroid continuation (n = 6859)	P-value
Induction therapy, %			$P < 0.001$
Thymoglobulin	50.58	33.04	
Alemtuzumab	27.66	3.79	
Basiliximab	10.35	28.24	
Other induction	2.90	10.29	
No induction	10.53	26.27	
Maintenance therapy, %			$P < 0.001$
Tacrolimus	90.57	76.69	
Cyclosporine	5.12	17.95	
Mycophenolic acid	90.39	90.77	
Azathioprine	0.18	1.14	
Sirolimus	7.49	5.69	

BMI, body mass index; ECD, expanded criteria donor; ESW, early steroid withdrawal; HLA, human leukocyte antigen; KDPI, Kidney Donor Profile Index; PRA, panel reactive antibody.

causes of graft loss. After undertaking further detailed analysis of the narratives, the incidence of graft loss due to IgA recurrence increased from 15.43% to 18.26%. The incidence of graft loss due to acute rejection and CAN also increased from 15.91% to 17.04% and from 35.54% to 39.82%, respectively. Nonetheless, 10.58% of the recipients with graft loss were still left with "other or uninformative" as their causes of graft loss (see Table S4). We created a new category: medical nonadherence, which included 3.23% of recipients with graft loss as it was unclear whether these recipients experienced acute rejection or CAN.

We then re-performed the competing risk analysis to assess the association of steroids and incidence of graft loss due to IgA recurrence, acute rejection, and CAN. In univariate analysis, the use of steroids was associated with a reduction in graft loss due to IgAN recurrence with a SHR of 0.725 (95% CI, 0.545–0.965; P = 0.027). This difference persisted in the multivariable model after adjusting for recipient age, sex, race, dialysis duration, donor age, sex, race, transplant type (deceased vs. living), and transplant eras, and steroid continuation was also significantly associated with a reduction in graft loss with a SHR of 0.715 (95% CI, 0.531–0.964; P = 0.028). Steroid therapy did not have any effect on graft loss due to acute rejection and CAN in multivariable models (Table S5).

Discussion

This analysis, which included 9690 single organ kidney transplants performed in the USA over 15 years, is the largest retrospective study to date evaluating the association of steroid continuation on kidney graft loss due to recurrent IgAN. Our study demonstrates that the use of steroids is strongly associated with reduced risk of graft loss due to recurrent IgAN, but does not influence graft or patient survival overall. Apart from steroids, we found no association between the use of other induction or maintenance immunosuppressive medications and the risk of graft loss due to IgAN.

An association between an increased risk of IgAN recurrence and ESW immunosuppression protocol has also been observed by others. Mulay *et al.* [20] examined the effect of immunosuppressive medications on allograft failure due to various subtypes of recurrent glomerulonephritis. In a subgroup analysis, steroid use was associated with HR for recurrent IgAN of 0.57 (95% CI 0.12–2.71; P = 0.48). It is plausible that the effect of steroids did not reach a statistically significant difference because the follow-up time was relatively short, and the cohort was conducted in the era (1990–2003) when ESW maintenance protocol was not widely used. As the number of recipients who were not on steroids was small, the study might not have had enough power to detect an effect of steroids on recurrent IgAN.

Kukla *et al.* [17] observed a higher risk of recurrence of primary glomerulonephritis with ESW regimen. At the 7-year follow-up period, there were 22% of patients in the ESW steroid group versus only 5.2% in the steroid continuation group that developed histologic recurrence (P = 0.02). Clayton *et al.* [18] conducted a retrospective study based on the Australia and New Zealand Dialysis and Transplant Registry and found that

steroid use was strongly associated with a reduced risk of graft loss due to IgAN recurrence (SHR 0.50, 95% CI 0.30–0.84, $P = 0.009$). Similarly, Visger *et al.* [19] observed a significantly higher risk of histologic IgAN recurrence with ESW regimens when compared to steroid continuation regimens (HR 8.59, 95% CI 3.03–24.38; $P < 0.001$).

Despite having less IgAN recurrence in the steroid continuation group, we have shown that the overall DCGS was not different from the ESW group. We attributed these effects to the recipients in steroid continuation group had proportionally more deceased donor transplantation, less preemptive transplantation, and were proportionally less likely to be identified as white. These factors are known to increase the risk of rejection [21–23]. As expected, the association of steroids on graft loss due to acute rejection and CAN dissipated after adjusting for the aforementioned covariates (see details in the supplement).

The lack of association between antithymocyte globulin (ATG) induction therapy and recurrent IgAN in our study is contrary to that reported by Berthoux *et al.*, who observed a lower risk of recurrent IgAN with ATG induction therapy [24]. In contrast to Berthoux *et al.* study, we had a significantly larger number of patients in our cohort. Visger *et al.* [19] did not find a significant association of lymphocyte depletion (ATG + OKT3) induction on the overall rate of recurrent IgAN, but the risk of recurrence appeared higher with non-lymphocyte depletion induction in multivariable analysis after adjusting for steroid therapy (RR 4.55, 95% CI 1.77–11.73; $P = 0.002$). In our study, ATG induction did not have any effect on graft loss due to IgA recurrence in univariate analysis.

In contrast to Visger *et al.* [19] which observed an increased risk of IgAN recurrence with sirolimus, we did not find any significant effect of sirolimus on graft loss due to IgAN recurrence. In that study, there was an overwhelmingly larger proportion of patients receiving sirolimus in the nonsteroid group compared to the steroid group, which made it difficult to extract out the impact of sirolimus itself from the ESW regimen on the risk of recurrence. Although not statistically significant, a larger percentage of patients on sirolimus underwent biopsy than those who were not on sirolimus. This is presumably a consequence of the high frequency of proteinuria observed with sirolimus use and could have led to detection bias. Similar to prior studies, we found no protective effect of mycophenolate to prevent IgA recurrence [25,26].

The study is limited by the use of registry data. While the UNOS/OPTN data are extensive, it lacks granularity and details that could have an effect on the studied outcomes. For instance, we used steroids upon discharge for our outcome analysis which might not represent a longitudinal use of steroids upon follow-up. In our study, more than 16% of recipients who were discharged without steroids ended up on steroids at a year follow-up presumably from rejection. However, this should have weakened the strength of observed association. Likewise, some recipients who were discharged with steroids might have ended up with a ESW regimen as some transplant centers withdraw steroids late after transplantation. Thus, we tried to address this concern by looking at steroid use at a year follow-up. Less than 8% of recipients were converted to a steroid-free regimen at a year follow-up, which should not have a significant impact on our outcome analysis. In addition, patients might get biopsies of their allograft and be restarted on steroids if there was evidence of IgAN (with or without subsequent graft loss), which might limit some of the potential benefit of this analysis.

Another major shortcoming of using the registry is that we were unable to fully assess the impact of steroid maintenance therapy as well as other induction and maintenance immunosuppressive medications given that we were only able to use graft loss for our outcome analysis. It is very plausible that the protective effect of steroid use would be even more pronounced if we take recipients' serum creatinine and proteinuria into account as some recipients may have developed histological recurrence of IgAN without graft loss. Additionally, several important covariates (race, preemptive transplantation, type of transplantation, transplant era, etc.) were significantly different between recipients treated with ESW and steroid continuation regimens, and multivariable adjustment for these covariates may not entirely eradicate those residual confounding effects.

We did not have information on whether the cause of graft loss was biopsy-proven; as a result, the cause of graft loss was arbitrarily coded to an extent which might reduce the accuracy of this endpoint. Some of the graft losses due to CAN may turn out to be undiagnosed IgAN recurrence. Similarly, some of the presumed graft losses due to IgAN recurrence may be misclassified as CAN. Physicians may have a lower threshold to pursue renal transplant biopsy in recipients on ESW regimens, and thus, they are more likely to be diagnosed with IgA recurrence. It is also important to note that we encountered many reports of graft loss due to "other specified" (23.51% of recipients who had

Table 2. Causes of graft loss stratified by steroid use upon discharge.

Causes	ESW (%) $n = 297$	Steroid continuation (%) $n = 941$	Total (%) $n = 1238$
IgA recurrence	61 (20.54)	130 (13.82)	191 (15.43)
Acute rejection	39 (13.13)	158 (16.79)	197 (15.91)
Chronic allograft nephropathy	84 (28.28)	356 (37.83)	440 (35.54)
BK nephropathy	9 (3.03)	24 (2.55)	33 (2.67)
Primary failure	13 (4.38)	42 (4.46)	55 (4.44)
Graft thrombosis	6 (2.02)	8 (0.85)	14 (1.13)
Infection	3 (1.01)	8 (0.85)	11 (0.89)
Urological complications	1 (0.34)	4 (0.43)	5 (0.40)
Other, specified	81 (27.27)	210 (22.32)	291 (23.51)

ESW, early steroid withdrawal.

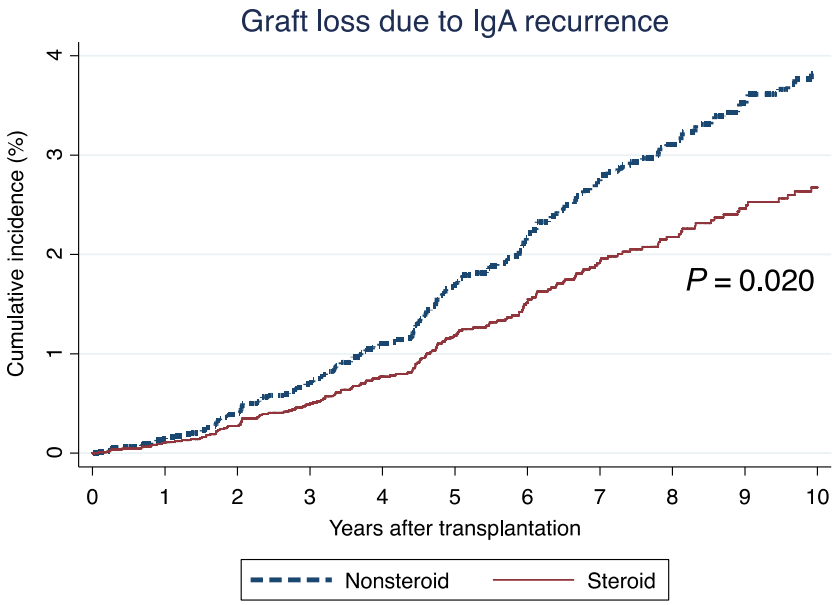

Figure 2 Ten-year unadjusted cumulative incidence of graft loss due to IgA recurrence stratified by steroid use upon discharge.

graft loss), which resulted in a lower cumulative incidence of graft loss due to IgAN recurrence than the prior study [25,26]. We tried to address this concern by reviewing all the free-text narratives of the recipients who experienced graft loss due to "other specified" and creating a new variable for causes of graft loss. We were able to identify slightly more than half of these recipients. After that, we were left with only 10.58% of the recipients whom the causes of graft failure were still either unknown or uncategorized. The competing risk analysis was re-performed based on this newly created variable, and the result continued to show a reduced risk of graft loss due to IgA recurrence with the use of steroids.

The strengths of this analysis are that it is the largest study to date on association between steroid use and IgA recurrence with a long follow-up time; thus, our study maybe better powered when compared to prior studies. The analysis includes all adult patients with IgAN undergoing solitary kidney transplantation within the United States; therefore, the study population fully represents the target population. Our analysis expands and strengthens the current available literature of using steroid maintenance therapy for prevention of recurrent IgAN. This may be useful for counseling IgAN patients on selecting post-transplant immunosuppressive regimens and designing strategies to prevent recurrent disease.

In summary, we find continued evidence that the use of early steroid-withdrawal regimen in recipients with IgAN is associated with a higher risk of graft loss due to disease recurrence. Future prospective studies are

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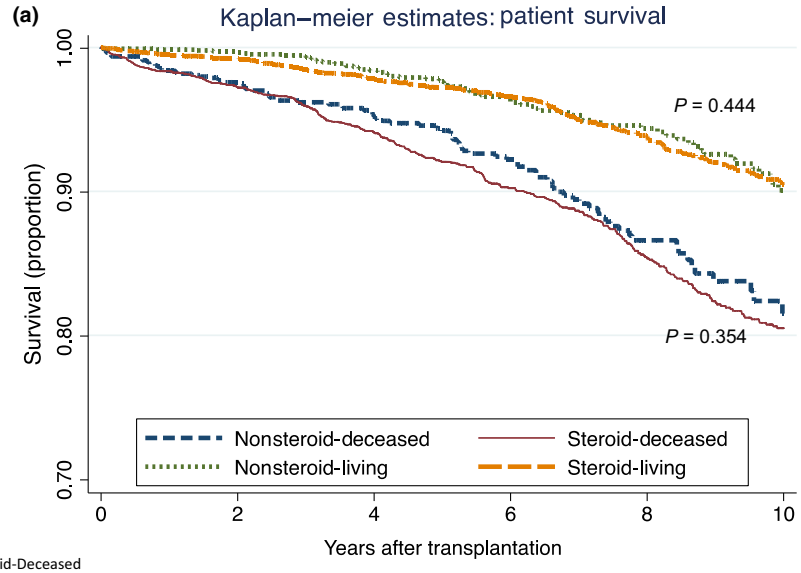
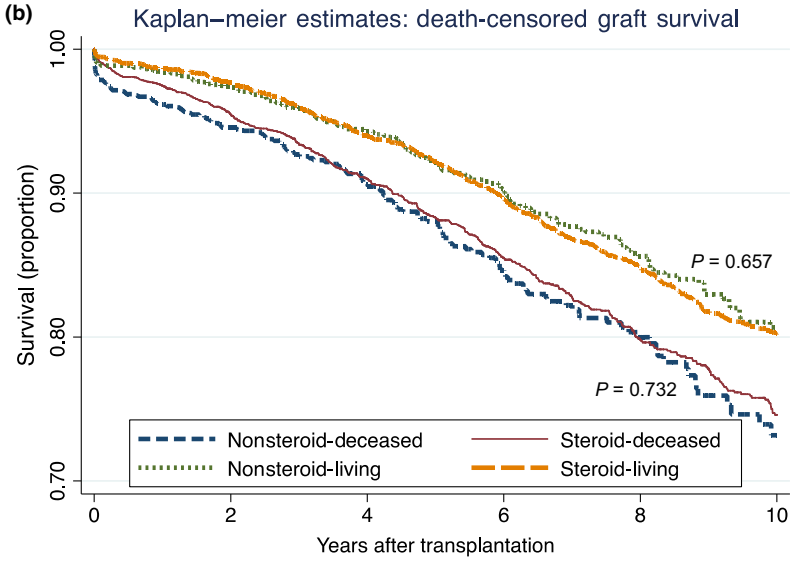
Table 3. Competing risk analysis of graft loss due to IgAN recurrence between ESW versus steroid continuation groups.

	Univariate analysis			Multivariate analysis		
	SHR	95% CI	*P*-value	SHR	95% CI	*P*-value
Steroid use	0.695	0.511–0.945	0.020	0.666	0.482–0.921	0.014
Recipient age	0.978	0.966–0.991	0.001	0.979	0.966–0.992	0.002
Recipient race						
Caucasian	1.444	1.050–1.987	0.024	Reference		
African American	1.212	0.673–2.182	0.521	0.899	0.480–1.685	0.740
Hispanic	0.712	0.427–1.186	0.192	0.709	0.377–1.330	0.284
Asian	0.540	0.328–0.887	0.015	0.499	0.271–0.920	0.026
Other	1.181	0.550–2.532	0.670	1.036	0.410–2.613	0.941
Recipient sex (male)	1.142	0.840–1.553	0.395	1.063	0.771–1.465	0.709
Zero mismatch	0.909	0.579–1.427	0.678			
Recipient BMI	1.007	0.982–1.033	0.594			
Diabetes	0.714	0.294–1.735	0.457			
Dialysis duration						
Preemptive	0.616	0.421–0.901	0.012	Reference		
0 to <1 year	1.697	1.264–2.278	<0.001	2.005	1.304–3.083	0.002
1 to <3 years	1.283	0.942–1.748	0.114	1.642	1.040–2.591	0.033
≥3 years	0.624	0.413–0.943	0.025	0.947	0.533–1.681	0.852
Donor age	0.998	0.987–1.010	0.756	1.001	0.989–1.013	0.891
Donor race						
Caucasian	1.172	0.839–1.638	0.353	Reference		
African American	1.376	0.812–2.332	0.236	1.486	0.872–2.533	0.145
Hispanic	0.694	0.422–1.143	0.151	0.846	0.459–1.560	0.593
Asian	0.717	0.365–1.385	0.316	1.176	0.518–2.667	0.6998
Other	1.128	0.419–3.035	0.811	1.129	0.358–3.557	0.836
Donor sex (male)	0.757	0.568–1.009	0.058	0.741	0.551–0.996	0.047
Donor type (living)	0.969	0.723–1.300	0.832	0.688	0.486–0.974	0.014
Induction therapy						
Thymoglobulin	0.975	0.720–1.320	0.871			
Alemtuzumab	1.210	0.735–1.995	0.454			
Basiliximab	0.963	0.684–1.357	0.830			
Other induction	0.969	0.616–1.525	0.893			
No induction	0.986	0.713–1.365	0.934			
Maintenance therapy						
Tacrolimus	1.231	0.878–1.723	0.227			
Cyclosporine	0.847	0.590–1.214	0.366			
Azathioprine	2.032	0.838–4.929	0.117			
Mycophenolate	0.760	0.516–1.119	0.164			
Sirolimus	1.251	0.790–1.981	0.339			
Transplant eras						
2000–2004	1.091	0.804–1.481	0.576	1.127	0.682–1.864	0.641
2005–2009	0.954	0.705–1.291	0.759	1.027	0.632–1.670	0.914
2010–2014	0.919	0.579–1.460	0.722	Reference		

ESW, early steroid withdrawal; IgAn, immunoglobulin A nephropathy; SHR, subdistribution hazard ratio.



Non-steroid-Deceased						
Number at risk	1101	896	637	406	230	91
Number of events	0	22	18	16	20	9
Steroid-Deceased						
Number at risk	3057	2570	1925	1371	944	602
Number of events	0	76	73	68	62	47
Non-steroid-Living						
Number at risk	1728	1483	1100	734	424	213
Number of events	0	4	15	20	11	14
Steroid-Living						
Number at risk	3802	3296	2566	1931	1388	943
Number of events	0	26	42	28	47	43



Non-steroid-Deceased						
Number at risk	1099	867	600	366	204	80
Number of events	0	37	32	34	15	13
Steroid-Deceased						
Number at risk	3053	2465	1790	1249	842	532
Number of events	0	116	103	93	72	45
Non-steroid-Living						
Number at risk	1727	1446	1050	695	400	198
Number of events	0	28	41	40	28	19
Steroid-Living						
Number at risk	3801	3227	2455	1817	1288	875
Number of events	0	67	110	103	86	62

Figure 3 (a) Unadjusted Kaplan–Meier patient survival curves in ESW groups compared to steroid continuation groups stratified by donor type. (b) Unadjusted Kaplan–Meier death-censored graft survival curves in ESW groups compared to steroid continuation groups stratified by donor type.

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warranted to further address which patients with IgAN would benefit from steroid continuation.

Authorship

NL: participated in research design, data analysis, the drafting of the manuscript and final approval of the manuscript. NG: participated in research design, interpretation of data for the work, technical editing and final approval of the manuscript. EVK: participated in revising of the manuscript and final approval of the manuscript. FC: participated in revising of the manuscript and final approval of the manuscript. MP: participated in research design, interpretation of data for the work, technical editing and final approval of the manuscript.

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Conflicts of interest

Dr. Pavlakis is on an endpoint adjudication committee for Shire Pharmaceuticals.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. (A) Cox proportional hazards model for patient survival in deceased donor kidney recipients between ESW versus steroid continuation groups. (B) Cox proportional hazards model for patient survival in living donor kidney recipients between ESW versus steroid continuation groups.

Table S2. (A) Cox proportional hazards model for death-censored graft survival in deceased donor kidney recipients between ESW versus steroid continuation groups. (B) Cox proportional hazards model for death-censored graft survival in living donor kidney recipients between ESW versus steroid continuation groups.

Table S3. Competing risk analysis of causes of graft loss between ESW versus steroid continuation groups.

Table S4. Causes of graft loss stratified by steroid use upon discharge after manually reviewing free-text narratives under the "cause of graft failure, other specified" variable.

Table S5. Competing risk analysis of causes of graft loss between ESW versus steroid continuation groups based on the newly created variable for causes of graft loss after manually reviewing free-text narratives under the "cause of graft failure, other specified" variable.

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