Dialysis prior to living donor kidney transplantation and rates of acute rejection

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Abstract

Background. The relationship between transplantation prior to chronic dialysis initiation and the pattern of acute rejection of kidneys from living donors (LDKT) has not been fully explored.

Methods. Using data provided by the United States Renal Data System, we performed a retrospective cohort study fitting multivariate proportional hazards models to characterize the association of chronic use of dialysis prior to transplantation [non-pre-emptive LDKT (non-PLDKT)] and acute rejection, and to examine if this association varies throughout the first year.

Results. Non-PLDKT was associated with a 2.5-fold higher rate of biopsy-confirmed rejection during the first month [adjusted HR 2.5, 95% confidence interval (1.85–3.33)], compared with no dialysis prior to transplantation. Increasing duration of pre-transplant dialysis was associated with increasing rate of biopsy-confirmed acute rejection during the first month (P < 0.001 for trend). Over the first year, there was a diminishing relationship between non-PLDKT and acute rejection: 2.5-, 2.22-, 2.13- and 1.78-fold elevation in the episodes of biopsy-confirmed acute rejection during the first, second, third through to the sixth and seventh through to the twelfth month post-transplant, respectively (P = 0.05 for trend).

Conclusions. The waning of the association of non-PLDKT with acute rejection over time supports the hypothesis that dialysis exposure prior to transplantation may modulate the immune system to increase the rates of acute rejection.

Keywords: dialysis; kidney; rejection; transplantation

Introduction

Patients with end-stage renal disease and who have potential living donors may have the opportunity to undergo pre-emptive living donor kidney transplantation (PLDKT), in contrast to the near universal timing of cadaveric kidney transplantation after the initiation of chronic dialysis. PLDKT is associated with a greater rate of allograft survival than transplantation from living donors after the commencement of chronic dialysis [1]. In a secondary analysis, an association with the reduction of biopsy-confirmed episodes of acute rejection after transplantation was proposed to be a partial explanation for the observed differences in allograft survival between these two timing strategies. Supporting the epidemiological data is in vitro evidence demonstrating that dialysis modifies immune processes, specifically the activity of T cells, among patients with renal failure [2–5]. We hypothesized that if dialysis exposure impacts the activation of the immune system, then the greatest difference in the activities of the immune systems between recipients undergoing pre-emptive transplantation and recipients of transplants received after initiation of dialysis should be associated with longer dialysis exposures and be manifest early during the post-transplant period closest to the prior dialysis exposure. Investigating these hypotheses was the principal objective of this study.

Subjects and methods

We conducted a retrospective cohort study comparing the rates of acute rejection during sequential time intervals in the first year after living donor transplantation among patients who were exposed previously to maintenance...
Dialysis and acute rejection

Dialysis of varying durations to patients who received transplants without prior dialysis. This study was approved by the Institutional Review Board of the University of Pennsylvania.

All patients in the USA who were 18 years of age or older when they received their primary kidney transplant from a living donor between January 1994 and June 1997 were potentially eligible for this study. Subjects were followed until the development of acute rejection, initiation of chronic dialysis, retransplantation, loss-to-follow-up, death or the end of the first year post-transplant, whichever occurred first. Patients with missing data on the date of first treatment for end-stage renal disease were excluded because of an inability to confirm the timing of LDKT relative to the exposure of dialysis.

Demographic and follow-up transplant data have been collected by the United Network for Organ Sharing and were supplied by the United States Renal Data System (USRDS). Potential confounding variables considered for this study included: recipient and donor age; gender and ethnicity (white, black or other); donor–recipient relationship (spouse, child, sibling, parent or other); number of human leukocyte antigen (HLA) haplotype matches (0, 1 or 2); most recent panel reactive antibodies (PRA, 0–100%); cause of native kidney disease [diabetes mellitus, hypertension, glomerulonephritis, cystic kidney disease, interstitial disease, or other (missing, unknown, other cause)]; use of antibody induction therapy; and delayed allograft function (DGF) defined as the use of dialysis in the first week post-transplant. Pre-emptive transplantation was defined as the absence of dialysis prior to LDKT and non-pre-emptive transplantation was defined as the administration of dialysis of any duration prior to transplantation.

Survival analysis was utilized to investigate the relationship between dialysis exposure prior to transplantation and the rate of biopsy-confirmed acute rejection following transplantation [6]. The primary endpoint was the first episode of acute rejection confirmed by biopsy. Allograft failure or patient death were considered censoring events. Acute rejection was indicated either by the International Classification of Diseases, Ninth Revision code 996.80 for transplant rejection or the code 996.81 for kidney rejection, in addition to a procedure code 55.23 for kidney biopsy. Potential predictors for multivariable modelling were screened in unadjusted Cox models. Variables that had a nominal relationship ($P < 0.10$) with allograft survival were eligible for inclusion in multivariable models. Multivariable Cox proportional hazards models were fit to adjust for potential confounders of the relationship between pre-transplant dialysis and acute rejection. We fit these models by first adding covariates using a forward stepwise algorithm and then removing variables that did not retain statistical significance by the Wald statistic ($P \leq 0.05$) [7]. Additionally, an indicator variable for the year of transplant was included to account for other aspects of the management of transplant recipients that had evolved over the period of the study. Further, an indicator for the annual volume of LDKTs performed at the transplant centre was included in each model. The assumption of proportional hazards was tested by graphical and weighted residuals testing [8], and by including time by predictor interaction terms as time-varying covariates. Standard errors for the rate ratios were calculated using the robust variance estimator to account for clustering of data by transplant centre [9]. The relationship between the duration of exposure to pre-transplant dialysis and acute rejection was explored using indicator variables generated based on the quartiles of time on dialysis prior to transplantation.

The general modelling strategy just described was initially used to examine the first month of follow-up post-transplant. Subsequently, we investigated the potential changing impact of non-PLDKT on the occurrence of acute rejection during the first year after transplantation. We divided follow-up during this year into four discrete and non-overlapping time periods: 0–30, 31–60, 61–180 and 181–365 days. We examined the associations between non-PLDKT and acute rejection separately within each period, conditional on rejection-free survival in previous time intervals. We used time by non-PLDKT interaction terms in the Cox model to assess whether the association of non-PLDKT with the rate of acute rejection during the first year remained constant or waned, as we had hypothesized.

Two supplemental analyses were performed to evaluate the stability of our findings. First, the analyses were repeated for acute rejection episodes defined less stringently by a diagnosis code with or without evidence of a transplant kidney biopsy. Secondly, using Medicare medical claims activity within the first year post-transplant, the analyses were limited to patients who had evidence that Medicare was their primary payer for medical insurance to minimize any bias in the verification of episodes of acute rejection among subjects undergoing chronic dialysis prior to LDKT related to insurance status.

Analyses were performed with the use of STATA 6.0 software (Stata Corporation, College Station, TX). $P$-values were two-sided and a value < 0.05 was considered to be significant.

Results

Demographics

Among the 9130 patients receiving a LDKT during the study period, 649 (7.1%) patients were excluded because of a missing date of first treatment for end-stage renal disease ($n = 65$) or because of prior transplantation ($n = 584$). Among the patients included in the analysis, 1819 (21.4%) received a kidney allograft from a living donor prior to the initiation of dialysis. The majority of the recipients in both groups of patients were white and male (Table 1). Siblings were the most common source of allografts and, accordingly, one match of the HLA haplotype was the most frequent in both groups. Cyclosporine-based immunosuppression regimens were prescribed in 8032 (94.7%) of the subjects at the time of discharge following transplantation.

Acute rejection in the first month

There was a higher frequency of biopsy-confirmed rejections in the non-pre-emptive group during all evaluated time points post-transplant (Table 2). Figure 1 displays a lower unadjusted rate of acute rejection-free allograft survival during the first month post-transplant among recipients of PLDKT ($P = 0.001$). After adjustment for donor–recipient gender
and ethnic relationships, PRA and DGF, non-PLDKT was associated with a 2.5-fold higher rate of rejection during the first month post-transplant [adjusted HR 2.5, 95% confidence interval (CI) (1.85–3.33)]. When other covariates that plausibly impact the risk of rejection (number of HLA haplotype matches, and the use of antibody induction therapy) were forced into the model, the elevation in the rate of acute rejection in the first month associated with non-PLDKT was unchanged [adjusted HR 2.5, 95% CI (1.85–3.45)]. Although the cause of end-stage renal disease was associated with the timing of transplantation relative to the initiation of dialysis, the inclusion of this covariate in the models did not significantly impact these findings.

Increasing duration of dialysis use prior to LDKT was associated with increasing rates of rejection within the first month (Table 3), rising from a 1.71-fold elevated rate for the lowest quartile of the duration of pre-transplant dialysis to a 3.95-fold higher rate for the highest quartile (P = 0.001, test for trend).

![Fig. 1. Kaplan–Meier curves for the proportion of recipients with episodes of biopsy-confirmed acute rejection in the first month according to the use of dialysis prior to kidney transplantation from a living donor.](https://academic.oup.com/ndt/article-abstract/18/1/172/1809156)
Rejections during the first year

The association of non-PLDKT and acute rejection was somewhat attenuated with increasing time after transplantation (Table 4). Over the first year post-transplant, non-PLDKT was associated with a 2.5-, 2.22-, 2.13-, and a 1.78-fold higher rate of biopsy-confirmed acute rejection during the first, second, third through to sixth and seventh through to twelfth months post-transplant, respectively ($P = 0.05$, test for trend). Furthermore, increasing duration of time on dialysis pre-transplant had less significant impact on the rates of acute rejection in each subsequent time period post-transplant (data not shown, $P = 0.05$ for trend). In the first year, 62 (0.73%) subjects had more than one episode of biopsy-confirmed rejection, which was unrelated to non-PLDKT ($P = 0.68$).

Supplemental analyses

The association of non-PLDKT and increase in the rate of acute rejections within the first month was essentially unchanged when the occurrence of rejection was defined by diagnosis codes with or without evidence of a kidney transplant biopsy [adjusted HR 2.12, 95% CI (1.52–3.03)] (Table 3). The analysis limited to the 3771 recipients who had evidence that Medicare was their primary payer of medical insurance yielded an association of non-PLDKT and rejection in the first month that was not substantively different than the primary analysis [adjusted HR 2.56, 95% CI (1.69–4.00)].

Table 3. Association of the duration of pre-transplant dialysis and biopsy-confirmed acute rejection in the first month

<table>
<thead>
<tr>
<th>Duration of dialysis prior to transplant</th>
<th>Adjusted HR$^a$ [vs pre-emptive (0 days)]</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>First quartile ( &gt; 0 and ≤174 days)</td>
<td>1.71</td>
<td>(1.21–2.41)</td>
</tr>
<tr>
<td>Second quartile ( &gt; 174 and ≤329 days)</td>
<td>2.09</td>
<td>(1.48–2.96)</td>
</tr>
<tr>
<td>Third quartile ( &gt; 329 and ≤623 days)</td>
<td>2.51</td>
<td>(1.80–3.50)</td>
</tr>
<tr>
<td>Fourth quartile ( &gt; 623 days)</td>
<td>3.95</td>
<td>(2.76–5.66)</td>
</tr>
</tbody>
</table>

$^a$Adjusted for donor–recipient ethnic and gender relationships, PRA, DGF, transplant centre and year of transplant. HR denotes hazard ratio.

Table 4. Association of non-pre-emptive transplantation and the rate of first acute rejection during sequential time intervals in the first year post-transplant

<table>
<thead>
<tr>
<th>Interval of time post-transplant (months)</th>
<th>Adjusted HR$^a$ [non-pre-emptive transplantation (vs pre-emptive)]</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>2.50</td>
<td>1.85–3.45</td>
</tr>
<tr>
<td>Second</td>
<td>2.22</td>
<td>1.54–3.23</td>
</tr>
<tr>
<td>Third to sixth</td>
<td>2.12</td>
<td>1.52–3.03</td>
</tr>
<tr>
<td>Seventh to twelfth</td>
<td>1.78</td>
<td>1.14–2.86</td>
</tr>
</tbody>
</table>

$^a$Adjusted for donor–recipient ethnic and gender relationships, PRA, DGF, transplant centre and year of transplant. HR denotes hazard ratio for the specified time interval.

Table 5. Supplemental analyses

<table>
<thead>
<tr>
<th>Diagnosis of rejection with or without biopsy</th>
<th>Adjusted HR$^a$</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited to Medicare recipients</td>
<td>2.56</td>
<td>(1.69–4.00)</td>
</tr>
</tbody>
</table>

$^a$Adjusted for donor–recipient ethnic and gender relationships, PRA, DGF, transplant centre and year of transplant. HR denotes hazard ratio for the specified time interval.

Discussion

This study demonstrates that dialysis before living donor kidney transplantation is associated with an increase in the rate of rejection episodes in the first year post-transplant, and that the greatest impact of prior dialysis was observed among patients with longer exposures and early on during the first year post-transplant.

This study’s findings are consistent with in vitro data assembled over the past five decades. As early as 1957, impaired immune processes have been known to exist in patients with chronic renal failure [10]. Descamps-Latscha et al. [5] were the earliest investigators to suggest that differences in T-cell activation exist among patients who were dialysis-dependent, and those patients who had chronic renal failure, but were not yet on dialysis. Dialysis exposure increased levels of markers of T-cell activation (sCD25), and lowered levels of inhibitors of T cells (IL-1Ra). Recently, Kaul et al. [11] followed a series of patients with advanced renal failure during a timeframe over which they transitioned from not requiring renal replacement therapy to becoming dependent on chronic dialysis. The impaired activation of T cells to phytohaemagglutinin preceding the initiation of chronic dialysis improved during the first 6 weeks of haemodialysis. These observations suggest that impaired immune responses present in uraemic, undialyzed patients improve after some time on dialysis. In addition, compared with healthy controls, patients who are dialyzed may have a larger percentage of their T cells comprised of the Th1 subset, further increasing their propensity to cellular rejection [12].

Our study is also consistent with an earlier clinical investigation that examined the association of dialysis exposure and rates of acute rejection in recipients of cadaveric renal allografts [13]. In this study, the risk
of acute rejection was the lowest among the group dialyzed for the shortest duration prior to transplantation. However, this study could not clarify the relationship between dialysis exposure and acute rejection, because pre-emptive transplant recipients were not analysed separately, and no multivariable analysis was performed. The rising risk of acute rejection associated with increasing duration of dialysis prior to transplantation that we observed is also consistent with observations made by Meier-Kriesche et al. [14] who detected an increasing relative risk of allograft failure with longer durations of dialysis prior to transplantation, compared with pre-emptive transplantation.

This study confirms and extends our prior report of increased odds of acute rejection with non-PLDKT [1]. We hypothesized that if the exposure to chronic dialysis prior to LDKT increased the risk of acute rejection by impacting biological processes, then the magnitude of the relationship between rejection events and dialysis prior to LDKT should decrease with time over the first year post-transplant. This study demonstrated such a time-varying association of prior dialysis and acute rejection, as well as a higher risk of acute rejection with increasing duration of dialysis prior to transplantation. Both of these observations provide further evidence that dialysis exposure may modulate the immune system.

The present investigation’s findings of differential rates of acute rejection between PLDKT and non-PLDKT may be explained, at least in part, by the difference in activation thresholds, cytolytic responses and survival characteristics between memory and naïve T cells [15,16]. Dialysis may lead to the non-specific activation of memory T cells that are maintained over long periods of time and are alloreactive to antigens in a renal allograft [17]. This observational study did not entail measurements of T-cell characteristics and, therefore, this explanation requires verification. If confirmed, the significance of these findings extends beyond renal transplantation and may also have implications for recipients of other solid organ transplants such as liver allografts.

The findings of this study should be viewed in the context of several limitations. First, we did not have access to data on the level of urea clearance by pre-transplant dialysis, residual function of native kidneys or transplant renal function. Examining the separate associations of a measure of immune competence with renal function provided by native kidneys or by the clearance from dialysis would provide useful information that was not collected in this study. Secondly, other than the use of antibody induction therapy and type of calcineurin inhibitor at the time of discharge for the transplant procedure, we did not have data on the time varying administration of immunosuppressive agents. Nonetheless, it is unlikely that subjects transplanted pre-emptively would have received an immunosuppressive regimen that systematically differed from the prescription of the non-pre-emptive cohort. Thirdly, we were unable to examine factors associated with the exposure to dialysis that may be contributing mechanisms to our findings, such as the number of blood transfusions, i.v. use of calcitriol or type of dialysis modality. Finally, despite the multivariable analysis, we cannot exclude the possibility of residual confounding from unmeasured characteristics.

In conclusion, we observed clinically significant increased rates of acute rejection post-transplant among patients undergoing kidney transplantation from living donors after initiation of chronic dialysis. Patients with longer exposures to dialysis before transplantation had higher rates of acute rejection. Over the first year post-transplant, the impact of pre-transplant dialysis was attenuated beginning after the first month, when the greatest difference of the immune system would be expected between pre-emptive and non-pre-emptive recipients. These observations provide evidence that the exposure to dialysis potentially impacts immune responses to increase the risk of rejection. Studies addressing the cellular events that are modulated by dialysis and level of renal function may elucidate the mechanisms underlying this study’s findings and provide novel insights into the regulation of the immune system.

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