Impact of Induction Therapy on Delayed Graft Function Following Kidney Transplantation in Mated Kidneys

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ABSTRACT

Background. Delayed graft function (DGF) is defined as the need for dialysis within 1 week of transplantation and occurs in 20%–50% of deceased-donor kidney transplant recipients. Although recovery from DGF often occurs within a few days, many cases may take weeks to months before the transplant function begins. The delay in function increases the complexity of recipient care, makes the diagnosis of acute rejection more difficult, prolongs length of stay, and increases hospital costs. Although several authors have proposed nomograms to predict DGF, there is no identifiable strategy to ameliorate it, except for the possible use of a specific type of induction therapy called Thymoglobulin.

Methods. In this retrospective analysis we included 407 subjects, of which 76 were mated (left and right kidney transplanted at Montefiore from the same donor). We used conditional logistic regression analysis while adjusting for the mated kidneys. We adjusted for age, gender, and race *a priori*, as well as cold ischemia time.

Results. There was a 36% decrease in odds of DGF when Thymoglobulin was used as induction when compared with basiliximab in mated kidneys 0.64 (0.10–4.05) (odds ratio [OR] with 95% confidence interval [CI]).

Conclusions. Thymoglobulin did have a protective effect in these data when analyzed in mated kidneys, however, we need a larger amount of data to concretely conclude this effect.

DELAYED graft function (DGF) is defined as the need for dialysis within 1 week of transplantation and occurs in 20%–50% of deceased-donor kidney transplant recipients [1]. It is a form of acute kidney injury resulting in post-transplantation oliguria, increased allograft immunogenicity and risk of acute rejection episodes, and decreased long-term survival [2]. Although recovery from DGF often occurs within a few days, many cases may take weeks to months before the transplanted kidney begins to function. The delay in function increases the complexity of recipient care, makes the diagnosis of acute rejection more difficult, prolongs length of stay, and increases hospital costs [3]. Although several authors have proposed nomograms to predict DGF, there is no identifiable strategy to ameliorate it, except for the possible use of a specific type of induction therapy called anti-thymocyte globulin (ATG) [4,5]. It is especially difficult to adjust for the preimplantation phase, which we define as the graft's procurement. This complex process introduces a magnitude of variables that significantly changes a graft's outcomes. We chose a mated kidney model to control for all donor factors to determine the association between induction and DGF.

Induction therapy is described as the intravenous immunosuppressive therapy given at the time of transplantation

The research described was supported by the National Institutes of Health/National Center for Advancing Translational Science Einstein-Montefiore Clinical and Translational Science Awards Program (CTSA) Grant Number UL1TR001073.

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0041-1345/17
http://dx.doi.org/10.1016/j.transproceed.2017.06.032

and has grown in use from 9% in 1992 to 59% in 1999 [6]. Currently, the two most used agents are Basiliximab, an interleukin (IL)-2 receptor monoclonal antibody that competes with IL-2 to bind to the alpha chain subunit of the IL-2 receptor on the surface of the activated T lymphocytes and thus prevents the receptor from signaling [7], and ATG, a lymphocyte-depleting polyclonal antibody that depletes T lymphocytes thus preventing them from replicating [8]. The intent of all induction therapies is to lower the incidence of acute rejection; however, some reports suggest an additional effect of ATG to prevent or reduce the incidence of DGF through the suppression of alloimmunity and ischemia reperfusion injury [9]. Whereas some previous reports have not shown an association of ATG with DGF [10,11], others have found a potential protective effect of ATG therapy with DGF [12,13].

We aimed to investigate the association between thymoglobulin and DGF. We hypothesized that thymoglobulin would be associated with decreased DGF.

METHODS

After institutional review board (IRB) approval, we retrospectively analyzed the charts of 407 deceased donor renal transplant subjects at the Montefiore Transplant Center from 2008 to 2015. Data collected included age at the time of transplantation, gender, race, history of hepatitis C infection, pretransplantation plasma-reactive antibody (PRA) class I and II, last recorded creatinine level (mean, 3 years post-transplantation), induction medication (thymoglobulin vs basiliximab), warm ischemia time (WIT), and cold ischemia time (CIT). We did not include donor factors because we have controlled for those variables by using a mated analysis. Seventy-six kidneys were mated, defined as both the left and right kidney from the same donor transplanted at our center (Fig 1). Discordant pairs were defined as mated kidneys where one kidney recipient received basiliximab as induction, whereas the other received Thymoglobulin. We evaluated continuous variables visually for any disturbances in normality. We examined all collected variables for bivariate associations as predictors of DGF using the *t* test, Mann-Whitney *U*, Kruskal-Wallis, and chi-square test as appropriate. We excluded WIT because there was no variability in the discordant paired kidneys used in the final model. We also excluded any pairs that did not use Thymoglobulin or basiliximab for induction (2 cases). We excluded hepatitis C infection from our final model because there were no paired kidneys with hepatitis C in our data. We defined our race variables as black and nonblack. There were no bivariate associations that were statistically significant, but we decided *a priori* to use age, gender, race, induction, and CIT in the model. We used a conditional logistic regression analysis to determine the association of DGF with Thymoglobulin while adjusting for age, gender, race, and CIT while controlling for donor factors by mating the kidneys in the model. We inserted all variables in a stepwise fashion into our model and defined confounding as a change in beta coefficient >10%. There was no effect modification in our model. Our power calculation showed an 88% power to detect a 10% difference in odds of DGF between our 38 matched sets of paired kidneys. All analysis was done using STATA v.14.2 (College Station, Tex, United States).

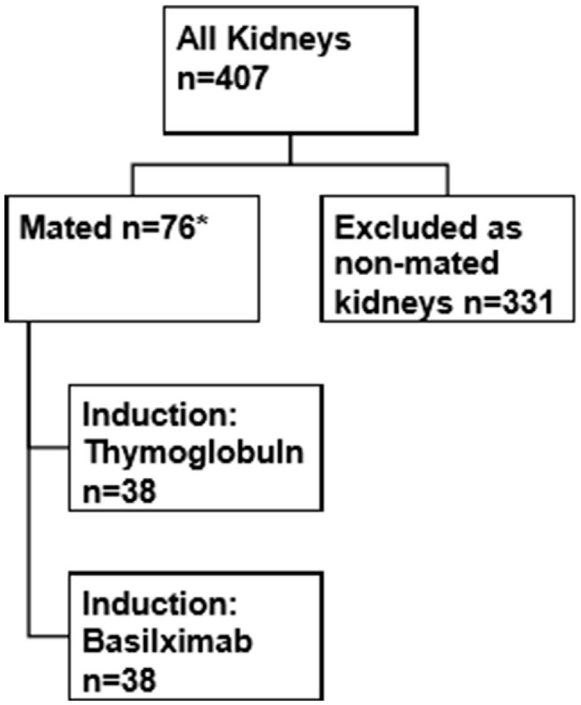

Fig 1. Four hundred seven deceased donor renal transplant subjects retrospectively evaluated from 2008–2015 at Montefiore Medical Center. *Mated is defined as 2 kidneys (left and right) from the same donor who underwent transplantation at Montefiore.

RESULTS

In our analysis of the 407 subjects who underwent transplantation from 2008 to 2015, 76 were mated kidneys. Of the 76 mated kidneys 38 received Thymoglobulin and 38 received basiliximab as induction therapy. There were no statistically significant differences between the ATG and basiliximab group when compared based on DGF, age, gender, race, and CIT (Table 1). There was a statistically significant difference in pretransplantation class I PRA for the basiliximab vs ATG groups (9% vs 17.5%; $P = .01$) and pretransplantation class II PRA approached statistical significance (2.5% vs 17%; $P = .06$). There were no statistically significant bivariate ($P < .05$) associations between DGF and induction type, CIT, 1-month postoperative creatinine level, nonblack race, age, or being female (Table 2). In the final model, there was a 35% decrease in odds of DGF when Thymoglobulin was used as induction therapy compared with basiliximab of 0.64% (0.10–4.05; odds ratio [OR] w 95% confidence interval [CI]), but the association was not statistically significant. Nonblack race was associated with a 46% decrease in odds of DGF when compared with black race of 0.54% (0.04–7.17; OR with 95% CI). Age was a confounder in our dataset and for every added year of age, there was a 5% decrease in odds of DGF of 0.94 (0.78–1.15; OR w 95% CI). Being female was associated with a 15%