Early Allograft Biopsies Performed During Delayed Graft Function May Not Be Necessary Under Thymoglobulin Induction

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Abstract

Objectives: **Delayed graft function affects up to 50% of kidney transplant recipients. Some guidelines recommend surveillance biopsies beginning 7 days after engraftment. This may be unnecessary with anti-thymocyte globulin induction.**

Materials and Methods: **We conducted a retrospective study of deceased-donor renal transplant recipients with delayed graft function.**

Results: **One hundred eleven patients met the inclusion criteria. The incidence of rejections during delayed graft function was 2.7%. They were diagnosed between 9 and 11 days after transplant. The subsequent incidence of rejection at 12-month follow-up was 13.5% (n=15). The median time to rejection after transplant was 10 weeks. Fourteen of 15 patients had subtherapeutic immunosuppression. The only risk factor associated with later rejection after delayed graft function was use of donors after cardiac death.**

Conclusions: **Early rejection during delayed graft function with anti-thymocyte globulin induction and maintenance immunosuppression with tacrolimus, mycophenolate mofetil, and steroids is rare. When later rejection occurs, it is at a median of 10 weeks after a transplant. Two of the 3 early rejections were antibody mediated. Later rejections were associated with subtherapeutic immunosuppression and donors after cardiac death. Biopsies need not be performed during the early postoperative period when anti-thymocyte globulin is used with tacrolimus, mycophenolate mofetil, and steroids.**

Key words: *Delayed graft function, Kidney, Transplant, Allograft, Thymoglobulin*

The shortage of organs has compelled centers to use kidneys from extended criteria donors (ECD) and donors after cardiac death (DCD). These kidneys have an increased risk of delayed graft function (DGF). Other risk factors for DGF include high panel reactive antibody, African American race, obesity, older donor and recipient age, prolonged cold ischemia time, and retransplant.[1] Delayed graft function is defined as *the need for dialysis in the first week after kidney transplant*, and is associated with increased hospital stay, costs, and psychologic and medical sequelae.[2]

Delayed graft function may be associated with an increased incidence of rejection. Puliatti[3] reported a rejection incidence of 18.8%. Moore cited an incidence of 28%.[4] Rejection may cause the decreased allograft survival reported in some publications.[5-7] In addition to DGF, risk factors associated with rejection (during DGF) include the number of human leukocyte antigen mismatches, the degree of sensitization, retransplant, and immunosuppressive regimens. Previous small studies regarding DGF vary in induction and maintenance immunosuppressive agents,[8] making it difficult to extrapolate results.

Rejection rates have decreased since the advent of newer induction and maintenance immunosuppressive agents. Many trials have shown that anti-thymocyte globulin (ATG) can reduce the

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incidence of rejection in the perioperative period.[9] It also may decrease the incidence of DGF by blocking various cytokines and chemokines.[10] A meta-analysis showed that ATG induction reduced the incidence of rejection. [11] According to UNOS data for transplants performed from 2007 to 2008, the incidence of rejection at the time of discharge was 2.6% with ATG and 3.7% without.

Maintenance immunosuppression regimens also have improved. Patients treated with tacrolimus and mycophenolate mofetil have displayed the lowest prevalence of rejection in some studies. [12, 13] Anti-thymocyte globulin use is associated with significant reduction in the incidence of acute rejection, graft loss, and patient death when used with tacrolimus, and mycophenolate mofetil, and with and without steroids.[14]

Renal allograft biopsy remains the criterion standard for diagnosing rejection. In the setting of DGF, it has been recommended that biopsies be performed at 1-week intervals, starting 7 days after surgery.[15, 16] It is unclear if with immunosuppression based on steroids, tacrolimus, and mycophenolate mofetil, biopsy guidelines should be modified to minimize hospital costs, decrease hospital stay, optimize hospital resources, and limit possible complications. Ideally, the biopsy should not be done when there is little clinical suspicion for and negligible chance of rejection.

We sought to investigate the use and appropriate timing of kidney allograft biopsies during DGF in the setting of ATG induction with maintenance immunosuppression with steroids, tacrolimus, and mycophenolate mofetil. We also searched for demographic and clinical variables associated with later onset rejection. Lastly, we questioned whether other findings discovered on biopsy were of clinical relevance.

Materials and Methods

This is a retrospective study approved by the Institutional Review Board of adult deceased-donor renal allograft recipients transplanted between January 2005 and June 2009; the protocols conform with the ethical guidelines of the 1975 Helsinki Declaration. Data were collected from a computerized database and paper records. One-year patient and allograft survival rates were collected, along with rejection rates during DGF and within 12 months after kidney transplant. We also reviewed the 1-year rejection rate and the 1-year patient and allograft survival for recipients who did not have DGF during this time.

The following patients were excluded: Patients who received combined liver-kidney or combined kidney-pancreas; patients who did not receive immunosuppression induction with ATG; and patients with immediate graft loss secondary to death, thrombosis, or primary nonfunction. Patients who had DGF for fewer than 7 days who did not require further maintenance dialysis were not biopsied and were excluded from the study.

Patients with DGF who underwent allograft biopsies within the first 14 days were included in this study.

Patients underwent allograft biopsies between days 7 and 14 if they required dialysis. They underwent frequent imaging to confirm vascular perfusion and to exclude urinary complications. All patients received induction with ATG. Anti-thymocyte globulin was dosed at 1.5 mg/kg/d for 4 to 7 days starting intraoperatively with a goal dosage between 5 to 6 mg/kg, titrated to avoid hematologic adverse events. All patients received maintenance immunosuppression with tacrolimus, mycophenolate mofetil, and prednisone. All patients were started on mycophenolate mofetil with doses ranging from 1 to 2 grams per day. The dosage was adjusted to avoid gastrointestinal adverse effects and leukopenia. Patients received methylprednisolone 400 to 500 mg intravenously (IV) intraoperatively followed by an oral prednisone taper to 5 mg/d by day 90. Tacrolimus was started by day 4. Target trough levels ranged between 7 to 11 ng/mL.

For pneumocystis jurevicus pneumonia prophylaxis, all patients received trimethoprim/sulfamethoxazole daily for at least 12 months after transplant, and 3 months after every rejection episode. In patients with sulfa allergies, dapsone or atovaquone was used. Fungal prophylaxis was provided by oral clotrimazole for 6 weeks. For *cytomegalovirus* prophylaxis, all patients received at least 6 months of valganciclovir with dosages ranging from 450 mg every other day to 900 mg daily, depending on renal function and established risk factors.

The Banff 97 classification was used to grade each biopsy specimen. Acute cellular rejection (ACR) grade 1 rejections were treated with IV methylprednisolone. Recalcitrant ACR grade 1 and

all ACR grade 2 rejections were treated with IV methylprednisolone and 5 to 6 mg/kg of ATG. Intravenous immunoglobulin and plasmapheresis were used for antibody-mediated rejections (AMR).

Statistical Analyses

Proportions, median (range), and mean (± SD) were used to summarize the data. Categorical variables were compared using chi-square tests. Continuous variables were analyzed with Mann-Whitney *U* tests. Statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 19.0, IBM Corporation, Armonk, New York, USA). Values for $P < .05$ were considered significant. The graft losses are death censored.

Results

Four hundred sixty-three recipients underwent renal transplant from deceased donors during the study. The overall incidence of DGF was 51.26% (242/463). One hundred thirty-one patients experienced DGF that recovered within 7 days and did not require biopsy. One hundred eleven patients met the inclusion criteria for this study of DGF requiring biopsy within 7 to 14 days after transplant.

Demographic variables are displayed in Table 1. The median recipient age at time of transplant was 56 years (range, 23-81 y). Fifty-seven percent were African American and 65% were male. Ninety-six patients were first-time recipients, 14 were second-time transplant recipients, and 1 patient received a fourth transplant. Twenty patients had a panel reactive antibody (PRA) over 20%. Twenty-seven out of 111 donor organs were machine perfused. The median body mass index (BMI) was 29.3 (range, 17.6-50.4 kg/m^2), and 45% of recipients were obese (BMI ≥ 30 kg/m^2). The most-common primary disease was hypertensive nephrosclerosis (49.6%).

Sixty-four donors were younger than 50 years old; 47 donors were older than 50 years. There were 50 recipients with ischemic times longer than 15 hours. Two patients received a pediatric kidney. Thirty-two donors (29%) were ECD, and 79 donors (71%) were standard criteria donor. A total of 39 donors (35%) were DCD, and 9 patients (8%) received an ECD/DCD.

The incidence of biopsy-proven rejection discovered in the initial biopsy during DGF was 2.7% (3/111). Two of these 3 rejections were AMR.

Table 1. Baseline characteristics of study population (n=111).

Variable	Rejection at 1 year		*P* value
	Yes (n=15) n (%)	No (n=96) n (%)	
Age (mean, y), (SD)	56.54 (12.23)	55.69 (11.45)	
Sex			.87
Male	10 (66.66)	62 (64.9)	
Female	5 (33.33)	34 (35.1)	
Race			.82
White	2 (13.3)	20 (20.83)	
African American	11 (73.3)	52 (54.16)	
Asian	1 (6.7)	3 (3.125)	
Hispanic	0	7 (7.29)	
Other	1 (7.14)	14 (14.58)	
Mean BMI (kg/m^2), (SD)	30.93 (8.54)	29.4 (5.91)	
Cause of ESRD			
Hypertensive	7 (46.66)	48 (50)	
Nephrosclerosis			
Diabetic nephropathy	6 (40)	35 (36.45)	
SLE	1 (7.14)	1 (1.04)	
FSGN	1 (6.66)	0	
IGA Nephropathy	0	2 (2.08)	
FSGS	1 (6.66)	1 (1.04)	
HCV GN	0	1 (1.04)	
GN Other	0	1 (1.04)	
Unknown	0	7 (7.29)	
Patients by number of transplant(s)			
First transplant	13 (86.7)	83 (86.45)	
Second transplant	2 (13.3)	12 (12.5)	
Third transplant	0	0	
Fourth transplant	0	1 (1.04)	
Machine perfusion	0	25	

Abbreviations: BMI, body mass index; ESRD, end-stage renal disease; FSGN, focal segmental glomerulonephritis; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; HCV GN, hepatitis C-virus-related glomerulonephritis; IGA, immunoglobulin A; SD, standard deviation; SLE, systemic lupus erythematosus

The first patient, a 61-year-old white woman with a history of end-stage renal disease owing to focal segmental glomerulosclerosis, a PRA of zero, and morbid obesity (BMI, 43.6), received a standard criteria donor kidney from a 49-year-old white man, with a zero DR match. This patient had an acute AMR. The second patient, a 36-year-old African American diabetic woman with a BMI of 50.4, PRA of 20%, and 1 DR match, received a standard criteria donor from a 36-year-old African American man, and developed an AMR. The last patient, a 48-year-old obese African American diabetic man with a BMI of 31.9 and PRA of 59% and 1 DR match received a standard criteria donor kidney from a 24-year-old African American man and experienced an ACR. The diagnosis was made 9 to 11 days after transplant. Owing to the small number of cases of early rejection, meaningful statistical comparisons and analyses could not be performed.

During the 12 months after transplant, there were 15 additional cases of rejection. Therefore, the incidence of rejection was 14% after the resolution of DGF (15/111). This included 1 acute antibody-mediated rejection and 14 acute cellular rejections. Of these 15 new rejections, 2 occurred in patients who had rejection uncovered with the initial DGF biopsy (1 AMR and 1 ACR with the same subsequent rejection). Eight of 15 rejections were diagnosed 7 to 12 weeks after the transplant. The median time to rejection of these 15 patients followed for 12 months was 10 weeks (range, 4-46 wk). The 2 repeat rejections happened 4 and 26 weeks after the first rejection.

The demographic and clinical characteristics of patients with rejection are summarized in Table 1. In the entire DGF cohort, 56.75% were African American. Thirteen of 15 patients who had subsequent rejection within 12 months after transplant were African Americans. We compared these demographic characteristics with the group without rejection at 12 months and found no statistically significant difference (Table 2).[17, 18] Of the patients who experienced rejection within 12 months after transplant, 11 of 15 were overweight, obese, or morbidly obese. Overall, in our study, 28 of 111 patients were obese (25.2%; $P = .5790$). Four of 15 patients, including the 1 patient who had AMR had elevated PRA. Seven of 15 patients had 0 DR matches, 6 patients had 1 DR match, and 2 had 2 DR matches. In our cohort, there was no relation between DR matches (0, 1, 2) and rejection at 1 year ($P > .05$). We also observed a higher rate of elevated PRA in the patients who developed rejection at 12 months compared with patients with no rejection at 12 months (27% vs 17%; $P > .05$). But this difference did not reach significance.

To summarize, there were no statistically significant associations between any of these recipient demographic variables and the presence of graft rejection at 12-months' follow-up. This includes retransplant.

Overall, 45 donors (41%) were older than 50 years. Sixty percent of patients who rejected in 1 year had received organs from donors older than 50 years, compared with 38% who did not have a rejection. This difference did not reach statistical significance ($P > .05$). Three of 15 patients received kidneys with a terminal serum creatinine more than 132.6 μmol/L (1.5 mg/dL). In our study, we found no association between rejection at 1 year and level of terminal creatinine ($P > .05$). The effect of type of donor on the rejection at 1 year is listed in Table 2. Donation after cardiac death was the only factor significantly associated with graft rejection at 12 months ($P = .017$). Machine perfusion did not show any statistically significant effect.

Table 2. Rejection risk factors and their statistical significance in our cohort.

	Rejection at 1 year		
Risk Factors	Yes (n=15)	No (n=96)	*P* value
PRA ≥ 20% (n=20)	4 (27)	16 (17)	.467
African American donors (n=92)	13 (86.7)	79 (82.3)	1.00
Donors older than 50 (n=45)	9 (60)	36 (37.5)	.098
Recipients older than 50 (n=31)	5 (33.33)	26 (27.1)	.757
Prolonged CIT (Longer than 15 h) (n=40)	8 (57.1)	32 (36.8)	.238
Retransplant (n=96)	13 (56.7)	83 (86.5)	1.00
Obesity (BMI ≥ 30) (n=61)	7 (46.7)	54 (56.8)	.579
ECD (n=32)	6 (18.8)	26 (81.3)	.361
DCD (n=39)	1 (2.6)	38 (39.6)	.017
ECD/DCD (n=9)	0 (0)	9 (9.3)	.606
Terminal creatinine ≥ 150.28 μmol/L (1.7 mg/dL)	3 (20)	22 (23)	.542

Abbreviations: CIT, cold ischemia time; DCD, donation after cardiac death; ECD, extended criteria donors; ECD/DCD, extended criteria donors/donors after cardiac death; PRA, panel reactive antibody

Fourteen of the 15 patients had subtherapeutic immunosuppression. Four of these 15 patients had subtherapeutic tacrolimus levels owing to patient nonadherence, intolerance, or concurrent infections. Fourteen patients had mycophenolate mofetil dosed at less than 1 g/d. Three patients had both nontherapeutic mycophenolate mofetil and tacrolimus.

One-year patient and graft survival of the patients who had later rejections were 93% (14/15) and 60% (9/15). Three of 5 graft losses were caused by rejection, and 2 causes of graft loss remain unknown. One-year patient and death censored graft survival for patients who did not have rejection (but did have DGF) were 86% (83/96) and 95% (91/96). The characteristics of patients who had rejections during 12 months after transplant are shown in Table 1. For comparison's sake, during the study, in the patients who did not have DGF, the 1-year patient survival and 1-year graft survival rates were 96.44% (217/225) and 93.77% (211/225). The 1-year graft rejection in this group is 7.1% (16/225), which is lower than the rate of graft rejection in the DGF group (14%) but not statistically significant ($P > .0564$).

One patient was found to have pyelonephritis on pathologic examination necessitating a change in

immunosuppression. There were no other significant biopsy findings that changed or decreased immunosuppressive therapy.

Discussion

The increased use of DCD and ECD kidneys plays a significant role in the increased incidence of DGF.[19, 20] The incidence of DGF is highest with DCD kidneys (44%), intermediate with ECD kidneys (33%), and lowest with standard criteria donor (21%).[2]

Delayed graft function is associated with cardiovascular morbidity,[21] prolonged hospitalization, increased health care costs, decreased short-term and long-term graft survival, and an increased risk of rejection.[2, 22] With the development of ATG induction and maintenance immunosuppression with mycophenolate mofetil, tacrolimus, and steroids, rejection rates have decreased.[9, 11-14]

Transplant kidney biopsy, the criterion standard for diagnosing rejection, is usually performed after the transplant in patients with DGF. The timing of these posttransplant biopsies in the setting of DGF remains controversial.

Ideally, biopsies should not be performed when the chance of rejection and clinical suspicion is low to minimize the chance of complications. The cost of biopsy can range between USD $1600 to $3000.[23] This must be weighed against the cost of missing a diagnosis of rejection.

Clinical suspicion for rejection also hinges upon many risk factors. Risk factors for rejection during DGF include HLA mismatches, sensitization, retransplant, and immunosuppressive regimen.[8] In our study, none of these recipient variables were statistically associated with rejection during DGF.

Like other studies, we found a higher incidence of rejection in those patients who had DGF compared to those who did not; this, however, was not statistically significant. We found DCD to be the only risk factor statistically associated with rejection in patients who experienced DGF.

African American transplant recipients are considered a high-risk population owing to the accelerated graft loss, independent of HLA matching. They have been shown to have an increased risk of complications including DGF, new-onset diabetes mellitus, infection, and recurrent disease.[18] In our cohort, 55.07% were African Americans. Two of 3 recipients who experienced rejection within 7 days after the transplant were African American. Eleven of 15 patients who had subsequent rejection within 12 months after the transplant were African Americans. However, the African American race was not a statistically significant risk factor for later rejection.

Recipients who are overweight or obese are also considered high risk for DGF, rejection, patient demise, and graft loss.[17, 24] In our cohort, 73.3% (11/15) were overweight or obese. This, however, was not a risk factor for subsequent rejection.

Machine perfusion has been reported to decrease the incidence and duration of DGF and is associated with improved graft survival in the first year after transplant.[16, 25] Despite longer cold ischemia times, recipients of ECD kidneys managed with pulsatile perfusion preservation had similar survival and functional outcomes, but experienced a marked reduction in the rate of DGF.[26] Not all authors agree.[27] In our cohort, 27/111 were machine perfused. The machine perfusion of donor organs was not a risk factor for DGF or later rejections.

There have been few studies concerning allograft biopsies performed early in the postoperative period. Many of the earlier reports regarding DGF and rejection were written in the cyclosporine era. Induction with polyclonal antibodies and maintenance immunosuppression was not uniform. Qureshi reported 50.8% rejection rates for 65 recipients with DGF on biopsies performed on days 7 to 10 in patients who received cyclosporine, azathioprine, mycophenolate mofetil, steroids with ATG induction.[7] Gaber and associates studied 71 patients who received a cyclosporine-based regimen with ATG induction and biopsies performed on days 7 to 10 after the transplant. Thirty percent of these biopsies uncovered rejection (8/21).[28]

The incidence of rejection during DGF depends on many donor and recipient risk factors, the duration of the DGF, and the immunosuppressive regimen. Rates vary from 18% to 48.5%.[7] An increased relative risk of acute cellular rejection with DGF was reported as 38% by Yarlagadda.[22] Although our incidence of rejection during DGF was low (2.8%), we found that our DGF patients were at subsequent risk for rejection within 12 months of transplant. This rejection also was associated with a high rate of graft loss. Two of the 3 DGF rejections

were seen in patients with elevated panel reactive antibodies. Two of the 3 rejections also were antibody mediated. They all were diagnosed between 9 and 11 days after the transplant. Two of these patients also had another subsequent rejection of the same type. Two out of these 3 (1 AMR and 1 ACR) lost their grafts after 104 days and 199 days. The small numbers of patients experiencing rejection during DGF precludes accurate statistical analysis, despite the fact that our entire DGF cohort represents one of the largest ever studied.

Patel[1] reported that patients with DGF continued to be at risk for rejection beyond the first year despite higher doses of ATG induction. This phenomenon may be a reflection of subsequent lower tacrolimus levels in the patient with a struggling kidney and lower mycophenolate dosages in patients with neutropenia. Animal studies also have suggested that ischemia enhances susceptibility to acute rejection by up-regulating antigen expression.[29] We showed a low rate of rejection on biopsies performed up to day 14 in patients who were dialysis dependent. This was similar to the experience of Kikic,[30] who performed 21 biopsies within the first week of DGF to uncover just 1 rejection. Qureshi[7] reported an increased incidence of rejection in patients with DGF at day 40, 24, of 65 first-time biopsies (performed between days 7-10) showed rejection. In their cyclosporine-based protocol, the median time from transplant to acute rejection was 16 days. Their DGF patients were also 2.86 times more likely to develop graft loss. In our study, 15 of 111 patients subsequently developed rejection in 12 months. The median time to development of rejection was 10 weeks (range, 4-46 wk). This rejection rate was higher than in our non-DGF comparison group, but it did not reach statistical significance. One-year graft loss was 40% (6/15) in those who subsequently experienced rejection. The only identifiable risk factor for rejection after DGF was a DCD.

In the remaining patients who did not reject in the DGF cohort, the 1-year patient and death censored allograft survival was 86% (83/96) and 95% (91/96). Overall, the DGF patient and death censored allograft 1-year survival were 87% (97/111) and 90% (100/111). Of patients with DGF, 13.51% (15/111) had rejection. Patient and allograft survival of the patients who experienced rejection was 93.33% (14/15) and 66% (10/15). The 1-year patient and allograft survival and rejection rates of the patients who did not have DGF were 96.44% (217/225), 93.77% (211/225), and 7.1% (16/225). This is consistent with the findings of other authors.[31]

One patient was found to have pyelonephritis on biopsy, and was subsequently treated with IV antibiotics, and discharged without mycophenolate mofetil. His renal function improved, and he did not experience rejection within 12 months posttransplant. There were no other significant biopsy findings that changed immunosuppressive therapy.

This study sought to determine the use and cost effectiveness of biopsies performed during DGF using immunosuppression with ATG, tacrolimus, mycophenolate, and prednisone. Our overall DGF rates were slightly higher than those reported by others (50.96% vs 23%-50%). This may be the result of an aggressive use of DCD and ECD kidneys or our patient population of obese, diabetic, and African American patients. The incidence of AR in our patient population found on biopsy completed for DGF was similar to that reported previously by UNOS (2.8% vs 2.6%).

In our DGF cohort, African American race, elevated PRA, DR mismatches, retransplant, and recipient obesity were not associated with rejection (Table 2; $P > .579$). Delayed graft function was the only risk factor for later rejection. In addition, inadequate immunosuppression also played a role, as 14 out of 15 patients had subtherapeutic immunosuppression for various reasons.

Limitations of this report include its retrospective nature, its relatively small patient numbers (yet larger than reported before), confounding variables, and short follow-up. We could not evaluate the possible role of pretransplant dialysis as a risk factor for DGF.[30] We could not examine the role of donor biopsies, donor inotropes, and donor blood pressure on the recipient's DGF. For the purposes of our study, we analyzed patients who had DGF and underwent allograft biopsies. The true definition of DGF is *the need for dialysis in the first week after transplant*, regardless of whether or not the biopsy was performed.

Conclusions

This study suggests that with ATG induction and maintenance immunosuppression with prednisone, mycophenolate mofetil, and tacrolimus, the incidence of early rejection during DGF is low. All patients had their rejection uncovered between 9 and 11 days after

transplant. Therefore, the cost:benefit ratio is in favor of not routinely performing biopsies in patients experiencing DGF if this regimen is used. However, a high degree of clinical vigilance should be maintained in such patients during weeks 7 to 12 after transplant, because they do have a higher risk of rejection compared with patients who did not experience early rejection. Donation after cardiac death was the only risk factor that was statistically significantly associated with rejection in the subsequent 12 months after DGF.

We recommend delaying the first surveillance biopsy during DGF after ATG induction with prednisone, mycophenolate mofetil, and tacrolimus maintenance immunosuppression. We also recommend maintaining a higher level of surveillance in patients who have experienced DGF and are DCD recipients and have not been administered full-dose immunosuppression. We believe this will lead to more efficient and less expensive care in the perioperative period.

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