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How Should Acute T-cell Mediated Rejection of Kidney Transplants Be Treated: Importance of Follow-up Biopsy

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Background. Limited published data exist to guide patient monitoring after the treatment of T-cell mediated rejection (TCMR) of kidney allografts. **Methods.** We reviewed the kidney function and histological outcomes after treatment of 163 first episodes of biopsy-proven TCMR between January 1, 2015, and July 31, 2020. **Results.** Of the 146 patients treated with steroid pulse alone, complete histological response was seen in 83% of patients with borderline rejection, 82.5% with grade 1A, 67% with grade 1B, and 50% with grade IIA. Of the 17 patients treated with steroids plus antithymocyte globulin, the complete histological response rate was 100% with grade 1A, 75% with grade 1B, 100% with grade IIA, and 57% with grade IIB. Among the patients with complete response as assessed by kidney function, 14% only had a partial or no response histologically. Among patients with no kidney function response, 68% had a complete response histologically. **Conclusion.** We thus find that responses based on kidney function alone do not correlate well with histological responses. If further treatment had been based solely on changes in estimated glomerular filtration rate, a significant number of patients would have been subsequently undertreated or overtreated. These results support the use of protocol follow-up biopsies after the treatment of TCMR.

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INTRODUCTION

Kidney transplantation is associated with improved mortality and improves the quality of life for patients with end-stage kidney disease (ESKD) compared with patients on dialysis.[1-3]

With advances in immunosuppression over the last few decades, the rate of acute rejection in kidney allografts has been significantly reduced; however, acute rejection continues to be an important cause of death-censored graft loss.[4-7] Greater histological severity of T-cell mediated rejection (TCMR) is associated with impaired response to rejection treatment and worse graft outcomes.[8] Many guidelines suggest treating acute TCMR of kidney allografts that is Banff grade I with steroids alone and Banff grade II with steroids plus antithymocyte globulin (ATG)[9]; however, high-quality studies providing histological support for this approach are lacking, particularly to guiding when patients need additional rejection treatment and when the additional treatment is not required. Some published literature recommends that kidney function response to the treatment should guide further rejection treatment after the initial treatment of TCMR.[9]

In this study, we share our experience with protocol follow-up biopsies performed after the treatment of TCMR. We analyze the response of each grade of rejection to different treatment modalities, as assessed both by changes in kidney function and histology.

MATERIAL AND METHODS

Study Population

The study was approved by the Health Sciences Institutional Review Board at the University of Wisconsin-Madison. Ethics approval or specific consent procedures were not required for this study. We included all kidney transplant recipients who

had a first episode of biopsy-proven TCMR with at least 1 protocol follow-up biopsy at our program between January 1, 2015, and July 31, 2020. None of our patients received treatment for non–biopsy-proven kidney rejection treatment before this episode of biopsy-proven rejection. Patients who had rejection on initial biopsy but had no follow-up protocol biopsy were excluded from the study. Also, patients with any histological component of antibody-mediated rejection, including c4d, g, or ptc >0 were excluded. Furthermore, patients with evidence of BK virus nephropathy or glomerulonephritis were also excluded from the study. Patients with primary graft dysfunction (defined as needing chronic dialysis within 3 mo posttransplant or graft nephrectomy) were also excluded. Recipients of multiorgan transplants, such as simultaneous liver and kidney, simultaneous pancreas and kidney, and simultaneous heart and kidney, were excluded from the study. All biopsies were reevaluated to conform to Banff's 2017 criteria.[10] Patients with borderline TCMR were also included in the study. Borderline TCMR was defined as foci of tubulitis (t1, t2, or t3) with mild interstitial inflammation (i1) or mild (t1) tubulitis with moderate to severe interstitial inflammation (i2 or i3).[11]

Death-censored kidney allograft failure was defined as the return of the patient to dialysis or retransplant.

Data Collection

We analyzed data on age; gender; race; retransplant status; the cause of ESKD; type of transplant; induction immunosuppression; maintenance immunosuppression; the reason for the biopsy; donor-specific antibodies (DSA) at time of biopsy; histology of the first and follow-up protocol biopsy; grade of rejection; baseline creatinine and estimated glomerular filtration rate (eGFR); creatinine and eGFR at time of rejection; creatinine and eGFR after treatment; the treatment received; graft loss; and patient death.

Immunosuppression

Patients undergoing kidney transplant received induction immunosuppression with either a T-cell depleting agent (ATG or alemtuzumab) or a nondepleting agent (basiliximab) based on immunological risk factors. Patients typically received a triple immunosuppressive regimen for maintenance immunosuppression, including a calcineurin inhibitor (usually tacrolimus), antiproliferative agent (mycophenolate mofetil or mycophenolic acid), and steroids. Low immunological risk patients receiving T-depleting induction were eligible for early steroid withdrawal. As previously described, the dose and drug level targets were adjusted based on the patient's clinical characteristics, including immunological risk, infections, malignancies, and rejections.[7]

Kidney Allograft Biopsies

Kidney allograft biopsies were performed for an unexplained rise in serum creatinine or a significant increase in urine protein to creatinine ratio. In addition, protocol biopsies were performed at months 3 and 12 for all patients with pretransplant DSA and patients who developed de novo DSA or a substantial rise in the level of DSA. Patients treated for rejection underwent protocol follow-up biopsy approximately 3 mo later. The biopsy was sometimes delayed for logistical reasons and was sometimes performed earlier because of concerns about poor response.

Acute kidney injury was defined based on the Kidney Disease Improving Global Outcomes guidelines, which define acute kidney injury as an absolute increase in serum creatinine level of ≥0.3 mg/dL within 48 h, ≥50% increase in serum creatinine level occurring over 1 to 7 d, or the presence of oliguria for >6 h.[12] As per the Banff recommendations, the biopsy sample was declared adequate if there were ≥10 glomeruli with at least 2 arteries.[13] The chronicity score was defined by the addition of c_i, c_t, c_v, and c_g scores ($c_i + c_t + c_v + c_g$) on the transplant kidney biopsy.

Rejection Treatment

TCMR treatment protocols at our institution are based on both the severity and Banff criteria. Borderline and Banff I TCMR are typically treated with steroid pulse. Treatment includes dexamethasone 100 mg the first day, 50 mg the second day, and then gradual taper of prednisone from 180 to 10 mg daily. Banff II and Banff III TCMR are typically treated with steroid pulse plus ATG (6–10.5 mg/kg in 4–7 divided doses). With any grade of TCMR, the baseline immunosuppression is usually increased.

Based on the immunological risk and infectious history, the rejection treatment was modified by the primary transplant nephrologists for some patients. Based on higher immunological risk, some opted to treat specific patients with Banff I TCMR with steroids and ATG. On the other hand, based on previous infectious history, some patients were treated with steroids alone, even with Banff II TCMR.

Histological and Kidney Function Response to the Rejection Treatment

Histological responses to rejection treatment were defined as complete response (CR; no residual rejection), partial response (PR; improved Banff grade but persistent rejection), or no response (NR; no change in Banff grade) on the follow-up biopsy.

Baseline eGFR was determined by visual inspection of the eGFRs within the past 3-mo period prior to the rejection episode. The eGFR at time of the first biopsy was used as the nadir eGFR. The eGFR at time of second biopsy was used to determine kidney function response to treatment. Kidney function responses were defined as follows: CR, eGFR returned to within 5 mL/min per 1.73 m2 of baseline eGFR; PR, improvement in eGFR by >5 mL/min per 1.73 m2 from the nadir eGFR; and NR, eGFR staying below a value that is 5 mL/min per 1.73 m2 higher than nadir eGFR. For example, if baseline eGFR was 50 mL/min per 1.73 m2 and dropped to 30 mL/min per 1.73 m2 at the time of the first biopsy, 30 mL/min per 1.73 m2 was the nadir eGFR. If the eGFR was lower than 35 mL/min per 1.73 m2 at the time of second biopsy, it was considered an NR. If eGFR was 35 to 45 mL/min per 1.73 m2 at the time of the second biopsy, it was considered a PR, and if the eGFR was >45 mL/min per 1.73 m2 at the time of the second biopsy, it was considered a CR.

There were a few patients with subclinical TCMR (biopsy was done per protocol). If their eGFR remained within 5 mL/min per 1.73 m2 of baseline at the time of the second biopsy, they were included with patients with CR in their kidney function.

Age at time of transplant; gender; race; living donor status; diabetes as cause of ESKD; induction agent; posttransplant cytomegalovirus, BK, and bacterial infections; grade of

rejection; histological response to the treatment; and kidney function response to the treatment were included in the univariate analysis.

Statistical Analysis

Data are reported as mean ± SD or percentages. Univariate and multivariate cox regression analyses were performed to determine the risk factors associated with death-censored kidney allograft loss. Variables were included in the multivariate analysis if the *P* value in univariate analysis was <0.05. Kaplan-Meier survival analyses were conducted to display graft survival. *P* values <0.05 were considered statistically significant. All analyses were performed using the MedCalc Statistical Software, version 16.4.3 (MedCalc Software Bvba, Ostend, Belgium; https://www.medcalc.org; 2016).

RESULTS

Baseline Characteristics

The total number of patients with TCMR during this era was 179, but 16 did not undergo follow-up biopsies, so 163 patients were included in the study (Figure 1). Baseline characteristics of the 163 patients are given in Table 1. The mean age at the time of transplant was 47.5 ± 14 y, 57% were male, and the majority were White (74%). A total of 53.4% of patients received ATG, 37% received basiliximab, and 10% received alemtuzumab as an induction agent. The mean time from transplant to the biopsy with the diagnosis of TCMR was 2.0 ± 3.0 y (median 0.96). Mean follow-up from transplant was 4.6 ± 3.0 y (median 4.2). Mean follow-up from the TCMR was 2.6 ± 1.5 y (median 2.7). Out of 163 patients, 77 (47%) had borderline, 43 (26%) had grade IA, 31 (19%) had grade IB, 4 (2%) had grade IIA, 7 (4.3%) had grade IIB, and 1 (0.6%) had grade III rejection. The mean time between the first and follow-up biopsy was 13.6 ± 8.5 wk.

At the time of biopsy, 43 (26%) patients had DSA, 6 to class I alone, 11 to class II alone and 26 to both class I and II.

Histological and Kidney Function Response To Treatment

Of 163 kidney recipients with TCMR, 146 were treated with steroid pulse alone (Tables 2–8). A total of 83% (64/77) of patients with borderline rejection, 82.5% (33/40) with grade 1A, 67% (18/27) with grade 1B, and 50% (1/2) with

grade IIA had a histological CR to treatment with steroids alone. Seventeen patients were treated with steroids plus ATG. The histological CR response rate was 100% (3/3) with grade 1A, 75% (3/4) with grade 1B, 100% (2/2) with grade IIA, and 57% (4/7) with grade IIB (Table 2).

Roughly similar rates were observed when assessing the response based on kidney function alone. Of 146 patients who received steroid pulse alone, 57% (43/77) patients with borderline rejection, 55% (22/40) with grade 1A, 44% (12/27) with grade 1B, and 100% (2/2) with grade IIA had a CR in kidney function. Out of 17 patients treated with steroids plus ATG, kidney function CR or PR rate was 67% (2/3) with grade 1A, 25% (1/4) with grade 1B, 100% (2/2) with grade IIA, and 28.5% (2/7) with grade IIB rejection (Table 3).

Among patients with CR by kidney function, 86% did have CR histologically, but 5% had PR, and 9% had NR histologically. Among patients with PR by kidney function, 74% had CR, 12% had PR, and only 14% had NR histologically. Among patients with NR by kidney function, 68% had CR, 9% had PR, and only 23% had NR histologically (Table 3).

Similar results were found in a subgroup analysis excluding patients with borderline TCMR (Table 5). Among patients with CR by kidney function, 84% did have CR histologically, but 9% had PR, and 7% had NR histologically. Among patients with PR by kidney function, 67% had CR, 18% had PR, and only 15% had NR histologically. Among patients with NR by kidney function, 67% had CR, 20% had PR, and only 13% had NR histologically.

The pattern of results was also similar in the subgroup analysis after excluding patients with subclinical TCMR (Table 6). Among patients with CR by kidney function, 83% did have CR histologically, but 6% had PR, and 11% had NR histologically. Among patients with PR by kidney function, 74% had CR, 10% had PR, and 15% had NR histologically. Among patients with NR by kidney function, 69% had CR, 8% had PR, and only 23% had NR histologically.

Decisions about whether or not to further treat patients were based on the histology, not kidney function, at the time of the second biopsy. Of the 34 patients without CR histologically on the first biopsy who underwent additional treatment with steroids, 27 (79.4%) achieved CR. The mean time between the second and third biopsy was 17.4 ± 19 wk (Table 7).
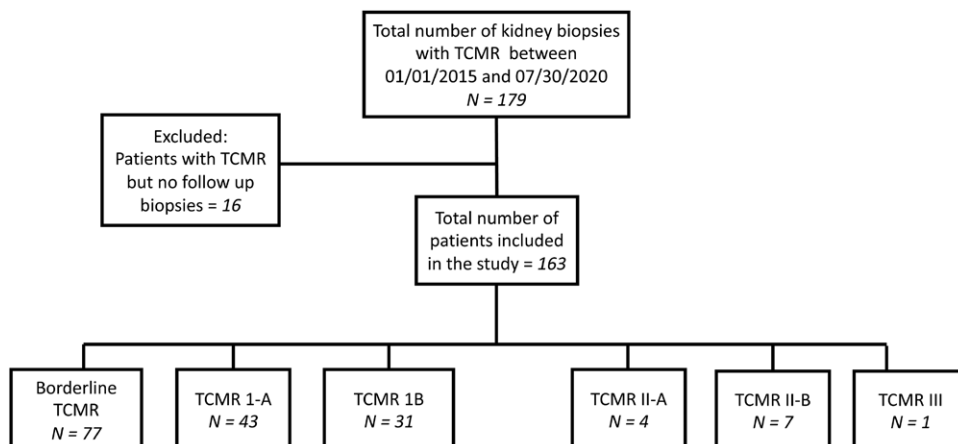

FIGURE 1. Flowsheet. TCMR, T-cell mediated rejection.

TABLE 1.
Baseline characteristics

Baseline characteristics	N = 163
Mean age at time of transplant, y	47.5 ± 14
Male, n (%)	93 (57)
White, n (%)	121 (74)
Diabetic ESRD, n (%)	32 (20)
Living donor transplant, n (%)	55 (34)
Induction immunosuppression	
Antithymocyte globulin, n (%)	87 (53.4)
Alemtuzumab, n (%)	16 (10)
Basiliximab, n (%)	60 (37)
Reason for biopsy	
Elevated creatinine, n (%)	131 (80)
Denovo DSA or worsening DSA, n (%)	18 (11)
High-risk protocol biopsy, n (%)	14 (9)
Type of rejection	
TCMR-borderline	77 (47%)
TCMR-1A	43 (26%)
TCMR-1B	31 (19%)
TCMR-IIA	4 (2 %)
TCMR-IIB	7 (4.3%)
TCMR-III	1 (0.6%)
Mean baseline creatinine, mg/dL	1.6 ± 0.5
Mean baseline eGFR, mL/min per 1.73 m2	45.5 ± 12
Mean time from transplant to biopsy, y	2.0 ± 3.0 (median = 0.96)
Mean follow-up from transplant, y	4.6 ± 3 (median = 4.2)
Mean follow-up from biopsy, y	2.6 ± 1.5 (median = 2.7)

DSA, donor-specific antibodies; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; TCMR, T-cell mediated rejection.

The histological characteristics of the initial and follow-up biopsies are given in Table 8. There was significant improvement in i and t scores on the follow-up biopsies ($P = 0.001$ and $P = 0.001$, respectively); however, cg score and total chronicity score were much worse on the follow-up biopsy ($P = 0.002$ and $P = 0.001$, respectively).

Graft Outcomes

Figure 2 shows death-censored graft survival after the first episode of TCMR. A total of 92% of patients still had functioning grafts 1 y after rejection, and 83% had graft function at 5 y (Figures 2–4A and B and Tables 9 and 10).

Complete histological and kidney function responses to treatment were associated with better graft outcomes than patients with PR or NR ($P = 0.03$ and 0.006, respectively; Figures 3 and 4A). After excluding the patients with subclinical rejection, the kidney function CR to treatment continues to be associated with better graft survival than patients with PR or NR ($P = 0.01$).

Multivariate analyses showed that every increase in the grade of rejection was associated with worse long-term graft outcomes (hazard ratio [HR] = 1.5, $P = 0.003$, 95% confidence interval [CI], 1.15-2). Histological and kidney function CR to treatment was associated with improved graft outcomes (HR = 0.6, $P = 0.03$, 95% CI, 0.15-0.94; HR = 0.5, $P = 0.01$, 95% CI, 0.32-0.84, respectively; Table 9). After excluding the patients with subclinical rejection, the multivariate analyses showed that every increase in grade of rejection was associated with worse long-term graft survival (HR = 1.6, $P = 0.003$, 95% CI, 1.17-2.19). Histological CR to treatment was associated with improved graft outcomes (HR = 0.5, $P = 0.04$, 95% CI, 0.18-0.98); however, the association between kidney function CR and graft outcomes no longer

TABLE 2.
Histological response to treatment

Rejection grade	Steroids alone			Steroids + ATG		
	Complete response	Partial response	No response	Complete response	Partial response	No response
TCMR-borderline (n = 77)	64/77 = 83%	NA	13/77 (17%)	NA	NA	NA
TCMR-1A (n = 43)	33/40 = 82.5%	2/40 = 5%	5/40 = 12.5%	3/3 = 100%	NA	NA
TCMR-1B (n = 31)	18/27 = 67%	6/27 = 23%	3/27 = 10%	3/4 = 75%	NA	1/4 = 25%
TCMR-IIA (n = 4)	1/2 = 50%	1/2 = 50%	NA	2/2 = 100%	NA	NA
TCMR-IIB (n = 7)	NA	NA	NA	4/7 = 57%	3/7 = 43%	NA
TCMR-III (n = 1)	NA	NA	NA	1/1 = 100%	NA	NA

ATG, antithymocyte globulin; NA, not available; TCMR, T-cell mediated rejection.

TABLE 3.
Kidney function response to treatment

Rejection grade	Steroids alone			Steroids + ATG		
	Complete response	Partial response	No response	Complete response	Partial response	No response
TCMR-borderline (n = 77)	43/77 = 57%	15/77 = 19.4%	19/77 = 24.6%	NA	NA	NA
TCMR-1A (n = 43)	22/40 = 55%	9/40 = 22.5%	9/40 = 22.5%	2/3 = 66.6%	1/3 = 33.3%	NA
TCMR-1B (n = 31)	12/27 = 44%	12/27 = 44%	3/27 = 11%	1/4 = 25%	1/4 = 25%	2/4 = 50%
TCMR-IIA (n = 4)	2/2 = 100%	NA	NA	2/2 = 100%	NA	NA
TCMR-IIB (n = 7)	NA	NA	NA	2/7 = 28.5%	4/7 = 57%	1/7 = 14%
TCMR-III (n = 1)	NA	NA	NA	1/1 = 100%	NA	NA

ATG, antithymocyte globulin; NA, not available; TCMR, T-cell mediated rejection.

TABLE 4.

Correlation between kidney function response and histological response to treatment

Kidney function response to treatment	Histological response to treatment		
N = 163	Complete response (N = 129)	Partial response (N = 12)	No response (N = 22)
Complete response (N = 87)	75/87 = 86%	4/87 = 5%	8/87 = 9%
Partial response (N = 42)	31/42 = 74%	5/42 = 12%	6/42 = 14%
No response (N= 34)	23/34 = 68%	3/34 = 9%	8/34 = 23%

TABLE 5.

Correlation between kidney function response and histological response to treatment (borderline rejections excluded)

Kidney function response to treatment	Histological response to treatment		
N = 86	Complete response (N = 65)	Partial response (N = 12)	No response (N = 9)
Complete response (N = 44)	37/44 = 84%	4/44 = 9%	3/44 = 7%
Partial response (N = 27)	18/27 = 67%	5/27 = 18%	4/27 = 15%
No response (N = 15)	10/15 = 67%	3/15 = 20%	2/15 = 13%

TABLE 6.

Correlation between kidney function response and histological response to treatment (subclinical rejections excluded)

Kidney function response to treatment	Histological response to treatment		
N = 131	Complete response (N = 102)	Partial response (N = 10)	No response (N = 11)
Complete response (N = 66)	55/66 = 83%	4/66 = 6%	7/66 = 11%
Partial response (N = 39)	29/39 = 74%	4/39 = 10%	6/39 = 15%
No response (N= 26)	18/26 = 69%	2/26 = 8%	6/26 = 23%

TABLE 7.

Histological response to treatment in patients who had no or partial response on the second biopsy

	Steroids alone			Steroids + ATG		
Rejection grade on second biopsy (n = 34)	Complete response	Partial response	No response	Complete response	Partial response	No response
TCMR-borderline (n = 13)	9/13 = 69%	1/13 = 7%	3/13 = 23%	NA	NA	NA
TCMR-1A (n = 7)	6/7 = 86%	1/7 = 14%	NA	NA	NA	NA
TCMR-1B (n = 10)	8/10 = 80%	NA	2/10 = 20%	NA	NA	NA
TCMR-IIA (n = 1)	1/1 = 100%	NA	NA	NA	NA	NA
TCMR-IIB (n = 3)	3/3 = 100%	NA	NA	NA	NA	NA

ATG, antithymocyte globulin; NA, not available; TCMR, T-cell mediated rejection.

TABLE 8.

Histological characteristics

Banff score	Index biopsy	Follow-up biopsy	*P*
i	1 ± 1	0.5 ± 1	0.001[a]
t	2 ± 1	0.3 ± 1	0.001[a]
v	0.04 ± 0.2	0	
ptc	0	0	
g	0	0	
mvi	0	0	
c4d	0	0	
ci	1 ± 1	1 ± 1	1
ct	1 ± 1	1.2 ± 1	0.08
cv	1 ± 1	1.1 ± 1	1
cg	0.05 ± 0.3	0.3 ± 1	0.002[a]
ci + ct + cv + cg	3 ± 2	4 ± 2.2	0.001[a]

[a]

reached statistical significance (HR = 0.7, P = 0.3, 95% CI, 0.46-1.30; Table 10).

Incidence of Infections After Rejection Treatment

The incidence of infections was analyzed within 1 y after the rejection treatment to look for adverse effects that might be attributable to ATG. For the patients treated with steroids alone (n = 146), 21% had bacterial infections including urinary tract infections and pneumonia, 5.4% had fungal infections, 15% had cytomegalovirus, and 9.6% had BK viremia. Of the patients treated with steroids plus ATG (n = 17), 23.5 % had bacterial infections, 6% had fungal infections, 18% had cytomegalovirus, and 12% had BK viremia. There was no statistical difference in the incidence of bacterial infections (P = 0.8), fungal infections (P = 0.7), cytomegalovirus infection (P = 0.7), and BK viremia (P = 0.6) in the year after rejection treatment among the patients treated with steroids alone or versus steroids plus ATG.
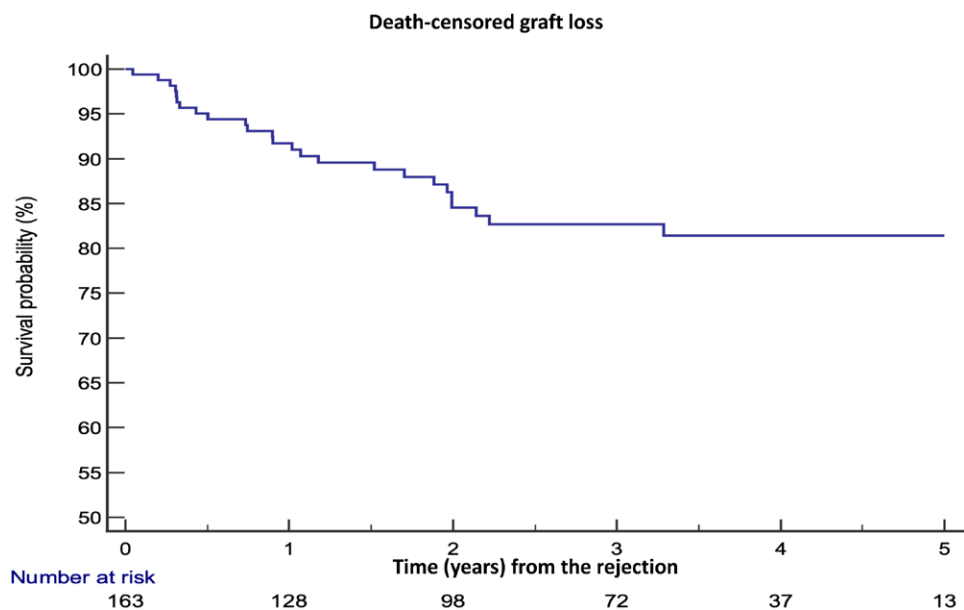
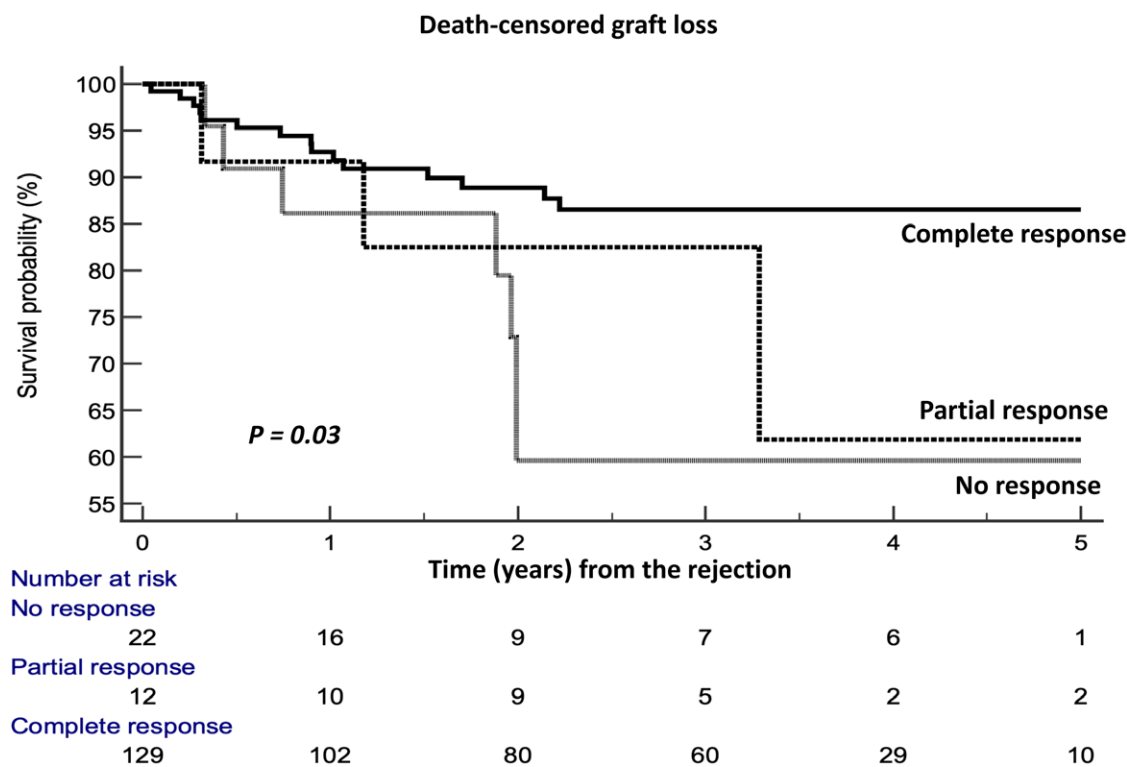**FIGURE 2.** Death-censored graft survival after T-cell mediated rejection.

FIGURE 3. Histological response and graft outcomes.

DISCUSSION

Our experience with 163 patients with biopsy-proven kidney rejection suggests that histological responses to treatment are generally consistent with available guidelines to treat TCMR grade II, and possibly grade IB, with steroids plus ATG. Most patients with grade IB or less responded to steroids alone; however, we also demonstrate that histological responses do not correlate well with kidney function responses. Out of 87 patients who had CR to treatment as assessed by kidney function, 5% had PR, and 9% had NR

histologically. None of these patients with CR by eGFR would have received further treatment if histology had been unavailable, but the protocol biopsy allowed the 14% with PR or NR histologically to receive further treatment. In addition, the availability of protocol biopsy results for the patients with NR by eGFR allowed 68% of them to avoid unnecessary treatment because the histology showed CR. Among the patients with PR by eGFR, biopsy results allowed 74% to avoid further treatment because the histology showed CR. Thirty-four patients who had PR or NR histologically after
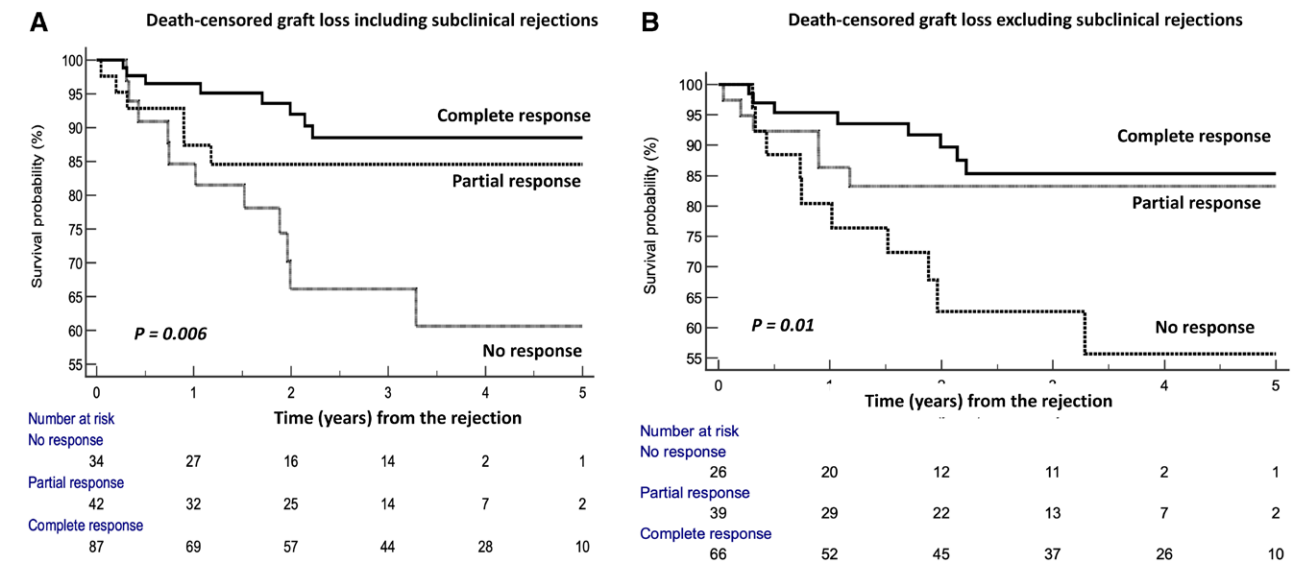
FIGURE 4. Kidney function response and graft outcomes.

TABLE 9.

Factors associated with death-censored graft loss

Variables	Univariate analysis			Multivariate analysis		
	HR	P	95% CI	HR	P	95% CI
Age at time of Txp	0.99	0.6	0.96-1.02			
White	0.72	0.4	0.31-1.67			
Male	0.76	0.5	0.35-1.68			
Living donor Txp	0.54	0.2	0.21-1.37			
DM cause of ESKD	0.75	0.6	0.25-2.20			
T-depleting vs IL-2 blockade induction	1.21	0.6	0.55-2.67			
CMV infection	1.35	0.5	0.50-3.61			
Bacterial infection	0.84	0.7	0.35-2.03			
BK viremia	0.45	0.2	0.13-1.51			
Positive DSA	0.92	0.86	0.32-2.2			
Grade of rejection	1.56[a]	0.003[a]	1.14-1.99[a]	1.5[a]	0.003[a]	1.15-2.00[a]
Histological response to treatment (CR vs PR/NR)	0.38[a]	0.01[a]	0.17-0.84[a]	0.6[a]	0.03[a]	0.15-0.94[a]
Kidney function response to treatment (CR vs PR/NR)	0.4[a]	0.02[a]	0.16-0.86[a]	0.5[a]	0.01[a]	0.32-0.84[a]

CI, confidence interval; CMV, cytomegalovirus; CR, complete response; DM, diabetes; DSA, donor-specific antibodies; ESKD, end-stage kidney disease; HR, hazard ratio; NR, no response; PR, partial response.
[a]

TABLE 10.

Factors associated with death-censored graft loss (subclinical rejections excluded)

Variables	Univariate analysis			Multivariate analysis		
	HR	P	95% CI	HR	P	95% CI
Age at time of transplant	0.99	0.63	0.96-1.02			
White	0.76	0.54	0.31-1.83			
Male	0.71	0.4	0.32-1.60			
Living donor Txp	0.44	0.08	0.17-1.12			
DM cause of ESRD	0.97	0.9	0.33-2.84			
T-depleting vs IL-2 blockade induction	1.01	0.98	0.45-2.25			
CMV infection	1.15	0.8	0.39-3.38			
Bacterial infection	0.90	0.8	0.37-2.18			
BK viremia	0.29	0.55	0.19-1.64			
Positive DSA	0.8	0.9	0.38-2.1			
Grade of rejection	1.5	0.006	1.11-1.94	1.6	0.003	1.17-2.19
Histological response to treatment (CR vs PR/NR)	0.35	0.02	0.15-0.84	0.5	0.04	0.18-0.98
Kidney function response to treatment (CR vs PR/NR)	0.5899	0.04	0.3707-0.9386	0.7	0.3	0.46-1.30

CI, confidence interval; CMV, cytomegalovirus; CR, complete response; DM, diabetes; DSA, donor-specific antibodies; ESRD, end stage renal disease; HR, hazard ratio; NR, no response; PR, partial response.

the initial rejection treatment received a second cycle of steroids with a 79% response rate, indicating that PR or NR histologically after initial treatment can usually be reversed with a repeat cycle of rejection treatment. Interestingly, none of these patients received ATG.

Diagnostic criteria and treatment of acute cellular rejection in kidney allografts are well established.[8] It is generally accepted that grade IA cellular rejection in a kidney should be treated with steroids alone, whereas grade II or higher cellular rejection should be treated with steroids plus ATG[8,14]; however, there are limited previous histological data demonstrating the success of this approach. A review by Brennan and Malone[9] recommends close monitoring of serum creatinine after the treatment of rejection and suggests that a reduction in creatinine be considered the endpoint for successful treatment of rejection. Woodle et al[15] found that a decrease in serum creatinine within 10% of the baseline level can be considered a successful reversal of rejection. Other studies have suggested that if the TCMR is without significant chronic histological findings, a favorable response to the treatment should be expected in 3 to 5 d of the treatment initiation[16,17]; however, we found a significant discrepancy between the histological and kidney function responses after rejection treatment. This suggests that monitoring only kidney function responses may be misleading and that a follow-up kidney biopsy after the treatment of TCMR provides important additional information. Although histology is subject to sampling error, it remains the gold standard for assessing rejection and is clearly more sensitive and specific for rejection than eGFR. These findings support the utility of routine follow-up biopsies after treatment of TCMR, as they help determine whether or not a response was achieved and, therefore, whether or not further treatment is indicated.

Studies have shown that acute rejection of the kidney allograft is associated with chronic graft dysfunction and has a negative impact on long-term kidney graft outcomes.[18,19] A higher grade of Banff rejection on the kidney biopsy is associated with inadequate response to the treatment and inferior graft survival.[20,21] Functional recovery after rejection treatment is an important prognostic factor for long-term outcomes[22,23]; however, the data on the impact of histological response after the treatment on long-term graft outcome are limited. Our findings demonstrate that better histological responses as well as kidney function responses to rejection treatment are associated with better long-term graft outcomes. Because the treatment response is associated with long-term graft survival, accurately diagnosing persistent rejection on the follow-up biopsies and treating appropriately should improve kidney graft outcomes.

Our report has all the potential limitations of a single-center cohort study. Our study population and approach to immunosuppression may not be the same as other centers. There are known limitations of histology as a gold standard for the diagnosis of rejection, including sampling error and variability in pathologist readings; however, a randomized control trial of treatment for TCMR is unlikely to be performed. Therefore, based on a protocolized approach to treat different grades of TCMR followed by a kidney biopsy to determine the success or failure of the treatment, we believe that our data provide the best guidance to date about how the response to treatment should be monitored. There may be instances where follow-up biopsies do not justify the risks, for example, in patients at high risk of bleeding whose eGFR ends up much better than baseline. These recommendations may need to be refined in the future as more information emerges regarding the optimal timing of the follow-up biopsies and how to approach resistant rejection.

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