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Original Article

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The Outcome of Tapered Steroid Regimen When Used to Treat Acute Borderline Cellular Rejection After Kidney Transplant: A Single-Center Experience

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Abstract

Background: Treatment of acute borderline cellular rejection (BCR) after kidney transplant has shown mixed results with no consensus on the necessity and modality of interventions.

Methods: The emphasis of our study was to assess the histopathologic response when BCR of kidney transplant is being treated with rapid steroid regimen. We analyzed all diagnosed acute BCR between 2018 and 2020. Patients were divided to a treatment responder group (RG) and non-responder group (NRG). All diagnosed BCR were treated with rapid steroid regimen and followed by a biopsy to assess response. Demographic data, recipients' comorbidities and clinical data, donor type, and induction immunosuppression regimen data were collected.

Results: Ninety-one patients had acute BCR and were treated with rapid steroid followed by a repeat biopsy. Sixty-three (69%) patients showed persistence BCR and were considered NRG. Age, gender, and race were similar between the two groups. Class I and II calculated panel reactive antibodies were similar between the groups. No significant difference in the median serum creatinine (SCr) was noted between the groups. RG and NRG had a median SCr of 1.6 mg/dL (1.2 - 2.1) and 1.5 mg/dL (1.4 - 2.0), respectively ($P < 0.79$). The median SCr at the time of the follow-up biopsy was not different between the groups: SCr of 1.6 mg/dL (1.2 - 2.0) vs. 1.4 mg/dL (1.2 - 2.2) for the RG and NRG, respectively ($P < 0.93$).

Conclusion: When rapid steroid regimen was used to treat acute BCR after kidney transplant, only smaller number of patients showed response based on the histology evaluation of the follow-up post-treatment biopsies.

Keywords: Kidney transplant; Cellular rejection; Steroid treatment

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Introduction

Acute borderline cellular rejection (BCR) is a diagnostic category of the Banff classification system. Acute BCR is characterized by infiltration of activated T cells into the interstitial and tubular compartments of a transplanted kidney with 10-25% cortical inflammation and mild tubulitis [1, 2]. "To treat or not to treat" has been the controversial question when a diagnosis of acute BCR is made on kidney allograft biopsy [3-5]. This dilemma is reinforced by multiple body of evidence to show beneficial long-term effect and others to show no gained benefit [6-9]. However, our transplant center follows a treatment approach and uses a rapid steroid regimen to treat all diagnosed acute BCR based on indicated or protocoled biopsies with a follow-up biopsy to assess the histopathologic response. In this study, we did not address the long-term benefit of acute BCR treatment and rather we tried to answer a specific question regarding the histopathologic response to rapid steroid treatment regimen if the decision to treat is implemented as the scenario at our transplant center.

Materials and Methods

This study was approved by the Institutional Review Board and is a retrospective analysis of all diagnosed acute BCR on indicated and protocoled kidney transplant biopsies done between January 2018 and December 2020. The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration. The protocoled biopsies at our institution are scheduled at 4-, 12-, 48-, and 96-month post-transplant. All protocoled and/or indicated biopsies were done after an informed consent was signed by the patients. All slides were diagnosed by nephropathologist and according to Banff criteria. Diagnosis of acute BCR was made based on Banff criteria: interstitial inflammation involving 10-25% of nonsclerotic cortex (Banff i1) with at least mild tubulitis ($t > 0$). Patients were included in the responsive group when the follow-up biopsy had interstitial inflammation involving less than 10% of nonsclerotic cortex ($i = 0$), with no tubulitis ($t = 0$). The treatment protocol for acute BCR at our transplant center is based on rapid steroid regimen with a follow-up biopsy to assess the response. The rapid steroid regimen consisted of methylprednisolone 500 mg IV once

Table 1. Demographics of the Study Population

	NRG (N = 63)	RG (N = 28)	P-value
Age (years)			0.40
Missing	0	0	
Median (Q1, Q3)	59.0 (47.0, 68.0)	61.5 (50.2, 71.2)	
Gender			0.36
Missing	0	0	
Female	26 (41.3%)	15 (53.6%)	
Race			0.50
Missing	0	0	
Non-Hispanic White	37 (58.7%)	16 (57.1%)	
Non-Hispanic Black	22 (34.9%)	8 (28.6%)	
Hispanic White	1 (1.6%)	2 (7.1%)	
Other	3 (4.8%)	2 (7.1%)	

NRG: non-responder group; RG: responder group; Q1: first interquartile range; Q3: third interquartile range.

a day for 3 days followed by 250 mg IV once a day on day 4, 125 mg IV once a day on day 5, start oral prednisone at 60 mg on day 6 and taper over 1 week by reducing the dose by 10 mg daily to the maintenance dose of 5 - 10 mg daily. Patients were divided, based on the repeat biopsy, into two groups: 1) treatment responder group (RG) who have a resolution of acute BCR and, 2) treatment non-responder group (NRG). Patients' characteristics including age, gender, race, immunosuppressive induction agent at time of transplant, and calculated panel reactive antibodies (cPRA) done before transplant were collected. The induction protocol at our institution is based on using basiliximab or alemtuzumab or thymoglobulin. Patients 65 years of age and older and/or two haplotype-matched donors or zero mismatch received basiliximab; patients 64 years of age and younger and/or no detected donor-specific antibodies (DSA) or detected DSA but with mean florescence intensity (MFI) < 2,000 received alemtuzumab; patients 64 years of age and younger with DSA at MFI ≥ 2,000 received thymoglobulin. All first indicated and protocoled biopsies and all follow-up biopsies (4 - 6 weeks after the initial biopsy with acute BCR) were evaluated based on Banff criteria and only patients with the diagnosis of acute BCR were included in the study. Data are presented as median and interquartile range (Q1/Q3). $P < 0.05$ was considered significant.

Results

We identified 91 patients who had a diagnosed BCR on protocoled and indicated biopsies (six patients diagnosed on indicated biopsies and 85 patients diagnosed on protocoled biopsies). All 91 patients were included in the study and their clinical data at the time of initial and follow-up biopsies were analyzed.

Demographics

Table 1 summarizes the characteristics of the patients' population included in the study based on their histological response to treatment. There were no significant differences between the two groups (NRG and RG) in term of age, gender, and ethnicity.

Comorbidities and immune risk phenotype

Table 2 presents patients comorbidities and immune risk phenotypes. It showed that 73% of the NRG and 82.1% of RG had received kidney allograft from deceased donors ($P < 0.43$). Furthermore, there were no significant differences between the groups for the diagnosis of hypertension and diabetes mellitus ($P < 0.79$ and $P < 0.63$, respectively). The two groups had non-significant differences in class I ($P < 0.64$) and II ($P < 0.29$) of cPRA prior to transplant. This could indicate similar immunogenicity prior to transplant between the two groups and minimal impact on the response to acute BCR after transplant. We found no differences between the two groups in term of induction therapy with alemtuzumab, thymoglobulin, and basiliximab. The time from transplant to first diagnosed acute BCR, and the time between the initial diagnostic biopsy and the follow-up post-treatment biopsy were also similar between the two groups. We followed kidney allograft function for 12 months post-biopsy and compared the serum creatinine (SCr) between the two groups at different follow-up time points. SCr at 1-, 2-, 3-, 6-, and 12-month post-biopsy showed no differences between the two groups (Table 3).

Treatment outcomes

We compared the persistence of acute BCR histological changes on the follow-up biopsies done after completing the rapid steroid regimen. We found 63 out of 91 patients to have persistent acute BCR despite treatment. Only 31% response rate to our steroid treatment regimen was achieved. The NRG showed similarities with RG in the tested variables including age, race, gender, hypertension, diabetes, cPRA, induction regimen, and

Table 2. Comorbidities and Immune Risk Phenotypes

	NRG (N = 63)	RG (N = 28)	P-value
Hypertension			0.79
Missing	9	1	
No	40 (74.1%)	19 (70.4%)	
Yes	14 (25.9%)	8 (29.6%)	
Diabetes mellitus			0.63
Missing	9	1	
No	35 (64.8%)	16 (59.3%)	
Yes	19 (35.2%)	11 (40.7%)	
Donor type			0.43
Missing	0	0	
Living donor	17 (27.0%)	5 (17.9%)	
Deceased donor	46 (73.0%)	23 (82.1%)	
Induction agent			0.74
Missing	1	0	
Alemtuzumab	22 (35.5%)	9 (32.1%)	
Basiliximab	15 (24.2%)	9 (32.1%)	
Thymoglobulin	25 (40.3%)	10 (35.7%)	
Class I cPRA			0.64
Missing	11	7	
Median (Q1, Q3)	1.5 (0.0, 32.0)	10.0 (0.0, 48.0)	
Class II cPRA			0.29
Missing	11	7	
Median (Q1, Q3)	0.0 (0.0, 37.0)	0.0 (0.0, 56.0)	
Time from transplant to first diagnosed acute BCR (in months)			0.21
Missing	0	0	
Median (Q1, Q3)	12.3 (4.3, 25.2)	17.5 (10.9, 47.9)	
Time between biopsies (in months)			0.78
Missing	0	0	
Median (Q1, Q3)	2.7 (1.6, 3.7)	2.5 (2.0, 3.5)	

BCR: borderline cellular rejection; cPRA: calculated panel reactive antibodies; NRG: non-responder group; RG: responder group; Q1: first interquartile range; Q3: third interquartile range.

donor type. The median tacrolimus (FK) level at the initial biopsy, the spot urine P/Cr and the follow-up urine P/Cr were also similar between the two groups.

Discussion

In the early 1970s, transplant professionals started to publish their experience using steroid for kidney allograft rejection in humans [10-12]. In 1971, Zurita et al used different steroid approaches to treat rejection in 55 kidney transplant patients. They used the following regimens: 1) prednisone, administered orally in doses ranging between 150 and 600 mg/day; 2) methylprednisolone, administered intravenously in doses of 0.5 to 1 g/day (total dose: 2 to 8 g); or 3) methylprednisone administered intravenously in the same dosage. They showed overall 60% rejection response without any apparent difference between the three treatment regimens [13]. Since the 1970s, significant new immunomodulator medications were developed and the use of steroid started to fade more. In addition, we believe that the growing consensus to minimize steroid therapy in transplant patients has supported the use of low-dose and rapid regimen of steroid when the decision to treat acute BCR is taken [14]. In our transplant center, we follow the Banff criteria to diagnose acute BCR and we use rapidly tapered steroid as the treatment regimen. Banff meeting for allograft pathology was held in September 2019, in Pittsburgh, PA (USA). The focus of kidney session was to harmonize the pathologic diagnosis of kidney transplant rejection and consequent therapeutic strategies [1]. Consensus

Table 3. Treatment Outcomes

	NRG (N = 70)	RG (N = 39)	P-value
Initial SCr			0.36
Median (Q1, Q3)	1.6 (1.2, 2.1)	1.5 (1.4, 2.4)	
1-month post-biopsy SCr			0.44
Median (Q1, Q3)	1.5 (1.2, 2.0)	1.5 (1.2, 2.1)	
2-month post-biopsy SCr			0.099
Median (Q1, Q3)	1.4 (1.1, 1.9)	1.7 (1.3, 2.1)	
3-month post-biopsy SCr			0.94
Median (Q1, Q3)	1.5 (1.2, 1.7)	1.3 (1.1, 1.8)	
6-month post-biopsy SCr			0.23
Median (Q1, Q3)	1.4 (1.1, 1.8)	1.6 (1.4, 1.9)	
12-month post-biopsy SCr			0.92
Median (Q1, Q3)	1.5 (1.2, 1.8)	1.5 (1.2, 1.6)	
Initial urine P/Cr			0.16
Missing	6	0	
Median (Q1, Q3)	0.1 (0.1, 0.3)	0.2 (0.1, 0.3)	
Follow-up urine P/Cr			0.55
Missing	16	4	
Median (Q1, Q3)	0.1 (0.1, 0.3)	0.2 (0.1, 0.3)	
Initial tacrolimus level			0.44
Missing	8	1	
Median (Q1, Q3)	7.0 (5.8, 8.2)	7.2 (6.1, 9.0)	
Follow-up tacrolimus level			0.60
Missing	9	1	
Median (Q1, Q3)	8.3 (7.0, 10.2)	8.1 (7.0, 9.3)	

NRG: non-responder group; RG: responder group; Q1: first interquartile range; Q3: third interquartile range; SCr: serum creatinine; P: plasmatic.

was achieved that the diagnostic threshold for acute BCR should include interstitial inflammation involving 10-25% of nonsclerotic cortex with at least mild tubulitis with minimum lesion for an acute BCR [15, 16]. Currently, in addition to the uncertainty regarding the clinical impact of treatment for acute BCR [17-19], the treatment modality, regimen, and approach are more debatable. In 2018, a clinical practice survey conducted in Canada and surveying 47 transplant providers showed that all respondents opted to treat borderline rejection but with different treatment options and approaches [3]. Here, we attempt not to address whether to treat or not to treat acute BCR, rather to address the response to steroid regimen used to treat. We did not address the long-term effect of treated acute BCR on kidney allograft function and survival. In a recent study, Dale et al used steroid to treat acute BCR and reviewed the response among 90 patients who had a biopsy proven diagnosis of acute BCR from 2008 to 2015. The regimen they used constituted of 500 mg IV daily for three doses followed by 250 mg IV on day 4, 125 mg IV on day 5, and 75 mg IV on day 6, and then oral prednisone tapering from 20 mg daily to 5 mg daily over the ensuing 2 weeks. They showed, with this rapid tapering of steroid, that the follow-up biopsies were negative for rejection in less than half of the patients [4]. This result is similar to ours in term of suboptimal histopathologic response to rapid tapering of steroid. Both our study and Dale et al have shown the suboptimal response to rapid tapering of steroid when the decision is made to treat the diagnosed acute BCR.

We analyzed the short-term outcome of rapid steroid regimen and found no differences in the kidney allograft function when measured by SCr and urine protein to creatinine ratio at the first biopsy and the follow-up one. These results add to the controversial discussion to whether a treatment is needed or not when acute borderline rejection is diagnosed [20]. As the median tacrolimus level at the initial biopsy, the spot urine P/Cr and the follow-up urine P/Cr were also similar between the two groups, these results could indicate a lack of response to treatment of kidney transplant acute BCR when rapid tapering of steroid is selected as the treatment regimen.

Limitations

The single-center nature of this study poses obvious limita-

tions. Most patients in our study were diagnosed with BCR on protocoled biopsy done at different time points post-transplant which could lead to a bias in the analysis of the outcome. Patients could have BCR for longer or shorter period of time before the biopsy and no current measures or clinical manifestations available to determine that. Nevertheless, our results support the design of subsequent longitudinal studies to directly examine the impact of different steroid-based therapeutic regimens when the decision is made to treat kidney transplant BCR.

Conclusion

The use of rapid tapered steroid regimen to treat acute BCR after kidney transplant showed to be effective in improving the pathologic findings on kidney biopsy in only smaller number of patients. Long-term and comparative studies are needed to evaluate different regimens of steroid when acute BCR is considered for treatment.

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Conflict of Interest

The authors do not have any conflict of interest to declare.

Informed Consent

All protocoled and/or indicated biopsies were done after an informed consent was signed by the patients.

Author Contributions

Abdullah Jebrini: data collection and analysis; data and results interpretation; manuscript writing. Ana Cecilia Farfan Ruiz: data collection; manuscript writing. Meray Hosni: data collection. Tambi Jarmi: hypothesis, methods, and design; data analysis; data and results interpretation; manuscript writing.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

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