2013 Banff Criteria for Acute Antibody-Mediated Rejection Are Superior to 2007 Banff Criteria in the Diagnosis and Assessment of Renal Allograft Outcomes

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ABSTRACT

Background. The 2013 Banff meeting updated the requirements for the diagnosis of acute/active antibody-mediated rejection (AAMR) in kidney allografts. There has been speculation that the changes lower the threshold for diagnosing AAMR, and may lead to possible unnecessary and expensive treatment.

Methods. We compared the 2013 Banff classification for AAMR to the previous 2007 Banff to determine if there was an increase in the number of patients receiving a diagnosis of AAMR and if the diagnosis affected allograft survival and post-biopsy 3-month and 6-month creatinine and eGFR values.

Results. A total of 212 renal allograft biopsies were compared to both 2007 and 2013 Banff classification requirements for AAMR. Ten patients (11 biopsies) met the 2007 criteria. An additional 15 patients (20 biopsies) met the 2013 criteria. These 2 groups showed no statistically significant demographic differences. By applying the 2013 Banff classification, we observed a 2.5-fold increase in the number of AAMR cases. One-year post-transplant allograft survival was higher in the 2013 group (.85 vs .55) and the 3-month and 6-month post-biopsy creatinine values were significantly lower for the 2013 group ($1.6 \pm .6$ vs 3.3 ± 2.2, P value .01, and $1.7 \pm .6$ vs 3.4 ± 2.8, P value .03). The 3-month and 6-month eGFR values were higher in the 2013 group, although not statistically significant.

Conclusions. These results suggest that use of Banff 2013 criteria in place of Banff 2007 may result in diagnosing milder and earlier cases of AAMR with the possibility of initiating earlier treatment and improving graft outcomes.

ACUTE/ACTIVE antibody-mediated rejection (AAMR) of kidney allografts has received a large amount of attention in the last few years. New treatments as well as the effectiveness of plasma exchange have made the early detection of acute AAMR critical in preserving long-term graft outcomes. Significant changes in the diagnostic criteria for AAMR were made in the Banff 2013 meeting. The diagnosis for AAMR requires 3 criteria: 1. morphologic evidence of active tissue injury by light microscopy; 2. evidence of antibody interaction with the vascular endothelium based on the presence of C4d, a glomerulitis plus capillaritis score (g + ptc) of at least 2, or gene expression of endothelial-associated transcripts (ENDATs); and 3. serologic evidence of circulating donor-specific antibodies

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(DSAs) specific to HLA or other antigens (Table 1) [1]. Compared to the 2007 Banff criteria (AAMR–2007), the most significant change made in the 2013 Banff criteria (AAMR–2013) pertains to requirement 2, related to the evidence of antibody interaction with the vascular endothelium. The threshold for C4d positivity was lowered to any C4d score >0 by immunohistochemistry or a C4d score of ≥ 2 by immunofluorescence. In addition, this criterion can now be fulfilled in C4d-negative patients who present with g + ptc score ≥ 2 or increased ENDATs [1–3]. Other changes introduced in AAMR–2013 affected the distinction between a glomerulitis score (g) of 2 vs g3.

The AAMR–2013 changes went into effect in August 2014 at our institution, and as of the time of analyzing and writing this article they were the current criteria used in our institution. Since then there has been anecdotal evidence that the changes have broadened the requirements for diagnosis and concerns have been raised that this would lead to an increasing number of AAMR diagnoses with a subsequent increase in unnecessary treatment [4]. No data currently exists on the incidence of AAMR in renal allografts with respect to AAMR–2013. Sis et al determined that death-censored graft survival was related to g + ptc score [5]; however, most of the reports on which the new criteria were based examined the effect of focal C4d staining or g + ptc on short-term worsening of renal function, DSA prediction, transplant glomerulopathy, or chronic, active antibody-mediated rejection [5–9].

In an effort to provide data regarding the incidence of AAMR in response to the AAMR–2013 changes and to move the management of AAMR forward, we evaluated renal biopsies at our institution to determine whether the changes were clinically relevant and can be used to guide therapy and improve patient outcomes. The purpose of this study was to determine if there truly was an increase in the number of biopsies receiving a diagnosis of AAMR. We also wanted to determine whether the AAMR–2013 changes positively affected allograft survival, post-biopsy 3- and 6-month serum creatinine, and estimated glomerular filtration rate (eGFR).

MATERIALS AND METHODS

Study Design and Population

This is a single-center, observational, retrospective cohort study of all patients who received a for-cause renal allograft biopsy between August 2012 and August 2016. The study was approved by the institutional review board (UTSW, STU 08216–041, expedited review). This period corresponds to the time during which the 2 renal pathologists that reviewed these biopsies began employment at this institution. During this period, 212 consecutive biopsies were evaluated by one of 2 renal pathologists using the AAMR–2007 criteria for acute/active antibody-mediated rejection for biopsies from August 2012 to August 2014 and AAMR–2013 criteria for AAMR for biopsies from August 2014 onward.

All 212 biopsies were reviewed and re-scored with AAMR–2007, regardless of the date of the biopsy, to determine the number of biopsies that would have received a diagnosis of AAMR under 2007 criteria. Afterwards, the biopsies were then reviewed and re-scored with AAMR–2013 in the same manner. Two separate groups were then compared, with first group composed of 11 biopsies that met AAMR–2007 and the second group composed of an additional 20 biopsies that only met AAMR–2013.

Table 1. Revised (Banff 2013) Classification of ABMR in Renal Allografts

Acute/active ABMR (All 3 Features Must Be Present for Diagnosis)
1. Histological evidence of acute tissue injury, including 1 or more of the following: • Microvascular inflammation ($g>0$ and/or $ptc>0$); • Intimal or transmural arteritis ($v>0$); • Acute thrombotic microangiopathy, in the absence of any other cause; and • Acute tubular injury, in the absence of any other apparent cause.
2. Evidence of current/recent antibody interaction with vascular endothelium, including at least 1 of the following: • Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by immunofluorescence on frozen sections, or $C4d>0$ by immunohistochemistry on paraffin sections); • At least moderate microvascular inflammation ($[g + ptc] \geq 2$); and • Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury, if thoroughly validated.
3. Serologic evidence of DSAs (HLA or other antigens)

Adapted from Haas et al [1].
Abbreviations: ABMR, antibody-mediated rejection; DSAs, donor-specific antibodies; g, glomerulitis; ptc, peritubular capillaritis; v, arteritis.

Definition of Outcome

The primary outcome was a comparison of the post-biopsy serum creatinine and eGFR at 3 and 6 months and the 1-year allograft outcomes between the 2007 Criteria and the 2013 Criteria groups.

RESULTS

Table 2 presents the baseline recipient and donor characteristics. Patients meeting AAMR–2007 only vs the additional cases identified using AAMR–2013 are presented separately for comparison. The recipient and donor characteristics were similar, with no statistical difference between groups for serum creatinine levels and proteinuria at biopsy.

Of the 212 consecutive graft biopsies performed between August 2012 and August 2016, 11 biopsies (5%) of the cohort met AAMR–2007. When the entire cohort was assessed using AAMR–2013, 31 biopsies (15%) met requirements for an AAMR diagnosis, an increase of 20 biopsies. Of these, 1 was positive only because of the new C4d threshold, 14 were positive because of the g + ptc score changes to criterion 2, and 5 were positive because of both the C4d and g + ptc scores (Fig 1).

Table 3 shows the 3- and 6-month post-biopsy serum creatinine and eGFR for the 2 groups. The 3- and 6-month post-biopsy creatinine values were significantly lower for the 2013 group ($1.6 \pm .6$ vs 3.3 ± 2.2, P value .01, and $1.7 \pm .6$ vs 3.4 ± 2.8, P value .03). The 3-month and 6-month eGFR values

Table 2. Baseline Donor and Recipient Characteristics

Donors	Banff 2007	Banff 2013	*P* Value
Age	41 ± 18	36 ± 15	.477
Sex			
Male	4 (50)	7 (50)	-
Female	4 (50)	7 (50)	
Race			
White	7 (87.5)	12 (85.7)	-
Black	1 (12.5)	2 (14.2)	
BMI	26 ± 7	26 ± 9	.967
Creatinine	1.08 ± .12	1.01 ± .5	.692
CMV			
Positive	6 (75)	10 (71.4)	-
Negative	1 (12.5)	2 (14.2)	
Recipients			
Age	45 ± 12	46 ± 15	.910
Sex			
Male	6 (75)	9 (64.2)	-
Female	2 (25)	5 (35.7)	
Race			
White	5 (62.5)	9 (64.2)	-
Black	3 (37.5)	4 (28.5)	
Pacific Islander	-	1 (7.1)	
BMI	25 ± 5	29 ± 5	.162
CMV			
Positive	5 (62.5)	5 (35.7)	-
Negative	3 (37.5)	8 (57.1)	
Transplant Type			
Kidney only	7 (87.5)	13 (92.8)	-
Kidney and liver	1 (12.5)	1 (7.1)	
Creatinine	7.21 ± 3.2	8.50 ± 5.5	.499
Warm ischemia time (min)	42.5 ± 9.1	36 ± 9.5	.168
Cold ischemia time (min)	15.1 ± 8.7	13.4 ± 8.5	.651
PRA	34.8 ± 40	21.3 ± 39	.527
HLA I/II Mismatch	5.3 ± .7	4.7 ± 1.1	.189

Abbreviations: BMI, body mass index; CMV, cytomegalovirus; PRA, panel reactive antibody.

were higher in the 2013 group, although not statistically significant (45 ± 16 vs 33 ± 18, *P* value .08 and 43 ± 15 vs 33 ± 18, *P* value .12). The Kaplan-Meier plot (Fig 2) illustrates the association between 1-year post-biopsy allograft survival and AAMR–2007 vs AAMR–2013. The AAMR–2013 group had better 1-year post-biopsy allograft survival (.85 vs .55), and was marginally significant (*P* value .07).

DISCUSSION

The diagnostic criteria for AAMR are regularly updated and refined based on the changing techniques available in both pathology and HLA laboratories [1–3]. Because there is no gold standard for the diagnosis of allograft rejection, challenging the value of the diagnostic criteria against clinical outcomes seems to be one of the most appropriate evaluations of their validity. Our study compared the 3- and 6-month post-biopsy serum creatinine and eGFR values, as well as the 1-year allograft survival for biopsies meeting AAMR-2007 vs AAMR-2013. We analyzed a cohort of patients with morphologic evidence of acute tissue injury.

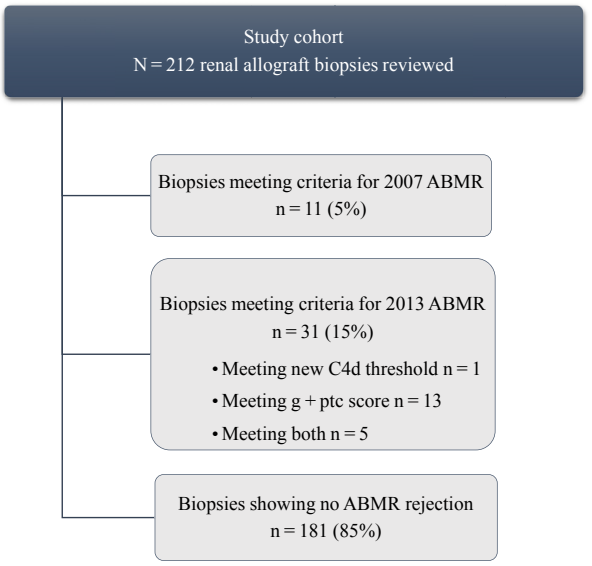

Fig 1. Chart of the study population meeting 2007 and 2013 criteria for ABMR and those with no rejection.

Use of AAMR-2013 increased the diagnosis of rejection by 2.5 times. A Kaplan-Meier curve analysis suggested that ABMR–2013 is associated with 3- and 6-month post-biopsy decreases in serum creatinine, increases in eGFR values, and better 1-year allograft survival than AAMR–2007.

Among the new components of the classification, the g + ptc component had the most impact on increasing the number of biopsies receiving a diagnosis of AAMR. This addition to criterion 2 has met with some controversy. De Serres et al [10] found no association between g + ptc > 2 and the composite end point in their study of chronic acute/active antibody-mediated rejection, and their data suggest that the lowering of the C4d threshold is the most important factor affecting allograft outcome. These findings are supported by several other reports [9–12]. In the DeKAF study, unsensitized patients with positive C4d staining were at higher risk of graft failure regardless of DSA; the threshold for C4d positivity was set at > 10% of peritubular capillary staining, corresponding to a Banff score of 2 for C4d [11].

Table 3. Post-biopsy 3-month and 6-month Creatinine and eGFR Values Associated With Biopsies Meeting Banff 2007 and Banff 2013 Criteria

	Biopsies Meeting Banff 2007 Criteria for ABMR	Biopsies Meeting Banff 2013 Criteria for ABMR	*P* Value
Creatinine at 3 mo (mg/dL)	3.3 ± 2.2	1.6 ± .6	.01
Creatinine at 6 mo (mg/dL)	3.4 ± 2.8	1.7 ± .6	.03
eGFR at 3 mo (mL/min/1.73 m^2)	36 ± 18	42 ± 19	.08
eGFR at 6 mo (mL/min/1.73 m^2)	32 ± 18	40 ± 16	.12

Abbreviations: ABMR, antibody-mediated rejection; eGFR, estimated glomerular filtration rate.

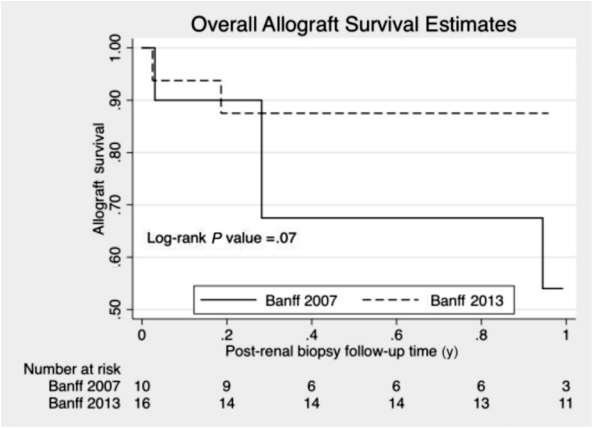

Fig 2. Kaplan-Meier survival plot of 1-year post-biopsy allograft survival for biopsies meeting the Banff 2007 criteria vs biopsies only meeting the Banff 2013 criteria.

Papadimitriou et al previously assessed the association between C4d staining on paraffin-embedded sections and graft dysfunction, defined as requiring for-cause biopsy [3]. They found that the presence of any C4d immunohistochemistry staining was significantly associated with graft dysfunction, with an increase in the odds ratio for C4d from 1 to 3; however, they reported no data on outcomes [3]. In >4500 biopsies gathered from 29 studies, Sapir-Pichhadze et al found that the presence of C4d was associated with inferior graft survival beyond DSA or g + ptc score. They also concluded that the simultaneous presence of all 3 criteria for acute AAMR is unlikely [12].

In contrast, Kozakowski et al reported in a retrospective study that a ptc > 3 was associated with graft loss [13,14]. The reference cited in the Banff 2013 meeting report for the inclusion of the g + ptc > 2 component is a study showing a trend toward an association between this threshold and the development of transplant glomerulopathy in DSA-positive patients even in the absence of C4d [1,15]. Importantly, glomerulitis and peritubular capillaritis are not specific for AAMR [16].

Notably, most of the patients with AAMR presented with mixed rejection: 91% of AAMR–2007 and 65% of AAMR–2013 also met criteria for borderline changes or T-cell mediated rejection. It is possible that the overlap of cellular rejection with antibody-mediated rejection confounds the findings, especially as more biopsies in the AAMR–2007 group experienced cellular rejection in addition to worsening clinical values. More analysis is needed.

This study is subject to a number of limitations. It is a single-institution, observational, retrospective study only spanning 4 years. As such, some of the cases that met the selection criteria during the time frame had very little follow-up data available. The sample size in both groups, while on par with previous studies (De Serres et al reviewed 1017 cases over a 7-year span and only found 22 cases meeting 2007 criteria and an additional 22 cases meeting 2013 criteria [10]) is still small, yielding a low power. Further review spanning a longer time period may increase the number of biopsies for review to increase the power of the findings. Collaboration with another institution may also prove useful in increasing the power of the study. Another limitation is the fact that the number of biopsies between the 2 groups is unequal. Any extreme outliers present in the AAMR–2007 group would affect the mean and standard deviation of the group's serum creatinine and eGFR values to a greater extent. Lastly, EM (electron microscopy) was not reassessed for all the 212 biopsies during the study period. The updates for chronic tissue injury in AAMR–2013 changed the peritubular capillary basement membrane multilayering definitions to be more restrictive than Ivanyi et al's [17] criteria, which was used for most of our cases; the percentage of cases with multilayering as their only form of chronic tissue injury would therefore likely be lower if we were to reinterpret the lesions according to the latest Banff criteria. This would probably lead to the inclusion of a few more cases that were previously labeled as chronic, active antibody-mediated rejection.

In summary, this study tested the AAMR–2007 vs the AAMR–2013 against clinical outcomes. Our findings indicate that the number of biopsies leading to a diagnosis of AAMR increased; they also suggested that the association with clinical outcomes improved with the new criteria, particularly the new g + ptc score. Additional studies with a similar design and possible collaboration with other institutions to increase the overall number of participants and improve the statistical power of the findings are needed to further confirm these observations.

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