I, Basma Sadaka, hereby submit this original work as part of the requirements for the degree of Master of Science in Clinical and Translational Research.

It is entitled:
Differences in histologic response between early and late antibody mediated rejection therapy: assessment by Banff component scoring

Student's name: Basma Sadaka

This work and its defense approved by:

Committee chair: Paul Succop, Ph.D.
Committee member: Rita Alloway, Pharm.D.
Committee member: Ervin Steve Woodle, M.D.
Differences in histologic response between early and late antibody mediated rejection therapy: assessment by Banff component scoring

A thesis submitted to the
Graduate School
of the University of Cincinnati
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Master of Science in Clinical & Translational Research

In the Department of Environmental Health
Division of Epidemiology & Biostatistics
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by Basma Sadaka

Doctor of Pharmacy, Northeastern University
Boston, Massachusetts, May 2009

Committee Chair: Paul Succop, PhD
Committee Members:
Rita R. Alloway, Pharm.D.
E. Steve Woodle, M.D.
OBJECTIVE: To analyze Banff component scoring in early and late antibody mediated rejection (AMR) treated with a proteasome inhibitor-based regimen as a mean for assessing therapeutic response in kidney transplant recipients.

METHODS: AMR was diagnosed using Antibody Working Group criteria. Biopsies were performed within 48 hours prior to and 14-21 days after AMR therapy initiation. Banff component scoring was performed using Banff ’97 criteria (update 2007). C4d capillary staining was considered positive if either focal or diffuse. Early AMR was defined as occurring within 6 months post-transplant and late AMR beyond 6 months. Early and late AMR were treated with a standardized regimen including 4 bortezomib doses (1.3 mg/m²) over 11 days with each dose immediately preceded by plasmapheresis and a single rituximab dose (375 mg/m²).

RESULTS: Fifty-five patients underwent AMR therapy (early AMR (n=18) and late AMR (n=37)). Composite Banff component scoring on initial AMR biopsy demonstrated that late AMR patients, as compared to early AMR patients, had higher t, i, and acute composite scores and higher ci, ct, cg, cv and chronic composite scores. In the entire patient population, AMR treatment provided statistically significant improvement in most individual acute component scores (t, i, g, ptc but not v) and in the acute composite score (t+i+g+v+ptc), but not individual chronic component scores (ct, ci, cg, and cv) or chronic composite score (ct+ci+cg+cv). C4d scoring also decreased significantly with AMR therapy. When analyzed separately, early and late AMR patients demonstrated differential histologic responses to AMR therapy. Early AMR patients demonstrated numerical (but not statistically significant) trends toward improvement in individual acute component and acute composite scoring, and statistically significant deterioration in ct, ci and chronic composite scores. Late AMR patients demonstrated significant improvements only in acute t and i scores, but not acute composite scores or individual chronic component or chronic composite scores.
CONCLUSION: Acute and chronic Banff component scoring demonstrates differences in early and late AMR at diagnosis and in response patterns to AMR therapy. These results indicate that Banff component scoring may provide a means for assessing AMR therapeutic responses in clinical.
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INTRODUCTION

Antibody mediated rejection (AMR) is an infrequent event following kidney transplantation, occurring in 1-5% of unsensitized patients, but may occur in 25% or more of highly sensitized patients.\(^2\)\(^-\)\(^6\) Importantly, responses to AMR therapy, particularly late AMR, are suboptimal. A potential explanation for the suboptimal therapeutic response in AMR is that traditional anti-humoral agents (including intravenous immunoglobulin (IVIg), plasmapheresis, immunoadsorption, rituximab, and rabbit anti-thymocyte globulin (rATG)) do not deplete plasma cells (which are the sole source of antibody production).\(^7\)\(^-\)\(^8\) Recently, bortezomib (Velcade, Millenium Pharmaceuticals, Cambridge, MA) has been used as an anti-humoral, plasma cell targeting agent in solid organ transplantation.\(^9\)\(^-\)\(^18\) Experience with the use of a bortezomib-based regimen has been reported for primary AMR as well as refractory AMR\(^19\)\(^-\)\(^21\) and has demonstrated differential responses in early and late AMR.\(^10\)

These differences in early and late AMR (defined as rejection occurring 6 months post-transplant) included differences in: 1) immunologic characteristics, 2) therapeutic response to proteasome inhibition, 3) renal function response, and 4) Immunodominant donor specific antibody (iDSA) [defined as the highest DSA level] response.\(^10\) However, histologic assessments in the earlier studies did not include a detailed analysis of individual Banff components.\(^9\)\(^-\)\(^21\) The purpose of the present study was to evaluate individual Banff component scoring and composite scores as an objective means for assessing AMR therapeutic responses.

The importance of this study is highlighted by a report from an FDA-organized open public workshop on AMR and desensitization that had a particular focus on clinical trial design issues. Deficits identified in this workshop included: 1) need for improved diagnostic criteria, 2) lack of defined endpoints, and 3) lack of FDA approved quantitative methods for measuring human leukocyte antigen (HLA) antibody
levels. Therefore, this study was conducted to evaluate histologic criteria as a means for assessing histologic responses to AMR therapy.
MATERIALS AND METHODS

Kidney transplant recipients who received a bortezomib-based therapy for AMR between July 2007 and July 2011 at the University Hospital and the Christ Hospital in Cincinnati, Ohio, were analyzed. Patients received treatment with at least one cycle of bortezomib (1.3mg/m$^2$ x 4 doses given on days 1, 4, 7, and 10) and a single dose of rituximab (375mg/m$^2$) immediately before the first bortezomib dose on day 1. Immediately prior to each bortezomib dose, patients underwent plasmapheresis (1.0 – 1.5 plasma volume) with anticoagulant citrate dextrose and 5% albumin replacement. Methylprednisolone was administered intravenously 30 minutes prior to each bortezomib dose (100 mg for the first and second doses and 50 mg for the third and fourth doses). Following the last bortezomib dose, post-treatment plasmapheresis was performed on days 14, 16, and 18. Maintenance immunosuppression was not changed during AMR treatment. Prior to bortezomib therapy initiation, the following prophylaxis were given to all patients: 1) valgancyclovir (225mg orally once a day for 90 days, adjusted based on renal function) for cytomegalovirus coverage, 2) nystatin (5mL orally three times a day for 90 days) for fungal coverage, and 3) trimethroprim/sulfamethoxazole (or pentamidine or dapsone) for 365 days for *Pneumocystis jirovecii* pneumonia coverage.

AMR was diagnosed if three of the following four criteria were present: 1) histologic evidence of microcirculatory inflammation (peritubular capillaritis and/or glomerular capillaritis), 2) presence of DSA, 3) allograft dysfunction in the absence of urinary obstruction or infection, or 4) the presence of C4d in the peritubular or glomerular. C4d was considered positive if linear circumferential peritubular capillary staining was identified in greater than 50% of peritubular capillaries, excluding scarred or necrotic areas.
Renal biopsies were graded using Banff ’97 criteria (update 2007), which was established by the Banff Working Classification of Renal Allograft Pathology in an attempt to standardize the interpretation and reporting of renal allograft biopsies. The following acute Banff components were graded by the pathologist and included in this study’s data collection: 1) tubulitis (t), 2) intimal arteritis (v), 3) interstitial inflammation (i), 4) glomerulitis (g), and 5) peritubular capillaritis (ptc). Chronic Banff components included: 1) interstitial fibrosis (ci), 2) tubular atrophy (ct), 3) allograft glomerulopathy (cg), and 4) vascular fibrous intimal thickening (cv). Acute composite score consisted of the sum of the t, v, i, g, and ptc; whereas the chronic composite score included the sum of ci, ct, cg, and cv. Acute microvascular inflammatory score consisted of the sum of g and ptc scores.

Donor specific anti-HLA antibody (DSA) levels (expressed in mean fluorescence intensity [MFI]) were obtained immediately before plasmapheresis on days 1, 4, 8, and 11 and quantified using single-antigen bead panels on a Luminex assay platform (Labscreen TM Single Antigen; One Lambda, Inc., Canoga Park, CA). Post-treatment DSA levels were also collected after post-treatment plasmapheresis (at least 48 hours after the final plasmapheresis session). Immunodominant DSA (iDSA) was defined as the DSA with the highest level.

Early post-transplant AMR was defined as occurring within the first 6 months after kidney transplantation, and late post-transplant AMR was defined as occurring more than 6 months post-transplant. Noncompliance was identified by detection of non-measurable tacrolimus levels, and/or by patient admission to coordinators or physicians.

All analyses were performed on an intention-to-treat basis. Each pre- and post-treatment biopsy was considered individually and Banff scores were collected for each patient’s in both groups. Variables
were compared between both groups using chi-square test for categorical variables and the Student’s t-test for continuous variables. Data was reported as mean ± standard deviation, or counts and percentage for proportion of patients that had any individual Banff component score >0. P values less than 0.05 were considered statistically significant. Institutional review board approval was obtained from the University Hospital and Christ Hospital (Cincinnati, OH), allowing for the use of patient data for publication. Statistical analyses were performed using the statistical package StatPac© version 12.1 (StatPac Inc, Bloomington, MN).
RESULTS

Fifty-five AMR episodes were treated with a proteasome inhibitor (PI)-based regimen. Examples of early and late AMR pre- and post-treatment on biopsies are shown in Figures 1a and 1b. Follow-up was similar between groups: a mean of 17.7±11 months for early acute AMR patients and 13.3±10.9 months for late acute AMR (p=0.167). Demographic data, rejection characteristics, DSA characteristics and response, and renal function response are presented in Table 1. A male predominance in late AMR and a female predominance in early AMR were observed (p=0.013).

Serum creatinine at rejection diagnosis and iDSA pre-treatment were not statistically significant between the two groups (Table 1). Patients with early AMR more commonly demonstrated class I denovo iDSA specificities (p=0.0002); whereas class II DQ iDSA specificity was predominant in patients with late AMR (p=0.0007). Approximately 59% of patients with early AMR achieved greater than 50% reduction in iDSA on treatment day 14 compared to 27% of patients with late AMR (p=0.024).

Proportion of patients with positive baseline Banff scores are presented in Table 2, distribution of acute and chronic Banff scores are presented in Figures 2a and 2c, and mean acute and chronic component Banff score are presented in Table 2 and Figure 2b and 2d. The proportions of patients with a Banff score that was positive (>0) was higher for the tubular (t) component (91.7% vs. 38.9%, p=0.0001) and interstitial (i) component (91.7% vs. 44.4%, p=0.0003) with late AMR in comparison to early AMR. However, glomerulitis (g) was more common in early AMR (38.9% vs. 28.6%, p=0.0001) and peritubular capillaritis (ptc) (71.4% vs. 38.9%, p=0.025) was more common in late AMR. As expected, early AMR patients had minimal evidence of chronic disease, whereas chronic Banff scores in patients with late AMR provided evidence of significant disease. The proportion of C4d positive biopsies was equivalent between both groups (Table 2).
With respect to the mean scores for all patients in early and late AMR, there was a greater degree of tubulitis and interstitial inflammation with the late AMR group (Table 2). A similar degree of glomerulitis but a trend towards more peritubular capillaritis was also noted in the late AMR group. The microvascular inflammatory score (g+ptc) was not different between the early and late AMR groups; however, the acute composite score (g+i+t+v+ptc) was statistically significant for the acute components between early and late rejection (p=0.0008). In terms of chronic Banff scores, as one might expect, a substantial difference was noted between early and late AMR (Table 2).

Acute Banff scores were evaluated and compared prior to and following AMR treatment in the early and late AMR groups (Figure 3a). In early AMR, statistically significant histologic improvement was not observed for individual acute Banff components or acute composite scores. Numerical trends towards improvement in tubular scores, microvascular inflammatory score (g+ptc), and composite acute scores were observed, but did not reach statistical significance. In contrast, late AMR showed improved acute Banff components, particularly t, i, and ptc scores (p=0.004, p=0.005, and p=0.012, respectively), as well as acute composite scores (p<0.0001).

Deterioration in ct, ci, and chronic composite scores were noted following treatment of early AMR (Figure 3b). However, the chronic composite chronic score in early AMR approached statistical significance, suggesting progression during AMR treatment. Late AMR showed deterioration in ct scores; whereas, remainder of the chronic scores (cg, ci, and cv) did not change. C4d positivity pre- and post-treatment was similar in early AMR, but showed a trend toward improvement with treatment in late AMR (p=0.149).
DISCUSSION

Registration trials for new immunosuppressive agents for AMR will require development and validation of new endpoints. Similar to traditional registration trials of immunosuppressive agents for cellular rejection\(^2\), clinical trials for AMR may likely require histologic and renal function endpoints. However, AMR trials may also include HLA-antibody levels as an additional endpoint. Anti-HLA antibody assays will need to be fully validated (a process that will likely require substantial collaborative efforts between academia and industry) to receive FDA acceptance as clinical trial endpoints.\(^2\) This highlights the importance of establishing the validity of histologic endpoints in AMR clinical trials.

Walsh et al\(^1\) demonstrated that early and late AMR are fundamentally distinct immunologic entities, with early AMR episodes demonstrating better results with a PI-based regimen in comparison to late AMR episodes. This difference was thought to be due to the underlying B cell and plasma cell immunobiology. Generally, early AMR results from a primary antibody response that generates a number of short-lived plasma cells, which have significant susceptibility to proteasome inhibition. In contrast, HLA-antibody levels in late AMR derive in large part from a niche resident long-lived plasma cell population that is more resistant to PI therapy. Contrary to early AMR, late AMR patients tend to have significant residual DSA levels after PI therapy, which could explain the worse long-term outcomes in this group.\(^1\)

We hypothesized that differences would be observed in histologic responses (i.e., Banff components) between early and late AMR due to differences in underlying biology. The present study demonstrated the ability of Banff component scoring to highlight these differences. The proportion of late AMR patients with a positive acute Banff component score (>0) was higher for the t and i components in comparison to early AMR patients, reflecting the relatively higher incidence of concomitant ACR and
mixed rejection in this population. Of interest, the microvascular inflammatory score (g+ptc) was not different between the two groups, but positive g scores were more common in early AMR and positive ptc scores were more common in late AMR. The overall acute composite score was statistically significant for the acute Banff components between early and late AMR episodes. These observations indicated that biologic differences exist between early and late AMR, and argue for additional studies that evaluate these differences.

Differences were also observed between early and late AMR in response to therapy. A trend toward improvement in t, g, ptc, and microvascular composite scores was observed in early AMR, but did not reach statistical significance. No differences were found in the individual chronic Banff scores in early AMR; however, the composite chronic score approached statistical significance, suggesting that a progression to fibrosis occurs with treatment of early acute AMR. Since early AMR presents with less inflammation than late AMR, observation of a treatment benefit should be more difficult with early AMR as compared to late AMR.

Late AMR demonstrated considerable acute inflammation at time of diagnosis. Improvements in t, i, and ptc scores, as well as the microvascular inflammatory score and the composite acute scores were observed following treatment. In late AMR, ct scores were noted to increase; however, no differences were observed in the ci, cv, cg, and the composite chronic scores. This may have resulted from the presence of significant chronic lesions at the time of AMR diagnosis. C4d positivity showed slight improvement post-treatment, but was not found to be statistically significant.

To our knowledge, Banff component scoring has not been used to evaluate differences in early and late AMR, nor to evaluate responses to therapy in early and late AMR. The present study provides evidence
that such differences do occur and indicates that the temporal distinction in when AMR occurs in the
potransplant patients is likely associated with either qualitative or quantitative differences.

The observations in this study have important implication for AMR clinical trials, as they indicate that
histologic component scoring may provide a means for assessing therapeutic responses. They also
indicate that the differences between early and late AMR are substantial enough to warrant
stratification at study entry and/or separation of the two groups for the purposes of statistical analysis.

For histologic parameters to be a viable as an endpoint in clinical AMR trials, they should demonstrate
trends that correlate positively with serum creatinine response (i.e., values for both decrease with
successful therapy) and also with DSA levels. For example, acute component scores should be expected
to decrease as renal function improves with successful therapy. One might expect chronic scores to
increase despite successful therapy, thereby providing a negative correlation. An additional validation
of histologic endpoints for AMR is reproducibility. As an example, significant differences are believed to
exist with respect to the two different methods for C4d staining (immunofluorescence and in situ
hybridization); therefore, central lab may be required to provide standardized histologic preparation.
Similarly, potential inter- and intra-observer (i.e., pathologist) differences should also be known or
evaluated within the context of the trial. Therefore, validation of Banff AMR component scoring is
needed as well as determination of inter- and intra-observer variability. Finally, these data may argue
for central pathology requirement of AMR clinical trials.

Widespread application of DSA testing has resulted in earlier recognition and diagnosis of AMR. We
believe that AMR is detected and diagnosed in our program at an early stage, which resulted in lower
levels of acute inflammation in early AMR in this study. Shifts in clinical management such as that seen
with early diagnosis will present additional challenges for continued development of histologic endpoints in AMR therapy.
BIBLIOGRAPHY


antibody-mediated rejection differs immunologically and in response to proteasome inhibition.


1754-1761.


Table 1: Demographic data, rejection characteristics, DSA characteristics and responses, and renal function responses data

<table>
<thead>
<tr>
<th>Demographic Data</th>
<th>Early AMR (n=18)</th>
<th>Late AMR (n=37)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient age at transplant (years)</td>
<td>42.1 ± 11.2</td>
<td>37.9 ± 13.9</td>
<td>NS</td>
</tr>
<tr>
<td>Male gender</td>
<td>7 (38.9)</td>
<td>28 (75.7)</td>
<td>0.013</td>
</tr>
<tr>
<td>African-American race</td>
<td>7 (38.9)</td>
<td>12 (32.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Deceased donor kidney transplant</td>
<td>7 (38.9)</td>
<td>17 (45.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up post-treatment (months)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>17.7 ± 11</td>
<td>13.3 ± 10.9</td>
<td>0.167</td>
</tr>
<tr>
<td>Range</td>
<td>15.4 (3.2 – 42.3)</td>
<td>31.9 (0.4 – 43.7)</td>
<td>–</td>
</tr>
</tbody>
</table>

| Rejection Characteristics                  |                  |                 |         |
| Time post-transplant to AMR (months)       |                  |                 | <0.0001 |
| Mean ± SD                                 | 1.6 ± 2          | 57.7 ± 43.7     |         |
| Range                                     | 0.5 (0.2 – 5.9)  | 41.5 (8.1 – 151.6)| –       |
| Serum creatinine at rejection diagnosis (mg/dL) | 2.66 ± 1.57     | 2.97 ± 1.44     | NS      |
| Rejection due to noncompliance             | 4 (22.2)         | 14 (37.8)       | NS      |

| DSA Characteristics                        |                  |                 |         |
| iDSA pre-treatment [untitered], (MFI),     | 9,498 ± 7,087    | 11,818 ± 6,844  | NS      |
| Number of HLA class I de novo specificities | 1.4 ± 1.1        | 0.7 ± 1        | 0.031   |
| Number of HLA class II de novo specificities | 1.2 ± 1.2        | 1.8 ± 0.9      | 0.054   |
| MHC class I iDSA specificity               | 9 (52.9)         | 2 (5.4)        | 0.0002  |
| MHC DQ specificity iDSA                    | 5 (27.8)         | 29 (78.4)      | 0.0007  |

| DSA Response Post-treatment                |                  |                 |         |
| Mean iDSA level at nadir on neat sera (MFI) | 3,001 ± 5,370    | 6,540 ± 5,374   | 0.026   |
| Mean reduction in iDSA level at nadir (%)  | 68.2             | 48.7           | 0.180   |
| Mean reduction in iDSA on treatment day 14 (%) | 58               | 36.7           | 0.140   |
| Patients with a >50% iDSA reduction on treatment day 14 (%) | 58.8 | 26.5 | 0.024 |

| Renal Function Response Post-treatment     |                  |                 |         |
| Baseline                                  | 1.14 ± 0.31      | 1.42 ± 0.39     | 0.010   |
| Day 14                                    | 2.01 ± 1.48      | 2.54 ± 1.00     | NS      |
| Month 1                                   | 1.55 ± 0.52      | 2.67 ± 1.43     | 0.007   |
| Month 6                                   | 1.92 ± 1.12      | 2.44 ± 0.86     | NS      |
| Year 1                                    | 1.65 ± 0.72      | 2.75 ± 1.18     | 0.004   |

Categorical variables are expressed as n (%) and continuous variables as mean ± SD
Table 2: Banff component scoring: early and late AMR

<table>
<thead>
<tr>
<th></th>
<th>Early AMR</th>
<th>Late AMR</th>
<th>p-value</th>
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<tr>
<td><strong>Proportion of patients with positive baseline Banff component scores</strong></td>
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<tr>
<td>Acute Banff scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t&gt;0</td>
<td>7 (38.9)</td>
<td>33 (91.7)</td>
<td>0.0001</td>
</tr>
<tr>
<td>i&gt;0</td>
<td>8 (44.4)</td>
<td>33 (91.7)</td>
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<td>g&gt;0</td>
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<td>10 (28.6)</td>
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<td>25 (71.4)</td>
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<td>v&gt;0</td>
<td>2 (11.8)</td>
<td>5 (14.3)</td>
<td>NS</td>
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<tr>
<td>Chronic Banff scores</td>
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<tr>
<td>ct&gt;0</td>
<td>3 (16.7)</td>
<td>34 (94.4)</td>
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<tr>
<td>ci&gt;0</td>
<td>5 (27.8)</td>
<td>32 (88.9)</td>
<td>&lt;0.0001</td>
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<tr>
<td>cg&gt;0</td>
<td>1 (5.6)</td>
<td>12 (33.3)</td>
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<tr>
<td>cv&gt;0</td>
<td>2 (11.8)</td>
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<td>0.0008</td>
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<td>C4d positive baseline biopsies</td>
<td>13 (72.2)</td>
<td>27 (73)</td>
<td>NS</td>
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<tr>
<td><strong>Baseline Banff component and composite scores</strong></td>
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<tr>
<td>Acute Banff scores</td>
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<tr>
<td>t</td>
<td>0.9 ± 1.2</td>
<td>2.1 ± 1</td>
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<tr>
<td>i</td>
<td>0.8 ± 1</td>
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<td>v</td>
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<tr>
<td>g</td>
<td>0.4 ± 0.6</td>
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<tr>
<td>ptc</td>
<td>0.6 ± 0.8</td>
<td>1 ± 0.8</td>
<td>0.096</td>
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<tr>
<td>g+ptc</td>
<td>1.1 ± 1.2</td>
<td>1.4 ± 1.4</td>
<td>NS</td>
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<td>composite scores (t+i+g+v+ptc)</td>
<td>2.9 ± 2.8</td>
<td>5.3 ± 2.5</td>
<td>0.0008</td>
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<td>Chronic Banff scores</td>
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<tr>
<td>ct</td>
<td>0.2 ± 0.4</td>
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<td>&lt;0.0001</td>
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<tr>
<td>ci</td>
<td>0.3 ± 0.4</td>
<td>1.7 ± 0.8</td>
<td>&lt;0.0001</td>
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<tr>
<td>cg</td>
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<td>cv</td>
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<td>4.8 ± 2.4</td>
<td>&lt;0.0001</td>
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</table>

Categorical variables are expressed as n(%) and continuous variables as mean ± SD
Figure 1a: Example of early AMR pre- and post-treatment on biopsy

Pre-treatment

Post-treatment

H&E

H&E

C4d

C4d
Figure 1b: Example of late AMR pre and post-treatment biopsies
Figure 2a: Acute Banff score distributions in early and late AMR
Figure 2b: Mean acute composite Banff score in early and late AMR

**Acute microvascular (g+ptc) composite score**

<table>
<thead>
<tr>
<th></th>
<th>Early AMR</th>
<th>Late AMR</th>
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<tbody>
<tr>
<td>Pre-treatment</td>
<td></td>
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<tr>
<td>Post-treatment</td>
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<tr>
<td>p=NS</td>
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<td>p&lt;0.0001</td>
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**Acute Composite score (i+t+g+v+ptc)**

<table>
<thead>
<tr>
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<th>Early AMR</th>
<th>Late AMR</th>
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<tbody>
<tr>
<td>Pre-treatment</td>
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<tr>
<td>Post-treatment</td>
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<tr>
<td>p=NS</td>
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<tr>
<td>p=0.011</td>
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Figure 2c: Chronic Banff score distributions in early and late AMR
Figure 2d: Mean chronic composite Banff score in early and late AMR

Chronic Composite score (ct+cg+cl+cv)

- Early AMR
  - Pre-treatment: 3, Post-treatment: 2
  - p = 0.061

- Late AMR
  - Pre-treatment: 5, Post-treatment: 5
  - p = NS
Figure 3a: Acute Banff component changes with treatment

Early Rejection

Late Rejection

Worsening

Improvement
Figure 3b: Chronic Banff component changes with treatment

**Early Rejection**

**Late Rejection**

- ct
- ci
- cg
- cv
- chronic composite (ct+ci+cg+cv)

- Improvement
- Worsening