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Bortezomib may Stabilize Pediatric Renal Transplant Recipients with Antibody-Mediated Rejection

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Abstract

Background—Current therapeutic strategies to effectively treat antibody-mediated rejection (AMR) are insufficient. Thus, we aimed to determine the benefit of a therapeutic protocol using bortezomib for refractory C4d+ AMR in pediatric kidney transplant patients.

Methods—We examined 7 patients with treatment refractory C4d+ AMR. Immunosuppression included antithymocyte globulin or anti-CD25 monoclonal antibody for induction therapy with maintenance corticosteroids, calcineurin inhibitor, and antimetabolite. Estimated glomerular filtration rate (eGFR) calculated by the Schwartz equation, biopsy findings assessed by 2013 Banff criteria, and human leukocyte antigen (HLA) donor specific antibodies (DSA) performed using the Luminex single antigen bead assay were monitored pre- and post- bortezomib therapy.

Results—Seven patients (86% male, 86% with ≥6/8 HLA mismatch, and 14% with pre-formed DSA) age 5 to 19 (median 15) years developed refractory C4d + AMR between 1–145 (median 65) months post-transplantation. All patients tolerated bortezomib. One patient had allograft loss. Of the six patients with surviving grafts (86%), the mean pre-bortezomib eGFR was 42 mls/min/1.73 m2 and the mean 1 year post-bortezomib eGFR was 53 mls/min/1.73m2. Five of 7 (71%) had improvement of histological findings of AMR, C4d staining, and/or acute cellular rejection. Reduction in HLA DSAs was more effective for Class I than Class II.

Conclusions—Bortezomib appears safe and may correlate with stabilization of eGFR in pediatric kidney transplant patients with refractory C4d+ AMR.

Keywords

bortezomib; proteasome inhibitor; antibody-mediated rejection; pediatric; transplant; kidney; nonadherence

Conflict of Interest: The authors declare that they have no conflict of interest.

Introduction

Antibody-mediated rejection (AMR) is a significant barrier to improving long-term kidney allograft survival [1–3]. Furthermore, AMR is the leading cause of allograft failure in pediatric kidney transplant patients, accounting for 35.6% of allograft losses with a mean time of approximately 3 years from diagnosis to failure [3–5]. Allograft failure from AMR increases sensitization which is associated with an increased risk of rejection and failure in subsequent allografts [3, 6], higher mortality [7] and longer transplant wait times [8]. Pediatric patients are particularly vulnerable to these complications given most will require re-transplantation in their lifetime.

Treatments for AMR include plasmapheresis, intravenous immunoglobulin (IVIG), and rituximab. These have varying efficacy for reducing human leukocyte antigen (HLA) Class I and II donor specific antibodies (DSA) [9–11]. Plasmapheresis has been shown to be beneficial in one randomized controlled trial [12] while two other randomized controlled trials found no benefit [13, 14]. Furthermore, there are no randomized controlled trials that support the benefits of IVIG for AMR despite its frequent use [15]. Additionally, rituximab has been shown in 2 small randomized controlled trials to improve short term estimated glomerular filtration rate (eGFR) 1 year post-treatment [16, 17]. These therapies, however, may be insufficient to treat AMR [18–22].

Bortezomib, a proteasome inhibitor, has been used with varying success [21, 23–34] to treat AMR, with the rationale that inhibition of plasma cells may more effectively decrease antibody production allowing recovery from AMR. Notably, patients treated for AMR with bortezomib have shown improvement in eGFR despite the persistence of DSAs [25, 26]. This suggests that bortezomib has additional immunomodulatory effects that may impact renal recovery from AMR [35–37]. In this case series, we aimed to report the safety and utility of bortezomib for stabilizing renal function, improving biopsy findings, and reducing DSA burden in 7 pediatric kidney transplant patients with treatment refractory C4d+AMR.

Materials and Methods

Clinical Protocols

All recipients of pediatric kidney transplants at UCLA undergo protocol biopsies at 6, 12, and 24 months posttransplantation or for clinical cause. Additionally, all patients are tested for DSA monthly for the first year, quarterly for the second year and biannually thereafter, for any change in clinical status, and /or for suspicion of medication non-adherence (MNA). All patients with *de novo* DSA undergo renal biopsies (MFI>1000 are considered positive) [38]. For DSAs alone without biopsy changes, treatment includes closer monitoring and high dose IVIG (2g/kg given over 2 days) for MFI > 2000. For DSA with biopsy changes (either histological evidence and/or C4d+), methylprednisolone pulse (10mg/kg/dose × 3 days), high dose IVIG, and rituximab (375mg/m^2) are given. For high MFI DSA (>5000) and creatinine increasing by > 50%, plasmapheresis 1x volume exchange with albumin replacement 3 times a week is initiated. Antithymocyte globulin (ATG) is given for concurrent acute cellular rejection (ACR) 1B or higher. Our bortezomib protocol is based on the protocol of the START collaborative [39]. Plasmapheresis is done on days

1,4,8,15,17,19, and 22 immediately prior to bortezomib administration. Rituximab 375 mg/m2 (day 1), 4 doses of bortezomib 1.3 mg/m^2/dose (days 1,4, 8,15), and IVIG 1g/kg on the last day of treatment (day 22) are given with each round of treatment. Rituximab is primarily given with the first round of therapy and is not readministered in patients who have received it previously. Each dose of bortezomib is preceded by methylprednisolone, acetaminophen, and diphenhydramine premedications. Valganciclovir and sulfamethoxazole/trimethoprim prophylaxis in addition to viral monitoring for BK virus, cytomegalovirus, and Epstein-Barr virus with PCR was initiated and continued for 1 year post-bortezomib protocol.

Patient Selection and Evaluation

This is a single center retrospective review of 7 pediatric kidney transplant patients with refractory C4d+ AMR treated with bortezomib at Mattel Children's Hospital, UCLA between November 2011 and January 2014. This retrospective chart review was performed in accordance with the UCLA institutional review board (IRB #11-003592) and formal patient consent is not required. Additionally, this report conforms with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The overall prevalence of biopsy proven C4d+ AMR in our patient population over the report period was approximately 12%. Patients were selected for treatment with the bortezomib protocol if their pre-bortezomib renal biopsy demonstrated C4d+ AMR and they were refractory to AMR treatment based on meeting 2 of 3 of the following criteria: 1) persistent or worsening biopsy findings, 2) persistent or increasing DSAs that did not decrease by 30% for MFI <10,000 or by 50% for MFI >10,000 or 3) declining graft function for 1 month despite treatment with the above described protocols. Persistent or worsening biopsy findings included progression from no rejection to AMR, progression from ACR to AMR, or persistence of AMR on biopsy.

The standard UCLA immunosuppressive regimen for pediatric transplant recipients included induction with either ATG for high risk patients (cPRA > 30% or delayed graft function) or anti-CD 25 monoclonal antibody for low risk patients cPRA<30%. Maintenance immunosuppression included steroid based immunosuppression, a calcineurin inhibitor, and an anti-metabolite. AMR at time of bortezomib treatment was considered early if it occurred < 6 months post-transplant and late AMR was defined as occurring > 6 months post-transplant [29]. In addition to the protocol surveillance biopsies mentioned above, patients underwent biopsies for cause based on positive DSAs with or without declining graft function. All biopsies were evaluated based on the 2013 Banff Criteria [40].

Patients underwent biopsies at the following time points: prior to any treatment for AMR, within 3 months prior to bortezomib treatment, and within 1 month after bortezomib protocol completion. The eGFR is reported as a measure of renal function and was calculated using the updated Schwartz equation [41]. Non-adherence was defined as physician and/or clinic staff documentation of patient report MNA, undetectable drug levels, or missed appointments [42]. We examined DSA and eGFR pre-bortezomib, at the time of post-bortezomib biopsy, and at 1 year following bortezomib treatment completion.

HLA Antibody Testing

HLA typing of recipient and donor was performed using molecular methods for HLA-A, -B, -DRB1,-DRB3/4/5, and - DQB1 loci by LABType SSO at intermediate resolution according to the manufacturer's specifications and the results were analyzed using HLA Visual software (One Lambda, Canoga Park, CA). Donors were further typed for HLA-Cw, DQA1, DPB1, or at high resolution (LABType SSO DNA typing) to define additional DSA or allele specific DSA. The detection and characterization of HLA antibodies were performed using a Luminex single antigen bead (SAB) assay (One Lambda Inc, Canoga Park, CA) and quantified by mean fluorescence intensity (MFI). Antibodies were considered positive when MFI was ≥1000 for HLA-A, -B, -DR, -DQ, and ≥2000 for HLA-C and –DP [38]. The immunodominant DSA (iDSA) for Class I and Class II was defined as the DSA with the highest MFI. A significant change in iDSA was defined as a 30% decrease for MFIs ≤ 10,000 and a 50% decrease for MFIs >10,000 to account for any variability in MFI secondary to bead saturation [43].

Results

Demographic and clinical information relevant to the initiation of bortezomib are summarized in Table 1 and Table 2. Five of 7 patients (71%) were deceased donor transplant recipients and 7 of 8 (86%) had poor HLA matching (≥6/8 HLA mismatch) (Table 1). Patient 1, a 5 year old patient, was treated for early AMR 1 month post-transplant. His post-transplant course was complicated by delayed graft function and delayed tacrolimus initiation due to concerns for worsening acute tubular necrosis (ATN). Bortezomib was initiated for a combination of increasing DSA MFI and progression from ATN to C4d+ AMR on biopsy (Table 2 and Table 3). The other six patients (86%) were adolescents with a median age of 16 (range 14–19) years and late AMR (Table 1). These patients had a median time of progression from our center's standard AMR treatment to the bortezomib protocol of 6.5 (range 3–20) months. In these patients, bortezomib was initiated at a median time of 65 (range 16–145) months post-transplant. Patient 2 was treated for AMR prior to bortezomib based on rapidly increasing MFI of DSA in association with previous ACR on biopsy (Table 2 and Table 3). Notably patient 6, was transplanted through preformed DSA and was successfully treated for AMR that occurred early post-transplant. However, her AMR recurred >6 months post-transplant after an extended period without follow up due to non-adherence, and she was treated with bortezomib. In contrast to the other 6 patients, she received rituximab with the bortezomib protocol despite having received it previously because of a dramatic reduction of her eGFR and attempt at rescue therapy (Table 2). The remainder of the patients (3–5, 7) had C4d+ AMR continuously from time of any treatment for AMR to time bortezomib was given (Table 2 and Table 3).

All 7 patients had C4d+ AMR associated with either Class I or Class II DSA at the time of bortezomib protocol treatment. Three of 7 (43%) with diffusely positive C4d staining had either partial or complete resolution in their post-bortezomib biopsies. One of 7 (14%), the sole patient with early AMR (Patient 1), had complete resolution of his C4d staining and histological evidence of AMR (Table 3). Additionally, 4 of 7 (57%) patients had

concomitant ACR on biopsy prior to treatment. Of these patients, 75% had improvement of Banff grade and 25% had complete resolution (Table 3).

Four of 7 (57%) patients treated with the bortezomib protocol had Class I DSA. Of those, 75% had a significant decrease in the Class I iDSA MFI after treatment with sustained resolution in 50% of patients 1 year post-treatment (Fig. 1a). All 7 patients treated with the bortezomib protocol had Class II DSA. Two (29%) had significant improvement of Class II iDSA after treatment. Only 1 patient (14%) had sustained resolution of Class II iDSA 1 year post-treatment (Patient 1) (Fig. 1b).

The bortezomib protocol was potentially associated with stabilization of the eGFR immediately post-treatment for 6 of 7 (86%) patients with refractory C4d+ AMR (Fig. 2). One of 7 (17%) with severe impairment of eGFR prior to treatment and MNA suffered allograft loss and returned to dialysis immediately following treatment (Patient 6). The remaining 5 patients with late AMR and the 1 patient with early AMR continued to have relatively stable eGFR 1 year post-treatment. The sole patient with early AMR (Patient 1) had significant recovery of eGFR from dialysis dependence to 73 ml/min/1.73m^2. There were no additional allograft failures (Fig. 2).

Overall, treatment with bortezomib was well tolerated. No patients had peripheral neuropathy, neutropenia, or thrombocytopenia associated with treatment. One patient (Patient 1) had a major infection, coagulase negative staphylococcus bacteremia, which responded to antibiotic therapy. Of note, this patient had also received ATG. Two patients (Patients 1 and 6) had diarrhea concurrent with bortezomib treatment. One patient (Patient 3) had pre-existing BK Viremia, which remained stable throughout treatment with a peak serum BK level of 1,474 copies/mL and was not associated with BK nephropathy. One patient (Patient 7) had a mild sinus infection treated successfully with oral azithromycin.

Discussion

Our report examined the safety and effectiveness of using a bortezomib protocol for treatment refractory C4d+ AMR in a group of pediatric kidney transplant patients composed primarily of adolescents with late AMR. Bortezomib was well tolerated in our patients. The sole patient with early AMR in our cohort had dramatic recovery with the use of bortezomib as rescue therapy, consistent with previous studies [19, 20, 29]. This included resolution of DSAs, improvement in biopsy findings, and recovery of renal function.

Notably, the addition of bortezomib may have been associated with stabilization of allograft function in 6 of the 7 patients with refractory C4d+ AMR, the majority having late AMR. Late AMR has been recognized as a clinically distinct entity from early AMR that is resistant to treatment and associated with poor allograft survival [18–22]. Previous authors have noted stabilization or improvement of late AMR with bortezomib [21, 26, 28, 29], but our case series is the first to report this finding in a cohort of mainly high risk adolescents. This potential effect was maintained 1 year after treatment, without any additional allograft losses in the year following treatment. Bortezomib was futile in one patient with late AMR, severely compromised graft function at the time of treatment initiation, and overt defiant

non-adherence with refusal to participate in clinic visits and laboratory monitoring. This is consistent with previous case reports [27, 44]. Our protocol may have correlated with a stabilization in renal function in patients with late AMR and eGFR > 30 ml/min/1.73m^2 at the time of treatment initiation. Therefore, we suggest that intensive DSA monitoring allowing for early detection and treatment of late AMR may maximize the benefit of bortezomib by allowing for treatment prior to significant allograft dysfunction.

Potential stabilization of eGFR in patients with refractory C4d+ AMR appeared to be independent of DSA response. Consistent with previous studies [45–47], reduction in iDSA with bortezomib treatment was more effective for Class I antibodies than Class II. In vitro studies have shown that bortezomib treated lymphocytes [47] and multiple myeloma cells [48] preferentially reduce HLA Class I expression and decrease stimulation for continued Class I antibody production [47]. The effect of bortezomib on cell surface expression of HLA Class I but not Class II may explain why this therapy has not produced dramatic recovery of renal function or biopsy findings in many patients with late AMR associated with HLA Class II DSAs [22, 49]. Interestingly, patients treated with bortezomib have shown modest improvement in eGFR despite the persistence of DSAs, which is consistent with our findings [25, 26]. This suggests that the immunomodulatory actions of bortezomib, such as modifying cell surface antigen expression and T-cell function, may contribute to its value as a therapy for AMR beyond its effect on the plasma cell and DSA production [47].

We also found that the addition of bortezomib may have been associated with an improvement in concomitant ACR in patients with refractory C4d+ AMR, which has been previously described [50]. Most of these patients had mild ACR (Ib or lower), however, which is generally not resistant to conventional therapy. More notably, the one patient with early AMR had concomitant ACR IIa which improved to borderline on follow up biopsy. This could represent a direct effect of bortezomib on T-cells. Bortezomib has been shown to suppress rapamycin resistant memory T cells while preserving the survival of T regulatory cells in vitro [35], and there is evidence that bortezomib reduces T lymphocyte numbers and the Th1/Th2 ratio in chemotherapy patients [36]. The observed effect on ACR may also be secondary to the use of corticosteroids as a premedication for bortezomib or the co-administration of ATG in some of our patients.

We recognize the limitations of our case series. One limitation is the wide range of timing and intensity of treatment for AMR prior to the initiation of bortezomib. Additionally, there is the possibility of observing effects from the multiple other treatments that were given prior to or concomitant with bortezomib in these results. Nonetheless, this is the largest reported pediatric case series describing the safety and potential benefits of a bortezomib protocol for refractory C4d+ AMR. Despite our small sample size, we were able to demonstrate that a bortezomib protocol can safely be used in the pediatric population, is potentially correlated with a stabilization of eGFR in adolescents with late AMR, and was effective rescue therapy for early AMR. Intensive DSA monitoring allowing for early detection and treatment may optimize the benefit of this protocol for late AMR by allowing for treatment prior to significant functional decline; however, our findings need validation in a larger randomized control trial.

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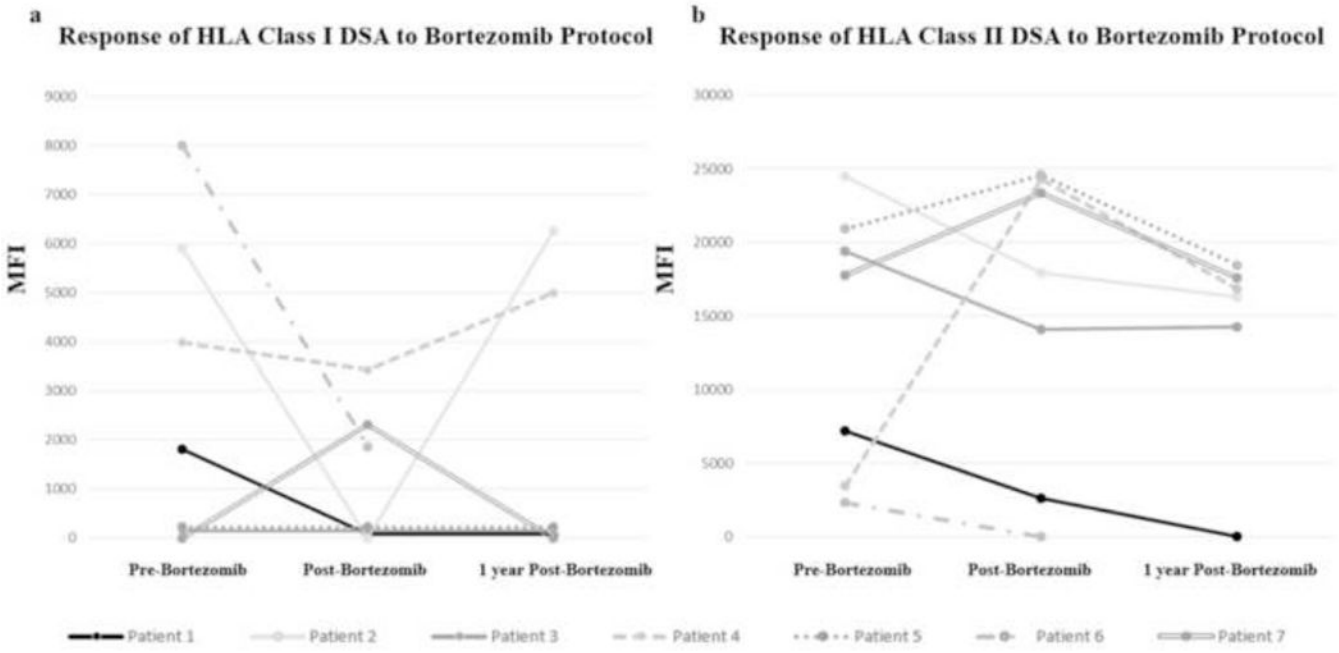

Fig. 1.

Change in immunodominant DSA (iDSA) over time in relation to treatment with bortezomib protocol. Data for all patients presented before and after treatment. Six patients with functioning grafts had one year follow up data available. (a) HLA Class I: Of 4 patients with Class I DSAs prior to treatment, 3 had a significant decrease in iDSA mean fluorescence intensity (MFI) after treatment. One patient developed Class I DSA after treatment. Two patients had rebound, 1 patient had resolution, and 3 patients were negative 1 year post-treatment. The iDSA was to the “A” locus in 3 patients and “Cw” in 2 patients. (b) HLA class II: All 7 patients had Class II DSAs and 2 had significant improvement of iDSA after treatment. One patient had resolution of Class II DSA and 5 patients had no significant change in iDSA 1 year post-treatment. The iDSA was to “DQ” in 5 patients and “DR” in 2 patients.

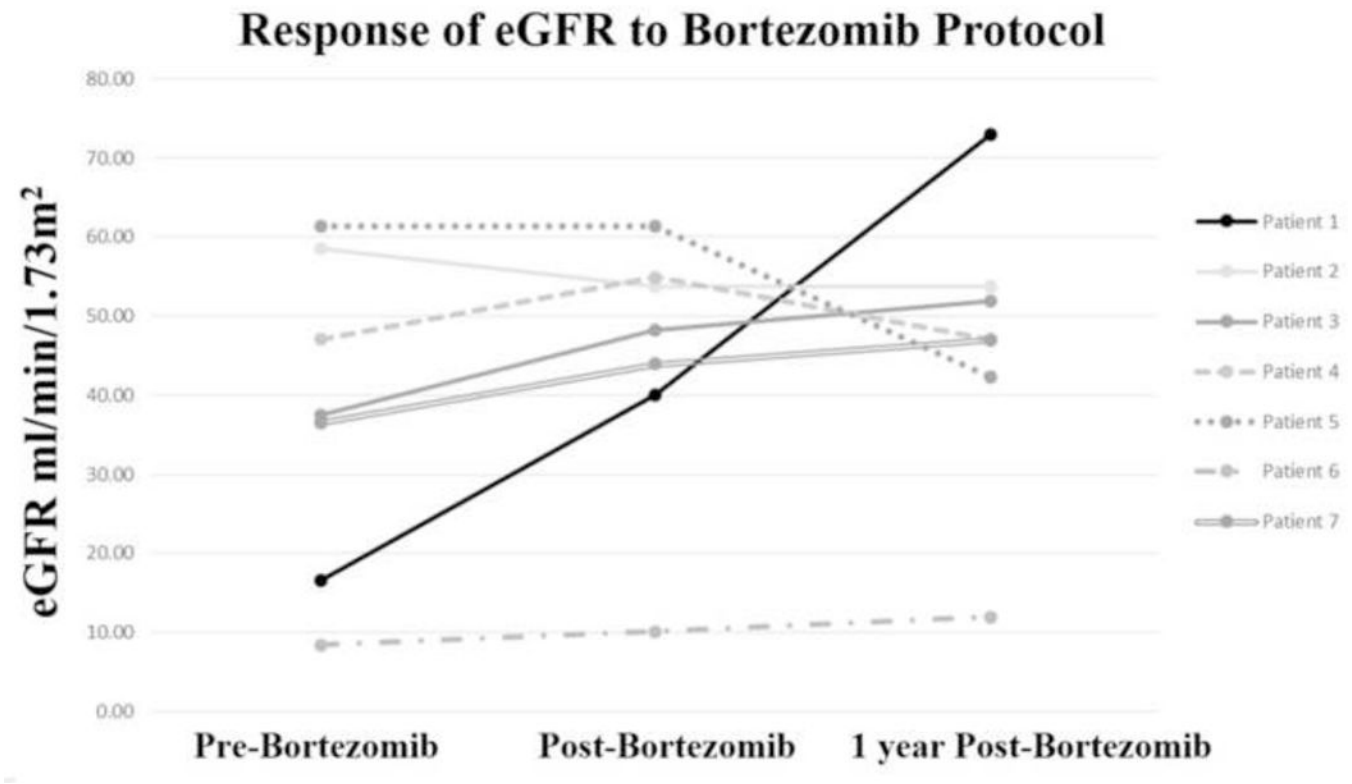

Fig. 2.

Estimated glomerular filtration rate (eGFR) over time in relation to treatment with bortezomib protocol.

Table 1

Patient Demographics

Pt #	Donor Type	Age at Bortezomib Protocol	Sex	HLA Mismatch A, B, DR (DQ)	Tx#	cPRA% HLA Class I/Class II	Etiology of ESRD	MNA
1	DD	5y	M	2,1,2 (2)	1	0/0	Hypoxia	No
2	DD	17y	M	2,2,2 (2)	1	0/0	ANCA GN	Yes
3	DD	15y	M	1,2,2 (2)	1	0/0	Indomethacin Toxicity	Yes
4	LRD	14y	M	1,1,1 (1)	1	0/0	Congenital Nephrotic Syndrome	Yes
5	LRD	14y	M	1,2,1 (2)	1	0/0	Congenital Nephrotic Syndrome	Yes
6	DD	18y	F	2,2,1 (1)	2	84/43	Neurogenic Bladder	Yes
7	DD	19y	M	1,2,2 (2)	1	0/0	Dysplasia	Yes

Pt patient, *DD* deceased donor, *LRD* living related donor, *y* year, *M* male, *F* female, *HLA* human leukocyte antigen, *Tx* transplant, *cPRA* calculated panel reactive antibody, *ESRD* end stage renal disease, *ANCA GN* anti-neutrophil cytoplasmic antibody glomerulonephritis, *MNA* medication nonadherence

Table 2

Immunosuppression, Timing of AMR Treatment and Bortezomib Protocol, and Indication for Bortezomib Protocol

Pt #	Induction IS	Maintenance IS at time of Bortezomib	Time Post-Tx AMR Treatment Initiated	Time Post-Tx of Previous AMR Treatments	Time Treated for AMR prior to Bortezomib Protocol	Time Post-Tx of Bortezomib Protocol	Indication for Bortezomib Protocol	Rounds of Bortezomib Protocol
1	ATG	FK MMF Steroid	0m	MP (0m) IVIG (0m) ATG (0m)	1m	1m	↑ DSA ATN→AMR	1
2	Basiliximab	FK MMF Steroid	13m	MP (13m) IVIG (13m, 15m)	3m	16m	↑ DSA ACR→AMR	3
3	Daclizumab	FK Leflunomide Steroid	65m	MP (65m) Rituximab (65m) IVIG (65m–70m)	5m	70m	↓ eGFR Persistent DSA Persistent AMR	2
4	Daclizumab	FK MMF Steroid	134m	MP (134m), Rituximab (134m), IVIG (134m, 138m)	6m	140m	↑ DSA Persistent AMR	2
5	Daclizumab	FK MMF Steroid	138m	MP(138m), Rituximab (138m) IVIG (138m & 142m)	7m	145m	↑ DSA Persistent AMR	2
6	ATG	FK MMF Steroid	0m	IVIG (0m–15m) PP (0m–15m) Rituximab (1m) MP (8m) ATG (8m)	19m	19m	↓ eGFR ↑ DSA AMR Recurrence	2
7	Daclizumab	CYA MMF Steroid	45m	MP (45m), Rituximab (45m) IVIG (45m, 51m, 63m–65m) PP (63m–65m)	20m	65m	↑ DSA Persistent AMR	2

Pt patient, *IS* immunosuppression, *FK* tacrolimus, *MMF* mycophenolate mofetil, *y* year, *m* months, *MP* methylprednisolone pulse, *IVIG* intravenous immunoglobulin, *PP* plasmapheresis, *ATG* antithymocyte globulin, *DSA* donor specific antibody, *eGFR* estimated glomerular filtration rate, *ATN* acute tubular necrosis, *AMR* antibody-mediated rejection, *ACR* acute cellular rejection. Ranges reflect multiple doses/treatments during a given time period.

Table 3

Biopsy Findings Before AMR Treatment, Before Bortezomib Protocol, and After Treatment with Bortezomib Protocol and Graft Outcome

Pt #	Pre-AMR Treatment Biopsy	Pre-Bortezomib Biopsy	Post-Bortezomib Biopsy	Graft Loss
1	No AMR or ACR, No IFTA, Severe ATN	C4d+ AMR, ACR IIA	No AMR, Borderline ACR	No
2	No AMR, ACR1A, No IFTA	C4d+ AMR, ACR1A, No IFTA	C4d+ AMR, Borderline ACR, No IFTA	No
3	C4d+ AMR, No ACR, Moderate IFTA	C4d+ AMR, No ACR, No IFTA	C4d+ AMR, No ACR, No IFTA	No
4	C4d+ AMR, No ACR, TG, No IFTA	C4d + AMR, No ACR, No IFTA	C4d+ AMR, No ACR, Mild IFTA	No
5	C4d+ AMR, No ACR, No IFTA	C4d+ AMR, Borderline ACR, No IFTA	C4d+ AMR, No ACR, Mild TG	No
6	C4d+ AMR, No ACR, No IFTA	C4d+ AMR, ACR1B, No IFTA	Decreased C4d, AMR, ACR 1B, Mild IFTA	Yes
7	C4d+ AMR, ACR1A, No IFTA	C4d+ AMR, No ACR, Mild IFTA	C4d- AMR, No ACR, No IFTA	No

Pt patient, *AMR* antibody-mediated rejection, *ACR* acute cellular rejection, *IFTA* interstitial fibrosis tubular atrophy, *ATN* acute tubular necrosis, *TG* transplant glomerulopathy