



Letter to the Editor

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Bortezomib-Containing Multimodality Treatment for Antibody-Mediated Rejection with Anti-HLA and Anti-AT1R Antibodies after Kidney Transplantation

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To the Editor:

For decades, the human leukocyte antigen (HLA) complex has been considered the primary target of antibody-mediated rejection (AMR), and treatment strategies have mainly focused on anti-HLA antibodies. Recently, other antibodies potentially causing organ damage and loss have been discovered. Conclusive evidence on treatment options for these subtypes of AMR is still lacking. After an experience previously reported in this journal,¹ we describe a case of late-onset AMR, with mixed anti-HLA and anti-angiotensin II type 1 receptor (AT1R) antibodies, that was successfully treated with a multimodal approach, including the use of the proteasome inhibitor bortezomib.

A 39-year-old Caucasian man received a live-related renal transplant in 2007. The donor and the recipient were blood group compatible with a 5 ABDRDQ-HLA-antigen mismatch. Pre-transplant panel reactivity antibody and direct microcytotoxicity cross-match were negative. For baseline immunosuppression, the patient received basiliximab, tacrolimus, enteric-coated mycophenolate sodium, and steroids. Postoperative course and follow up were uneventful. Seven years after transplantation, the patient was hospitalized with worsening graft function and low calcineurin inhibitor levels (Table 1), reflecting occasional non-compliance with immunosuppres-

sants. Antibody screening showed anti-HLA sensitization, with *de novo* donor-specific antibodies (DSAs) against B58 and DQ9, and high titers of anti-AT1R antibodies (>50 U/L). Interestingly, both anti-HLA DSAs were unable to fix C1q, suggesting that anti-AT1R antibodies played a toxic role, in this specific setting. Histopathologic examination confirmed AMR. The patient received an initial multimodality treatment based on a combination of steroids, plasma exchange, and intravenous immunoglobulins. Then, bortezomib (Velcade[®], Takeda, Osaka, Japan) was administered at 1.3 mg/m² of body surface area, on days 1, 4, 8, and 11, to directly inhibit antibody production through plasma cell depletion.² Following anti-rejection treatment, anti-HLA DSA and anti-AT1R antibodies promptly disappeared, and SCr stably decreased. One year later, the patient is doing fine, with stable graft function, no proteinuria, and undetectable DSA and anti-AT1R antibodies (Table 1).

Despite surgical innovations and novel immunosuppressive regimens, long-term kidney allograft survival has not significantly improved during last decades, since we are now losing organs mainly due to AMR.³ Recently, in addition to anti-HLA antibodies, new antibodies have been discovered in transplant recipients experiencing rejection, supporting the hypothesis that anti-HLA antibodies may not be the only effectors of alloimmune humoral response. Among them, anti-AT1R antibodies seem to be particularly significant.

AT1R is the main receptor for angiotensin II. Anti-AT1R antibodies can mimic angiotensin II and trigger multiple autoreactive and alloreactive responses, eventually leading to cell damage, apoptosis, and hypertension due to allosteric activation of AT1R.⁴ Anti-AT1R antibodies can act independently or synergistically with other effectors of the rejection pathway.⁵

Our patient experienced AMR seven years after transplantation due to non-compliance. An association between anti-HLA and anti-AT1R antibodies has been already described in un-

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Table 1. Clinical Parameters before, during, and after Bortezomib Administration

Parameters	Normal range	Before rejection	Detection	Bortezomib administration				Day 90	Day 180	Day 365
				Day 10	Day 13	Day 17	Day 20			
SCr (mg/dL)	0.6–1.2	1.1	1.89	1.6	1.8	1.6	1.5	1.7	1.5	1.55
eGFR (mL/min)	>90	80	40	48	42	48	53	47	53	50
Proteinuria (mg/24 hr)	28–141	30	94	-	-	-	177	48	74	46
WCC (cell×10 ³ /μL)	4.8–10.8	-	7.0	8.2	9.3	6.5	6.3	6.9	13.0	7.58
NLR (#)	/	-	1.9	7.8	4.6	2.1	1.9	1.3	3.9	2.0
CRP (mg/L)	<0.5	-	-	-	-	0.03	0.03	-	-	-
Anti-HLA Class I Abs (%)	/	0	11	0	-	-	-	0	0	0
Anti-HLA Class II Abs (%)	/	0	26	0	-	-	-	0	0	0
DSA B58 (MFI)	/	-	2755	-	-	-	-	-	-	-
DSA DQ9 (MFI)	/	-	3800	-	-	-	-	-	-	-
Anti-AT1R Abs (U/l)	/	-	>50	-	-	-	14	-	0	0
Prednisone (mg/day)	/	5	5	20	20	20	20	10	10	10
Sodium mycophenolate (mg/day)	/	1440	1440	1440	1440	1440	1440	1440	1440	1440
Tacrolimus (mg/day)	/	3	3	5	5	5	5	6.5	5.5	5.5
Tacrolimus CO (ng/mL)	/	6.1	3.2	5.6	6.8	4.4	5.2	8.3	5.7	4.6
Diuresis (mL/24 hr)	/	-	3500	4500	-	3000	3300	3500	3300	4000

Abs, antibodies; AT1R, anti-angiotensin II type 1 receptor; CO, trough level; CRP, C-reactive protein; DSA, donor-specific antibodies; eGFR, estimated glomerular filtration rate; HLA, human leukocyte antigen; MFI, mean fluorescence intensity; NLR, neutrophil-to-lymphocyte ratio; WCC, white cell count.

der-immunosuppressed kidney transplant recipients.⁵ *De novo* anti-AT1R antibodies have been also detected after episodes of allosensitization,⁶ being consistently associated with rejection and poor graft and patient survivals.⁷ However, testing for non-anti-HLA antibodies is not routinely performed, such that their real incidence and prevalence in the transplant population are basically unknown.⁷

What may trigger the development of anti-AT1R antibodies after transplantation is still under investigation. Several factors have been proposed: 1) genetic polymorphisms affecting the structure of AT1R extra-cellular domain; 2) genetic polymorphisms altering the geometric shape of the receptor; 3) antigenic exposure secondary to death perturbations; and 4) cell damage caused by alloimmune response, which modifies AT1R expression into the graft exposing previously hidden epitopes.⁵

Meanwhile, several therapeutic options have been proposed to treat early-onset anti-HLA AMR. Some combination strategies have shown good results in the short term, although no clear benefit of one specific regimen has been demonstrated, and long-term results are sub-optimal. Experience with late-onset non-anti-HLA AMR is even more limited.⁸ Inhibition of B-cells and antibody production by administration of anti-CD20 monoclonal antibodies (e.g., rituximab) or proteasome inhibitors (e.g., bortezomib) may represent a promising option together with apheresis techniques and intravenous immunoglobulins.⁹

Optimal treatment of late-onset acute AMR is still a matter of debate. Reports on anti-AT1R AMR are anecdotal: some authors support the role of apheresis combined with intravenous normal human immunoglobulins, rituximab, and high-dose AT1R-blockers.¹⁰ This journal has already published a

first successful experience with bortezomib.¹ Our experience with a multimodality treatment, including bortezomib, confirms its efficiency in stably clearing not only anti-HLA but also anti-AT1R antibodies, halting renal function deterioration even in the longer term.

Further investigations are warranted to better address the role of proteasome inhibition in the setting of anti-HLA and non-anti-HLA AMR and to assess the contribution of bortezomib to overall efficacy.

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