# Effective Therapy for Acute Antibody-Mediated Rejection With Mild Chronic Changes: Case Report and Review of the Literature

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## Abstract

**To reduce the long-term toxicities of immunosuppressant drugs, corticosteroid-sparing and calcineurin-inhibitor–sparing immunosuppression protocols have become increasingly popular in managing kidney transplant recipients. The most vexing clinical condition caused by antibodies in organ transplants is antibody-mediated rejection. Limitations of the current antibody-mediated rejection therapies include (1) antibody-mediated rejection reversal tends to be gradual rather than prompt, (2) expense, (3) rejection reversal rates below 80%, (4) common appearance of chronic rejection after antibody-mediated rejection treatment, and (5) long-term persistence of donor specific antibodies after therapy. Because these limitations may be due to a lack of effects on mature plasma cells, the effects of bortezomib on mature plasma cells may represent a quantum advance in antihumoral therapy.**

**Our experiences represent the first clinical use of bortezomib as an antihumoral agent in renal allograft recipients in Kuwait. We present 2 cases with resistant-acute antibody-mediated rejection to the standard therapies that were managed successfully with bortezomib.**

**Key words:** *Antibody-mediated rejection, Bortezomib, Renal transplant*

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***Experimental and Clinical Transplantation (2012) 4: 406-409***

The most vexing clinical condition caused by antibodies in organ transplants is antibody-mediated rejection (AMR).[1, 2] Evidence of AMR can be found in 20% to 30% of episodes of acute rejection.[3]

Current anti-humoral therapies (plasmapheresis, intravenous [IV] immune globulin), and polyclonal antilymphocyte antibodies, including rabbit anti-thymocyte globulin lack direct effects on the major antibody producing cell (the mature plasma cell). Although B-lymphocyte specificity has been provided with rituximab (an anti-CD20 monoclonal antibody), it does not deplete plasmablasts or mature plasma cells, which represent the major source of antibody production.[4]

Bortezomib is a first in a class of proteosomal inhibitor, which is Food and Drug Administration-approved, for treating multiple myeloma (a plasma cell neoplasm).[5]

Limitations of the current AMR therapies include the following: (1) AMR reversal tends to be gradual rather than prompt, (2) expense, (3) rejection reversal rates below 80%, (4) common appearance of chronic rejection after AMR treatment, and (5) long-term persistence of donor-specific antibodies after therapy. Because these limitations may be due to the lack of effects on mature plasma cells, the effects of bortezomib on mature plasma cells may represent a quantum advance in anti-humoral therapy,[6] but the diagnosis of AMR is sometimes challenging. Although antibodies specific for the donor are sometimes found in the circulation, such antibodies are not often found, at least not at high levels.[7]

In contrast to prior reports suggesting that rituximab leads to decreased serum alloantibody levels in sensitized recipients,[8] we contend that accumulating data suggest that rituximab likely plays little beneficial role in preventing ongoing antibody production in sensitized renal allograft candidates.



**DOI: 10.6002/ect.2011.0153**

A growing dissatisfaction with the results of standard AMR therapies led to a search for anti-humoral agents with activity against plasma cells. This search led to identifying bortezomib as an anti-plasma cell agent. In addition to anti-plasma cell properties, proteosomal inhibitors suppress T-cell function.[9] Therefore, they also have the potential for treating or preventing cell-mediated allograft rejection.

**Aim of the work**

The experience described herein represents the first clinical use of bortezomib as an anti-humoral agent in renal allograft recipients in Kuwait. We present 2 cases with acute resistant AMR to the standard therapies that were managed successfully with bortezomib therapy.

**Case Reports**

**Case** 1

A 19-year-old Syrian man with end-stage renal disease, secondary to chronic tubulo-interstitial disease, underwent live-related renal transplant from his father on July 29, 2007. He received basiliximab as an induction and was maintained on a steroid, mycophenolate mofetil, and cyclosporine. He had a smooth postoperative course and his graft function was normal. In view of good human leucocyte antigen match, he was shifted to sirolimus. On April 2010, he developed graft dysfunction and graft biopsy revealed acute AMR with mild chronic changes. This episode was treated by our adopted antirejection protocol: 10 sessions of 1 volume plasma exchange, 2 g/kg IV immunoglobulin in 5 divided doses, and 1 dose of rituximab 375 mg/m$^2$—together with intensification of his maintenance immuno - suppression by conversion to tacrolimus. Despite this, his creatinine did not touch baseline values. Two months later, rebiopsy of the graft revealed the same findings. In view of low total CD count with complete depletion of CD19 lymphocytes, we gave him 1 cycle of bortezomib to extend plasma exchange to 20 sessions, but the level of donor antibodies (anti-human leucocyte antigen class II) did not improve (Table 1). After 2 months of completing antirejection therapy, he developed legionella bronchopneumonia that was managed successfully. His graft function showed progressive improvement over the next few months (mean creatinine, 140 ± 15 μmol/L).

**Case 2**

A 40-year-old Kuwaiti lady with end-stage renal disease, secondary to IgA nephropathy, underwent preemptive live-related renal transplant from her brother on July 4, 2008. She received basiliximab as induction and was maintained on a steroid, mycophenolate mofetil, and cyclosporine. She had smooth postoperative course and her graft function was normal. Unfortunately, BK viremia and viruria were detected by June 2009. She was managed by reduction of her immunosuppression (calcineurin inhibitor minimization), and she became aviremic after 3 months. On April 2010, she developed acute graft dysfunction that was managed by an empiric pulse steroid. However, a graft biopsy done after 3 days showed acute AMR with mild chronic changes. Again, our adopted antirejection protocol was applied, together with intensification of her maintenance immunosuppression, by conversion of cyclosporine to tacrolimus. Despite this, her creatinine continued to rise, with a low total CD count and complete depletion of CD19 lymphocytes, so we decided to give her 1 cycle of bortezomib and to extend plasma exchange for 4 more sessions. After 4 months, her graft function showed progressive improvement (mean creatinine, 120 ± 12 μmol/L).

**Table 1.** Summary of The 2 Cases With AMR Treated With Bortezomib

| | Case I | Case 2 | |
|---|---|---|---|
| Original kidney disease | Chronic TID | IgA nephropathy | |
| Donor | Live-related | Live-related | |
| **Immunosuppression** | | | |
| Induction | Basiliximab | Basiliximab | |
| Maintenance | Steroid, MMF, and cyclosporine | Steroid, MMF, and cyclosporine | |
| First conversion | CsA to rapamycin | CNI minimization | |
| Second conversion | Rapamycin to tacrolimus | CsA to tacrolimus | |
| First biopsy result | Acute AMR with chronic changes | Acute AMR with chronic changes | |
| Management | PE + IVIG + rituximab | PE + IVIG + rituximab | |
| Second biopsy | Acute AMR with chronic changes | Not done | |
| Further management | PE up to 20 sessions + bortezomib (1 cycle) | PE up to 20 sessions + bortezomib (1 cycle) | |
| **PRA-date** | | **Class I (%)** | **Class II (%)** |
| May 17, 2010 | | 40 | 43 |
| September 6, 2010 | | 0 | 53 |
| June 30, 2010 | | 0 | 43 |
| May 9, 2010 | | 0 | 63 |
| **Creatinine μmol/L** | | | |
| Basal | 180 | 88 | |
| Peak | 178 | 134 | |
| Last | 140 | 90 | |

***Abbreviations:*** AMR, antibody-mediated rejection; CNI, calcineurin inhibitor; CsA, cyclosporine; IgA, immunoglobulin A; IVIG, intravenous immunoglobulin; PE, plasma exchange; PRA, panel reactive antibody TID, total ionizing dose

**Antirejection therapy**

After completing a course of conventional AMR therapy, and after a detailed discussion, and getting the written consent of the Hamed Al-Essa organ transplant center of Kuwait according the ethical guidelines of the 1975 Helsinki Declaration, the 2 cases received treatment with bortezomib. We adopted the following bortezomib protocol that consisted of plasmapheresis sessions (1.0-1.5 plasma volumes) under heparin anticoagulant with 5% albumin replacement. After each plasmapheresis, bortezomib was given (1.3 mg/m$^2$) IV over 3 to 5 seconds. Bortezomib was redosed on treatment days 4, 8, and 11 with plasmapheresis performed immediately before each dose. Methylprednisolone was given IV 30 minutes before each bortezomib dose (100 mg for first and second doses, and 50 mg for third and fourth doses).

## Discussion

To reduce the long-term toxicities of immunosuppressant drugs, corticosteroid and calcineurin inhibitor-sparing immunosuppression protocols have become increasingly popular in managing kidney transplant recipients. Nevertheless, these strategies may increase the risk of acute and chronic allograft injury that may worsen the fate of transplant recipients.[10]

Randomized controlled trials in which calcineurin inhibitors were replaced a few months after transplant by sirolimus reported improved graft function among sirolimus-treated patients, but such a treatment was complicated by iatrogenic toxicity. Late replacement of calcineurin inhibitors with sirolimus did not produce an advantage and again, it was complicated by more frequent adverse effects. Based on these trials, it seems that calcineurin inhibitor elimination can trigger rejection or adverse effects.[11]

Because we had a good human leucocyte antigen match in our first case, with the advantages of conversion to sirolimus, we proceeded in that way, but 6 months later, the patient developed an acute rejection episode of AMR despite keeping the drug level within the accepted therapeutic window. This rejection episode was resistant to the conventional means of treatment, and the graft was about to be lost. This was matched with a report by Cantarovich and Vistoli 2008,[12] who concluded that calcineurin inhibitors as well as corticosteroids may induce adverse effects, and despite the benefits from their withdrawal, minimization, or avoidance, this could be dangerous and result with a graft loss (ie, antibody-mediated process).

We tried to minimize calcineurin inhibitor for controlling polyoma virus BK nephropathy in the second case and again, this strategy was complicated with a resistant episode of acute antibody-mediated rejection. A finding that was matched with that reported by Höcker and Tönshoff in 2009,[13] who showed that reduction of immunosuppression is the cornerstone in treating polyoma virus BKV-induced nephropathy. However, specific antiviral agents such as cidofovir and leflunomide are known to inhibit BKV. Moreover, cidofovir is nephrotoxic and should be administered cautiously. Complete calcineurin inhibitor avoidance seems inappropriate because other relatively potent immunosuppressant agents, such as lymphocyte depleting antibodies, are needed for rejection prophylaxis and are frequently accompanied by a higher incidence of infections.

Flechner and associates,[14] concluded that a bortezomib-containing regimen demonstrated activity in AMR but seems to be most effective before the onset of significant renal dysfunction (serum creatinine < 249 μmol/L) or proteinuria (< 1 g/d). Only 25% returned to their baseline renal function before AMR. They added that it should be evaluated in controlled trials using dosing strategies that include longer courses or retreatment schedules.

Trivedi and associates,[15] showed that bortezomib elicited a substantial reduction in both donor-specific antibody and non–donor-specific antibody levels in 11 patients with anti-human leucocyte antigen alloantibodies. At a mean follow-up of 6 months after treatment, all patients had stable graft function, with minimal transient adverse effects such as gastrointestinal toxicity, thrombocytopenia, and paresthesias.

Moreover, in another study of 5 patients (2 kidney/pancreas and 3 kidney transplant recipients) with AMR and coexisting acute T-cell–mediated rejection ACR, treatment with bortezomib (median follow-up, 6.9 months) led to prompt reversal of ACR and AMR. Patients were treated after other known anti-humoral therapies had failed to reverse the acute rejection episode. Donor-specific antibody levels decreased significantly in all patients (except 1 patient with short follow-up). Adverse effects of

bortezomib included a transient grade III thrombocytopenia in 1 patient and mild-to-moderate gastrointestinal toxicities in 3 of 5 patients. No opportunistic infections were observed.[4]

Therefore, we were confronted by 2 cases of resistant acute AMR with mild chronic changes. The available therapies for AMR lack direct effects on the major antibody producing cell (the mature plasma cell). Although B-lymphocyte specificity has been provided with rituximab, it does not deplete plasmablasts or mature plasma cells, which represent the major source of antibody production.[4] Each case was managed by 1 cycle of bortezomib with partial response and satisfactory 1-year graft survival despite the sustained anti-human leucocyte antigen antibodies. The first case was complicated by legionella pneumonia but neither of them developed any of its specific adverse effects. The partial response in both of them might be attributed to chronic changes in the biopsy that could be overcome if they was used earlier as concluded by Flechner and associates 2010,[14] who used bortezomib-containing regimen in 20 patients with established AMR, but they added that it seems to be most effective before the onset of significant renal dysfunction (serum creatinine < 249 μmol/L) or proteinuria (< 1 g/d).

## Conclusions

Immunosuppression minimization carries the risk of acute resistant AMR, and renal grafts can be rescued by earlier bortezomib use, especially in the absence of chronic changes.

## References


1. Takemoto SK, Zeevi A, Feng S, et al. National conference to assess antibody-mediated rejection in solid organ transplantation. *Am J Transplant.* 2004;4(7):1033-1041.
2. Bustos M, Saadi S, Platt JL. Platelet-mediated activation of endothelial cells: implications for the pathogenesis of transplant rejection. *Transplantation*. 2001;72(3):509-515.
3. Mauiyyedi S, Colvin RB. Humoral rejection in kidney transplantation: new concepts in diagnosis and treatment. *Curr Opin Nephrol Hypertens.* 2002;11(6):609-618.
4. Everly MJ, Everly JJ, Susskind B, et al. Proteasome inhibition reduces donor-specific antibody levels. *Transplant Proc*. 2009;41(1):105-107.
5. Kyle RA, Rajkumar SV. Multiple myeloma. *N Engl J Med.* 2004;351(18):1860-1873. Erratum in: *N Engl J Med.* 2005;352(11):1163.
6. Everly MJ, Everly JJ, Susskind B, et al. Bortezomib provides effective therapy for antibody- and cell-mediated acute rejection. *Transplantation*. 2008;86(12):1754-1761.
7. Chang AT, Platt JL. The role of antibodies in transplantation. *Transplant Rev (Orlando).* 2009;23(4):191-198.
8. Vieira CA, Agarwal A, Book BK, et al. Rituximab for reduction of anti-HLA antibodies in patients awaiting renal transplantation: 1. Safety, pharmacodynamics, and pharmacokinetics. *Transplantation*. 2004;77(4):542-548.
9. Wang X, Luo H, Chen H, Duguid W, Wu J. Role of proteasomes in T cell activation and proliferation. *J Immunol*. 1998;160(2):788-801.
10. Helal I, Chan L. Steroid and calcineurin inhibitor-sparing protocols in kidney transplantation. *Transplant Proc*. 2011;43(2):472-477.
11. Ponticelli C, Scolari MP. Calcineurin inhibitors in renal transplantation still needed but in reduced doses: a review. *Transplant Proc*. 2010;42(6):2205-2208.
12. Cantarovich D, Vistoli F. Minimization protocols in pancreas transplantation. *Transpl Int*. 2009;22(1):61-68.
13. Höcker B, Tönshoff B. Treatment strategies to minimize or prevent chronic allograft dysfunction in pediatric renal transplant recipients: an overview. *Paediatr Drugs*. 2009;11(6):381-396.
14. Flechner SM, Fatica R, Askar M, et al. The role of proteasome inhibition with bortezomib in the treatment of antibody-mediated rejection after kidney-only or kidney-combined organ transplantation. *Transplantation*. 2010;90(12):1486-1492.
15. Trivedi HL, Terasaki PI, Feroz A, et al. Abrogation of anti-HLA antibodies via proteasome inhibition. *Transplantation*. 2009;87(10):1555-1561.