

Renal Transplantation and Renovascular Hypertension

Bortezomib Provides Effective Therapy for Antibody- and Cell-Mediated Acute Rejection

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Background: Current antihumoral therapies in transplantation and autoimmune disease do not target the mature antibody-producing plasma cell. Bortezomib is a first in class proteasomal inhibitor, that is Food and Drug Administration approved, for the treatment of plasma cell-derived tumors that is multiple myeloma. We report the first clinical experience with plasma cell-targeted therapy (bortezomib) as an antirejection strategy. **Methods:** Eight episodes of mixed antibody-mediated rejection (AMR) and acute cellular rejection (ACR) in six transplant recipients were treated with bortezomib at labeled dosing. Monitoring included serial donor-specific antihuman leukocyte antigen antibody (DSA) levels and repeated allograft biopsies. **Results:** Six kidney transplant patients received bortezomib for AMR and concomitant ACR. In each case, bortezomib therapy provided (1) prompt rejection reversal, (2) marked and prolonged reductions in DSA levels, (3) improved renal allograft function, and (4) suppression of recurrent rejection for at least 5 months. Moreover, immunodominant DSA (iDSA) (i.e., the antidonor human leukocyte antigen antibody with the highest levels) levels were decreased by more than 50% within 14 days and remained substantially suppressed for up to 5 months. One or more additional DSA were present at lower concentrations (non-iDSA) in each patient and were also reduced to nondetectable levels. Bortezomib-related toxicities (gastrointestinal toxicity, thrombocytopenia, and paresthesias) were all transient. **Conclusions:** Bortezomib therapy: (1) provides effective treatment of AMR and ACR with minimal toxicity and (2) provides sustained reduction in iDSA and non-iDSA levels. Bortezomib represents the first effective antihumoral therapy with activity in humans that targets plasma cells.

Editorial Comment: Antibody mediated rejection has received increased attention in the last several years. The currently available treatments include plasmapheresis, intravenous immunoglobulin and B cell depleting antibody. Each of these treatments, as well as various permutations and combinations of these treatments, has been used with unreliable success. Plasmapheresis mechanically reduces antibody levels, which may rebound following treatment. The mechanism for effectiveness of intravenous immunoglobulin is multifactorial and empirical evidence demonstrates usefulness.¹ B cell depletion disrupts only the precursor to plasma cells, not the antibody producing cells themselves.

Bortezomib is a proteasomal inhibitor approved for use in the treatment of plasma cell derived tumors (multiple myeloma). This study represents the initial use of a drug targeting inhibition of the antibody producing cell itself in the setting of antibody mediated rejection. In this series 6 patients were treated for antibody mediated rejection with bortezomib. Conventional treatment had failed in all 6 patients. Bortezomib was effective at controlling rejection and reliably decreased the level of circulating donor specific antibody. It will be interesting to see expanded clinical use of this drug.

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1. Jordan SC, Vo AA, Peng A, Toyoda M and Tyan D: Intravenous gammaglobulin (IVIG): a novel approach to improve transplant rates and outcomes in highly HLA-sensitized patients. *Am J Transplant* 2006; **6**: 459.