BORTEZOMIB FOR THE TREATMENT OF RENAL CHRONIC ANTIBODY MEDIATED REJECTION IN PEDIATRIC AGE

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INTRODUCTION AND AIMS

The standard approach to treatment of chronic Antibody Mediated Rejection (AMR) is derived from that of acute AMR and includes plasmapheresis or immunoadsorption, intravenous immunoglobulin (IVIG) and Rituximab. These therapeutical attempts, however, are not always able to reverse the chronic AMR, that leads to irreversible damage with substantially impaired graft survival.

Several studies describe successful Bortezomib-based therapies in the setting of acute AMR while unsatisfactory results characterize case reports about the use of this drug in case of chronic AMR. The experience with the proteasome inhibitor in pediatric patients is limited and covers only cases of acute AMR. We describe two cases in which bortezomib was used as rescue therapy for chronic AMR.

METHODS

Patient 1 is an adolescent affected by Autosomal Recessive Polycystic Kidney Disease (ARPKD) who received a 3 mismatch renal transplant from his mother at the age of 13.6 years. Maintenance immunosuppression protocol consisted of tacrolimus, mycophenolate mofetil (MMF) and prednisone. His serum creatinine remained stable at baseline until the fourth year after transplantation, when rose to 1.5 mg/dl. Kidney biopsy showed a transplant glomerulopathy and positive immunostaining for C4d. Donor-specific antibodies (DSA) levels against DQB1 05:02 were significantly increased, with Mean Fluorescence Index (MFI) values of 18000.

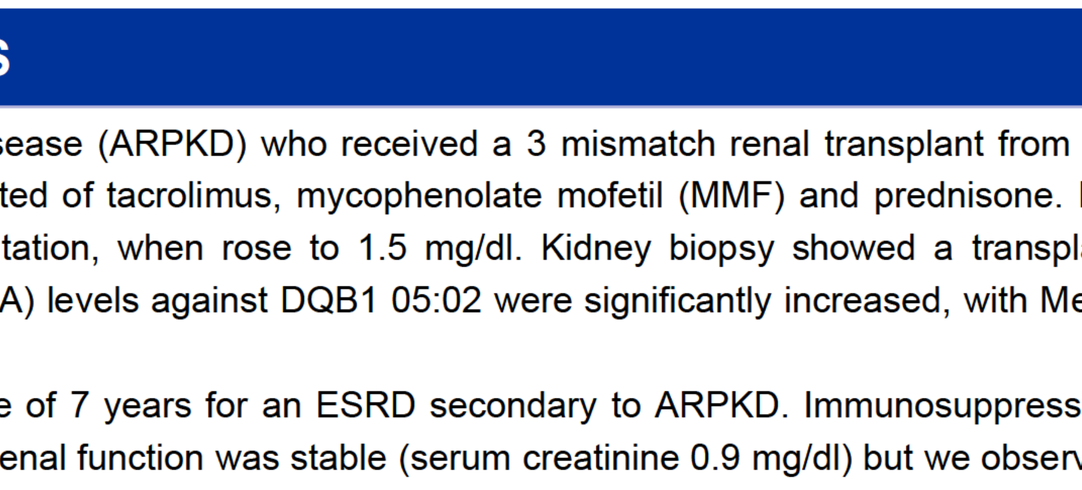
Patient 2 is a girl who received a 4 mismatch cadaveric renal transplant at the age of 7 years for an ESRD secondary to ARPKD. Immunosuppression protocol included tacrolimus, MMF and prednisone. Five years after transplantation renal function was stable (serum creatinine 0.9 mg/dl) but we observed a persistent proteinuria (uPr/uCr >1 mg/mg). The biopsy showed a chronic allograft nephropathy associated with a suspected chronic AMR. Immunostaining for C4d was positive and DSA titres against HLA class I and II increased (MFI values up to 3500). Treatment of chronic AMR for both patients consisted of plasmapheresis, IVIG and Rituximab.

The failure of all these measures (MFI values above 3000) prompted the use of 4 doses of bortezomib (1.3 mg/m^2) over a 4 weeks period.

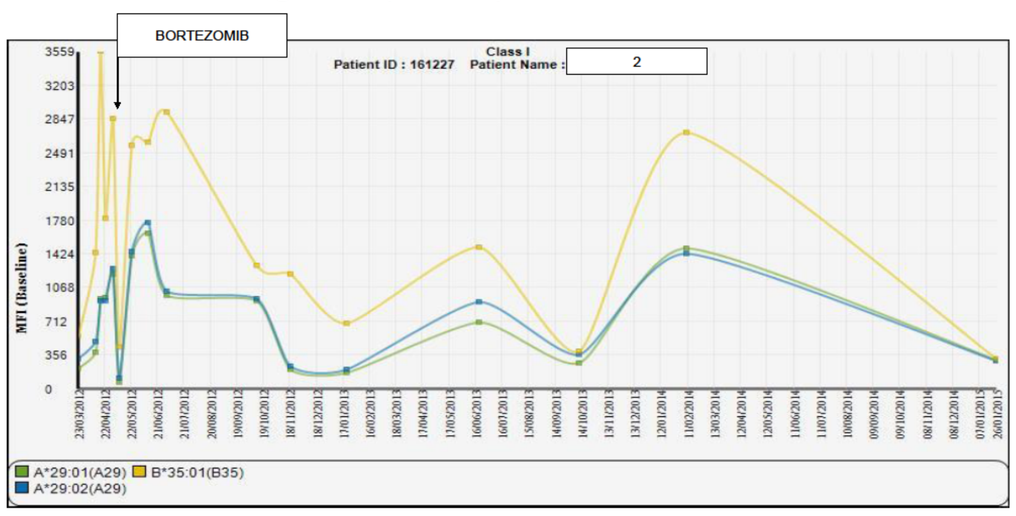
RESULTS

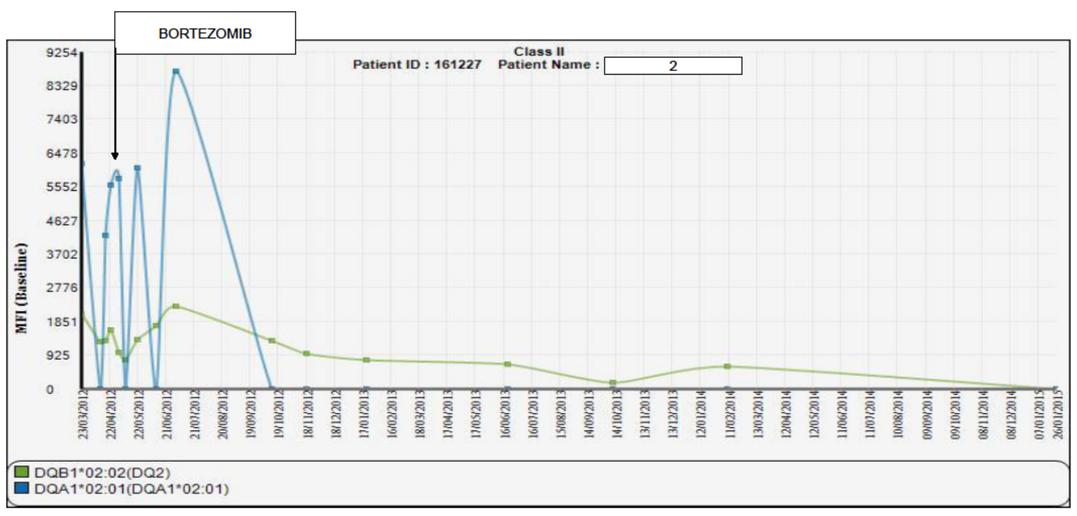
Patient 1 DSA persisted post treatment with little change in MFI values.

At last follow up visit (35 months) renal function was stable with a creatinine value of 1.35 mg/dl. DSA against DQB1 05:02 were still detectable (MFI slightly <15000).



One month after bortezomib infusion **patient 2** antibodies were still detectable (DSA against HLA-A2 and DQA1+0201 with MFI values of 3000 and 8700 respectively). At most recent follow up (32 months), she had a stable renal function with a creatinine value of 1.01 mg/dl, uPr/uCr 0.17 mg/mg. MFI for class I and class II was negative (<1000).





CONCLUSIONS

Both patients have a stable renal function and Bortezomib led to advantages on antibody levels only in patient 2. We do not know yet the potential harmful role of the antibodies and of their type or strength at the time of rejection episode. The long-lived plasma cells probably involved in the pathogenesis of the chronic rejection may be less responsive to proteasome inhibition. Further studies and data, investigating, for example, the need for repeated cycles or combination therapies, are needed to clarify the impact of bortezomib on the clinical course of chronic AMR.

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