SP 687

Do we know how to treat resistant antibody-mediated rejection effectively? A single centre experience

Janka Slatinska[1], Vladimir Hanzal[1], Eva Honsova[2], Petra Bohacova[3], Petra Hruba[4], Michaela Zelinova[1], and Ondrej Viklicky[1,4]

[1]Department of Nephrology, [2]Department of Pathology, [3]Department of Immunology, [4]Transplant Laboratory

Institute for Clinical and Experimental Medicine, Videnska 1958/9, Prague 4, 140 21, Czech Republic

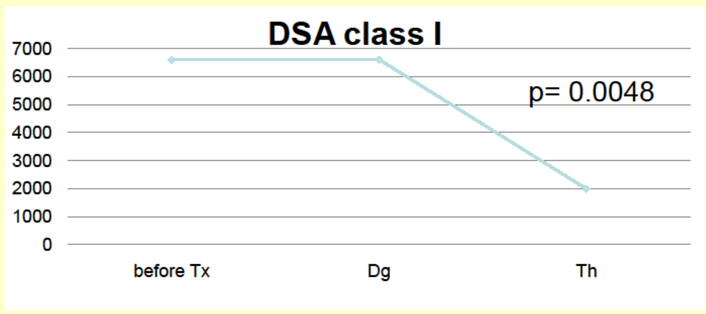
OBJECTIVES

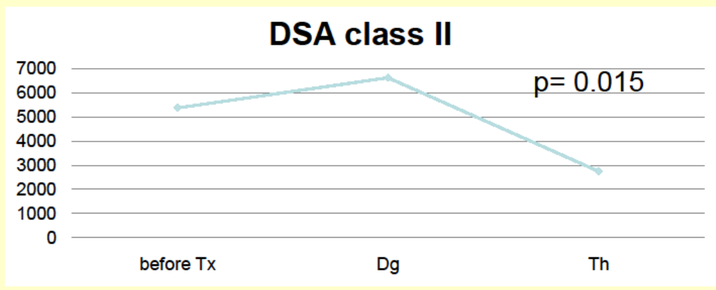
Acute antibody-mediated rejection (AMR) remains one of the major barriers to successful long-term outcomes. Previously reported therapeutic superiority of combination of plasmapheresis (PP) and intravenous immunoglobulin (IVIG) may however fail in some resistant cases. Thus, the aim of this work was to analyze the efficacy and safety of administration of bortezomib and rituximab-based treatment of resistant AMR.

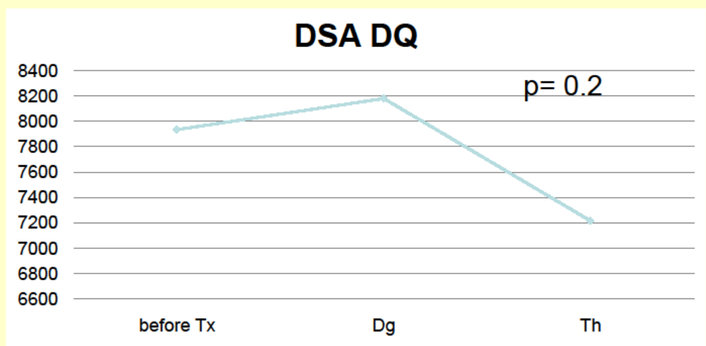
METHODS

We retrospectively analyzed documentation of 772 patients who underwent renal transplantation between 1/2012-6/2015. Novel therapeutic approach to resistant acute AMR in kidney transplant recipients was applied in 23 patients (3%) based on administration of bortezomib [1 cycle of 4 doses of bortezomib (1.3 mg/m2)], small doses of intravenous corticosteroids, plasmapheresis and a dose of rituximab (375mg/m2). This protocol was administrated after conventional treatment had failed. Resistant AMR was defined as a persisting deterioration or non-function of renal allograft in patients with histological verification of AMR, positive C4d staining and detection of donor specific antibodies (DSA) receiving standard antirejection treatment with PP + IVIG. Patients were followed for 6-48 months.

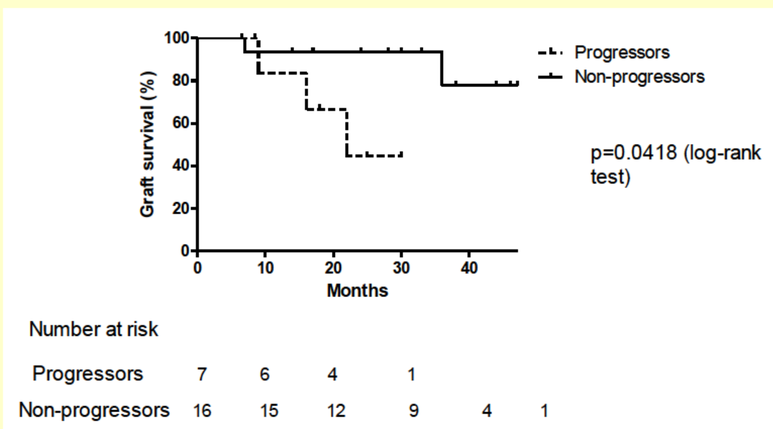
Resistant AMR	n= 23
Donor age (years)	47.7 ± 10.2
Recipient age (years)	47.4 ± 8.7
Gender: male	74%
PRA max %	54.2 ± 32.2
PRA act. %	33.9 ± 31
Dialysis therapy median (years)	6 (0 -17)
CIT (hours) median	16 ± 5.9
Mismatch HLA A	1.4 ± 0.6
Mismatch HLA B	1.5 ± 0.6
Mismatch HLA DR	1.2 ±0.6
AMR onset (POD) median	14 (7 – 60)
First transplantation	13%
Retransplantations	87%
Delayed graft function	26.1%
Induction of basiliximab	4.3%
Induction of thymoglobuline	95.7%







Adverse events of the treatment	n= 23 (%)
Thrombocytopenia	78.3
Leucopenia	56.5
Urinary tract infection	34.8
Sepsis	30.4
Polyneuropathy	26.1
Fluid retention	21.7
CMV replication	17.4
BKV replication	13
Diarrhea	13
Hepatopathy	13
Pneumonia	13



RESULTS

Therapy of resistant acute AMR was administered to 23 patients after kidney transplantation with median peak PRA 52%, actual PRA 36%, mean HLA mismatch in HLA-A 1.4 ± 0.6, HLA-B 1.5 ± 0.6, HLA-DR 1.2 ± 0.6, with median of 6 years on dialysis. 3 patients underwent 1st kidney transplantation, while 20 patients retransplantation (2nd Tx n=10, 3rd Tx n=6, 4th Tx n=4). Immunosuppressive protocol consisted of induction with antithymocyte globulin (n=22) or basiliximab (n=1), all patients have maintenance immunosuppression with tacrolimus, mycophenolate mofetil/ enteric-coated mycophenolate sodium and corticosteroids. Diagnosis of resistant acute AMR was made on 14.th POD (7- 60 days).

Based on therapeutic effect, 15 patients received 1 cycle, 7 patients 2 cycles and 1 patient was treated with 3 cycles of bortezomib. We observed delayed graft function in 26.1%.

Using bortezomib regimen in treating resistant acute AMR led to decrease in DSA quantity in HLA especially in class I (p=0.005), class II (p = 0.015), but not in DQ (p= 0.2). No significant improvement of renal function was observed during the follow-up.

The patients with the levels of serum creatinine increased more than 25% of baseline level in 6 months after administration of protocol with bortezomib, are progressors (n=7). The progressors graft survival was 57% in 20 months. The quantity of MFI DQ antibodies was significantly higher than in patients with stable renal function (non progressors).

The side-effects observed were urinary tract infection (35%), colitis (13%), polyneuropathy (26%), hepatotopathy (13%), fluid retention (22%), thrombocytopenia (78%), leucopenia (56.5%), sepsis (30.4%).

CONCLUSIONS

Traditional AMR therapeutic strategies have focused on antibody removal and B-cell depletion while not directly focusing on plasma cell depletion. Bortezomib was effective against HLA I and II class antibodies, the problem with DQ antibodies is still unsolved. Bortezomib-related toxicities (thrombocytopenia and peripheral neuropathy) were all transient and responded to conservative management.

References

Walsh RC, Aloway RR, Woodle ES, Proteasome inhibitor-based therapy for antibody-mediated rejection Kidney Int. 2012 Jun;81(11):1067-74

Walsh RC, Everly JJ, Aloway RR, Woodle ES, Proteasome inhibitor-based primary therapy for antibody-mediated renal allograft rejection Transplant 2010 Feb 15;89(3):277-84.

DOI: 10.3252/pso.eu.53era.2016

ePosters supported by F. Hoffmann- La Roche Ltd.