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# Proteasome inhibitors in Kidney Transplantation

**Jong Cheol Jeong**
*Seoul National University Bundang Hospital, Republic of Korea*

Depleting monoclonal antibodies which target surface marker during the B cell development have been investigated for the treatement and desensitization strategies. However, Rituximab, an effective anti-CD 20 monoclonal antibody, lacks efficacy to plasma cell which lacks CD20. Proteasomes play a necessary role in cell survival, normal cellular function and in the degradation of misfolded or mutated proteins. Plasma cell has high protein turnover with IgG, which can be a target for proteasome inhibitors (PIs).

Early clinical series showed benefits of bortezomib, a first generation of proteasome inhibitor, as the additional treatment agent to acute antibody mediated rejection. However, in BORTEJECT trial, the investigators failed to prove the efficacy of isolated bortezomib as first line treatment agent to the late antibody mediated rejection. While the reasons why BORTEJECT trial have failed was critically appraised, other proteasome inhibitors have been tried.

Carfilzomib is a second generation proteasome inhibitor, with irreversible inhibition and without boronation, which expected to increas the efficacy and decrease the neurotoxicity. Addition of carfilzomib prolonged allograft survival in sensitized non-human primate kidney transplantation model. Nevertheless, it did not prevent late rebound of donor specific antibody and repopulation of plasma cell and follicular helper T cells. Clinical application of carfilzomib was investigated in the iterative trial of desensitization, which showed 73% reduction of median maxiaml immunodominant antibody MFI strengths. However, cessation of carfilzomib was also associated with rebound of anti-HLA antibodies.

Other strategies combining anti-plasma cell therapy with plasma cell mobilization (Plerixafor, selective CXCR4 inhibitor), costimulation blockader (Belatacept, CD28 axis inhibition) have been tried.

Ixazomib, another second generation proteasome inhibitor as a oral formulation, was tested in Phase II clinical trial (IXADES). The trial recruited highly sensitized kidney transplant candidates and applied Ixazomib 12 monthly cycles. Ixazomib reduced class II DQ and DP

antibodies. However, DR antibodies showed paradoxical increment and there was no efficay in HLA A antibodies.

A review of the publications will be given during the lecture.