Immunoproteasome Inhibition Reduces Donor Specific Antibody Production and Cardiac Allograft Vasculopathy in a Mouse Heart Transplantation Model

Authors:
Allison M Schwalb[1,*], Imran Anwar[1,*], Isabel DeLaura[1,*], Joseph M. Ladowski[1], Janghoon Yoon[1], Rafaela Belloni[1], Mingqing Song[1], Carolyn Glass[2], Stuart Knechtle[1], Jean Kwun[1,†]

Objective: Cardiac Allograft Vasculopathy (CAV), a process of vascular damage accelerated by antibody-mediated rejection (AMR), is the leading cause of cardiac transplant failure. Proteasome inhibitors (PIs) are utilized to treat AMR; however, PI-associated toxicity limits their therapeutic utility. Novel immunoproteasome inhibitors (IPIs) have higher specificity for immune cells and have not been investigated for AMR in cardiac transplant patients. We sought to evaluate the effect of an IPI in a cardiac transplant model.

Methods: Fully MHC mismatched C57BL/6 (H-2^b) to huCD52Tg (H-2^k) heterotopic heart transplantations were performed (n=28). Recipients were treated with alemtuzumab (10mg, IP) on days -2, -1, 2, and 4 and anti-CD25mAb (PC61 clone, 100mg, IP) on day 7 to accelerate AMR development with (n=20) or without (n=8) IPI, ONX-0914 (15m/kg, SQ), administered on transplant day and three times a week thereafter. Surviving animals were sacrificed around 7 weeks post-transplantation for histological and immunological analysis.

Results: Of animals that reached the study endpoint, those without IPI gradually developed post-transplant DSA and showed a significantly elevated DSA level compared to animals receiving IPI. (TCXM 48.86 vs. 14.17; p=0.0291, BCXM 43.53 vs. 6.114; p=0.0031). Accordingly, H&E staining of allograft showed reduced evidence of AMR with IPI compared to controls (P=0.0410). Notably, increased mortality was observed in the IPI treated group.

Conclusion: This study demonstrated the ability of ONYX-194, an IPI, to control post-transplant DSA production and AMR development in a heart transplant model. IPI-resistant DSA production was also observed and increased mortality among IPI recipients raises concerns about potential toxicity. Further investigation is warranted to assess the utility and potential risk associated with the use of IPI as a post-transplant maintenance immunosuppression.