Evaluating Immunoproteasome Inhibition in Murine Cardiac Transplant Recipients: Can a Novel Therapeutic with Enhanced Specificity Reduce Toxicity and Prevent Antibody-Mediated Damage?

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Background

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.

Objective

To evaluate the impact of immunoproteasome inhibition following cardiac transplant on Donor-Specific Antibody (DSA) production, Antibody-Mediated Rejection (AMR), and Graft Vasculopathy.

Methods

Fully MHC mismatched heterotopic heart transplantations were performed. Recipients were initially treated with alemtuzumab and anti-CD25mAb to accelerate AMR development with (n=20) or without (n=8) IPI treatment three times weekly thereafter. (Figure 2A)

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.

Discussion

In our chronic AMR model, while prolonged post-transplant IPI treatment reduced DSA production and AMR development, it was also associated with toxicity and variable efficacy. Further characterization of IPI pharmacodynamics will enhance the understanding of its safety and efficacy, thereby improving utility for clinical application.

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Immunoproteasome inhibitors can reduce antibody-mediated damage to heart transplants; however, toxicity profiles may not be significantly better than proteasome inhibitors.

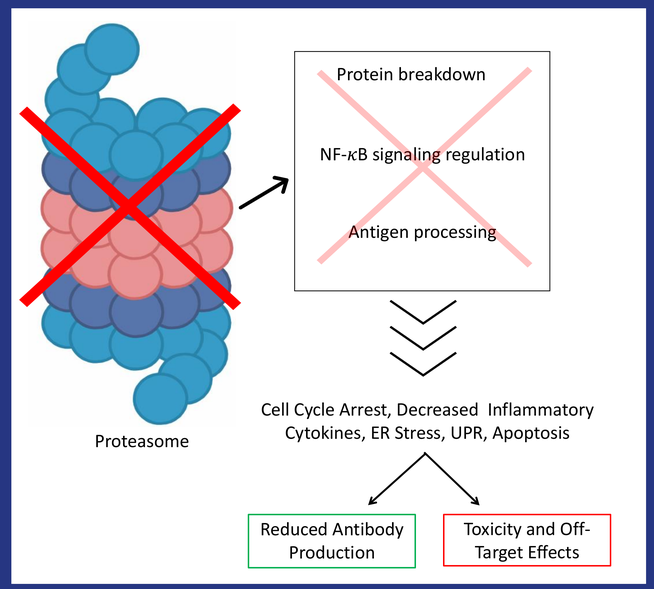

Figure 1: Mechanism and effects of proteasome inhibition.

Figures

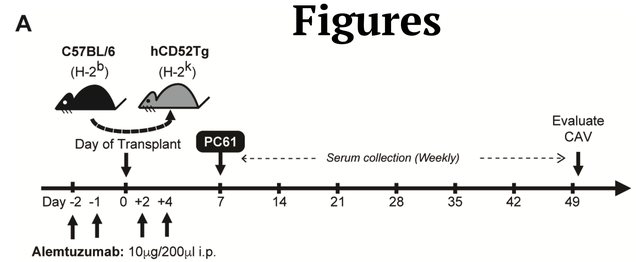

Figure 2: Schema of experimental design (A). Graft survival (B) and recipient survival (C) comparison between IPI and control groups.

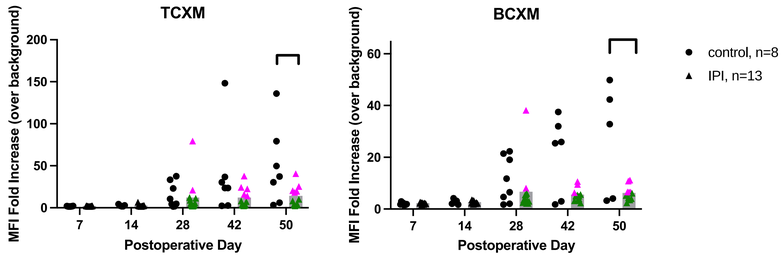

Figure 3: DSA production measured in TCXM and BCXM throughout study period.

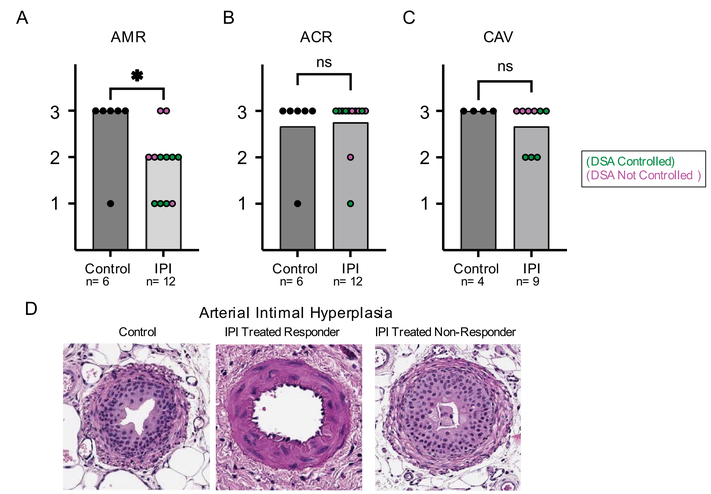

Figure 4: Antibody mediated rejection (A), acute cellular rejection (B), and coronary allograft vasculopathy (C) score comparison between IPI and control group allografts. Representative H&E images of arteries identified within allografts (D).