Combination of HDAC6 and SGLT2 Inhibitors Provides Additive Benefit vs Either Alone, Improves Diastolic Dysfunction without Reducing Ejection Fraction

Gene Expression Analysis Shows Differentiated Profile for HDAC6 Inhibitor; Highlights Orthogonal Mechanism of Action

INTRODUCTION

Background

Heart failure with preserved ejection fraction (HFpEF) is a form of heart failure characterized by diastolic dysfunction and associated with high morbidity, mortality and significant unmet need.

We have previously demonstrated that selective inhibition of histone deacetylase 6 (HDAC6) has directed and systemic effects on multiple pathways in HFpEF pathophysiology. In a mouse model of HFpEF using a high-fat diet (HFD) and L-NAME, positive effects on diastolic dysfunction and left ventricular thickness of the heart, as well as overall improvements in systemic inflammation and metabolism, were achieved. Empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor approved for the FDA for HFpEF patients, works as expected in this model, confirming the potential clinical translatability of results seen with HDAC6 inhibitors. In head-to-head studies, the beneficial effects of HDAC6 inhibitors have been shown to be comparable to empagliflozin, while demonstrating a distinct mechanism of action in gene expression analysis. (1) 

Toh-301, a highly selective HDAC6 inhibitor, is being advanced into clinical development for the potential treatment of HFpEF. In a Phase 1 clinical trial, Toh-301 has been well-tolerated across a broad range of doses and demonstrated target engagement. In a preclinical setting, the development for the potential treatment of HFpEF. In a Phase 1 clinical trial, Toh-301 has been well-tolerated across a broad range of doses and demonstrated target engagement. This study, utilizing TYA-018 (a TN-301-like HDAC6-specific inhibitor) we investigate the additive or synergistic effects of combining HDAC6 and SGLT2 inhibition to improve cardiac function in a two-hit mouse model of HFpEF.

STUDY DESIGN

A. Mice were evaluated at 0-, 4-, and 8-weeks post-dosing by echocardiography and by terminal PV loop at end point (8 weeks), with cardiac tissue harvested and used for transcriptional profiling by RNA-Seq.

B. Treatment doses are selected empirically and in the lower treatment dose range to allow for demonstrating the additive or synergistic effects of combining HDAC6 and SGLT2 inhibition to improve cardiac function in a two-hit mouse model of HFpEF.

RESULTS

CARDIAC FUNCTIONAL IMPROVEMENTS OBSERVED AT 8-WEEKS OF TREATMENT

End-of-Study Echocardiographic Assessment of Cardiac Function by Non-invasive Doppler Analysis Conducted at 8 Weeks and Terminal PV Loop Analysis at 9 Weeks in Control and HDAC6-NAME Model of HFpEF

A. Echocardiography measurements (E/A, E/e', IVRT) and Levocarbidol Relaxation Time (LVRT) demonstrated that the doses of HDAC6- and SGLT2-inhibition did not reliably improve diastolic dysfunction, with only the combined treatment group showing consistently significant improvement relative to vehicle.

B. Combination therapy specifically improved OXPHOS and normalized to -1 with the HFpEF effect. Our findings exhibit the substantial normalization of transcriptional changes at gene level in Toh-301 and Combination treatment groups.

CONCLUSIONS

In our comprehensive review on TN-301, a highly selective HDAC6 inhibitor for HFpEF treatment, we observed significant benefits. Both in vivo pharmacology and whole transcriptome RNA-seq analyses revealed additive and synergistic benefits of HDAC6 and SGLT2 inhibition. These effects significantly improved diastolic function and gene expression in the HFpEF heart. Further analysis emphasized distinct and complementary mechanisms of action from HDAC6 inhibition, reinforcing its potential as a standalone therapeutic and in conjunction with SGLT2 inhibitors. Comorbid previous data, it’s evident that HDAC6 inhibitors, like TN-301, are potent treatments for HFpEF, and in select cases, surpass SGLT2 inhibitors. The synthesis of these findings underscores the potential of TN-301 for HFpEF treatment, both as a singular or combined approach.