Comparative effectiveness of the new calpain inhibitor NPO-2270 versus enalapril in pressure overload-induced heart failure

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Background: Studies performed in multiple preclinical models support the contribution of the Ca²⁺-dependent cysteine proteases calpains to ventricular remodelling and heart failure (HF). However, pharmacological calpain inhibition has not yet been tested in patients with HF mainly due to the limitations of available inhibitors.

Purpose: To determine the effect of NPO-2270 (NPO), a new ketoamide derivative calpain inhibitor, in a mouse model of pressure-overload and compare its effectiveness with that of enalapril.

Methods: C57BL6 mice were subjected to transverse aortic constriction (TAC) for 4 weeks. Mice were randomised to receive orally administered NPO or enalapril at the dose of 10 mg/kg/day once a day, or vehicle, starting at day 7 after TAC surgery. The combination of both drugs and the effect of NPO starting 1 day after surgery were tested in additional TAC mice. Echocardiographic data, markers of hypertrophy, fibrosis, calpain activity and cleavage of calpain substrates were measured at different time points.

Results: TAC increased calpain-1 and -2 expression and activity. Administration of NPO and enalapril prevented the progression of hypertrophy and interstitial fibrosis induced by TAC with no statistically significant differences between the two treatments. However, ongoing ventricular dysfunction was less severe in the NPO group than in the enalapril group (27% of LVEF reduction in control group, 6% in NPO group and 16% in the enalapril group after TAC. \( P=0.024 \) between NPO and enalapril groups). The combined treatment or the administration of NPO from the first day after TAC surgery was not superior to NPO alone starting 7 days after TAC. These differences in LVEF correlated with better preservation of cadherin-based cell adhesion complex in mice treated with NPO-2270. No adverse effects associated with long-term NPO administration were observed in a sham group.

Conclusions: The new calpain inhibitor NPO-2270 prevents the development of hypertrophy and fibrosis with similar efficacy than enalapril but prevents cardiac dysfunction more effectively in a preclinical model of pressure overload when given orally at equivalent doses.