PDE-5 Inhibition Has No Effect on Measures of Heart Failure

Written by Wayne Kuznar

The phosphodiesterase type 5 (PDE-5) inhibitor sildenafil failed to improve peak exercise capacity in patients with diastolic heart failure (HF) in a double-blind, placebo-controlled, randomized clinical trial.

Results from the Evaluating the Effectiveness of Sildenafil at Improving Health Outcomes and Exercise Ability in People With Diastolic Heart Failure trial [RELAX; Redfield MM et al. *JAMA* 2013] did not replicate the cardiovascular benefits of PDE-5 inhibition obtained in studies of experimental HF and small clinical studies, said Margaret M. Redfield, MD, Mayo Clinic, Rochester, Minnesota, USA.

RELAX included 216 patients with NYHA Class II to IV symptoms, an ejection fraction ≥50%, and objective evidence of HF. Additionally, patients at entry were required to have significantly reduced maximum oxygen consumption (VO_2max; <60% predicted for age and sex) with adequate effort and an elevated level of N-terminal pro-B-type natriuretic peptide (NT-proBNP; ≥400 pg/mL) or an elevated pulmonary capillary wedge pressure with normal levels of NT-proBNP. Subjects were randomized to sildenafil (20 mg TID for 12 weeks and then uptitrated to 60 mg TID for 12 weeks) versus placebo. The primary endpoint of the study was change in peak VO_2 from baseline to Week 24. In addition, patients underwent intensive cardiopulmonary exercise testing evaluation, 6-minute walk test (6MWT), echocardiography, biomarker assessment, cardiac magnetic resonance imaging and completed the Minnesota Living with Heart Failure Questionnaire (MLHFQ).

At baseline, peak VO_2max was <12 mL/kg/min in each group, which was 41% of the predicted normal value for age and sex. Left ventricular ejection fraction was 60% in both groups. The 6MWT distance was 305 meters in the placebo group and 308 meters in the sildenafil group.

There was no significant difference in the change in peak VO_2 between groups (p=0.90), a finding that was unchanged after performing a sensitivity analysis to account for missing data (multiple imputation p=0.98; last observation carried forward p=0.98). There was also no significant difference between groups in the change in 6MWT distance (p=0.92) and the mean clinical rank score (mean anchor value approximately 95 in both groups; p=0.85). An anchor value of 95 indicates no treatment effect.

Three deaths occurred in the sildenafil group and none in the placebo group, a difference that was not significant. There were no significant differences between groups in the rates of cardiovascular or cardiorenal hospitalizations, adverse events, and serious adverse events.

The proportion of patients who withdrew or were unwilling or unable to complete cardiopulmonary exercise testing at 24 weeks was twice as great in the sildenafil group versus the placebo group (16% vs 8%), but this difference did not achieve significance. There were no significant differences in left ventricular mass or changes in filling pressure and pulmonary artery systolic pressure between the groups. Patients treated with sildenafil experienced greater increases in creatinine and cystatin C, and these changes were associated with significantly greater increases in NT-proBNP, endothelin-1, and uric acid.

In conclusion, in this small randomized placebo-controlled trial, 12 weeks treatment with a PDE-5 inhibitor did not improve peak exercise capacity or other functional measures in patients with diastolic HF. Whether longer term therapy might favorably effect functional status or clinical events would require further investigation.

First Clinical Evidence Offered That Inhibiting P-Selectin May Limit Myocardial Damage During PCI

Written by Wayne Kuznar

A single dose of inclacumab, a fully human recombinant monoclonal antibody directed against P-selectin, appears to reduce myocardial damage in patients undergoing percutaneous coronary intervention (PCI) as measured by biomarker concentration. Results from a randomized Phase 2 trial showed a reduction in levels of troponin I at 16 and 24 hours post PCI with a single dose of incalcumab 20 mg/kg when administered prior to PCI.

P-selectin is an adhesion molecule expressed on activated endothelial cells. It modulates interactions between white blood cells and platelets, acting as a crossroads of inflammation and thrombosis. It has been hypothesized that inhibition of P-selectin may reduce myocardial damage in the setting of PCI through both anti-inflammatory and anti-thrombotic effects.

The effect of a single dose of inclacumab on myocardial damage was examined in the Study of RO4905417 in Patients With Non ST-Elevation Myocardial Infarction (NSTEMI) Undergoing Percutaneous Coronary Intervention [SELECT-ACS; Tardif JC et al. *J Am Coll Cardiol* 2013]. Results were presented by Jean-Claude Tardif, MD, Montreal Heart Institute, Montreal, Quebec, Canada.

SELECT-ACS randomized NSTEMI patients to a single infusion of 5 or 20 mg/kg of inclacumab or matching placebo, administered 1 to 24 hours prior to PCI. To be eligible, patients had to be scheduled for catheterization and intended to undergo PCI. The primary endpoint was the change in troponin I (Tn-I) at 16 and 24 hours post PCI.