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.

Of the 544 patients randomized, the efficacy analysis included 322 patients who received study medication, underwent PCI and had biomarkers assayed at all timepoints.

The duration of PCI and rates of drug-eluting and bare-metal stent deployment were similar between the 3 arms, as were use of concomitant medications.

The mean percent change in Tn-I was −22.4% at 16 hours (p=0.07) and −24.4% (p=0.05) for patients receiving inclacumab 20 mg/kg relative to those receiving placebo. Peak Tn-I was numerically reduced by 23.8% with this dose (p=0.05). There was no significant difference in Tn-I concentration observed with inclacumab 5 mg/kg at either timepoint.

The percent change in Tn-I at 24 hours with inclacumab 20 mg/kg versus placebo was similar in patients with or without diabetes (–33.2% and vs –31.6% respectively; p=0.03 in patients without diabetes; Table 1).

Table 1. Change in Troponin I at 24 Hours

Troponin I (Tn-I)	Placebo n=115	Inclacumab 5 mg/kg n=95	Inclacumab 20 mg/kg n=112
Baseline geometric mean IQR	1.03 0.24-4.69	0.71 0.17-3.44	0.82 0.19-3.73
24 hours post-PCI	1.76	1.21	0.99
Change from baseline[1]	57.7%	55.5%	19.1%
Placebo-adjusted change[2] 95% CI; p value	-- --	-1.4% (-26.7, 32.7) 0.93	-24.4% (-43.1, 0.4) 0.05

PCI=percutaneous coronary intervention; IQR=interquartile range.

[1] Adjusted geometric mean percent change (based on repeated ANCOVA model).

[2] Placebo-adjusted geometric mean percent change obtained by exponentiating the delta adjusted mean from repeated ANCOVA, then subtracting 1 and X100.

The change in creatine kinase-myocardial band (CK-MB) was similar to the findings for troponin with a borderline significant result in favor of high-dose inclacumab (–17.4% vs placebo; p=0.06). The incidence of CK-MB increases more than 3 times the upper limit of normal was 18.3% in the placebo group and 8.9% in the inclacumab 20 mg/kg group (p=0.05).

Safety data were collected at 120 days, at which time there was no increase in the rates of infection or bleeding with inclacumab. Of note, there were higher numbers of deaths (6 vs 0) and nonfatal MI (11 vs 2) in patients randomized to inclacumab versus placebo but the study was not adequately powered to detect differences in clinical endpoints.

While these findings show a favorable pattern in biomarker concentration with high-dose inclacumab in the setting of PCI for NSTEMI, the clinical relevance of these findings is not clear from this Phase 2 study. Further clinical investigation is required to determine the clinical impact of inclacumab administration in patients presenting with MI.

Eplerenone Post Myocardial Infarction Plus Standard Treatment May Prevent Adverse Cardiovascular Outcomes

Written By Rita Buckley

Early administration of eplerenone added to standard treatment in postmyocardial infarction (MI) patients appears to reduce the risk of adverse cardiovascular (CV) outcomes and heart failure (HF), according to results from the Impact of Eplerenone on Cardiovascular Outcomes in Patients Post-Myocardial Infarction trial [REMINDER; NCT01176968].

The randomized double-blind REMINDER trial included 1102 patients with ST-segment elevation myocardial infarction (STEMI) in the absence of HF. The lead investigator for the study, Gilles Montalescot, MD, PhD, Pitié-Salpétrière Hospital, Paris, France, reported that the provision of a mineralocorticoid receptor antagonist early in the acute phase of MI suggests a potential long-term CV benefit.

Eligible patients were identified following emergency room or ambulance evaluation and diagnosis of acute STEMI without HF. Key exclusion criteria were a known left ventricular ejection fraction (LVEF) <40%, any previous known history of HF, uncontrolled hypotension (systolic blood pressure <90 mm Hg), and known renal insufficiency (eGFR ≤30 mL/min/1.73m^2). Patients were randomized to eplerenone (25 to 50 mg QD; n=506) or placebo (n=506), with the first dose of the study drug administered within 24 hours of symptom onset, and if possible, within 12 hours. All patients otherwise were to receive standard medical therapy.

The primary endpoint was a composite of CV mortality, rehospitalization or extended initial hospital stay due to HF, sustained ventricular tachycardia or ventricular fibrillation, LVEF ≤40% after 1 month post randomization, or elevated brain natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) at 1 month post randomization.

Baseline characteristics were well balanced between the 2 treatment arms; the mean age of participants was 58 years, 17% were female, and 35% had anterior STEMI on presentation. Patient background medical therapy was representative of guideline-recommended practice (approximately 98% received aspirin, 98% P2Y12 antagonist, 79% heparins or fondaparinux, 29% a GPIIb/IIIa inhibitor); approximately 85% received primary percutaneous coronary intervention.

After a mean follow-up of 10.5 months, the primary composite endpoint was significantly lower in the eplerenone (18.4%) versus placebo group (29.6%; HR, 0.58; 95% CI, 0.45 to 0.75; p<0.0001; Figure 1). However, the main driver and only statistically significant component of the