Results of the PROTECT Trial

Results from the PROTECT (A Placebo-controlled Randomized study of the selective A_1 adenosine receptor antagonist KW-3902 for patients hospitalized with acute heart failure and volume Overload to assess Treatment Effect on Congestion and renal function Trial) trial, presented at the European Society of Cardiology's annual meeting in Barcelona, Spain, by Professor Marco Metra, MD, University of Brescia, Brescia, Italy, failed to meet both the primary and secondary endpoints of the study.

The objectives of PROTECT were to assess the efficacy and safety of the adenosine A_1 receptor antagonist rolofylline versus placebo on symptoms, renal function, and short-term morbidity and mortality in 2033 patients who were hospitalized with heart failure (HF) within 24 hours with signs of fluid overload, impaired renal function (estimated GFR 20-80 ml/min), and high serum levels of B-type natriuretic peptide (BNP >500 pg/mL) or N-terminal fragment of B-type natriuretic peptide (NT-proBNP >2000 pg/mL). Rolofylline 30 mg/day or placebo (2:1 ratio) was administered in a double-blind fashion as a 4-hour daily infusion that was repeated for 3 days. Subjects were predominantly male (67%) who had a mean age of 70 years, mean creatinine clearance ~50 mL/min, and mean serum creatinine (SCr) 1.5 mg/dL. Most subjects were receiving multiple HF medications within the 2 weeks prior to study enrollment, including ACE inhibitor or ARB (75%), beta-blocker (76%), aldosterone inhibitor (43%), and digoxin (28%).

The primary study outcome was a three-category ordered outcome: treatment success (moderate to marked improvement of dyspnea at 24 and 48 hours with no evidence of treatment failure); subject unchanged; or treatment failure (death or readmission for HF through Day 7, or worsening signs/symptoms of HF occurring >24 hours after the start of the study through Day 7 or discharge, or persistent renal impairment [SCr increase ≥0.3 mg/dL at Days 7 and 14, or the initiation of hemofiltration or dialysis through Day 7]). Secondary outcomes included time to death or rehospitalization for renal or cardiovascular causes through Day 60 and the proportion of subjects with renal impairment, as defined in the primary endpoint.

There was no significant difference in the primary endpoint, wherein 40.6% of rolofylline subjects versus 36% of placebo subjects achieved treatment success, 37.5% versus 44.2% remained unchanged, and 21.8% versus 19.8% were classified as treatment failures (OR, 0.92; 95% CI, 0.78 to 1.09; p=0.35), nor was a difference observed in the secondary endpoint of persistent renal impairment (15.0% vs 13.7%, OR, 1.11; 95% CI, 0.85 to1.46; p=0.44). Furthermore, rolofylline appeared to increase neurological complications, including seizures (11 subjects [0.8%] vs no subjects on placebo), stroke (16 [1.2%] vs 3 [0.5%]), and serious adverse events that involved the nervous system (1.5% vs 0.6%).

Although the smaller PROTECT Pilot trial had shown promise for rolofylline in preventing dyspnea and renal failure, due to the lack of efficacy and apparent increase in nervous system disorders in this larger trial, further study of rolofylline in HF has been halted. Additional studies with alternative selective adenosine A_1-receptor antagonists are ongoing.

Irbesartan Fails to Prevent Most Vascular Events in Patients with AF

In the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-I; NCT00249795), treatment with irbesartan failed to lower the risk of stroke, myocardial infarction (MI), and vascular death compared with placebo in patients with atrial fibrillation (AF). However, irbesartan may have a role in preventing heart failure (HF), recurrent embolic events, and cardiovascular (CV) hospitalizations in patients with AF.

The ACTIVE program comprised three clinical trials that enrolled patients with documented AF and at least one additional risk factor for stroke, including ACTIVE-W (clopidogrel plus aspirin vs warfarin), ACTIVE-A (clopidogrel plus aspirin vs aspirin monotherapy), and ACTIVE-I. Salim Yusuf, MD, DPhil, McMaster University, Ontario, Canada, presented preliminary results from the ACTIVE-I trial, which was designed to evaluate the effect of additional blood pressure (BP) reduction with an angiotensin receptor blocker (ARB) on common complications of AF, including HF, stroke, and other embolic events.

In ACTIVE-I, patients who had a systolic BP >110 mm Hg and were not being treated with an ARB were randomly assigned to irbesartan at a target dose of 300 mg/day (n=4518) or placebo (n=4498). At baseline, patients generally were treated with multiple CV medications, including angiotensin-converting enzyme (ACE) inhibitors (60%), aspirin (59%), beta-blockers (54%), diuretic therapy (54%), vitamin K antagonists (38%), digoxin (35%), calcium channel blockers (27%), and antiarrhythmics (23%).

On top of this extensive background therapy, irbesartan provided an additional reduction in BP (6.8/4.5 mm Hg)