EFFECTS OF THE ADENOSINE A1-ANTAGONIST ROLOFYLLINE ON RENAL FUNCTION IN ACUTE HEART FAILURE PATIENTS: RESULTS FROM THE PROTECT STUDY

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Background: Small studies have indicated that adenosine A1 receptor antagonists enhance diuresis and may improve renal function in patients with chronic heart failure. We studied the effects of rolofylline on renal function in patients with acute heart failure (AHF) and renal dysfunction randomized in PROTECT, a pivotal phase III clinical trial.

Methods: A total of 2,033 patients with ADHF, volume overload, an estimated creatinine clearance (eCrCl; Cockcroft-Gault) between 20 and 80 ml/min, and elevated natriuretic peptide levels were randomized within 24 hours of hospital admission in a 2:1 ratio to receive rolofylline 30 mg/day or placebo IV for up to 3 days. Renal function was measured daily up to 7 days and at day 14. Persistent worsening renal function (WRF) was defined as an increase in serum creatinine ≥ 0.3 mg/dL at both day 7 and 14, or initiation of dialysis or death by day 7.

Results: At baseline, mean (SD) eCrCl was 51.0 (20.5) ml/min in the placebo and 50.4 (20.0) ml/min in the rolofylline group. There was no difference in the change in creatinine or eCrCl between placebo- and rolofylline-treated patients during hospital admission or at day 14. After 4 days, mean body weight was reduced by 2.6 kg and 3.0 kg in the placebo and rolofylline treated patients, respectively (p=0.005). Persistent WRF occurred in 13.7% of the placebo group and 15.0% of the rolofylline group (OR (95% CI) vs. placebo: 1.11 (0.85, 1.46); p = 0.44). In multivariable analysis, adjusted for baseline variables, only the presence of anemia, but not use of placebo/rolofylline, was independently associated with persistent WRF. Persistent WRF was associated with an increased risk of death (HR 2.54; 95% CI 1.73-3.71) and death or cardiovascular or renal re-hospitalization through day 60 (HR 1.32; 95% CI 1.04-1.67).

Conclusions: In this large phase III clinical trial, the adenosine A1 receptor antagonist rolofylline did not prevent persistent WRF in AHF patients with volume overload and renal dysfunction. In the overall study, persistent WRF was independently associated with adverse clinical outcomes at 60 days.