Pilot Study of Natriuretic Versus Standard Doses of Mineralocorticoid Receptor Antagonists in Heart Failure and Loop Diuretic Resistance in Outpatients

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Study Design

We conducted a pilot, prospective, single-center, double-blind, randomized, placebo controlled trial assessing the effects of high dose spironolactone in addition to intensified loop diuretic therapy vs. standard medical therapy in outpatients with ADHF. Our primary outcome was defined as weight change over the seven day study period. Based on data from a non-randomized intervention study, we aimed to recruit a total sample size of 40 subjects to detect a difference in our primary outcome of weight loss of 1.5kg difference between treatment and control.

On Day 1, all potential subjects were evaluated with complete medical history and physical examination, review of home medications, measurement of vital signs and body weight with a calibrated scale, serum collection for basic metabolic panel, liver function test, biomarkers of congestion, and electrocardiogram. "Imminent hospitalization" was determined by two independent HF specialists to assess the need for hospitalization for intravenous diuretics. Home MRAs were discontinued and potassium supplementation held if baseline serum potassium was >4.0mmol/L. Beta-blockers, ACE-I or angiotenin II receptor blockers were continued at home dose. Loop diuretic dosage was increased by two-fold. Patients were seen at two office visits in total, baseline at day 1 and final visit on day 7. On day 3, participants had serum basic metabolic panel to assess potassium levels and renal function for safety assessment.

Intervention

Enrolled patients were randomly assigned in a 1:1 ratio to high-dose (100mg/day) or standard-dose (25mg/day) spironolactone treatment groups.

Randomization, Allocation and Blinding

Randomization was stratified by sex and EF<45% in blocks of size 4. 2 by 2 randomization was performed via computer model generated by a study investigator. Allocations were concealed via the locked research pharmacy and the research team was blinded to treatment arm. All treatment medications were labeled in a blinded fashion. Subjects received 2 capsules per day (if standard dose: 25mg and placebo, if high dose: two 50mg) dispended in vials of 2 capsules.

Study Endpoints

The primary endpoint for the study was defined as change in total body weight at day 7 of the study period. Multiple secondary endpoints from day 1 to 7 were assessed. These included a) changes in dyspnea assessment scores; Visual Analogue Scale and 7-Likert scale, b) signs of congestion (i.e. JVP, peripheral edema and respiratory rales), c) 6MWT, d) serum and urinary creatinine, sodium, potassium and plasma aldosterone and renin activity and biomarkers of congestion and neurohormonal activation, e) furosemide equivalent of treatment loop diuretics doses, e) hospitalization at 30-, 60- and 90-days.

Six-minute walk test was performed per American Thoracic Society guidelines, along with Borg scores for dyspnea and fatigue at day 1 and 7. Serum and urinary creatinine, potassium, and sodium, plasma aldosterone and renin activity, and pro-BNP were assessed at days 1 and 7.

Other biomarkers of peripheral congestion (CD146), inflammation (interleukin-6, tumor necrosis factor-α, endothelin-1) oxidative stress (isoprostane) and endothelial activation (vascular cell adhesion molecule-1) were assessed at day 1 and 7 and analyzed by ELISA or LC-MS.

A data monitoring committee of two independent cardiologists was established to evaluate safety, with a pre-specified stopping rule for harm but not for efficacy. Safety endpoints included changes in serum creatinine levels, eGFR, and the incidence of hyperkalemia during the 7 day treatment period. Safety was assessed by tracking adverse events including new or worsening renal dysfunction, and hyperkalemia. Serious adverse events were defined as death and all-cause hospitalization.