improved survival. Allogeneic mesenchymal stem cells (MSCs) have been shown to reduce the severity of and improve the recovery from AKI in preclinical studies.

Madhav Swaminathan, MD, Duke University Health System, Durham, North Carolina, USA, discussed A Study to Evaluate the Safety and Efficacy of AC607 for the Treatment of Kidney Injury in Cardiac Surgery Subjects [NCT01602328]. The objective of this phase 2 randomized double-blind study was to compare the time to kidney recovery (TKR) with AC607 (human MSCs that have been isolated and expanded, then administered via catheter in the groin) vs placebo in the setting of postcardiac surgery.

The study included patients who were undergoing cardiac surgery, including cardiopulmonary bypass (CPB) surgery, with a baseline creatinine within 30 days of surgery. Postoperative AKI was defined as a ≥0.5-mg/dL rise in serum creatinine from baseline within 48 hours after CPB. The primary end point was TKR (creatinine return to preoperative baseline). The secondary end point was all-cause mortality or dialysis at 30 or 90 days. Exploratory end points included length of stay, intensive care unit stay, and in-hospital mortality.

Of 26 548 patients tracked, 1990 were eligible, and 156 patients were randomly assigned to AC607 (2×10^6 human MSCs per kg; n = 77) or placebo (n = 79). Equal numbers in each group completed 30 (n = 60) and 90 days (n = 57) of follow-up. Patients were well matched for baseline characteristics, including age, sex, and baseline renal function.

There was no difference between treatment groups for any of the following parameters: median TKR (15 days–treatment vs 12 days–placebo), TKR for patients whose CPB time was >120 minutes, TKR recovery by CPB time quartiles, or TKR by timing of dosing (<24, >24 to 36, or >36 hours).

All-cause mortality or dialysis at day 30 for AC607 vs placebo was 11 vs 8, respectively; at day 90, it was 12 vs 9. All-cause mortality for AC607 vs placebo at day 30 was 6 vs 5, respectively; at day 90 it was 8 vs 6. In-hospital mortality for AC607 vs placebo was 7 vs 4 days, respectively; dialysis at day 30 for AC607 vs placebo was 7 vs 5; and median hospital length of stay for AC607 vs placebo was 14 vs 12 days. There was no statistical difference between treatment groups for any of these events.

Although AC607 appears safe and well tolerated in postcardiac surgery patients with AKI, it did not reduce the TKR compared with placebo. The low event rates make it difficult to observe a treatment effect without a large study population—but a large study would require investigators to screen a prohibitive number of patients for randomization.

Patiromer Controls RAASi-Associated HK in Patients With Diabetes and CKD

Written by Lynne Lederman

Renin-angiotensin-aldosterone system inhibitors (RAASis) are beneficial and recommended for patients with chronic kidney disease (CKD) and type 2 diabetes mellitus (T2DM) [ADA. *Diabetes Care*. 2014]. However, hyperkalemia (HK) often limits RAASi therapy [Einhorn LM et al. *Arch Intern Med*. 2009]. Current treatment options for chronic management of HK are limited [Fordjour KN et al. *Am J Med Sci*. 2014; Harel Z et al. *Am J Med*. 2013], and an unmet need remains for safe and effective HK treatment.

Patiromer has previously been shown to normalize serum potassium (s-K^+) and prevent HK recurrence compared with placebo in A Two-Part, Single-Blind, Phase 3 Study Evaluating the Efficacy and Safety of Patiromer for the Treatment of Hyperkalemia [OPAL-HK; NCT01810939]. Matthew R. Weir, MD, University of Maryland, Baltimore, Maryland, USA, presented poster FR-PO792, which described the prespecified analysis of the subgroup with T2DM in OPAL-HK.

In part A (4-week treatment phase), patients with CKD with and without T2DM on stable doses of ≥1 RAASi with mild HK (s-K^+ 5.1 to <5.5 mEq/L; n = 92) received patiromer 4.2 g BID; those with moderate-to-severe HK (s-K^+ 5.5 to <6.5 mEq/L; n = 151) received patiromer 8.4 g BID. After 4 weeks, patients with moderate-to-severe HK continued on to the 8-week withdrawal phase (part B) and were randomly assigned to patiromer plus RAASi (n = 55) or placebo plus RAASi (n = 52).

End points included change in s-K^+ from baseline to week 4, percentage of patients with s-K^+ within target at week 4, between-group difference in s-K^+ change over the first 4 weeks, and percentage of patients with recurrent HK.

T2DM was present in 138 (57%) of patients assessed for the primary end point. The mean change from baseline to week 4 for patients with T2DM was –1.00 ± 0.04 (95% CI, –1.08 to –0.92; $P < .001$); for those without T2DM it was –1.02 ± 0.05 (95% CI, –1.12 to –0.92; $P < .001$); ($P = .77$ for interaction). In a secondary end point, 78% and 73% of patients with and without T2DM, respectively, had s-K^+ within range at week 4.

The median increase in s-K^+ from baseline at week 4 of the withdrawal phase was larger for the placebo group (n = 33; 0.69 mEq/L; 95% CI, 0.19 to 1.29) than for the patiromer group (n = 34; 0.03 mEq/L; 95% CI, –0.20 to 0.30; $P < .001$) in patients with T2DM ($P < .001$).

Patiromer increased the time to first recurrent HK event vs placebo in patients with T2DM. Through week 8 of the withdrawal phase, significantly ($P < .001$) more T2DM patients on placebo (62%) vs patiromer (19%) had at least 1 recurrent HK event.

Patiromer was well tolerated in patients with T2DM, with mild-to-moderate constipation being the most common adverse event (13% in Part A, 6% in Part B).

For patients with CKD, T2DM, and HK who are taking RAASis, patiromer may provide an option for HK management.

REPRISE 3b Study in Enrollment Phase

Written by Maria Vinall

The Efficacy and Safety of Tolvaptan in Subjects With Chronic Kidney Disease Between Late Stage 2 to Early Stage 4 Due to Autosomal Dominant Polycystic Kidney Disease [REPRISE 3b; NCT02160145] study is a multinational, phase 3b, randomized-withdrawal, placebo-controlled, double-blind, parallel-group trial. It is currently enrolling patients in 22 countries and expanding. The objective of the trial is to compare the efficacy of tolvaptan, a selective arginine vasopressin V_2 receptor antagonist, with placebo in adults with autosomal dominant polycystic kidney disease (ADPKD). Vicente E. Torres, MD, PhD, Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota, United States, presented the REPRISE study design in a poster session.

ADPKD is the most common inherited kidney disease in adults and is the fourth-leading cause of end-stage renal disease. It affects approximately 1 in 2500 adults in Europe and the United States. The Tolvaptan Phase 3 Efficacy and Safety Study in ADPKD [TEMPO3/4; NCT00428948] demonstrated the efficacy of tolvaptan to slow the increase in total kidney volume and the decline in kidney function over a 3-year period in subjects with chronic kidney disease (CKD) stage 1 to 3 due to ADPKD [Torres VE et al. *N Engl J Med.* 2012]. Currently, tolvaptan is only approved in Japan for the treatment of patients with ADPKD and rapidly progressive disease.

The REPRISE trial plans to enroll approximately 1300 tolvaptan-naïve ADPKD patients with CKD in late stage 2 to early stage 4. Subjects will be randomized to receive either tolvaptan or placebo for 13.5 months. Subjects may be randomly switched back and forth between treatments (to establish tolerance) at different times for defined intervals and are eligible for open enrollment after the end of the study. Men and women aged 18 to 55 years with an estimated glomerular filtration rate (eGFR) between 25 and 65 mL/min/1.73 m^2 or aged 55 to <66 years with an eGFR between 25 and 44 mL/min/1.73 m^2 are eligible for the enrollment. Diagnosis of ADPKD is performed with the modified Pei-Ravine criteria including age and number of renal cysts in patients both with and without a family history. Patients with hepatic impairment or liver function abnormalities other than those associated with ADPKD, advanced diabetes, or other significant renal issues (kidney cancer, surgery, or injury) are not eligible to participate.

The primary purpose is to compare the efficacy of tolvaptan with placebo in reducing the change in eGFR from pretreatment (baseline) to post-treatment follow-up. Secondary objectives are to compare tolvaptan to placebo in reducing the decline of annualized eGFR slope, overall and hepatic safety (monthly monitoring of liver abnormalities), and the incidence of ADPKD complications. It is expected that outcomes will support the previous TEMPO findings that tolvaptan is successful in slowing cyst growth and deterioration of kidney function in ADPKD patients in stages 1 to 3. One caution noted was the higher levels of transaminase (>3 times the upper level of normal) in the TEMPO trial. Close monitoring of transaminase will be performed in the current study. Screening for the REPRISE trial began on May 21, 2014.

It is hoped that this trial will not only confirm previous findings, but will also extend understanding of the safety and efficacy of tolvaptan to later stage (3b and 4) CKD.