Effects of Renin-Angiotensin-Aldosterone System Blockade in Patients with End-Stage Renal Disease

Teresa Slomka, MD, Emily S. Lennon, MS, Hina Akbar, MD, Elvira O. Gosmanova, MD, Syamal K. Bhattacharya, PhD, Carrie S. Oliphant, PharmD and Rami N. Khouzam, MD

ABSTRACT

Blockers of the renin-angiotensin-aldosterone system (RAAS), such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are routinely used in patients with chronic kidney disease because of their cardiovascular (CV) and renoprotective effects. However, there are no uniform recommendations about RAAS blockers for CV protection in the end-stage renal disease (ESRD) population other than the preferred drug class for blood pressure control. This uncertainty stems from the fact that patients with ESRD were generally excluded from randomized controlled trials evaluating the cardioprotective benefits of RAAS blockers. It is important to weigh the potential harms associated with the use of RAAS blockers, such as electrolyte disturbances and worsening anemia, with their role in protection of residual kidney function, alleviation of thirst and potential CV benefits. The objective of this review is to summarize the current knowledge about the use of RAAS blockers in patients with ESRD.

Keywords: Angiotensin-converting enzyme inhibitor; Angiotensin receptor blocker; End-stage renal disease; Heart failure; Hypertension. **[Am J Med Sci 2016;351(3):309–316.]**

INTRODUCTION

Within the category of renin-angiotensin-aldosterone system (RAAS) blockers, the role of the angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) in the management of hypertension and heart failure (HF) has been well established. In addition to their effect on blood pressure (BP) and decreased cardiac muscle's oxygen demand, ACEI and ARB inhibit the RAAS, which plays an important role in the progression of chronic kidney disease (CKD).

Activation of the RAAS is known to contribute to cardiovascular (CV) complications, and patients with end-stage renal disease (ESRD) have both an upregulated RAAS and a high burden of CV disease. Therefore, ACEI and ARB are attractive therapeutics in ESRD. The Kidney Disease Outcomes Quality Initiative recommends using RAAS blockers for treating elevated BP in ESRD.[1] However, beyond BP lowering effects, there is paucity of data advocating their use to reduce CV morbidity and mortality. In addition, RAAS blockers have many "extracardiac" effects, such as preservation of residual renal function (RRF) and alleviation of excessive thirst.[2] However, RAAS blockers may also raise serum potassium levels, and, therefore, arrhythmia is of concern with their use. The aim of this report is to summarize the current literature highlighting the CV and non-CV effects of ACEI and ARB in patients with ESRD.

NON-CV EFFECTS OF RAAS BLOCKERS IN ESRD

Potential Beneficial Effects

Residual Renal Function

The loss of RRF is an important predictor of morbidity and mortality in patients with ESRD on dialysis.[3] RRF is crucial in maintaining fluid balance and better nutrition, controlling phosphorus levels and removing mid–molecular weight toxins. Patients with RRF have fewer complications with potassium homeostasis, whereas, the decline in RRF contributes significantly to anemia, inflammation and malnutrition.[4]

It has been demonstrated that RRF is associated with mortality benefits in patients with ESRD. In the Netherlands Cooperative study on the Adequacy of Dialysis, the contribution of RRF to the overall survival of patients who underwent hemodialysis (HD) was significant.[5] The CANUSA study (Canada-USA Peritoneal Dialysis Study Group) demonstrated that for every 250 mL increment in 24-hour excretion in urine volume there was a 36% corresponding decrease in the relative risk of death.[6] Furthermore, it is strongly recommended to preserve RRF by avoiding potentially nephrotoxic medications and judicious use of intravenous contrasts.[7]

Several studies have evaluated the effects of ACEI on RRF, and ACEI use has been shown to preserve RRF.[8] Xydakis et al[9] evaluated whether enalapril would

slow the rate of decline of RRF in patients with incident ESRD starting HD. At the end of the 12-month study period, patients receiving enalapril had a slower decline of glomerular filtration rate (GFR) and higher daily urine output than the control group. Urine volume remained at 690 ± 270 mL/24 hours in the treatment group and declined to 330 ± 160 mL in the control group. This study suggests that a single morning dose of enalapril exerted a significant beneficial effect on preserving RRF in patients starting dialysis. Another prospective observational study by Itoh et al,[10] demonstrated that RAAS inhibitors were independently associated with RRF preservation in patients after 1 year of HD, especially when used continuously (more than 80% of the time). Moreover, Reyes-Marin et al,[11] in their randomized controlled study investigating preservation of RRF with enalapril or losartan, found no significant difference between these agents, and therapy with any of them being useful. In another randomized controlled trial evaluating patients with continuous ambulatory peritoneal dialysis was shown to slow the rate of decline in RRF by 0.93 mL/min/1.73 m^2 per year and progression to anuria.[12] However, not all studies have found benefit of RAAS blockade in preservation of RRF. In a recently published randomized controlled trial, irbesartan administered for 1 year in patients with ESRD did not affect the decline in RRF, as measured by combined urea and creatinine clearance.[13] Although not statistically significant, the urine volume was greater in the ARB group and decline in GFRs were lower than expected. This study has several limitations such as small sample size and high dropout rate (only 56 of 82 patients completed the study after 1 year). Another retrospective study involving 401 pediatric patients found that the use of RAAS blockers was associated with elevated risk of RRF decline, as compared with the no use of RAAS blockers; however, the association did not reach statistical significance (hazard ratio = 1.60; 95% CI: 0.98-2.63; $P = 0.06$).[14]

The potential mechanisms of RRF protection by RAAS blockers are not well studied in patients with ESRD. RAAS blockers were consistently shown to slow progression of GFR decline in patients with diabetic and nondiabetic CKD via improving renal hemodynamic adaptation, antifibrotic action and reducing proteinuria and oxidative stress.[15] Therefore, similar mechanisms may be involved into preservation of RRF in patients with ESRD.

RAAS Blockers and Thirst

Patients with ESRD often experience increased thirst, which in turn, leads to excessive fluid intake and large interdialytic weight gain (IDWG). Excessive IDWG correlates with increased mortality in patients receiving dialysis and low sodium diet is the preferred intervention to reduce thirst and IDWG.[16,17] Angiotensin II (AngII) levels have been shown to correlate with fluid intake and, not surprisingly, intravenous infusion of AngII has been found to increase thirst in experimental studies.[2,18] In patients receiving dialysis, AngII levels were found to be elevated not only after dialysis, which could be owing to a volume-related mechanism of thirst activation, but also between dialysis sessions despite progressive volume expansion.[19] As a result, RAAS blockers may offer a beneficial role in reducing fluid intake by reducing the AngII-mediated activation of thirst mechanism. In all, 2 ACEI, captopril and enalapril, were tested in patients with ESRD and found to reduce thirst and IDWG.[20,21] Although these results are inconsistent[22] and ARB have not been evaluated in this setting, RAAS blockers may offer ancillary benefit for reducing IDWG.

Potential Hazardous Effects

Hyperkalemia

Hyperkalemia is an important concern with the use of RAAS blockers in the ESRD population due tosuppression of AngII and lower aldosterone levels. If the level of aldosterone is diminished, potassium would be retained potentially leading to hyperkalemia. As with other electrolyte imbalances, there are adverse systemic effects that can be life threatening, such as affected neuromuscular impulse conduction velocity and cardiac rhythm abnormalities. However, the degree to which RAAS blockers contribute to hyperkalemia in patients with ESRD, especially with no RRF is uncertain. Enterocytes also have aldosterone receptors, and may play a role in potassium secretion in patients with ESRD.[23]

Patients on HD receiving either ACEI or ARB have a significantly higher risk of developing hyperkalemia compared to patients with ESRD who are not receiving these medications, even after adjusting for other risk factors.[24] Hyperkalemia is observed in about 10% of patients receiving HD and was found to be the most common indicator for additional HD in the emergency department, excluding patients with HF.[25,26] However, several studies have found no significant difference in the rate of hyperkalemia in patients receiving HD receiving RAAS blocking agents compared with control.[27-30] A possible explanation could be that increased gut elimination of potassium in patients with ESRD is likely mediated by increase in colonic secretion of potassium.[31-34]

Nevertheless, the use of ACEI and ARBs requires caution in patients with inadequate dialysis or peritoneal dialysis with low solute transporter membrane characteristics, as well as in dietary noncompliant patients.[24] Although dialysis is the definitive treatment of hyperkalemia through intravenous bicarbonate or cation exchange resins, these strategies are not always effective in lowering serum potassium in the acute setting. Dietary compliance and avoidance of medications that may promote hyperkalemia are the best strategies to prevent hyperkalemia-associated complications.[35] Newer oral potassium binders have been