Mineralocorticoid Receptor Antagonists in ESKD

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Introduction

There is an urgent need for interventions that reduce cardiovascular risks in patients with ESKD. Recently there has been considerable interest in whether blocking the effects of the mineralocorticoid aldosterone could be such an intervention.

Since the 1980s, we have known that plasma aldosterone levels rise in CKD and that this effect persists even with extracellular volume expansion. More recently, investigators have reported elevated plasma aldosterone concentrations in patients undergoing hemodialysis. In 2013, a *post hoc* analysis of the German Diabetes Dialysis Study showed that aldosterone excess was strongly associated with cardiovascular and all-cause mortality in patients on chronic hemodialysis (1).

Pivotal clinical trials report that mineralocorticoid receptor antagonists reduce the risks of cardiovascular death or heart-failure hospitalization in the non-ESKD population with heart failure (2). Because aldosterone excess is associated with worse outcomes in ESKD, could blocking the effects of aldosterone with mineralocorticoid receptor antagonists improve clinical outcomes in ESKD? A growing body of evidence, in the form of several hypothesis-generating studies, suggests that this may be the case.

Aldosterone Pathophysiology and Rationale of Using Mineralocorticoid Antagonists in ESKD

The main stimuli for aldosterone synthesis and release from the adrenal cortex are angiotensin II, serum potassium, and adrenocorticotropic hormone. Once released, aldosterone mediates most of its effects through its binding to the mineralocorticoid receptor in the cytosol, which causes it to translocate to the nucleus, promoting changes in gene expression ("genomic" pathway). Aldosterone also activates specific molecular pathways within minutes through "nongenomic" pathways, which could be either dependent or independent of mineralocorticoid receptor activation. Mineralocorticoid receptors are expressed in the distal renal tubule, vascular endothelium, colon, heart, brain, and the vascular smooth muscle cells in the aorta, coronary arteries, mesenteric, and renal interlobar arteries.

Mineralocorticoid receptor blockers competitively inhibit the effects of aldosterone mediated *via* mineralocorticoid receptors, which include all genomic and most nongenomic pathways. Aldosterone mediates profibrotic, prohypertrophic, and antinatriuretic effects through both genomic and nongenomic pathways. In addition to being a key regulator of body ion composition, aldosterone stimulates the increased expression of proinflammatory cytokines that recruit inflammatory cells, augments the production of TGF and plasminogen activator inhibitor-1, and consequently induces endothelial dysfunction and myocardial and vascular fibrosis.

Although angiotensin II is a key driver of aldosterone production, 30%–50% of patients on long-term angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy have increased levels of serum aldosterone; a condition referred to as "aldosterone breakthrough" (3). The underlying mechanisms for this phenomenon remain unknown but may explain the survival benefit of aldosterone blockade therapy as an add-on therapy to angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy in patients with heart failure (2). Aldosterone breakthrough is especially important in patients with CKD and ESKD, which are states of relative hyperaldosteronism despite extracellular volume expansion. Indeed, the greatest survival benefit from aldosterone blockade in heart failure is seen in patients with CKD (4).

Metabolic studies performed in the 1960s showed enhanced fecal potassium losses in ESKD, raising the possibility that this adaptive response helps maintain normokalemia. Aldosterone stimulates potassium secretion across mammalian colon (5), portending that blocking its effects on mineralocorticoid receptors expressed in colonic epithelium could increase serum potassium levels even in anephric patients.

Aldosterone Antagonists in ESKD

The two commonly used mineralocorticoid receptor antagonists are spironolactone and eplerenone, although these agents are currently not approved by the US Food and Drug Administration for use in ESKD. Spironolactone is more potent, whereas eplerenone is more specific for the mineralocorticoid receptor. Spironolactone has a molecular weight of 416.6 g/mol but is 90% protein bound; therefore, it is unlikely to be significantly removed by hemodialysis, although its pharmacokinetics have not been reported in ESKD. Although spironolactone has a $t_{1/2}$ of only 1.4 hours, the $t_{1/2}$ of its active metabolites, which are primarily cleared renally, are much longer (13–17 hours).

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Limited pharmacokinetic data shows that approximately 10% of eplerenone (molecular weight of 414.5 g/mol and 50% protein bound) is dialyzed during a standard hemodialysis session.

Data for aldosterone blockade in ESKD are modest. An early double-blind, placebo-controlled, randomized, controlled trial (RCT) examining aldosterone blockade in ESKD showed improvements in BP control by spironolactone in eight oligoanuric patients on chronic hemodialysis. A subsequent study using eplerenone showed similar results. Over the following decade, several RCTs with sample sizes ranging from 16 to 158 participants investigated the effects of add-on mineralocorticoid receptor antagonist therapy on intermediate cardiovascular outcomes in ESKD. Most of these studies showed decreases in BP, left ventricular mass index (LVMi), and carotid intima-media thickness as well as increased left ventricular ejection fraction, as well as demonstrating relative safety concerning hyperkalemia. Nonetheless, some studies yielded negative results, including showing no benefit in BP control or reductions in LVMi, which gave us pause on drawing firm conclusions. This past year saw the publication of two more RCTs, safety and cardiovascular efficacy of spironolactone in dialysis-dependent ESRD (SPin-D) (6) and Mineralocorticoid Receptor Antagonists in End-Stage Renal Disease (MiREnDa) (7), examining the effects of spironolactone in patients on chronic hemodialysis. Although both these RCTs showed relative safety regarding hyperkalemia, they failed to show improvements in cardiac diastolic function over 36 weeks (6) or in LVMi over 40 weeks (7) with spironolactone use.

Two recent RCTs reported benefits in more definitive cardiovascular end points. A study by Matsumoto *et al.* (8) showed that spironolactone 25 mg daily reduced the combined end point of cardiovascular death or hospitalization by 62% over 3 years in 309 oligoanuric patients on chronic hemodialysis. Serious hyperkalemia leading to treatment discontinuation occurred only in three out of 157 patients in the treatment group. However, the control arm in this study did not receive a placebo. Another RCT by Lin *et al.* (9) showed a 58% reduction in the combined end point of cardiovascular death or cardiac arrest and a 48% reduction in all-cause death in 253 patients on either hemodialysis or peritoneal dialysis without heart failure for over 2 years, on spironolactone 25 mg daily. The authors of these two studies conjectured that the mechanisms of the cardiovascular protective effects of spironolactone in patients receiving dialysis are reduction in progression of atherosclerosis (8,9), decrease in arrhythmogenesis caused by mineralocorticoid receptor activation in ESKD (8), and attenuation of myocardial fibrosis (9). Which of these mechanisms plays the greatest cardioprotective role, and under what conditions, remains unknown.

Safety data for the use of mineralocorticoid receptor antagonists in ESKD are largely derived from clinical trials, although their safety profile may be different in routine clinical practice. With that caveat, several trials suggest that spironolactone at a daily dose of 25 mg is likely to be safe in ESKD. However, the risk of hyperkalemia seems elevated with the 50-mg daily dose (6). Safety profile may be more favorable in peritoneal dialysis, where hyperkalemia is less of a concern compared with hemodialysis (10). Gynecomastia develops in 10%–15% of patients on spironolactone, for which switching over to eplerenone could be an option. Larger studies are needed to confirm these conjectures.

Conclusions and Future Considerations

The two respective RCTs by Matsumoto *et al.* and Lin *et al.* (8,9) show significant clinical benefits with aldosterone blockade in ESKD, although some smaller RCTs report conflicting effects on intermediate end points. This apparent discrepancy may be owing to the potential of aldosterone blockade to improve cardiovascular outcomes through multiple distinct mechanisms that individual intermediate end points fail to capture, and/or the small sample sizes and short follow-up durations in some studies. We need larger, well designed RCTs to provide definitive conclusions.

Two large, ongoing RCTs will likely provide valuable clinical-efficacy and safety data on the use of spironolactone in ESKD. The Aldosterone Antagonist Chronic Hemodialysis Interventional Survival Trial (ALCHEMIST; Clinicaltrials.gov identifier NCT01848639), which plans to recruit 825 patients undergoing chronic hemodialysis and is projected to be completed in 2024, aims to establish the effects of spironolactone (versus placebo) on the composite end point of nonfatal myocardial infarction, acute coronary syndrome, heart failure hospitalization, nonfatal stroke, or cardiovascular death. An even larger trial, projected to be completed in 2023, the Aldosterone Blockade for Health Improvement Evaluation in ESKD trial (ACHIEVE; Clinicaltrials.gov identifier NCT03020303) plans to enroll 2750 patients undergoing chronic hemodialysis or peritoneal dialysis and compare the effects of spironolactone versus placebo on cardiovascular death or hospitalization.

While we await the results from ALCHEMIST and ACHIEVE, there are several questions that remain unresolved regarding the efficacy and safety of mineralocorticoid receptor antagonist use in ESKD. (*1*) Would monthly monitoring of serum potassium, as performed in most clinical practice, be adequate to assure safety? (*2*) Is there a subset of the ESKD population (*e.g.*, peritoneal dialysis or heart failure) in which the risk–benefit ratio for aldosterone blockade is particularly favorable? (*3*) Which mineralocorticoid receptor antagonist is most suitable for use in ESKD? Newer agents, such as finerenone, may have a better safety profile, although this needs further study. (*4*) Does the concomitant use of mineralocorticoid receptor antagonists and the newer agents for hyperkalemia and heart failure alter their safety profiles? (*5*) What effect does aldosterone blockade have on quality-of-life in ESKD? The ALCHEMIST and ACHIEVE trials will answer some, but not all of these outstanding questions.

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