Mineralocorticoid Receptor Antagonists in End-Stage Renal Disease: Efficacy and Safety

Andrew S. Bomback

Department of Medicine, Division of Nephrology, Columbia University College of Physicians and Surgeons, New York, NY, USA

Key Words

Aldosterone · Spironolactone · Eplerenone · Hyperkalemia

Abstract

Mineralocorticoid receptor antagonists (MRAs) that block aldosterone's effects on both epithelial and non-epithelial receptors have become a mainstay of therapy for chronic heart failure. Given that cardiovascular events remain the leading cause of death for patients with end-stage renal disease (ESRD), the question of whether these MRAs can be employed in dialysis patients arises. This review summarizes the rationale for blocking aldosterone in patients with chronic and end-stage kidney disease and surveys the data on both the efficacy and safety of using MRAs in the ESRD population. A small but growing body of literature suggests that use of MRAs by ESRD patients is associated with lower blood pressure, reduced left ventricular (LV) mass, and improved LV ejection fraction. Recently, a large randomized trial found an overall 3-year mortality rate of 6.4% in ESRD patients on spironolactone 25 mg daily vs. 19.7% in ESRD patients on no MRA therapy ($p = 0.002$), without a significantly increased risk of hyperkalemia.

© 2016 S. Karger AG, Basel

Introduction

Interruption of the renin-angiotensin-aldosterone system (RAAS) with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) has become a leading strategy in slowing the progression of chronic heart and kidney disease. In the last two decades, mineralocorticoid receptor antagonists (MRAs) that target aldosterone have emerged as important additive therapies in treating chronic heart and kidney disease. Indeed, spironolactone and eplerenone, given in combination with ACE inhibitors or ARBs, are now standard treatments in managing congestive heart failure and have become increasingly used in the care of proteinuric CKD patients. As cardiovascular disease remains the leading cause of death among patients with end-stage renal disease (ESRD), the logical question is whether MRAs will be able to show equally impressive performance in the ESRD population.

Rationale for Aldosterone Blockade in ESRD

Numerous animal studies have shown that despite RAAS blockade with ACE inhibitors or ARBs, aldosterone infusion leads to profound cardiovascular and renal

disease [1–3], circumventing even dual prior RAAS blockade [1]. Although blockade of the RAAS has traditionally been performed with ACE inhibitors or ARBs, and more recently direct renin inhibitors have been tried [4], 30–50% of patients on long-term therapy have unexpected elevations of serum aldosterone levels, a phenomenon termed ‘aldosterone breakthrough’ [4–7]. This paradoxical elevation in aldosterone levels in some ways mirrors animal studies in which aldosterone is infused over the background of ACE inhibitors or ARBs. This breakthrough leads to the progression of cardiac and renal disease, as ACE inhibitors and ARBs may not adequately block the MR component [8–11].

The phenomenon of aldosterone breakthrough, well described in the cardiac and renal literature [4, 7, 8, 12], may explain the mortality benefit of aldosterone blockade as add-on therapy to ACE inhibitors or ARBs in congestive heart failure (CHF) [13–15]. Following myocardial infarction, patients in the highest quartile of aldosterone levels have double the event rate of death, resuscitated cardiac arrest, recurrent or extended myocardial infarction, recurrent ischemia, CHF, and stroke [16]. Patients with systolic CHF who have aldosterone breakthrough despite ACE inhibition have significantly lower peak oxygen uptake and percent-predicted oxygen uptake [17]. In essence, this breakthrough may attenuate the end-organ benefits of RAAS blockade.

In healthy humans consuming variable quantities of dietary sodium, a reciprocal relationship exists between serum aldosterone concentration and daily urinary sodium excretion, a surrogate measure of extracellular volume (ECV). The physiological elevations in renin, angiotensin II, and aldosterone in response to low ECV states do not cause hypertension or vascular inflammation. In healthy individuals, angiotensin II is a primary regulator of aldosterone secretion, which, in turn, is regulated by renin released by the juxtaglomerular apparatus in response to changes in effective arterial blood volume. These homeostatic effects are mediated by the classical action of aldosterone on the MR located on epithelial cells of the distal convoluted tubule and cortical collecting duct.

Aldosterone levels, in relation to a cofactor of plasma renin activity, increase as GFR falls (fig. 1), and thus CKD and ESRD are considered states of relative hyperaldosteronism [18–20] in which aldosterone breakthrough may be particularly noxious. The inverse relationship between ECV and serum aldosterone concentration suggests that in the setting of low dietary sodium intake, levels of renin, angiotensin II, and aldosterone increase but do not cause inflammation and end-organ damage [21]. However,

Fig. 1. Plasma aldosterone levels rise as GFR falls. In CKD stages 3–5, although ECV expansion manifests clinically as hypertension with or without edema, plasma aldosterone levels (in reference to a cofactor of plasma renin activity) rise, establishing CKD as a state of relative hyperaldosteronism. The degree of aldosteronism is most pronounced in CKD 5, marking the dialysis population as a prime target for aldosterone-targeted drugs. Based on data from Hené et al. [19].

CKD [22, 23] and ESRD [24] are notable states of relative hyperaldosteronism despite ECV expansion – that is, aldosterone levels are not sufficiently suppressed for the degree of ECV expansion (fig. 2) – leading to proinflammatory MR activation [22, 23, 25, 26]. In experimental studies, some of the adverse tissue effects of inappropriate MR activation occur at non-epithelial MR receptors, develop rapidly, are non-genomic, and have the potential to be attenuated by the use of MRAs.

Efficacy of Aldosterone Antagonists in ESRD

Spironolactone and eplerenone have become mainstays of treating CHF due to the large clinical trials, RALES and EPHEUS [13, 14]. These MRAs have become increasingly used in proteinuric CKD management, but the evidence stems from smaller studies, many of which are uncontrolled [27, 28]. An even more modest literature exists on the use of MRAs in patients with ESRD. Two of the earliest, smallest studies confirmed a non-diuretic mechanism of MRAs in blood pressure control. In a double-blind, placebo-controlled RCT of 8 oligoanuric hemodialysis patients, spironolactone 50 mg

Fig. 2. Chronic and end-stage kidney disease are states of relative hyperaldosteronism. Increased sodium intake, and subsequent volume expansion, should suppress the renin angiotensin aldosterone system, with an inverse relationship between daily salt loads and plasma aldosterone concentrations. This relationship still exists as renal function declines, but aldosterone is inadequately suppressed in CKD and ESRD patients compared to individuals with preserved GFRs. This relative hyperaldosteronism creates a high aldosterone-high sodium state that can activate non-epithelial mineralocorticoid receptors to produce inflammatory and fibrotic effects in the cardiovascular and renal systems. Adapted from Volk et al. [26].

twice daily led to a decline in pre-dialysis SBP from 142 to 131 mm Hg [29]. In a similar cohort that was given eplerenone 25 mg twice daily, pre-dialysis SBP dropped from 166 to 153 mm Hg [30].

Targeting aldosterone in the CKD population should yield benefits beyond proteinuria and blood pressure reduction, given the numerous avenues of injury that aldosterone's actions have in the cardiovascular system, making ESRD patients a potentially prime target population for MRA therapy. The absolute mortality benefit for spironolactone in CHF appears highest among patients with CKD [31]. Similar reductions in CV morbidity and mortality should be seen in ESRD patients if treated with MRAs. In the CRIB-II study, spironolactone added to an ACE inhibitor for 10 weeks resulted in significant reductions in LVMI (11.4%), left ventricular (LV) mass (11.8%), and LVH prevalence (50%), whereas the placebo-treated group showed no change [32]. ESRD patients typically have LVH, and LVMI correlates with aldosterone levels in non-diabetic patients on hemodialysis [33, 34]. In a recent study of 328 hemodialysis patients, the median serum aldosterone level was 18.4 ng/dl, and the highest ter-

tile (level >28 ng/dl, as compared with level <14 ng/dl) was associated with a doubling of mortality and cardiovascular events in euvolemic patients [24].

In a small double-blind, placebo-controlled RCT of 11 hemodialysis patients with systolic CHF, those given spironolactone (25 mg thrice weekly after dialysis) for 6 months had a significant improvement in LV ejection fraction (mean absolute increase 6% vs. no change with placebo) and LV mass (mean decrease 8.4 g/m² vs. no change with placebo) [35]. In peritoneal dialysis subjects, spironolactone conferred similar benefits, with a 30% improvement in ejection fraction (and no benefit with placebo) after 6 months of therapy in an RCT [36]. A subsequent placebo-controlled study in hemodialysis patients without CHF found no improvement in echocardiographic measures after 4 months on spironolactone but showed significant improvement in endothelial function as measured by increased reactive hyperemia (from 80% at baseline to 152% on spironolactone) with prolonged duration (35 to 48 s, respectively). Heart rate variability, a known mortality risk factor [37], was also significantly decreased [38].

Spironolactone given for 3 years attenuated vascular calcification as determined by aortic computed tomography in five hemodialysis patients [39]. Probing carotid intima-media thickness via ultrasonography in the carotid arteries, 53 non-diabetic, hemodialysis patients were followed for 2 years to examine the effect of MR activation on atherosclerosis progression. Spironolactone-treated patients (50 mg thrice weekly after dialysis) had statistically significant stabilization (5 of 6 areas evaluated) and even some improvement (left internal carotid artery, mean 1.15–0.84 mm), while the placebo-treated group had diffuse progression over time in most areas [40].

Safety of Aldosterone Antagonists in ESRD

These small studies are important as much for their efficacy data as their safety signal. Although, in general, serum potassium levels rise with MRA administration in hemodialysis patients, only rarely does therapy lead to clinically meaningful hyperkalemia requiring medication or dialysate adjustments [41–43]. Patients on continuous ambulatory peritoneal dialysis [36] and continuous cycler-assisted peritoneal dialysis [44] have safely received spironolactone for systolic CHF without significant hyperkalemia.

A 6-month pilot study with the specific goal of determining the risk of hyperkalemia during spironolactone

therapy was conducted in 50 Japanese, oligoanuric, chronic hemodialysis patients who did not have a hyperkalemic episode in the 2 months preceding the trial [45]. Pre-dialysis serum potassium was checked at baseline, 2 weeks, 4 weeks, 2 months and 6 months after administration of spironolactone 25 mg daily. No changes were made during the trial in existing therapy with ACE inhibitors, ARBs, loop diuretics, cation exchange resins, dialysis prescription or dietary potassium restriction. Mean potassium levels increased from 4.96 ± 0.72 to 5.26 ± 0.76 mEq/l during the study period, but no individual measurement was >6.8 mEq/l, nor was hyperkalemia a reason for stopping treatment with spironolactone. Development of gynecomastia in 3 patients led to study withdrawal.

The same authors have recently reported a prospective, randomized study in which 309 hemodialysis patients received spironolactone 25 mg daily vs. no MRA therapy for 3 years [46]. The primary objective of this study was to gauge spironolactone's effect on cardiovascular and cerebrovascular mortality or hospitalization. The incidence of the primary outcome in the spironolactone cohort was 5.7% compared to 12.5% in the control cohort ($p = 0.017$). The secondary outcome of death from all causes was similarly reduced in the treatment group, 6.4%, compared to the non-MRA group, 19.7% ($p = 0.002$). Hyperkalemia (defined as >6.5 mEq/l) occurred in 2% and gynecomastia in 10% of the spironolactone patients.

Currently, a randomized, placebo-controlled study of spironolactone in hemodialysis patients is in progress (Aldosterone Antagonist Chronic HEModialysis Interventional Survival Trial, ALCHEMIST), hoping to enroll

more than 800 patients, with the primary endpoint of time until first nonfatal myocardial infarction or hospitalization for heart failure or nonfatal stroke or cardiovascular death. This study, in addition to providing the best evidence to date on MRA efficacy in the ESRD population, will provide crucial data on the safety of these agents in patients on dialysis.

Conclusion

Blocking aldosterone's classical and non-genomic actions using MRAs such as spironolactone and eplerenone is an important part of managing patients with CKD and CHF. Extending the use of these agents to the dialysis population appears beneficial from the small-scale studies that have been performed to date. Of equal importance, these studies have provided important and reassuring data about the safety of MRAs in dialysis patients. Larger trials of using MRAs in ESRD patients are currently underway and, if they confirm the results of these preliminary studies, could transform the standard of care in treating blood pressure and cardiovascular disease in ESRD.

Acknowledgments

None.

Disclosure Statement

No conflicts of interest to declare.

References

- Greene EL, Kren S, Hostetter TH: Role of aldosterone in the remnant kidney model in the rat. *J Clin Invest* 1996;98:1063–1068.
- Rocha R, Chander PN, Zuckerman A, Stier CT Jr: Role of aldosterone in renal vascular injury in stroke-prone hypertensive rats. *Hypertension* 1999;33(1 pt 2):232–237.
- Rocha R, Stier CT Jr, Kifor I, et al: Aldosterone: a mediator of myocardial necrosis and renal arteriopathy. *Endocrinology* 2000;141:3871–3878.
- Bomback AS, Rekhman Y, Klemmer PJ, Cannaletta PA, Radhakrishnan J, Appel GB: Aldosterone breakthrough during aliskiren, valsartan, and combination (aliskiren + valsartan) therapy. *J Am Soc Hypertens* 2012;6:338–345.
- Sato A, Hayashi K, Naruse M, Saruta T: Effectiveness of aldosterone blockade in patients with diabetic nephropathy. *Hypertension* 2003;41:64–68.
- Horita Y, Taura K, Taguchi T, Furusu A, Kohno S: Aldosterone breakthrough during therapy with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in proteinuric patients with immunoglobulin A nephropathy. *Nephrology (Carlton)* 2006;11:462–466.
- Bomback AS, Klemmer PJ: The incidence and implications of aldosterone breakthrough. *Nat Clin Pract Nephrol* 2007;3:486–492.
- Struthers AD: Aldosterone escape during angiotensin-converting enzyme inhibitor therapy in chronic heart failure. *J Card Fail* 1996;2:47–54.
- Naruse M, Tanabe A, Sato A, et al: Aldosterone breakthrough during angiotensin II receptor antagonist therapy in stroke-prone spontaneously hypertensive rats. *Hypertension* 2002;40:28–33.
- Lakkis J, Lu WX, Weir MR: RAAS escape: a real clinical entity that may be important in the progression of cardiovascular and renal disease. *Curr Hypertens Rep* 2003;5:408–417.
- Schjoedt KJ, Andersen S, Rossing P, Tarnow L, Parving HH: Aldosterone escape during blockade of the renin-angiotensin-aldosterone system in diabetic nephropathy is associated with enhanced decline in glomerular filtration rate. *Diabetologia* 2004;47:1936–1939.

- 12 Pitt B: 'Escape' of aldosterone production in patients with left ventricular dysfunction treated with an angiotensin converting enzyme inhibitor: implications for therapy. *Cardiovasc Drugs Ther* 1995;9:145–149.
- 13 Pitt B, Zannad F, Remme WJ, et al: The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized aldactone evaluation study investigators. *N Engl J Med* 1999;341:709–717.
- 14 Pitt B, Remme W, Zannad F, et al: Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;348:1309–1321.
- 15 Zannad F, McMurray JJ, Krum H, et al: Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;364:11–21.
- 16 Beygui F, Montalescot G, Vicaute E, et al: Aldosterone and long-term outcome after myocardial infarction: a substudy of the French nationwide observatoire sur la prise en charge hospitalière, l'Evolution à un an et les caractéristiques de patients présentant un infarctus du myocarde avec ou sans onde Q (OPERA) study. *Am Heart J* 2009;157:680–687.
- 17 Ciccoira M, Zanolla L, Franceschini L, et al: Relation of aldosterone 'escape' despite angiotensin-converting enzyme inhibitor administration to impaired exercise capacity in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 2002;89:403–407.
- 18 Berl T, Katz FH, Henrich WL, de Torrente A, Schrier RW: Role of aldosterone in the control of sodium excretion in patients with advanced chronic renal failure. *Kidney Int* 1978;14:228–235.
- 19 Hené RJ, Boer P, Koomans HA, Mees EJ: Plasma aldosterone concentrations in chronic renal disease. *Kidney Int* 1982;21:98–101.
- 20 Reams GP, Bauer JH: Effect of enalapril in subjects with hypertension associated with moderate to severe renal dysfunction. *Arch Intern Med* 1986;146:2145–2148.
- 21 Bombardier AS, Klemmer PJ: Mineralocorticoid receptor blockade in chronic kidney disease. *Blood Purif* 2012;33:119–124.
- 22 Bombardier AS, Kshirsagar AV, Ferris ME, Klemmer PJ: Disordered aldosterone-volume relationship in end-stage kidney disease. *J Renin Angiotensin Aldosterone Syst* 2009;10:230–236.
- 23 Schrier RW, Masoumi A, Elhassan E: Aldosterone: role in edematous disorders, hypertension, chronic renal failure, and metabolic syndrome. *Clin J Am Soc Nephrol* 2010;5:1132–1140.
- 24 Hung SC, Lin YP, Huang HL, Pu HF, Tarng DC: Aldosterone and mortality in hemodialysis patients: role of volume overload. *PLoS One* 2013;8:e57511.
- 25 Bombardier AS, Klemmer PJ: Interaction of aldosterone and extracellular volume in the pathogenesis of obesity-associated kidney disease: a narrative review. *Am J Nephrol* 2009;30:140–146.
- 26 Volk MJ, Bombardier AS, Klemmer PJ: Mineralocorticoid receptor blockade in chronic kidney disease. *Curr Hypertens Rep* 2011;13:282–288.
- 27 Bombardier AS, Kshirsagar AV, Amamoo MA, Klemmer PJ: Change in proteinuria after adding aldosterone blockers to ACE inhibitors or angiotensin receptor blockers in CKD: a systematic review. *Am J Kidney Dis* 2008;51:199–211.
- 28 Navaneethan SD, Nigwekar SU, Sehgal AR, Strippoli GF: Aldosterone antagonists for preventing the progression of chronic kidney disease. *Cochrane Database Syst Rev* 2009;3:CD007004.
- 29 Gross E, Rothstein M, Dombek S, Juknis HI: Effect of spironolactone on blood pressure and the renin-angiotensin-aldosterone system in oligo-anuric hemodialysis patients. *Am J Kidney Dis* 2005;46:94–101.
- 30 Shavit L, Neykin D, Lifschitz M, Slotki I: Effect of eplerenone on blood pressure and the renin-angiotensin-aldosterone system in oligo-anuric chronic hemodialysis patients – a pilot study. *Clin Nephrol* 2011;76:388–395.
- 31 Vardeny O, Wu DH, Desai A, et al: Influence of baseline and worsening renal function on efficacy of spironolactone in patients with severe heart failure: insights from RALES (randomized aldactone evaluation study). *J Am Coll Cardiol* 2012;60:2082–2089.
- 32 Edwards NC, Steeds RP, Stewart PM, Ferro CJ, Townsend JN: Effect of spironolactone on left ventricular mass and aortic stiffness in early-stage chronic kidney disease: a randomized controlled trial. *J Am Coll Cardiol* 2009;54:505–512.
- 33 Sato A, Funder JW, Saruta T: Involvement of aldosterone in left ventricular hypertrophy of patients with end-stage renal failure treated with hemodialysis. *Am J Hypertens* 1999;12(9 pt 1):867–873.
- 34 Steigerwalt S, Zafar A, Mesiha N, Gardin J, Provenzano R: Role of aldosterone in left ventricular hypertrophy among African-American patients with end-stage renal disease on hemodialysis. *Am J Nephrol* 2007;27:159–163.
- 35 Taheri S, Mortazavi M, Shahidi S, et al: Spironolactone in chronic hemodialysis patients improves cardiac function. *Saudi J Kidney Dis Transpl* 2009;20:392–397.
- 36 Taheri S, Mortazavi M, Pourmoghadam A, Seyrafi S, Alipour Z, Karimi S: A prospective double-blind randomized placebo-controlled clinical trial to evaluate the safety and efficacy of spironolactone in patients with advanced congestive heart failure on continuous ambulatory peritoneal dialysis. *Saudi J Kidney Dis Transpl* 2012;23:507–512.
- 37 Fukuta H, Hayano J, Ishihara S, et al: Prognostic value of heart rate variability in patients with end-stage renal disease on chronic haemodialysis. *Nephrol Dial Transplant* 2003;18:318–325.
- 38 Flevari P, Kalogeropoulou S, Drakou A, et al: Spironolactone improves endothelial and cardiac autonomic function in non heart failure hemodialysis patients. *J Hypertens* 2013;31:1239–1244.
- 39 Nitta K, Akiba T, Nihei H: Aldosterone blockade and vascular calcification in hemodialysis patients. *Am J Med* 2003;115:250.
- 40 Vukusich A, Kunstmann S, Varela C, et al: A randomized, double-blind, placebo-controlled trial of spironolactone on carotid intima-media thickness in nondiabetic hemodialysis patients. *Clin J Am Soc Nephrol* 2010;5:1380–1387.
- 41 Chua D, Lo A, Lo C: Spironolactone use in heart failure patients with end-stage renal disease on hemodialysis: is it safe? *Clin Cardiol* 2010;33:604–608.
- 42 Baker WL, White WB: Safety of mineralocorticoid receptor antagonists in patients receiving hemodialysis. *Ann Pharmacother* 2012;46:889–894.
- 43 Reikhtman Y: Mineralocorticoid receptor-associated hypertension and target organ damage: clinical relevance for resistant hypertension in end stage renal disease. *Curr Hypertens Rev* 2012;8:267–275.
- 44 Hausmann MJ, Liel-Cohen N: Aldactone therapy in a peritoneal dialysis patient with decreased left ventricular function. *Nephrol Dial Transplant* 2002;17:2035–2036.
- 45 Matsumoto Y, Kageyama S, Yakushigawa T, et al: Long-term low-dose spironolactone therapy is safe in oligoanuric hemodialysis patients. *Cardiology* 2009;114:32–38.
- 46 Matsumoto Y, Mori Y, Kageyama S, et al: Spironolactone reduces cardiovascular and cerebrovascular morbidity and mortality in hemodialysis patients. *J Am Coll Cardiol* 2014;63:528–536.