

# Mineralocorticoid receptor blockade for renoprotection

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Extensive animal and clinical studies have demonstrated that inhibition of the renin–angiotensin–aldosterone system (RAAS) has a widespread protective role in various tissues. Although angiotensin II is the primary mediator of RAAS in the kidney, the effects of blockade with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor antagonists (ARB) are limited with respect to prevention of end-stage renal disease.

Previous studies have shown that administration of mineralocorticoid receptor antagonists (MRAs) including spironolactone and eplerenone has beneficial effects in a variety of renal injury animal models, such as unilateral ureteral obstruction, cyclosporine-induced nephrotoxicity, and hypertensive renal injury [1]. In addition, recent observations also demonstrate that MRAs improved renal function in animal models of transplant vasculopathy and ischemia reperfusion injury [2]. Furthermore, many animal and clinical studies showed that MRAs have additional benefit independent of renin-angiotensin system (RAS) blockade in diabetic kidney disease [3].

Aldosterone induces tissue injury by inflammation, oxidative stress, and fibrosis mechanisms, and MRAs may prevent renal fibrosis via suppression of transforming growth factor  $\beta$ 1, plasminogen activator inhibitor-1, oxidative stress, and endothelial dysfunction. Mineralocorticoid receptors (MRs) are widely expressed in

endothelial cells, mesangial cells, podocytes, and renal fibroblasts as well as distal tubular cells, and accumulating evidence suggests the important role of MRs in these cells as a mediator of renal injury [4]. Interestingly, recent evidence suggests that MR signaling is increased by Rac1 activation, independent of ligand binding to MR, and that Rac1 was shown to be activated by angiotensin II and diabetic conditions [5]. Altogether, these data suggest the possibility that MR signaling may be activated by several mechanisms, including increased aldosterone concentration, upregulation of MRs, and activation of Rac1 in the kidney, all of which have been reported as pathological mediators in chronic kidney disease (CKD).

There are many convincing data suggesting that MRAs may provide additional reno-protective effects in patients experiencing the aldosterone escape phenomenon during RAS blockade treatment [6]. A recent meta-analysis by a Cochrane systematic review included 27 studies (1,549 patients) of CKD patients (stage 1–4) and reported that adding an MRA on ACEi or ARB (or both) significantly reduced proteinuria (standardized mean difference [MD],  $-0.61$ ; 95% confidence interval [CI],  $-1.08$  to  $-0.13$ ) and reduced both systolic and diastolic blood pressure (BP) at the end of treatment (systolic BP: MD,  $-3.44$  mmHg; 95% CI,  $-5.05$  to  $-1.83$ ; diastolic BP: MD,  $-1.73$  mmHg; 95% CI,  $-2.83$  to  $-0.62$ ) compared with ACEi or ARB (or both) therapy. However, MRA treatment accelerated the glomerular filtration rate (GFR) decline rate (MD,  $-2.55$  mL/min/1.73 m<sup>2</sup>; 95% CI,  $-5.67$  to  $0.51$ ), doubled the risk of hyperkalemia, and increased the risk of gynecomastia compared to ACEi or ARB (or both) [7]. The major barrier for using MRAs in more advanced stages in CKD patients is the safety concern about hyperkalemia. Spironolactone and eplerenone are steroidal MRAs that have side effects including significant hyperkalemia. Recently, a highly selective and potent non-steroidal MRA (finerenone) has

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been developed and introduced as a promising new MRA in patients with CKD because early clinical trials demonstrated albuminuria reduction with a lower incidence of significant hyperkalemia [8,9].

In this issue of *Kidney Research and Clinical Practice*, Yu et al [10] reported that adding a low dose spironolactone on ARBs reduced proteinuria in patients with glomerulonephritis, mostly immunoglobulin A (IgA) nephropathy. In this retrospective study, they evaluated the effect and safety of low dose of spironolactone (12.5 mg/day) treatment for one year in 42 patients with biopsy-proven glomerulonephritis whose proteinuria was not adequately controlled by ARBs. The underlying diseases of the patients were IgA nephropathy (n = 30), thin basement membrane disease (n = 4), focal segmental glomerulosclerosis (n = 3), minor glomerular disease (n = 2), obesity related glomerulonephritis (n = 2), and membranous glomerulonephritis (n = 1). Proteinuria decreased significantly from 592 to 335 mg/g at 3 months and 378 mg/g at 12 months after treatment with spironolactone. Although there were no statistical differences, serum creatinine and potassium levels were elevated, and decreases in systolic and diastolic BP and estimated GFR were noted after spironolactone therapy. Based on these findings, Yu et al [10] concluded that low dose spironolactone in combination with an ARB may be another therapeutic option in patients with glomerulonephritis in whom proteinuria was not optimally controlled by ARBs. However, it is worth noting that this study was retrospectively performed over a relatively short duration with a small sample size. In addition, this study did not have a control group that received just an ARB.

Although recent clinical trials with novel nonsteroidal MRAs showed encouraging results for albuminuria reduction without significant hyperkalemia, we are left with negative findings on hard renal outcomes for using MRAs in proteinuric kidney disease.

### Conflicts of interest

The author has no conflicts of interest to declare.

### References

- [1] Blasi ER, Rocha R, Rudolph AE, Blomme EA, Polly ML, McMahon EG. Aldosterone/salt induces renal inflammation and fibrosis in hypertensive rats. *Kidney Int* 63:1791-1800, 2003
- [2] Sánchez-Pozos K, Barrera-Chimal J, Garzón-Muvdi J, et al. Recovery from ischemic acute kidney injury by spironolactone administration. *Nephrol Dial Transplant* 27:3160-3169, 2012
- [3] Zhou G, Johansson U, Peng XR, Bamberg K, Huang Y. An additive effect of eplerenone to ACE inhibitor on slowing the progression of diabetic nephropathy in the db/db mice. *Am J Transl Res* 8:1339-1354, 2016
- [4] Nagase M. Activation of the aldosterone/mineralocorticoid receptor system in chronic kidney disease and metabolic syndrome. *Clin Exp Nephrol* 14:303-314, 2010
- [5] Shibata S, Nagase M, Yoshida S, et al. Modification of mineralocorticoid receptor function by Rac1 GTPase: implication in proteinuric kidney disease. *Nat Med* 14:1370-1376, 2008
- [6] Bombardier AS, Klemmer PJ. The incidence and implications of aldosterone breakthrough. *Nat Clin Pract Nephrol* 3:486-492, 2007
- [7] Bolignano D, Palmer SC, Navaneethan SD, Strippoli GF. Aldosterone antagonists for preventing the progression of chronic kidney disease. *Cochrane Database Syst Rev* 29(4): CD007004, 2014
- [8] Pitt B, Kober L, Ponikowski P, et al. Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. *Eur Heart J* 34:2453-2463, 2013
- [9] Bakris GL, Agarwal R, Chan JC, et al; Mineralocorticoid Receptor Antagonist Tolerability Study—Diabetic Nephropathy (ARTS-DN) Study Group. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. *JAMA* 314:884-894, 2015
- [10] Yu BC, Lee MS, Moon JJ, et al. Efficacy of low-dose spironolactone in patients with glomerulonephritis. *Kidney Res Clin Pract* 37:257-265, 2018