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Editorial

Novel Nonsteroidal Mineralocorticoid Receptor Antagonists a Promising Strategy for Chronic Kidney Disease Patients and Diabetic Nephropathy

Merita Rroji and Myftar Barbullushi

University Department of Nephrology, Faculty of Medicine, University of Medicine Tirana, Tirana, Albania

The story of mineralocorticoid receptor antagonists (MRAs) started initially with 'aldosterone antagonists (AAs)' as the report of the first AAs during the 1950s being encouraged by identifying inhibitors aldosterone activity in animals and humans.

The 60 years of MRA research and progress was a journey with three waves. It started with the identification of steroid-based spironolactone as the first anti-mineralocorticoid, shortly after the purification of aldosterone. Continued with the discovery of more specific steroidal anti mineralocorticoids. And in the last two decades, we are facing the ultimate goal of identifying novel nonsteroidal MRAs with individualized pharmacokinetic and pharmacodynamic qualities for use as safe and efficacious drugs for a broad spectrum of diseases [1].

The third and fourth-generation MRAs share a nonsteroidal structure, where finerenone and esaxerenone are currently being evaluated in clinical trials, while no clinical data are available for apararenone. Finerenone is thought to have higher potency and less rick for hyperkalemia than steroidal MRAs such as spironolactone and eplerenone due to the differential distribution of the drug in the heart and kidney [2]. The renal elimination of finerenone is minimal, although in moderate and severe renal impairment, there is increased exposure to unbound finerenone by 57% and 47%, respectively, possibly due to renal impairment and nonrenal routes of elimination [3].

Inappropriate activation of the mineralocorticoid receptor (MR) plays a crucial role in the development of hypertension, cardiovascular disease (CVD) and chronic kidney disease (CKD).

The adrenal cortex's primary stimuli for aldosterone synthesis and release are angiotensin II, serum potassium and adrenocorticotropic hormone. However, other factors such as nitric oxide, endothelin and various pituitary and adipose-tissue factors can stimulate aldosterone synthesis. 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 "non-genomic" ways, which could be either dependent or independent of mineralocorticoid receptor activation [4].

MR expression has been detected in classical and non-classical tissues. The classic effect of aldosterone is exerted in the epithelium of the aldosterone-sensitive distal nephron (ASDN), where MR activation stimulates renal sodium reabsorption and potassium excretion binding to the MR and controls sodium reabsorption and potassium secretion. Besides the traditional role in ion and water transport, these functions of mineralocorticoid receptors have also been detected in other cell types, especially in cardiac and vascular tissues. MR expression has also been identified in non-classical tissues, such as podocytes, fibroblasts, cardiomyocytes, endothelial, vascular smooth muscle cells, adipocytes and macrophages. Although known to be pathophysiological, its activation in non-classical tissues is not always due to the action of aldosterone, as 11β-HSD2 is not always expressed. MR expression may be upregulated in some pathological conditions, such as diabetes, heavy proteinuria, vascular aging, and hypertension, thus amplifying MR signaling [2,5,6].

Aldosterone promotes hypertension through sodium retention. This sound-known action remains a potential mechanism for both cardiac and renal injury. However, some of the impairment attributable to aldosterone and the benefits observed with its suppression and antagonism are complex and partially beyond their blood pressure lowering effects.

A rapid nongenomic mechanism initiated by mineralocorticoid receptor activation involves PI-3 kinase, protein kinase B, and heat shock protein 90-mediated stimulation showed that aldosterone inhibits depolarization-induced vasoconstriction in renal afferent arterioles of NO generation [7].

Nonhemodynamic actions of aldosterone may also participate in its renal and cardiac fibrotic consequences. Although the distal tubules are usually considered the targets of aldosterone action in the kidney, transcripts for the mineralocorticoid receptor have been detected in glomeruli, albeit at lower levels than in the distal tubular epithelium, most probably mediating fibrogenesis and sclerosis. There are rather old reports in vitro that

Correspondence to: Merita Rroji University Department of Nephrology, Tirana, Albania;
Mob Phone: 00355692314086; Email address: meritarroji@yahoo.com

showed that aldosterone does stimulate type IV collagen synthesis by mesangial cells and that vascular smooth muscle cells contain mineralocorticoid receptors that respond to aldosterone. It seems that an increasing number of locally and systemically acting factors have been associated with progressive renal injury [8]. Plasminogen activator inhibitor-1 levels were enhanced by aldosterone in the kidney and circulation, promoting thrombosis and extracellular matrix accumulation. Besides, data indicate that the TGF-β message is associated with aldosterone, suggesting that increased production of the profibrotic cytokine TGF-β is likely to be at least partly attributable to a direct action of aldosterone on renal tissue and not late nonspecific response to hypertensive renal injury [9]. Both TGF-β and the renin-angiotensin-aldosterone system (RAAS) participate in progressive renal damage, although the effect may be complex and may depend on hemodynamic and more direct actions. On the other hand, aldosterone and TGF-β1 added together produced dramatic synergistic effects on PAI-1 production and subsequent ECM accumulation. Thus, the activation of the elevated aldosterone induced by the renin-angiotensin-aldosterone system may amplify renin-angiotensin-aldosterone system profibrotic actions [10]. Therefore, both hypertensive and more direct cellular actions of aldosterone, including scarring, may account for its contributions to glomerulosclerosis and interstitial fibrosis.

Beyond organ fibrosis, some reports showed that mineralocorticoid receptors play a significant point in oxidative stress and inflammation. Due to genomic and non-genomic effects, it is raised reactive oxygen species (ROS) production (expressly by the enzyme NADPH oxidase), inflammation, and fibrosis, promoting tissue remodeling, vascular stiffening, and endothelial dysfunction being engaged in hypertension and cardiac and kidney damage [11].

Both macrophages and T cells have expressed MR, functioning as an essential transcriptional cellular phenotype and function regulator. In pathological conditions, this is being initiated even with normal or low aldosterone levels [12,13].

It was also noted that MR expression is enhanced in adipose tissue of murine models of obesity and obese human subjects. Different studies using MR antagonists and adipocyte-specific MR transgenic mice have demonstrated a crucial role of MR in insulin signaling and inflammation [14].

Although Angiotensin II plays an essential role in increased aldosterone level, it was shown that plasma aldosterone levels tend to grow with the duration of an ACE treatment (aldosterone breakthrough), suggesting that treatment with an ACE inhibitor was not sufficient in suppressing aldosterone synthesis [15,16]. In addition to ACE inhibition, that aldosterone blockade has an additional benefit in preventing organ damage. Besides reported studies in the heart, Bianchi *et al.* [17], more than a decade ago, showed that treatment with spironolactone might reduce proteinuria in patients with CKD. The newer and novel approaches to counteract this aldosterone breakthrough while emphasizing these agents' antihypertensive, antiproteinuric, anti-inflammation, and antifibrotic effects would be perfect, and mineralocorticoid receptor antagonists look to fit in this hole quite well, especially in CKD and diabetic nephropathy [18]. However, on the other hand, it is essential to note that steroidal MRAs are not indicated for treating patients with CKD and T2D. Their use is frequently associated with hyperkalemia, antiandrogenic adverse effects such as gynecomastia (for the nonselective MRA spironolactone), and eplerenone is contraindicated in hypertensive patients with creatinine clearance <30 mL/min and diabetic patients T2 with albuminuria [19]. Strategies to diminish aldosterone activation make sense, and drugs that interfere with the binding of aldosterone to its receptor to affect CKD is a relatively novel concept. Recently, we have had promising clinical trials with a new nonsteroidal structure of MRA [20].

Mineralocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy (ARTS-DN) was the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 2b study which compared finerenone (at the initial dose of 1.25 mg daily titrated up to 20 mg) with placebo in patients with type 2 diabetes and urinary albumin to creatinine ratio (UACR) ≥30 mg/g already being treated with an ACEI or an ARB. A significant decrease in UACR was detected with all doses of finerenone compared with placebo at 90 days. However, it would be noted that long-term effects on CKD progression or antifibrotic and anti-inflammatory properties have not been evaluated due to the short duration of the study where hyperkalemia but was observed in 6.3% of patients who received the maximal dose of finerenone in CKD stage 3 patients [21]. The largest metanalysis on the field including 31 studies presented by Sarafidis *et al*. [22,23], showed that using an MRA (alone or on top of RAS blockade) is linked with a significant proportional decrease in urine albumin or protein excretion from baseline. All three of spironolactone, eplerenone, and finerenone appear to reduce albuminuria potently. According to the analysis, using an MRA is associated with a mean increase in serum potassium by 0.22 mEq/l, increased more significantly with spironolactone than eplerenone and finerenone. Promising data of phase III clinical trial (ESAX-DN study) has also demonstrated the safety and efficacy of esaxerenone in patients with type 2 diabetes and microalbuminuria. Recently, we have an available very enthusiastic data of the FIDELIO-DKD trial (randomized, double-blind, placebo-controlled, parallel-group, multicenter trial which enrolled patients with an eGFR of 25-75 ml/min/1.73m2 and a UACR of 30-5000 mg/g). It was reported that finerenone, delayed the progression of kidney disease and improved cardiovascular outcomes in patients with advanced kidney disease and type 2

diabetes [24,25]. Moreover, Finerenone, in addition to standard medical therapy in patients with less-severe CKD and type 2 diabetes, reduced the risk of the study's primary endpoint of kidney failure or death from renal causes and reduced the risk of CV mortality, MI, stroke, or heart failure hospitalization among a population of about 7,400 patients which are the top results of FIGARO-DKD study [26].

Based on recent evidence, it is logical to suspect that if safe, MR blockade may contribute additional benefit when added to monotherapy with a RAS blocker by attenuating aldosterone breakthrough and through inhibition of deleterious effects aldosterone, such as renal inflammation and fibrosis and significantly retarding kidney disease progression. Preclinical and clinical studies indicate that MRAs reduce morbidity and mortality by reducing renal and cardiovascular risk [27]. Novel nonsteroidal MRAs are very selective and specifically inhibit MR, causing minimal hyperkalemia. The recent clinical trials of finerenone and esaxerenone in patients with kidney disease indicated a potential therapeutic role of nonsteroidal MRAs in CKD patients, especially with the new perspectives offered from novel treatments for hyperkalemia.

Conflict of interest statement. None declared.

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