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Review

THE CHANGING LANDSCAPE OF MINERALOCORTICOID RECEPTOR ANTAGONISTS – FINERENONE IN CARDIOVASCULAR AND RENAL HEALTH

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ABSTRACT

Finerenone is a novel non-steroidal mineralocorticoid receptor antagonist (MRA) with high selectivity and affinity to mineralocorticoid receptor (MR). Steroidal MRAs, like spironolactone and eplerenone, have been in use for decades. They have an established position in the management of hypertension and heart failure with reduced ejection fraction (HFrEF). There are studies showing that MR antagonism has anti-inflammatory and anti-fibrotic effects resulting in cardiovascular and renal protection. However, broader use of steroidal MRAs is seriously limited by antiandrogenic side effects and the risk of hyperkalemia. The differences in structure as well as pharmacokinetic and pharmacodynamic properties between steroidal and non-steroidal MRAs result in reduced risk of side effects while offering the benefit of cardiorenal protection. Finerenone is currently the only non-steroidal MRA approved by European Medicines Agency (EMA). It is indicated for patients with chronic kidney disease (CKD) with albuminuria and type 2 diabetes mellitus (DM2). Several studies showed a reduction of the risk of cardiovascular and renal events in this group of patients compared to placebo. The risk of hyperkalemia was increased resulting in discontinuation of treatment in more patients than placebo, but the risk of serious adverse events did not differ significantly. The other indications for finerenone, including heart failure (HF) management, are currently being researched.

KEYWORDS: chronic kidney disease, finerenone, heart failure, mineralocorticoid receptor antagonists, cardiorenal protection

1. Introduction

Steroidal mineralocorticoid receptor antagonists (MRAs) have been used in medicine for decades. The first steroidal MRA, spironolactone, has been introduced in the 1960s. Originally labeled as aldosterone antagonist it was used mainly for its diuretic properties in edemas, primary hyperaldosteronism and hypertension [1-3]. After the discovery of mineralocorticoid receptor (MR), the mechanism of action of spironolactone was associated with binding with MR [1]. Despite its positive properties in various conditions, spironolactone use has serious limitations. It is structurally similar to progesterone and has progestogenic and antiandrogenic effects resulting in gynecomastia, abnormal menstrual cycles and impotence [4, 5]. Eplerenone was approved in 2002 by Food and Drug Administration (FDA), 40 years after the approval of spironolactone, as a second oral MRA in the US [6]. The steroidal structure of its molecule has been modified to reduce the affinity to androgen and progesterone receptors [1]. Compared to spironolactone, it has higher selectivity to MR and lower chance of inducing antiandrogenic side effects. Indications for its use include hypertension and heart failure [6, 7]. Nevertheless, the use of eplerenone, as well as spironolactone, is still associated with an increased risk of

hyperkalemia [8, 9]. The latest research in the field of MRAs concerns non-steroidal molecules. Inhibition of MR offers a possibility of cardiovascular and renal protection by reducing inflammatory and fibrotic response [10-12]. Although steroidal MRAs like spironolactone and eplerenone have been shown to reduce albuminuria, they lack efficacy concerning clinical outcomes in chronic kidney disease (CKD) [13]. Their use is also limited due to possible side effects. Non-steroidal molecules could combine the cardiorenal protection benefits with a limited chance of serious side effects, including the risk of hyperkalemia. In 2022, the European Medicines Agency (EMA) approved the first and currently only non-steroidal MRA, finerenone. It is indicated in patients with CKD with albuminuria associated with type 2 diabetes mellitus (DM2) [14]. The aim of this article is to review the current information on finerenone and its indications and efficacy in cardiovascular and renal protection.

2. The mineralocorticoid receptor

MR is a nuclear hormone receptor that is activated by aldosterone and cortisol [15, 16]. It is present in kidneys, heart, blood vessel walls, brain, lungs, sweat and salivary glands and other organs [16, 17]. In kidneys, it plays a role in homeostasis of sodium, potassium and fluid mainly in connection to aldosterone as a part of renin-angiotensin-aldosterone system (RAAS). It is present in renal epithelial cells, but also podocytes, mesangial cells and smooth muscle cells [15]. Physiological activation by aldosterone induces water and sodium retention [18]. In the heart, MR is present in cardiomyocytes, cardiac fibroblasts and epithelial cells [16]. Overactivation of MR is an effect of excessive aldosterone concentration and up-regulation of the MR itself [16]. Overactivation of renal MR promotes kidney injury and loss of glomerular filtration rate (GFR) by inducing fibrosis, proteinuria and glomerulosclerosis [15, 19-21]. MR overactivation in cardiovascular system induces cardiomyocyte hypertrophy and apoptosis, fibrosis, oxidative stress and negatively affects vascular function [12, 16, 22-25]. Overall, MR overactivation plays a significant role in CKD as well as cardiovascular injury.

3. Steroidal MRAs

Both steroidal MRAs are widely used in heart failure with reduced ejection fraction (HFrEF). Spironolactone has been demonstrated to reduce mortality and hospitalization rate in those patients in the RALES study published in 1999 [26]. The same was later observed for eplerenone, with EPHESUS and EMPHASIS-HF studies revealing a significant decrease in mortality and morbidity among patients suffering from HFrEF [27, 28]. On the other hand, spironolactone use in patients with heart failure with preserved ejection fraction (HFpEF) did not result in reduction of cardiovascular deaths or hospitalization due to heart failure exacerbation as was demonstrated by TOPCAT study in 2014 [29]. These findings are represented by a current standard of care. The ESC 2021 Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure recommend MRAs as first-line treatment in all patients with HFrEF without contraindications [7]. Moreover, there is evidence suggesting that spironolactone administration offers renal protection and reduction of proteinuria. The blockade of RAAS in the form of ACE-inhibitors or angiotensin receptor blockers (ARB) is the standard treatment in patients with CKD with proteinuria aimed to reduce the urinary protein excretion. Spironolactone was proven in several studies to provide additional benefit in those patients by further decreasing proteinuria and delaying the loss in estimated glomerular filtration rate (eGFR) [30]. These studies did not show a significant increase in hyperkaliemia, but a subsequent meta-analysis showed a 4.3 times higher relative risk of developing hyperkalemia with the use of spironolactone on top of RAAS blockade [13]. Similar qualities have been confirmed for eplerenone. Several studies indicated further reduction of albuminuria as an effect of eplerenone used additionally to RAAS blockade [31, 32].

4. Properties of finerenone

Finerenone is currently the only non-steroidal MRA approved in Europe. There are other compounds in various stages of clinical trials. They include for example esaxerenone and aparenone as well as other substances [15]. Finerenone is a compound with high selectivity and affinity to MR. This reduces the risk of anti-androgenic and progestogenic effects. It acts as an antagonist of MR but has a specific binding mode that changes the conformation of the MR inducing a different cofactor-binding profile in comparison to other MRAs [15, 33]. Finerenone induces the protrusion of helix 12 of the MR that creates an unstable receptor-ligand complex reducing the possibility of transcriptional coregulators recruitment. This results in a specific gene regulation that promotes less pro-inflammatory and pro-fibrotic transcription profile compared to the inhibition by steroidal MRAs [34, 35].

There are also differences in pharmacokinetic properties between finerenone and steroidal MRAs. Finerenone has a much shorter plasma half-life compared to steroidal MRAs. Finerenone's plasma half-life is about 2-3 hours, while spironolactone has a half-life of more than 20 hours and eplerenone between 4 and 6 hours [15, 36]. This is partly attributed to the fact that finerenone, unlike spironolactone, has no active metabolites. Finerenone is also significantly less lipophilic than steroidal MRAs. Because of that, it is unable to cross the blood-brain barrier and penetrate to central nervous system [15]. It was also demonstrated that finerenone has a balanced distribution between heart and kidneys, while spironolactone and eplerenone tend to accumulate predominantly in the kidneys [37]. Finerenone is metabolized mostly by CYP3A4 and to some extent by CYP2C8, but the metabolites are excreted mainly through kidneys [15, 38]. As a result, finerenone's elimination is prolonged in patients with worse kidney function. The recommended initial dose is dependent on the eGFR. The starting dose for patients with eGFR > 60 ml/min/1.73m^2 is 20 mg, for patients with eGFR of 25-60 ml/min/1.73m^2 it is reduced to 10 mg and eGFR less than 25 ml/min/1.73m^2 is a contraindication for the initiation of finerenone treatment [14].

Table 1. The comparison of chosen properties of spironolactone, eplerenone and finerenone. Abbreviations: MR – mineralocorticoid receptor, CNS – central nervous system.

	Spironolactone	Eplerenone	Finerenone
Structure	Steroidal	Steroidal	Non-steroidal
MR-selectivity	Low	Higher	High
MR-affinity	High	Low	High
Plasma half-life	>20 h	4-6 h	2-3 h
Active metabolites	Yes	No	No
CNS penetration	Yes	Yes	No
Tissue distribution	Kidney > Heart	Kidney > Heart	Balanced
Hormonal side effects	Yes	Reduced	No

5. Clinical evidence

Phase II program concerning finerenone includes ARTS, ARTS-HF and ARTS-DN trials. The tolerability and safety profile of finerenone in patients with HFrEF and mild or moderate CKD was investigated by the ARTS trial. Its primary outcome was the change in serum potassium level with the use of finerenone (doses 2.5, 5 and 10 mg per day) versus spironolactone (25 or 50 mg per day) versus placebo. The increase in serum potassium concentration was significantly smaller for finerenone at all doses compared to spironolactone. In comparison to placebo, lower doses of finerenone (2.5 and 5 mg per day) did not result in a significant increase in potassium levels. Only the higher dosage (10 mg per day) was associated with a significant increase in serum potassium levels compared to placebo. Moreover, finerenone at doses 5-10 mg per day was non inferior to spironolactone in decreasing levels of hemodynamic stress biomarkers [39]. It is worth noting, however, that the maximum dosage of finerenone in this study was half the recommended dose as per finerenone's product information [14].

ARTS-HF was a randomized, double-blind, active-comparator-controlled study. It was designed to compare the use of finerenone in different dosages with eplerenone in patients with HFrEF and concomitant DM2 and CKD. The primary endpoint was the percentage of patients with a 30% or greater reduction in serum NT-proBNP concentration. There were no significant differences between groups in primary endpoint occurrence. However, finerenone was superior to eplerenone in an occurrence of composite endpoint of all-cause death, cardiovascular hospitalizations or emergency presentation for HF exacerbation. This effect reached statistical significance only in a group of patients treated with 10 mg of finerenone increased to 20 mg on day 30 [40].

ARTS-DN was a randomized, double-blind, placebo-controlled study investigating the use of finerenone in patients with albuminuria (urinary albumin-creatinine ratio [UACR] ≥ 30 mg/g) and DM2 who were receiving angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. The addition of finerenone on top of this treatment proved to be effective in reducing UACR at 90 days. The reduction of UACR was dose-dependent [41].

Phase III trials included FIDELIO-DKD, FIGARO-DKD and a pooled analysis of those two trials – FIDELITY. FIDELIO-DKD was a randomized, double-blind, placebo-controlled trial. Patients with CKD and DM2 were included in the study. The primary endpoint was a composite of kidney failure, a sustained > 40% decrease in eGFR or death from renal causes. Finerenone successfully reduced the occurrence of primary endpoint (hazard ratio [HR]: 0.82; 95% confidence interval [CI]: 0.73-0.93; p = 0.001) [42]. Moreover, finerenone proved to reduce the risk of cardiovascular events [42, 43]. The cardiovascular endpoint, which was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke or hospitalization from heart failure, was also significantly less common in the finerenone group (HR: 0.86; 95% CI: 0.75-0.99; p = 0.03) [42]. This was also confirmed in FIGARO-DKD trial. Finerenone reduced the occurrence of cardiovascular endpoint compared to placebo (HR: 0.87; 95% CI: 0.76-0.98; p = 0.03) and the greatest effect was demonstrated for lowering the incidence of hospitalizations for heart failure (HR: 0.71; 95% CI: 0.56-0.90) [44]. It was also reported that finerenone reduced the incidence of novel heart failure in patients with CKD and DM2 [45]. Nevertheless, both trials excluded patients with symptomatic HFrEF and only a small proportion of patients had a history of HFpEF (7.7% in FIDELIO-DKD and 7.8% in FIGARO-DKD) [46]. The impact on cardiovascular risk was unrelated to the previous history of HF [46]. Patients treated with finerenone more often than those treated with placebo discontinued the treatment because of hyperkalemia, but the risk of serious adverse events was similar [42, 44]. FIDELITY, the subsequent pooled analysis of these two trials confirmed the reduction in cardiovascular and renal risk as well as the safety profile [47].

Currently ongoing study, FINEARTS-HF (ClinicalTrials identifier: NCT04435626), is designed to evaluate the safety and efficacy of finerenone in patients with symptomatic HF and left ventricle ejection fraction (LVEF) ≥ 40%. It is a randomized, double-blind, placebo-controlled trial. The primary outcome is the number of cardiovascular deaths and heart failure events. The results of this study could fill the gap in our knowledge about the position of finerenone in terms of HF treatment. The study completion is planned for 2024.

6. Conclusions

The role of MR overactivation in the progression of cardiovascular and renal disease is well-documented.

Because of that, inhibition of the MR is currently an important aspect of treatment in these conditions. Steroidal MRAs already have an established position in treatment of HFrEF. Non-steroidal MRAs, such as finerenone, provide a different profile of action that was proven to be beneficial in selected populations of patients. Finerenone reduces albuminuria and reduces the risk of CV and renal events in the group of patients with CKD and DM2. Unlike steroidal MRAs it does not have antiandrogenic adverse events and carries smaller risk of inducing hyperkalemia, although there is little data comparing head-to-head the safety profile of finerenone to spironolactone or eplerenone. There is convincing evidence that finerenone administration in patients with CKD with albuminuria and DM2 should be considered. Nevertheless, those studies had some limitations. The heterogeneity was not sufficient and the exclusion criteria were strict which might result in different outcomes in real-world clinical setting. Undoubtedely, further studies are needed to assess long-term efficacy and safety profile of this drug. Also, some studies suggest positive impact on CV risk in patients with HF. In this case, convincing data is still lacking. The possible use of finerenone in different populations, including patients with HFrEF or HFpEF, is still not studied sufficiently. The results of currently ongoing FINEARTS-HF study could bring advancement in that area.

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