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Administration of finerenone in chronic kidney disease

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ABSTRACT

Spirolactone is a first-generation and non-selective mineralocorticoid receptor antagonist (MRA). It is extensively well-studied and recommended due to increased accessibility for patients. Unfortunately, it is often discontinued in several cases due to its association with hyperkalemia. The apparent benefit of eplerenone over spironolactone is its mineralocorticoid receptor (MR) selectivity. However, it is also characterized by low-potency and higher cost compared to spironolactone. The high adverse-effect profile of spironolactone and eplerenone has led to the innovation of novel medications such as non-steroidal MRAs. Among these medications, finerenone is the most advanced agent. Finerenone is associated with decreased proteinuria, reduced risk of hyperkalemia and increased preservation of renal function with comparable benefit in heart failure compared to selective and nonselective MRAs. The nonsteroidal structure of finerenone affects mineralocorticoid receptor binding, lipophilicity and polarity which have potent effects on distribution, the degree of attachment to blood proteins, transportation, and tissue diffusion.

Implication for health policy/practice/research/medical education:

The available non-selective mineralocorticoid receptor antagonist (MRA) such as spironolactone and eplerenone have high adverse-effect profiles. Therefore, novel non-steroidal MRAs have been studied and discovered during recent years. Among these drugs, finerenone is associated with decreased proteinuria, reduced risk of hyperkalemia, and increased preservation of renal function with comparable benefits in heart failure to selective and nonselective MRAs.

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Introduction

The expression of mineralocorticoid receptors (MRs) has been detected in approximately all kidney regions including vascular endothelial cells, podocytes, fibroblasts, mesangial cells and vascular smooth muscle cells (1). MR activity influences sodium and potassium renal reabsorption which contributes to the maintenance of ion balance in the body. MR expression and aldosterone signaling is enhanced in metabolic diseases, specifically diabetes, hypertension and nephropathy. Growing evidence indicates that activation of MR leads to atherosclerosis, micro-angiopathy in renal blood vessels, activation of Rac1/Rho kinase (mediators of podocyte injury) and progression of chronic kidney disease (CKD) (2). Additionally, diabetic nephropathy is suggested to be associated with MR activity by mesangial

expansion, albuminuria, tubulointerstitial lesions, and macrophage infiltration.

Aldosterone is the most effective agonist of MR. The effect of aldosterone levels on renal function is influenced by MR activation. In several diseases, primary hyperaldosteronism may result in increased urinary protein excretion without hypertension (3). MR activation induces aldosterone that promotes a pro-inflammatory factor, nuclear factor kappa B (NF- κ B), synthesis of pro-fibrotic cytokines and matrix proteins, and also oxidative stress in the kidney (4). Aldosterone has also been reported to advance the deterioration of renal function, glomerulosclerosis, and proteinuria in a remnant kidney model (5).

Numerous preclinical and clinical studies have

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utilized mineralocorticoid receptor antagonists (MRAs) in treatments for acute kidney injury (AKI), diabetic nephropathy, CKD and renal fibrosis. MRAs are categorized as selective or non-selective and specific or non-specific types. Non-selective MRAs present a risk of gynecomastia that is not present in selective MRAs despite both being effective treatments. Furthermore, the presence of a steroidal nature distinguishes specific MRAs from non-specific MRAs.

Spironolactone is a first-generation and non-selective MRA that is extensively well-studied and recommended due to the ease of accessibility for patients. However, it is discontinued in most patients due to its association with hyperkalemia. The apparent benefit of eplerenone over spironolactone is its MR selectivity. However, it also demonstrates a low-potency and higher cost in comparison to spironolactone.

The high adverse-effect profile of spironolactone and eplerenone initiated the advancement of innovative drugs such as non-steroidal MRAs. They are characterized by decreased proteinuria, decreased risk of hyperkalemia, and increased preservation of renal function with comparable efficacy to selective and nonselective MRAs in heart failure. Examples of nonsteroidal MRAs that are utilized in various clinical trials of patients with kidney disease include finerenone, aparenone, esaxerenone, SM-368229, AZD9977, PF-03882845, DSR-30192, KBP-5074, DSR-71167, LY2623091, and BR-4628. Among these medications, finerenone has been shown as the most advanced and promising nonsteroidal MRA (6).

Methods

For this narrative review the international databases comprising PubMed, Scopus, Google Scholar, Web of Science and DOAJ (Directory of Open Access Journals) were searched using the following keywords; finerenone, chronic kidney disease, mineralocorticoid receptor, and acute kidney injury.

Finerenone

In 2004, it was reported that some para-dihydropyridines may operate as MRA *in vitro*. Subsequently, the chemical development of dihydropyridines led to the discovery of a dihydronaphthyridine compound, finerenone (BAY94-8862). Finerenone ($C_{21}H_{22}N_4O_3$) acts as a bulky antagonist on the MR which utilizes a passive mechanism that differs from steroidal MRAs. It also possesses exceptional selectivity (at least 500- fold toward MR) compared to all other steroid hormone receptors (such as glucocorticoid receptors, progesterone receptors, androgen receptors, and estrogen receptors), eplerenone, and 65 important receptors and ion channels involving the L-type calcium channel (7). Additionally, the IC₅₀ value of finerenone

is 17.8 nM, which is noticeably lower compared to spironolactone (IC₅₀ 24.2 nM) and eplerenone (IC₅₀ 990 nM) (8). The nonsteroidal structure of finerenone affects MR binding, lipophilicity, and polarity which have a potent effect on distribution, the degree of attachment to blood proteins, transportation, and tissue diffusion (9).

Finerenone is also characterized by its distribution. Unlike the first- and second-generation MRAs that favorably concentrate in the kidney over the heart, finerenone is more balanced and evenly distributed amongst the two organs with almost similar drug concentrations. The equivalent tissue distribution and different pharmacological metabolism properties contribute to decreased adverse effects related to serum potassium level and renal function (10,11). Finerenone possesses superior polarity and 6- to 10-fold less lipophilicity compared to steroidal MRAs (6). Absorption and pharmacological properties of finerenone at fasting states were also further evaluated. Researchers established that finerenone was quickly absorbed at tolerable states, with plasma concentration increased in 0.5-1 hour, alongside a rapid plasma elimination half-life of 1.7–2.83 hours under dose-linear pharmacokinetics. Up to 80 mg of finerenone was established as tolerable in healthy individuals at non-fasting states. Additionally, finerenone was shown to not affect laboratory factors such as urinary electrolytes, serum aldosterone, and angiotensin II (12). Finerenone is primarily metabolized and cleared by the enzymes cytochrome P450 (CYP) 3A4 (90%) and CYP2C8 (10%) found in the gut wall and liver. Patients with impaired kidney function possessed prolonged elimination half-lives dependent on creatinine clearances as illustrated; eGFR (estimated glomerular filtration rate) <30 mL/min/m² (180 minutes), 30–50 mL/min/m² (173 minutes), 50–80 mL/min/m² (140 minutes), and > 80 mL/min/m² (134 minutes). Finerenone is also influenced by serum proteins levels, specifically albumin. Therefore, in conditions with hypoalbuminemia, there may be augmented serum levels of finerenone due to a significant degree of finerenone binding to serum proteins (12).

Available data from numerous clinical trials on over 2000 patients with renal diseases treated with finerenone have confirmed the low rates of adverse effects such as hyperkalemia and renal damage. Finerenone appears to have lower rates of hyperkalemia than spironolactone. However, they both possess similar effects on N-terminal pro-B-type natriuretic peptide (NT-proBNP) and albuminuria (13). A study with 1066 participants compared finerenone to eplerenone in patients with CKD and heart failure. The finerenone group demonstrated reduced cardiovascular hospitalization, a composite of death, or acute heart failure compared to the eplerenone group. However, they were similar in regards to NT-proBNP reduction and the risk of hyperkalemia (14). A preclinical

study on deoxycorticosterone acetate (DOCA) treated rats displayed that the administration of finerenone protected against cardiac and renal damage despite reduced systolic blood pressure. Finerenone decreased cardiac hypertrophy, proBNP and proteinuria more proficiently than eplerenone at almost equivalent doses (11). Some head-to-head studies have also suggested the utilization of finerenone instead of spironolactone in patients with chronic heart failure and CKD. In addition, it has been reported that once-daily oral consumption of finerenone at lower doses was associated with a more prominent anti-hypertrophic/-fibrotic effect alongside reduced hyperkalemia risk, NT-proBNP, deterioration of renal function, and urinary albumin (15,16). Kolkhof et al demonstrated that survival and nephroprotection improved in hypertensive rats that were administered finerenone (17). Aldosterone blocker administered concurrently with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blocker (ARB) may be beneficial in the reduction of proteinuria or reduction in the rate of decreased renal function. However, it is also associated with potential added adverse effects (hyperkalemia and AKI). Similarly, finerenone combined with ACEI/ARB displayed a dose-dependent decrease in albuminuria and urinary albumin-creatinine ratio (UACR) in patients with diabetic nephropathy and mild hypertension (18). Finerenone also reduced the expression of the pro-fibrotic gene in DOCA-salt hypertensive rats (19). A recent clinical trial reported a potential beneficial role of nonsteroidal MRAs (finerenone and esaxerenone) in CKD patients as well. MRAs may inhibit the development of AKI to CKD by decreasing inflammation and oxidative stress. Finerenone administration reduced intrinsic arterial stiffness in mesenteric arteries in genetic CKD model rats, which is associated with reduced albuminuria. Furthermore, finerenone improved endothelial dysfunction by enhancing the activity of vascular and renal superoxide dismutase (SOD) (a main superoxide anion blocker) as well as increasing the bioavailability of nitric oxide (NO) (20, 21). This study demonstrated that treatment with finerenone for 90 days improved myocardial perfusion, oxidative stress, proteinuria, and NO bioavailability. However, systolic blood pressure (BP) and heart rate were not improved (22).

Acute kidney injury

Remarkable evidence has developed on the potential nephroprotective effects of finerenone. Lattenist et al investigated a murine model with ischemia-reperfusion AKI after pre-treatment with finerenone for three days. Decreased AKI biomarkers (kidney injury molecule-1 and neutrophil gelatinase, associated with lipocalin-2, a mediator of tissue inflammation) and reduced creatinine,

urea, proteinuria, and oxidative stress in ischemia-reperfusion AKI were observed. Finerenone prevented the transition from AKI induced by ischemia-reperfusion to CKD (23). The central targets of finerenone in ischemia-reperfusion AKI are vessel smooth muscle cells which decrease the generation of reactive oxygen species and amplified the synthesis of nitric oxide in endothelial cells. A study by Barrera-Chimal et al showed that finerenone limited ischemia-reperfusion AKI by influencing the Rac1-mediated MR signaling (24).

The study by Dutzmann et al investigated the functional effect of finerenone in *in vitro* vascular cells. They reported that finerenone considerably prevented the apoptosis of endothelial cells while simultaneously increasing the proliferation of smooth muscle cells resulting in augmented endothelial recovery. In addition, the effect of finerenone was also investigated on *in vivo* vascular remodeling following acute vascular injury. Finerenone was shown to repair vascular integrity following vascular injury and reduce rates of the reendothelialization process. Therefore, finerenone restricts the inflammatory factors and has an inhibitory effect on vascular remodeling (25). A meta-analysis displayed a 31% decrease in proteinuria or albuminuria following treatment with a steroidal MRA in patients with CKD (26). This study showed that finerenone possesses superior anti-inflammatory and anti-fibrotic effects in preclinical models compared to other steroidal MRAs (27,28).

The Aldosterone Blockade for Health Improvement Evaluation in end-stage kidney disease (ESKD) trial (ACHIEVE; NCT03020303, 2017) that is estimated to complete in 2023 included 2750 dialysis patients where spironolactone and placebo were compared for outcomes such as cardiovascular death or hospitalization. While results from ACHIEVE are not yet available, results outlining the type and efficiency of MRAs recommended for use in ESKD would be of great value. Finerenone requires further study regarding its role, performance, and safety profile in the context of ESKD (29).

Trials on finerenone

There are several barriers that limit the implementation of finerenone treatment in clinical practice. For example, there are limited phase III trials due to deficiencies in suitable RCTs (randomized controlled trials), lack of medication development, and the absence of Food and Drug Administration (FDA) recommendations. There is well-established evidence that supports finerenone as a suitable option for MRA treatment, especially for renal function, proteinuria, and hyperkalemia. These results are supported predominantly by RCTs that include the FIDELIO-DKD, FIGARO-DKD, ARTS-DN, ARTS-DN Japan and ARTS-HF trials (Table 1).

The Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD, NCT02540993)

This double-blinded, placebo-controlled, and phase III randomized trial investigated over 5734 patients with progressive CKD and type 2 diabetes on finerenone and ACE/ARB therapy that were followed up for at least one month (30). They studied the effect of finerenone on the onset of renal failure, continued reduction in creatinine clearance and decreased cardiovascular disease-related death.

The Efficacy and Safety of Finerenone in Subjects with Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease (FIGARO-DKD, NCT02545049)

This trial also included 7437 patients with diabetic nephropathy on ACEI/ARB treatment that were followed up for 5.5 years. This study evaluated the safety and effectiveness of finerenone compared to placebo. Two doses (10 and 20 mg/d) of finerenone were investigated to assess morbidity and mortality, hospitalizations, the progression of renal disease considering the onset of kidney failure and the variation in UACR and eGFR amongst patients (31). This active phase III randomized, double-blinded and placebo-controlled trial uncovered finerenone to decrease the composite outcome by almost 18% in comparison to placebo.

The Miner Alocorticoid Receptor Antagonist Tolerability Study (ARTS; NCT01345656)

Finerenone has been examined in numerous phase 2 RCTs, such as the ARTS trial. These multicenter, randomized, double-blinded, placebo-controlled and parallel-group (8,16) studies that investigated finerenone safety on registered patients with heart and renal disease compared creatinine clearances, proteinuria and hyperkalemia in two arms (finerenone versus placebo, and finerenone versus spironolactone). The study demonstrated finerenone to cause a superior decrease in hyperkalemia and decreased rate of reduced renal function compared to spironolactone with a similar degree of proteinuria reduction (8).

Safety and Efficacy of Different Oral Doses of BAY94-8862 in Subjects with Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Nephropathy (ARTS-DN, NCT1874431)

This study provides further support for finerenone as a substitute for first- and second-generation MRAs in patients with diabetic nephropathy (32). This dose-dependent phase 2b study of finerenone included 823 patients followed for 90-days at 148 sites in 23 countries. Finerenone added to ACEIs or ARBs in CKD achieved its primary outcome of a dose-dependent reduction in UACR. This trial displayed finerenone to improve UACR in comparison to placebo with minimal effects on blood pressure (32).

Safety and Efficacy of Different Oral Doses of BAY94-8862 in Japanese Subjects with Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Nephropathy (ARTS-DN Japan, NCT019686681)

This multi-center, randomized, adaptive, double-blinded, placebo-controlled and parallel-group design trial investigated Japanese diabetic patients with diabetic nephropathy. Finerenone reduced UACR at 90 days compared to placebo with insignificant increases in serum potassium. Hyperkalemia was not detected amongst their cohort, even among patients receiving the highest doses of finerenone (18).

MinerAlocorticoid Receptor antagonist Tolerability Study-Heart Failure (ARTS-HF, NCT01807221)

This was a phase 2b trial that investigated the safety of finerenone on 1058 patients with heart failure and/or CKD who were followed for 90 days. Based on serum potassium and eGFR levels, patients were randomized to receive finerenone or eplerenone treatment at increasing doses. Finerenone and eplerenone were equally effective regarding the reduction of NT-proBNP (almost 30%) (13).

Other trials

A non-randomized, observational trial conducted in

Table 1. Some of the trials that have investigated finerenone in patients with chronic kidney disease

Trial name	NCT#	Study completion year	Phase	No. of Participants
FIGARO-DKD	NCT02545049	2019	Phase 3	7437
FIDELIO-DKD	NCT02540993	2019	Phase 3	5734
ARTS-HF	NCT01807221	2016	Phase 2	1058
ARTS-DN	NCT1874431	2015	Phase 2	823
ARTS-DN Japan	NCT01968668	2014	Phase 2	96

Abbreviation: NCT #: National Clinical Trial number.

Germany studied the pharmacokinetics of 10 mg of finerenone administered in patients with varying renal injuries. This trial concluded that moderate and severe renal injury amplified exposure to unbound finerenone by 57% and 47%, respectively, without significant effects on maximum plasma concentration. However, the mild renal injury did not affect finerenone exposure (33).

Conclusion

The high adverse-effect profile of spironolactone and eplerenone has led to the advancement of innovative drugs. Finerenone is the most promising drug considering renal function, proteinuria, and hyperkalemia. These results are primarily supported by RCTs including the FIDELIO-DKD, FIGARO-DKD, ARTS, ARTS-DN, ARTS-DN Japan, and ARTS-HF trials that were summarized in this review.

Authors' contribution

Conceptualization: MAS, MRR, EE.

Validation: MAS, EE, SH & MRR.

Investigation: AAJ, SH.

Resources: MRR.

Data Curation: MRR, MAS.

Writing—Original Draft Preparation: MAS, EE & MRR.

Writing—Review and Editing: SH, AAJ.

Visualization: SH.

Supervision: SH, MRR.

Project Administration; MRR.

Funding Acquisition; MRR.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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