The Role of Finerenone in the Management of Diabetic Nephropathy

Stavroula Veneti · Konstantinos Tziomalos ⓘ

ABSTRACT

Diabetic nephropathy (DN) is the leading cause of chronic kidney disease. Even though mineralocorticoid receptor antagonists (MRA) induce incremental reductions in urine albumin excretion when added to angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, this combination is infrequently used because of an increased risk of hyperkalemia. In this context, finerenone, a novel selective MRA that appears to be associated with lower risk for hyperkalemia compared with other MRAs (spironolactone and eplerenone), might represent a useful tool in patients with DN. A recent large randomized trial suggested that finerenone delays the progression of DN and might also reduce cardiovascular morbidity in patients with DN. However, more data are needed to clarify the safety and efficacy of finerenone in this high-risk population.

S. Veneti · K. Tziomalos (✉)
First Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA Hospital, 1 Stilponos Kyriakidi street, 54636 Thessaloniki, Greece
e-mail: ktziomalos@yahoo.com

Key Summary Points
Finerenone is a novel, selective mineralocorticoid receptor antagonist.
Finerenone delays the progression of diabetic nephropathy.
Finerenone appears to reduce cardiovascular morbidity in patients with type 2 diabetes mellitus.
Finerenone appears to be safer than other mineralocorticoid receptor antagonists.

DIGITAL FEATURES

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INTRODUCTION

Diabetic kidney disease (DKD) constitutes the lion's share of patients with chronic kidney disease (CKD). It is expected that 40–45% of patients with type 1 diabetes mellitus (DM) and 30% of patients with type 2 DM will eventually develop nephropathy [1]. Diabetic nephropathy (DN) is characterized by albuminuria and progressive reduction in glomerular filtration rate (GFR). The major lesions observed in the kidneys of patients with DN are glomerulosclerosis, thickening and hypertrophy of the glomerular basement membrane, hypertrophy of renal cells, expansion of mesangial cells, and tubulointerstitial fibrosis [2]. DKD is a progressive condition characterized by an early stage of hyperfiltration and renal hypertrophy, followed by a stage of incipient nephropathy with microalbuminuria and hypertension [3]. Gradually, patients present overt nephropathy with proteinuria and reduction of GFR and some develop end-stage kidney disease (ESKD) [4]. DKD is a potentially life-threatening disease not only because patients progress to ESKD but also because they have increased risk for cardiovascular events and a greater susceptibility to infections [5]. For this reason, early identification and management of DKD is of outmost importance. The two major established risk factors for DKD are hyperglycemia and hypertension. Moreover, age, ethnicity, family history, and obesity are also associated with increased risk for DN [5].

Multifactorial treatment is essential for preventing DKD and for delaying its progression and its cornerstone is strict glycemic and blood pressure control [6, 7]. Regarding glycemic control, sodium–glucose cotransporter 2 inhibitors are recommended in patients with estimated glomerular filtration rate (eGFR) of at least 30 ml/min/1.73 m^2 and urinary albumin greater than 300 mg/g creatinine [6, 7]. The agents of choice for the management of hypertension in patients with DKD are angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin II receptor blockers (ARBs) [6, 7]. More recently, additional blockade of the renin–angiotensin system with mineralocorticoid receptor antagonists (MRAs) has been shown to reduce albuminuria in short-term studies in patients with DM and micro- or macroalbuminuria treated with ACE-Is or ARBs [6]. Indeed, MR overactivation is a key determinant of DKD progression by increasing intraglomerular pressure and also by non-hemodynamic actions, including direct proinflammatory and profibrotic effects as well as Klotho deficiency [8]. However, combination therapy with MRAs and ACE-Is or ARBs increases the risk of serious adverse effects, especially hyperkalemia, and this represents a major barrier in the use of MRAs. On the other hand, finerenone, a recently developed selective MRA, appears to be both safe in patients with DKD and to exert beneficial effects on kidney function. In the present review, we discuss the role of finerenone in the management of DKD. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

SEARCH STRATEGY

The PubMed database was reviewed for papers published until March 2021 using the terms "finerenone", "diabetes", and "kidney". The references of pertinent articles were also hand-searched for relevant papers. Only papers published in English were considered.

CLINICAL PHARMACOLOGY OF FINERENONE

The nonsteroidal MRA finerenone, initially called BAY 94-8862, is characterized by a very strong binding potential to the mineralocorticoid receptor [9]. Finerenone is an inverse agonist of the mineralocorticoid receptor whereas the steroidal MRAs spironolactone and eplerenone are partial agonists of this receptor [10]. Even though finerenone is mainly metabolized by CYP3A4 (90%), kidney function and serum albumin levels also affect serum levels of the drug, which is mostly excreted by the kidneys [10, 11]. Absorption is independent of food

intake and the half-life of finerenone, which has no active metabolites, is about 2 h [11, 12]. On the other hand, eplerenone, which also has no active metabolites, has a half-life of 4–6 h, whereas the active metabolites of spironolactone have half-lives of 14–16 h [13, 14]. Importantly, finerenone does not appear to have clinically relevant interactions with substrates of cytochrome P450 [15] and does not require dose modification in patients with mild or moderate hepatic impairment [16]. On the other hand, exposure to finerenone is increased in patients with moderate and severe renal impairment but not in those with mild renal impairment [17].

EFFECTS OF FINERENONE ON KIDNEY FUNCTION: ANIMAL STUDIES

Animal studies have shown that finerenone reduces albuminuria and has a positive impact on endothelial function and arterial elasticity through an increase in nitric oxide bioavailability [18, 19]. It was also reported that finerenone prevents progression of acute kidney injury to chronic kidney disease by exerting anti-inflammatory and antioxidant effects [20–22]. Furthermore, finerenone appears to improve glucose tolerance in high-fat diet-fed obese mice [23]. Notably, in rats with deoxycorticosterone acetate/salt-induced renal injury, finerenone was more effective than eplerenone in preventing glomerular, tubular, and vascular damage in the kidneys, in suppressing the renal expression of pro-inflammatory and profibrotic genes, and in reducing proteinuria [24].

EFFECTS OF FINERENONE ON DKD: CLINICAL STUDIES

Accumulating data support a role for finerenone in the management of DKD (Table 1). In an early randomized, double-blind study conducted at 148 sites in 23 countries, 823 patients with type 2 DM and DN who were on ACE-Is or ARBs were randomly assigned to receive finerenone (1.25, 2.5, 5, 7.5, 10, 15, or 25 mg/day) or matching placebo ($n = 94$) for 90 days [25]. Finerenone induced dose-dependent decreases in albuminuria, which were significant at doses of at least 7.5 mg/day [25]. Hyperkalemia leading to discontinuation of treatment was not observed in the placebo and finerenone 10-mg/day groups and occurred in 2.1%, 3.2%, and 1.7% of the finerenone 7.5-, 15-, and 20-mg/day groups, respectively [25]. The incidence of estimated GFR decrease of at least 30% or other adverse events did not differ between the placebo and finerenone groups [25]. In another multicenter, randomized, double-blind, placebo-controlled, phase 2b study in 96 Japanese patients with type 2 DM and DN who were treated with ACE-Is or ARBs, finerenone reduced albuminuria more than placebo at day 90 whereas the change in serum potassium levels was similar in the two groups; notably, no patient developed hyperkalemia [26]. More recently, the results of the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial were reported [27]. This double-blind, multicenter trial was conducted in 48 countries and randomized 5734 patients with type 2 DM and CKD (defined as urinary albumin-to-creatinine ratio (UACR) 30–300 mg/g, eGFR 25–60 ml/min/1.73 m^2, and a history of diabetic retinopathy or as UACR 300–5000 mg/g and eGFR 25–75 ml/min/1.73 m^2) treated with ACE-Is or ARBs at the maximum tolerated dose and with serum potassium level of at most 4.8 mmol/l to receive finerenone 20 mg/day (10 mg/day in patients with eGFR 25–60 ml/min/1.73 m^2) or placebo [27]. After a median follow-up of 2.6 years, the incidence of the primary outcome [a composite of kidney failure (defined as initiation of long-term dialysis for at least 90 days, kidney transplantation, or eGFR less than 15 ml/min/1.73 m^2), sustained decrease of at least 40% in the eGFR from baseline over a period of at least 4 weeks, or death from renal causes] was 18% lower in the finerenone group [27]. It was estimated that 29 patients had to be treated with finerenone for 3 years to prevent one primary outcome event [27]. Moreover, finerenone was associated with a 31% greater reduction in UACR than placebo [27]. The incidence of the key secondary

Table 1 Major randomized, double-blind, placebo-controlled studies evaluating the effects of finerenone on diabetic kidney disease

References	Number of patients	Follow-up	Efficacy	Safety
[25]	823	90 days	Finerenone induced dose-dependent decreases in albuminuria (significant at doses ≥ 7.5 mg/day)	Incidence of hyperkalemia leading to discontinuation of treatment in the finerenone 7.5-, 10-, 15-, and 20-mg/day and placebo groups: 2.1%, 0.0%, 3.2%, and 1.7%, respectively
[26]	96	90 days	Finerenone reduced albuminuria more than placebo	Similar changes in serum potassium levels in the finerenone and placebo groups No patient developed hyperkalemia
[27]	5734	2.6 years	The incidence of the primary outcome (kidney failure), sustained decrease ≥ 40% in the eGFR, or death from renal causes) was 18% lower in the finerenone group The incidence of the key secondary outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure) was 14% lower in the finerenone group Finerenone reduced albuminuria by 31% more than placebo	Incidence of hyperkalemia leading to treatment discontinuation in the finerenone and placebo groups: 2.3% and 0.9%, respectively Incidence of serum potassium levels > 5.5 mmol/l in the finerenone and placebo groups: 21.7% and 9.8%, respectively

outcome (a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure) was also 14% lower in patients treated with finerenone [27]. The reduction in cardiovascular events was similar in patients with established cardiovascular disease (CVD) and in those without CVD [28]. Finerenone reduced blood pressure by 2.1/0/9 mmHg more than placebo whereas body weight and HbA_{1c} did not differ between the two groups [27]. On the other hand, the incidence of hyperkalemia leading to treatment discontinuation was higher in patients treated with finerenone 20 mg/day (10 mg/day in patients with eGFR 25–60 ml/min/1.73 m^2) (2.3% vs. 0.9% in the placebo group) and the incidence of serum potassium levels greater than 5.5 mmol/l was also higher in the former (21.7% vs. 9.8% in the placebo group) [27]. To prevent hyperkalemia, patients with serum potassium level of 4.8 mmol/l or below were excluded from the study, patients with eGFR 25–60 ml/min/ 1.73 m^2 received a lower dose of finerenone (10 mg compared with 20 mg in patients with eGFR 61–75 ml/min/1.73 m^2), and serum potassium levels were frequently monitored [27]. Notably, in a recent meta-analysis, the combination therapy of finerenone plus ACE-Is or ARBs was not associated with hyperkalemia whereas spironolactone and eplerenone increased the risk for hyperkalemia by 4.58 and

2.81 times, respectively, when combined with ACE-Is or ARBs [29]. The ongoing Finerenone in Reducing CV Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial will evaluate the effects of finerenone on cardiovascular and renal events in 7437 patients with type 2 DM and less advanced CKD [30].

EFFECTS OF FINERENONE IN HEART FAILURE

In addition to its beneficial effects on renal function, finerenone also appears to exert cardioprotective actions. In animal models, finerenone was shown to prevent myocardial fibrosis and remodeling by attenuating the expression of connective tissue growth factor and transforming growth factor-β [31] and also to improve myocardial diastolic dysfunction [32, 33]. Importantly, finerenone reduced cardiac hypertrophy and brain natriuretic peptide (BNP) levels more than eplerenone did; moreover, finerenone improved systolic and diastolic left ventricular function whereas eplerenone had no effect [24]. In addition, in a mouse model of cardiac fibrosis induced by short-term isoproterenol injection, cardiac fibrosis and macrophage invasion were blocked by finerenone, whereas eplerenone had no effect [34]. Clinical studies also reported promising results. In a randomized study in 392 patients with heart failure and reduced ejection fraction and mild to moderate CKD, finerenone reduced BNP levels as much as spironolactone but was associated with smaller increase in serum potassium concentration and lower incidence of hyperkalemia than the latter [35]. In another randomized study in 1066 patients with worsening heart failure and reduced ejection fraction and CKD and/or DM, finerenone was similarly effective with eplerenone in reducing BNP levels and was associated with comparable rates of hyperkalemia with the latter [36].

CONCLUSIONS

Finerenone appears to delay the progression of DKD and might also reduce the risk of cardiovascular events in this high-risk population. Even though finerenone increases the incidence of hyperkalemia, it appears to be safer than other MRAs. However, close follow-up is required in patients treated with a combination of finerenone and ACE-Is or ARBs. The results of the ongoing FIGARO-DKD trial will provide additional insight into the role of finerenone in the management of DKD.

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