



Renoprotective Effect of the Mineralocorticoid Receptor Antagonist Esaxerenone

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Background: The effects of mineralocorticoid receptor antagonists, including the newly introduced esaxerenone, on renal function remain uncertain.

Methods and Results: This retrospective study was performed on patients who received esaxerenone for resistant hypertension between November 2019 and June 2020. Trends in the estimated glomerular filtration rate (eGFR) were compared between the 6-month period before esaxerenone treatment (pre-treatment period) and the 6-month treatment period on esaxerenone. Twenty-six patients (15 men), with a median age of 70 years (interquartile range [IQR] 51–73 years) and a median systolic blood pressure of 146 mmHg (IQR 139–156 mmHg), were included in the study and completed 6 months of esaxerenone therapy without any adverse events. eGFR decreased significantly during the pre-treatment period (from 66.6 to 59.5 mL/min/1.73 m²; P=0.003), whereas eGFR was unchanged during the treatment period (from 59.5 to 61.8 mL/min/1.73 m²; P=0.15). The median change in eGFR differed significantly between the treatment and pre-treatment periods (3.8 [IQR –4.2, 6.8] vs. –6.1 [IQR –11.1, 1.8] mL/min/1.73 m², respectively; P=0.008).

Conclusions: Esaxerenone may have renoprotective effects when administered to treat hypertension. Further studies are needed to understand which patient populations may see greater renoprotective benefits with esaxerenone.

Key Words: Blood pressure; Chronic kidney disease; Mineralocorticoid receptor antagonist

Patients with hypertension refractory to various anti-hypertensive agents, including β -blockers, renin-angiotensin system (RAS) inhibitors, and diuretics, are clinically challenging to manage.^{1–3} Mineralocorticoid receptor antagonists (MRAs) are tried in cases of such refractory hypertension. However, conventional MRAs, including spironolactone and eplerenone, can cause sex hormone-related adverse events and hyperkalemia, necessitating discontinuation.^{4,5} Furthermore, these medications may have a negative effect on preserving renal function.⁶ Of note, eplerenone is contraindicated for those with an estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m².^{1,2} The interplay of untreated hypertension and chronic kidney disease can make clinical management very challenging.⁷

Esaxerenone is a recently introduced MRA that specifically inhibits excessive mineralocorticoid receptor activity.⁸ A recent Phase III study demonstrated that adding esaxerenone to existing RAS inhibitors in patients with Type 2 diabetes and microalbuminuria improved albuminuria.⁹ We hypothesized that mid-term esaxerenone therapy may

suppress the gradual progression of renal impairment and, in the present study, investigated the effect of esaxerenone therapy on the preservation of eGFR by comparing a period prior to esaxerenone therapy (pre-treatment period) to a period on esaxerenone among a hypertensive cohort.

Methods

Patient Selection

Consecutive patients who received esaxerenone for the treatment of resistant hypertension between November 2019 and June 2020 were considered for inclusion in this retrospective study. Patients with an eGFR <30 mL/min/1.73 m² or those with serum potassium >5.0 mEq/L were not given esaxerenone. Patients with malignancy or secondary hypertension were excluded from the study. Patients without comprehensive clinical data obtained at 3 time points (in the 6 months before esaxerenone, at baseline, and after 6 months esaxerenone treatment) were also excluded. The study protocol was approved by the University of Toyama Ethics Committee (No. RCOI2019584). All participants

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provided written informed consent beforehand.

Clinical Management

All patients were managed at every clinic visit once per month. Clinical decisions to administer esaxerenone and

Table 1. Baseline Characteristics	
Demographics	
Age (years)	70 [51–73]
Male sex	15 (58)
Body surface area (m ²)	1.63 [1.55–1.78]
Atrial fibrillation	6 (23)
Heart failure	6 (23)
Ischemic heart disease	2 (8)
Diabetes	5 (19)
Hemodynamics	
SBP (mmHg)	146 [139–156]
DBP (mmHg)	81 [73–93]
Heart rate (beats/min)	77 [67–92]
Medications	
β-blocker	10 (38)
ACEI/ARB	20 (77)
Calcium channel blocker	15 (58)
Diuretics	9 (35)
Laboratory data	
Serum potassium (mEq/L)	4.1 [3.8–4.3]
UACR (mg/g creatinine)	26.5 [22.5–31.5]
eGFR (mL/min/1.73m ²)	59.5 [49.7–70.5]

Data are given as the median [interquartile range] or as n (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor II antagonist; DBP, diastolic blood pressure; SBP, systolic blood pressure; UACR, urinary albumin-to-creatinine ratio.

its dose were at the discretion of the attending physicians, and esaxerenone therapy was performed according to the institutional protocol of the Second Department of Internal Medicine, University of Toyama, as described below.

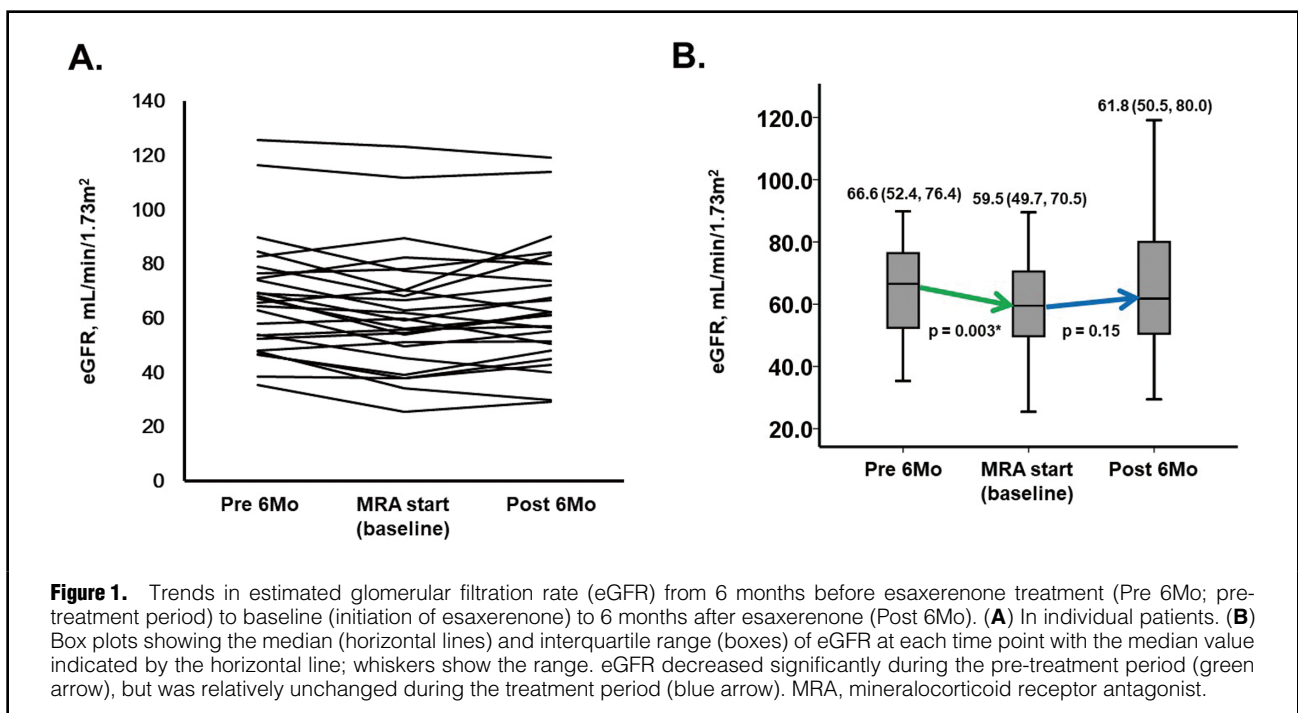
Esaxerenone was initiated at a dose of 2.5 mg/day, except in patients with an eGFR between 30 and 60 mL/min/1.73 m², in whom esaxerenone was initiated at a dose of 1.25 mg/day. Systemic blood pressure (SBP) and serum potassium concentrations were followed up at least once per month. When the serum potassium concentration exceeded 5.0 mEq/L, down-titration of the dose of esaxerenone was considered. When serum potassium concentrations exceeded 5.5 mEq/L, stopping esaxerenone was considered.

Data Collection

Information on patient demographics, medications, hemodynamics, and laboratory data, including eGFR, serum potassium concentrations, and the urinary albumin-to-creatinine ratio (UACR), at the time of esaxerenone initiation (which was defined as baseline), was retrieved from patient records. Similarly, laboratory data were retrieved 6 months before and after the initiation of esaxerenone. The primary outcome in this study was the trend in eGFR during the observational period (i.e., during the pre-treatment period, at baseline, and then after 6 months treatment).

Statistical Analyses

Continuous variables are presented as median values with the interquartile range (IQR). Categorical variables are presented as numbers and percentages. Trends were assessed using the Friedman test and ad hoc Wilcoxon signed-rank test or the Cochran Q test and ad hoc McNemar test. Logistic regression analyses were used to investigate factors associated with any increases in eGFR during esaxerenone therapy. Variables with P<0.10 in the univariate analysis were included in the multivariate analysis.



Statistical analyses were performed using SPSS Statistics 22 (IBM Corp., Armonk, NY, USA). Two-sided $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

In all, 26 patients (median age 70 years [IQR 51–73 years]; 15 men) were included (Table 1). Six patients had heart failure, 6 had atrial fibrillation, and 5 had diabetes. All patients had hypertension; the median SBP was 146 mmHg (IQR 139–156 mmHg). Eight patients were receiving ≥ 3 antihypertensive agents. No patients had received MRAs previously. The Median eGFR was 59.5 mL/min/1.73 m² (IQR 49.7–70.5 mL/min/1.73 m²) and the median serum potassium concentration was 4.1 mEq/L (3.8–4.3 mEq/L).

Esaxerenone was administered at a dose of 2.5 mg/day in 16 patients and at 1.25 mg/day in 10 patients. All patients continued esaxerenone therapy for the entire 6-month observational period without any obvious adverse events.

Trends in eGFR (Primary Outcome)

Trends in eGFR in individual patients during the entire study period are shown in Figure 1A. During the 6-month period prior to the initiation of esaxerenone, eGFR decreased significantly from 66.6 to 59.5 mL/min/1.73 m² ($P = 0.003$; Figure 1B), with the median change in eGFR being -6.1 mL/min/1.73 m² (IQR $-11.1, 1.8$ mL/min/1.73 m²; Figure 2).

eGFR did not change during the 6-month period when patients were on esaxerenone: from 59.5 to 61.8 mL/min/1.73 m² ($P = 0.15$; Figure 1B). The median change in eGFR was 3.8 mL/min/1.73 m² (IQR $-4.2, 6.8$ mL/min/1.73 m²; Figure 2), which was significantly higher than the change during the pre-treatment period ($P = 0.008$).

Trends in Other Data

SBP decreased significantly following the initiation of esaxerenone ($P = 0.034$; Table 2); however, the prescription rates of antihypertensive agents remained unchanged ($P > 0.05$ for all). Serum potassium concentrations increased significantly from 4.1 to 4.2 mEq/L ($P = 0.013$) after the initiation of esaxerenone, but no patient had serum potassium

> 5.0 mEq/L during esaxerenone therapy. UACR did not change during the pre-treatment period ($P = 0.10$), but decreased significantly following the initiation of esaxerenone ($P = 0.001$).

Factors Associated With Any Increases in eGFR

Among all baseline variables, a smaller body surface area ($P = 0.053$) and the dose of esaxerenone ($P = 0.040$) were significantly associated with any increases in eGFR. In the multivariate analysis, the association of these two variables with any increase in eGFR did not reach statistical significance ($P = 0.059$ and $P = 0.051$ for body surface area and dose of esaxerenone, respectively).

Discussion

In this study we investigated the effect of esaxerenone

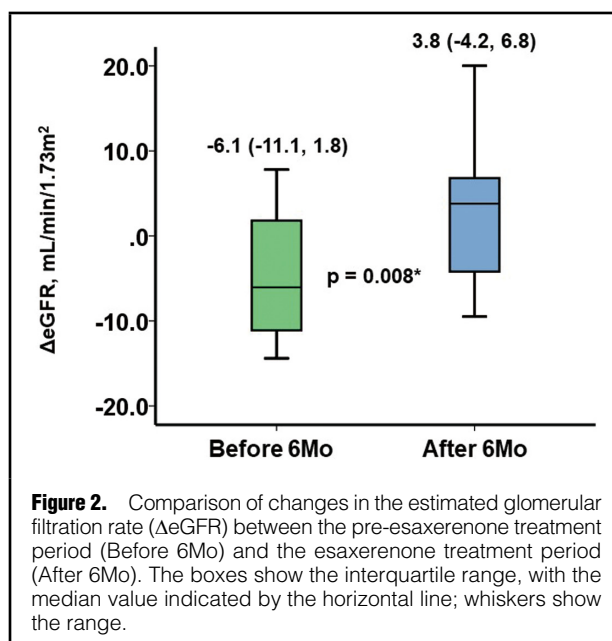


Figure 2. Comparison of changes in the estimated glomerular filtration rate (Δ eGFR) between the pre-esaxerenone treatment period (Before 6Mo) and the esaxerenone treatment period (After 6Mo). The boxes show the interquartile range, with the median value indicated by the horizontal line; whiskers show the range.

Table 2. Trends in Clinical Variables From 6 Months Before Esaxerenone Treatment (Pre 6Mo) to Baseline (Initiation of Esaxerenone) to 6 Months After Esaxerenone (Post 6Mo)				
	Pre 6Mo	Baseline	Post 6Mo (on MRA)	P value
Hemodynamics				
SBP (mmHg)	137 [128–162]	146 [139–156]	134 [126–144]	0.034*
DBP (mmHg)	84 [71–91]	81 [73–93]	79 [68–88]	0.26
Heart rate (beats/min)	75 [69–85]	77 [67–92]	76 [71–84]	0.15
Medications				
β -blocker	10 (38)	10 (38)	8 (31)	0.37
ACEI/ARB	19 (73)	20 (77)	18 (69)	0.37
Calcium channel blocker	17 (65)	15 (58)	15 (58)	0.61
Diuretics	9 (35)	9 (35)	8 (31)	0.85
Laboratory data				
Serum potassium (mEq/L)	4.1 [4.0–4.3]	4.1 [3.8–4.3]	4.2 [4.1–4.4]	0.013*
UACR (mg/g creatinine; n=16)	26.5 [24.0–30.0]	26.5 [22.5–31.5]	22.5 [20.0–25.0]	$< 0.001^*$

Data are given as the median [interquartile range] or as n (%). MRA, mineralocorticoid receptor antagonist. Other abbreviations as in Table 1. * $P < 0.05$.

therapy on renal function in patients with hypertension. The major findings of the study were that: (1) esaxerenone decreased blood pressure without any adverse events during the 6-month observation period; (2) the median change in eGFR was significantly higher during the 6-month therapeutic period on esaxerenone than during the pre-treatment period; and (3) UACR decreased significantly following the initiation of esaxerenone.

Efficacy and Safety of Esaxerenone Therapy

SBP decreased by 12 mmHg during the 6-month period of esaxerenone therapy in this study. This is relatively lower than the 18-mmHg decrease reported in a study that included patients with chronic kidney disease¹⁰ and the 17-mmHg decrease reported in the Phase III study that included patients with normal kidney function.⁹ This discrepancy may stem from a relatively lower baseline SBP (median <150 mmHg) in the present study. A median SBP of 134 mmHg during the post-treatment period would be an acceptable value to prevent an increase cardiovascular disease risk.^{1,2}

Hyperkalemia is a well-known adverse event and a leading cause of the discontinuation of MRAs.⁴ The incidence of hyperkalemia during esaxerenone therapy is quite low. In the Phase III study that included patients with diabetic kidney disease, serum potassium increased only 0.2 mEq/L during the esaxerenone therapy.¹⁰ In that study, esaxerenone was discontinued in only 4% of patients. In the present study, the median increase in serum potassium concentrations was 0.1 mEq/L, and no patient discontinued esaxerenone. Another study including patients with chronic kidney disease reported comparable results.¹⁰ Lower baseline eGFR and higher baseline serum potassium concentrations are reported to be risk factors for hyperkalemia during esaxerenone therapy.⁹

Effect of Esaxerenone Therapy on Renal Function

Albuminuria is associated with the development of end-stage kidney disease.¹¹ A treatment-related reduction in albuminuria reduces the risk of end-stage kidney disease.¹² Therefore, a change in albuminuria is considered as a surrogate marker of kidney function. Spironolactone and eplerenone decrease albuminuria, although both these agents increase the risk of hyperkalemia, thus leading to premature discontinuation.⁴ As observed in the present study, previous Phase IIb and Phase III studies have demonstrated that esaxerenone reduces albuminuria and is associated with few adverse events, namely hyperkalemia, independent of the degree of blood pressure reduction.^{9,13}

In this study we observed a relative improvement in eGFR during the 6-month period of esaxerenone therapy compared with the 6-month pre-treatment period. This study was designed based on the concept that eGFR declines gradually. Consistently, a Phase III study observed a statistically comparable trend in eGFR between the esaxerenone arm and the placebo arm.⁹

Further studies are needed to analyze the mechanism of the potential renoprotective effects of esaxerenone. Given the initial drop in eGFR observed during a 12-week period of esaxerenone therapy in the Phase III study,⁹ an improvement in glomerular hyperfiltration may be a major mechanism.¹⁴ Understanding the comparative differences in renoprotective effects among different MRAs remains an area in need of further study. Determining which patients are most likely to benefit from specific MRAs requires

further large prospective clinical trials. Given our findings, aggressive up-titration of esaxerenone, if tolerable, may be an option for resistant hypertension while also allowing for a unique renoprotective effect.

Study Limitations

In this small study we examined comprehensive clinical data obtained 6 months before and after the initiation of esaxerenone. This is a proof-of-concept study for the newly introduced MRA esaxerenone. Further larger-scale studies are needed to validate our findings. We lack monthly trends in clinical data, including eGFR and urinalysis. We performed intragroup comparisons (pre- vs. post-treatment) but lacked a control group. Although the medications remained unchanged during both periods, nevertheless there may have been uninvestigated confounders or covariates that may have had unmeasured clinical effects. In our study, most patients did not have diabetes or proteinuria and had relatively preserved renal function (>60 mL/min/1.73 m²). Our findings are not generalizable to those patient subsets.

Conclusions

Esaxerenone may have renoprotective benefits when administered for the treatment of resistant hypertension. Further studies are needed to understand the ideal patient subset that may experience clinical benefit from esaxerenone.

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None.

Disclosures

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IRB Information

This study was approved by the University of Toyama Ethics Committee (No. RCOI2019584).

Data Availability

The deidentified participant data will not be shared.

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