INVESTIGATING THE IMPACT OF FINERENONE ON RETINAL VASCULAR DYSFUNCTION IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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ALEXANDRIA UNIVERSITY

Suggested Proposal

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Degree: PhD Department: Clinical Pharmacy and Pharmacy Practice

Specialty: Clinical Pharmacy

Proposed Thesis Title:

Investigating the impact of finerenone on retinal vascular dysfunction in patients with chronic kidney disease

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Proposal Supervisor Committee:

Name	Position	Affiliation	Signature
Prof. Dr. Labiba Khalil El-Khordagui	Professor of Pharmaceutics	Faculty of Pharmacy, Alexandria University	
Prof. Dr. Ahmed Fathi El-keraie	Professor of Internal Medicine	Faculty of Medicine, Alexandria University	
Prof. Dr. Ahmed Abdelkareem El-Masry	Professor of Ophthalmology	Faculty of Medicine, Alexandria University	
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Assoc. Prof. Noha Alaa Eldine Hassan Hamdy	Associate Professor of Clinical Pharmacy	Faculty of Pharmacy, Alexandria University	

Role of Supervisors:

Name	Role
Prof. Dr. Labiba Khalil El-Khordagui	• Main supervisor • Supervise the implementation of the research protocol • Assist the researcher in analyzing the results • Review of the writing of the thesis
Prof. Dr. Ahmed Fathi El-keraie	• Follow up on all matters related to the selection of patients and their inclusion in the study and recording their data. • Help the researcher in measuring the parameters to be measured as proposed in the protocol. • Participate in the development and implementation of work plan.
Prof. Dr. Ahmed Abdelkareem El-Masry	• Follow up on all matters related to the selection of patients and their inclusion in the study and recording their data. • Help the researcher in measuring the parameters to be measured as proposed in the protocol. • Participate in the development and implementation of work plan.
Prof. Dr. Ahmed Fawzy El-Yazbi	• Providing guidance on the pharmacological rationale for using finerenone in CKD patients. • Offering consultation on interim analyses when needed. • Providing mentorship, fostering a robust academic and research environment. • Assisting in the interpretation of study results and contributing to the preparation of manuscripts for peer-reviewed journals or conference presentations.
Assoc. Prof. Noha Alaa Eldine Hassan Hamdy	• Follow up with the researcher • Help in overcoming the obstacles encountered, analyzing the results and performing the appropriate statistical analysis. • Help the researcher in arranging the results and writing the thesis.

Introduction

It has been observed that kidneys and eyes are significantly interlinked, due to the substantial overlaps in pathways of development, structural anatomy, physiological and pathological characteristics (Wong et al., 2014, Elias et al., 2016). For instance, the glomerulus and choroid possess comparable vascular circulation, and similar pathological mechanisms are involved in the development of CKD and many ocular disorders, such as oxidative stress, inflammation, atherosclerosis, endothelial dysfunction and vascular remodeling (Nusinovici et al., 2019). Additionally, both diabetic and non-diabetic kidney disease patients have been characterized by lower thickness of peripapillary and parafoveal retinal nerve fiber layer (RNFL), peripapillary choroidal, and central macular thickness (Balmforth et al., 2016, Basiony et al., 2023, Zeng et al., 2021). The risk of retinal vascular disease (RVD), major eye diseases and impaired vision has been shown to be significantly increased in patients with CKD (Grunwald et al., 2010, Jonas et al., 2017, Lin et al., 2021).Vision impairment and visual loss can be caused by RNFL defects (RNFLDs) ,which can be non-invasively detected using fundus photography or optical coherence tomography (OCT), and significantly associated with other systemic conditions including CKD (Wan et al., 2024). Accordingly, it has been suggested that ocular manifestations have been shown to be the mirror of CKD development (Benitez-Aguirre et al., 2012, Wong et al., 2004).

Finerenone, a novel orally administered selective non-steroidal MRA demonstrates stronger affinity to the mineralocorticoid receptor (MR) in comparison with eplerenone and spironolactone resulting in better efficacy in aldosterone's inhibition (Palanisamy et al., 2022). As demonstrated by FIDELIO-DKD (NCT02540993; n = 5674) and FIGARO-DKD (NCT02545049; n = 7352) randomized phase 3 trials, slower progression of CKD and reduced risk of cardiovascular outcomes were associated with administration of finerenone versus placebo in patients with CKD and type 2 diabetes (T2D) (Bakris et al., 2020, Pitt et al., 2021). Based on these trials, clinical practice guidelines recommended finerenone as part of the pharmacological treatment to prevent kidney disease progression and cardiovascular events in CKD patients with T2D (de Boer et al., 2022, Blonde et al., 2022). Regarding non-diabetic CKD patients, FIND-CKD trial, a phase 3 randomized controlled trial of finerenone in patients with CKD of non-diabetic etiology, verified the safety and efficacy of finerenone in this population (Heerspink et al., 2024). According to a recent comprehensive review, finerenone possesses different or superior multiple mechanisms of action to traditional MRAs as indicated by both animal and cell-based studies (Zhai et al., 2024).

Regarding vision-threatening complications, it was proven using a mouse model of oxygen-induced retinopathy (OIR) that finerenone reduced the retinal levels of IL-1β, ICAM-1 and VEGF, vascular leakage, retinal neovascularization as well as the density of retinal microglial cells, while increasing regulatory T cells (Tregs) in the retina, spleen and blood (Jerome et al., 2023). Finerenone has demonstrated beneficial effects in the retina of rodents with diabetes and ischemic retinopathy, reducing the hallmark features of vision-threatening vascular injury including neovascularization, in addition to alleviating retinal inflammation (Jerome et al., 2023). Moreover, positive effects were achieved in patients with non-proliferative diabetic retinopathy according to pooled analysis of two studies from clinical trial participants (ReFineDR/DeFineDR) (Rossing et al., 2023). However, definitive conclusions could not be drawn as the study was exploratory in nature and based on routine ophthalmological examinations. Data reported so far suggest that finerenone might be a potential novel oral treatment for patients suffering from retinal vascular dysfunction. This can be further confirmed by more randomized clinical trials with adequate power based on more comprehensive and accurate functional and structural assessments of retinopathy.

AIM OF THE STUDY

To examine the potential protective effects of finerenone compared to standard treatment (based on patient's symptoms and condition) on retinal vascular dysfunction in CKD patients.

PLAN OF THE STUDY

Study setting: CKD Patients will be recruited from the outpatients' clinics and/or inpatients wards in Alexandria University hospitals and other private hospitals (if possible).
Study design: Open labelled, prospective, two-arm, parallel group, non-placebo controlled clinical trial. Included patients will be divided into 2 parallel groups randomly.

Treatment arm: will receive oral finerenone in addition to standard treatment.

Initial dose of finerenone will be determined according to eGFR:

eGFR>= 60 mL/min: 20 mg once daily.

eGFR>25 mL/min, <60 mL/min: 10 mg once daily

eGFR<15 mL/min: use is contraindicated

Maintenance dose will be determined by the serum potassium level measured 4 weeks after initiation of therapy or dose adjustment according to CKD progression.

Control arm: will receive standard treatment according to patient's condition and symptoms.

Type of the trial: Open labelled randomized controlled clinical trial with parallel design.

Inclusion and exclusion criteria

Inclusion criteria

- ✓ Age: above 18 years
- ✓ Diabetic and non-diabetic non-hemodialysis CKD patients (Stage 2 – Stage 4).

Exclusion criteria

- ✓ Patients on hemodialysis (HD).
- ✓ Serum potassium level > 5.5 mEq/L
- ✓ Prior/planned ocular interventions (retinal laser treatment, intravitreal injection or vitrectomy).
- ✓ Pregnant and lactating women
- ✓ Malignancy

Target population: CKD patients.

Sample size: Will be calculated using suitable software to achieve the study objective

Outcome assessment:

Primary outcomes

To elucidate the difference in field vision and optical coherence tomography (OCT) metrics 1 month, 3 months and 6 months after treatment initiation compared to baseline findings; OCT metrics include macular thickness and retinal nerve fiber layer (RNFL) thickness.

Secondary outcomes

- To examine the effect on eGFR slope, defined as the mean rate of change in eGFR from baseline to month 6 of treatment.
- Mean change from baseline scores of routine laboratory investigations of CKD patients including serum creatinine, urea, uric acid, urinary albumin to creatinine ratio (ACR), complete blood count (CBC), and serum albumin.
- Mean change from baseline values of metabolic parameters including random blood glucose (RBG), glycated hemoglobin (HbA1C), lipid profile and liver enzymes (ALT and AST) in addition to mean change in body weight.
- To examine the metabolic regulatory effects exhibited by finerenone by measuring the mean change from baseline levels of adipokine leptin.
- Safety will be assessed at all scheduled visits and includes assessment of vital signs and adverse events. Hyperkalemia is an adverse event of special interest in this study. Serum potassium and hyperkalemia will be characterized through monitoring the change from baseline in serum potassium and identification of the number of patients with serum potassium levels >5.5 mmol/L and >6.0 mmol/L.

Type of sample and method of selection:

Ocular examinations will be performed by expert ophthalmologists in addition to blood and urine samples that will be collected at baseline and after the follow-up duration to conduct laboratory investigations.

Data collection methods and tools:

Screening of patients according to the inclusion and exclusion criteria. Included patients will be interviewed to gather their demographic data, full patient history (medical and medication history) and assessment of their baseline characteristics.

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RESEARCH TIME LINE

Objective	Activities	Months				
		1-3	3-6	6-9	9-12	>12
Ethical considerations	• The researcher will seek the approval of the Ethics Committee of Alexandria University for conducting the research. • The researcher will comply with the International Guidelines for Research Ethics and declaration of Helsinki. • The researcher declares that there is no conflict of interest.	√				
Profiling of patients	• Screening of patients and collection of demographic data. • Recruitment of patients based on specific inclusion and exclusion criteria. • Patients divided randomly into 2 parallel groups (control versus intervention). • Samples collection from patients to determine baseline levels of selected parameters. • Follow-up of patients and re-measurement of selected parameters after completion of follow up duration	√	√	√		
Results	Statistical analysis will be conducted based on the results of the follow-up				√	
Documentation and publication of results	Writing thesis Publishing paper in scientific journal					√