Study Protocol

Official Title:

Study of the Cardio Renal Effects of SGLT2 Inhibitors Among Diabetic and Non-diabetic Lupus Nephritis Patients

ClinicalTrials.gov Identifier (NCT Number):

NCT05748925

Date of Document:

May 11, 2024

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Study of the cardio renal effects of SGLT2 inhibitors among diabetic and non-diabetic lupus nephritis patients.

Thesis submitted as partial fulfillment of M.D in Nephrology

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2021

Introduction

Sodium-glucose cotransporter 2 inhibitors have been the recent focus in a large number of diseases, not only type 2 diabetes but also congestive heart failure and chronic kidney disease. (1)

Latest studies show that sodium-glucose cotransporter 2 inhibitors originally approved for glycemic control in patients with type 2 diabetes (2).

SGLT2i also exert protective renal effects independently from their effects on blood glucose level (2).

Recently it is obvious that SGLT2i treatment can be effective in patients with non-diabetic chronic kidney disease, including primary and secondary glomerular diseases. (3)

Glomerular diseases can result from either immune or nonimmune mediated damage, it appears that SGLT2i would not target the mechanism of immune-mediated glomerular diseases; it may improve the source of injury from the original glomerular damages. (4)

It is still not obvious at what point of the mechanism of specific glomerular diseases (either immune or nonimmune mediated) SGLT2i can be beneficial. So, more studies targeting nondiabetic primary and

secondary glomerular diseases are ensured to assess the efficacy and safety of SGLT2i in patients with glomerular diseases. (4)

SLE is a chronic inflammatory disease that has renal effect in about half of patients. Lupus nephritis is a major risk factor for morbidity and mortality in patients with SLE, and in spite of strong anti-inflammatory and immunosuppressive therapies still ends in CKD or ESRD. (5)

Based on this observation, we aim to determine the effect of SGLT2i treatment in patients with glomerulonephritis secondary to SLE who either is diabetic or non-diabetic.

Aim of the work

This study aims to assess SGT2i role in regression of ongoing kidney and cardiac diseases among lupus nephritis patient either diabetic or non-diabetic under different immunosuppressive therapy.

Patients and methods

Technical design:

Study sitting: .1

Nephrology and renal transplant unit at urology and nephrology center in Mansoura University.

It will include 100 patients with lupus nephritis, Diagnosis of glomerulonephritis was performed by renal biopsy, and all of the renal biopsies were carried out at urology and nephrology center.

Patients with an estimated glomerular filtration rate (eGFR) >30 ml/min/1.73m2 will be randomized into two groups

- Study group will receive SGLT2i inhibitor as add on drug or replace another drug according to patient clinical situation, Dapagliflozin 10 mg and 25 mg will be used once daily with or without food.
- Control group will be maintained on placebo.

The primary endpoint will be sustained decline in eGFR ≥50%, ESKD, or kidney or cardiovascular death

We will follow up all patients for 12 months and compare their results.

2. Inclusion criteria:

1. Patients aged more than 16 year.
2. Willing to sign informed consent.
3. Diagnosis of SLE according to EULAR/ACR classification criteria.
4. Renal biopsy showed lupus nephritis.
5. Patient with eGFR > 30 ml/min/1.73m2 by cockcroft-gault equation.

3. Exclusion criteria:

1. Patients with eGFR <30 ml/min per 1.73 m2.
2. Current pregnancy or lactation.
3. Medical history of chronic disease (CLD, cancer, severe respiratory distress, gastrointestinal tract lesions).
4. Patients refusing to participate in the study or lost follow up.
5. Evidence of urinary obstruction of difficulty in voiding at screening.

6. Patients who are receiving high dose diuretics or combined ACEI, ARBS.

7. Patients who have frequent hypotensive episode or SBP <100 mmHg.

Operational design:

Study Protocol:

- Patients included in the study will treated with dapaglifilozin initiated at a total daily dosage of 10 mg/kg per day.

Study design:

Type of the study: randomized controlled study.

The following data will be gathered and evaluated for all patients:

I-before intervention:

1. Serum creatinine, Creatinine clearance.
2. 24 hour urine protein, urine protein/creatinine ratio.
3. Urine analysis.
4. HBA1c.
5. HGB.
6. Uric acid and lipid profile.
7. Lupus serology.

II-after intervention: All patients will be evaluated monthly regarding:

.1 Serum creatinine, creatinine clearance.

.2 24 hour proteinuria, protein/creatinine ratio.

.3 Fasting, random and postprandial glucose levels.

.4 CNI trough level if used.

.5 Urine analysis.

.6 HGB level.

.7 Uric acid, lipid profile.

.8 Lupus serology.

.9 **Cardiovascular assessment:**

ECCHO.

Atherosclerosis and vascular calcification incidence (NCCT model).

Regular measurement of blood pressure each visit.

Outcomes:

1. Effect of dapagliflozin compared to placebo on eGFR.
2. Effect of dapagliflozin compared to placebo on systolic/diastolic blood pressure.
3. Effect of dapagliflozin compared to placebo on body weight.
4. Safety of dapagliflozin vs. placebo - the number of hypoglycemia episodes between groups and serious adverse events.

Statistical Analysis:

Qualitative data were displayed in cross tabulations, and quantitative data were described in terms of arithmetic mean ± SD. Bivariate techniques were used for initial evaluation of contrasts. Thus, the chi-square and Fisher's exact tests were used for comparisons of frequencies of qualitative variables; the Mann-Whitney test and the unpaired t-test were used for comparisons of means of two quantitative variables. A p-value <0.05 was considered significant. Graft and patient survival rates were assessed using the Kaplan-Meier method. All analyses were carried out using the computer package SPSS for windows, release 16 SPSS Inc. Chicago, III, USA.

Administrative design •

Informed consent will be obtained from all subjects and the approval will be obtained from institutional review board (IRB) in Faculty of Medicine, Mansoura University. There is no funding.

Research question

The main research question is: Does use of SGLT2i will show superiority over conventional lines of treatment of lupus nephritis patient as regard efficacy and safety.

Rationale and justification

The rational of this study is that SGLT2i are now one of the common lines in regression of chronic kidney disease either is diabetic or not.

Large trials on this issue exclude patient with glomerulonephritis, so we will study its renal efficacy in patient with secondary glomerulonephritis to SLE to prove their efficacy and safety in this group of patients.

Objectives

The main objective of this study is to:

- To compare use of SGLT2i versus standard care in regression of chronic kidney disease in patient with LN.
- To study the safety and efficacy of this drug group with use of immunosuppression and possible interaction.

Hypothesis

SLE is the one of the leading causes of secondary glomerulonephritis. Despite the use immunosuppressive and antiproteinuric drugs, a number of patients are at risk of progressing to end-stage kidney disease. Additional therapies to slow kidney function decline are highly desired. The DAPA-CKD trial demonstrated that the sodium glucose co-transporter 2 inhibitor dapagliflozin significantly reduced the risk of kidney failure and prolonged survival in participants with chronic kidney disease with and without type 2 diabetes. The DAPA-CKD population excluded patients with lupus nephritis, so we determined the long-term efficacy and safety of dapagliflozin on major kidney and cardiovascular outcomes in these patients.

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