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ERA Long-Term Research Fellowship Project

ERAKI

Project's key info

Title of the project	**SGLT-2 inhibitors to prevent Acute Kidney Injury**
Working Group involved in the project	European Renal Acute Kidney Injury Working Group (ERAKI)
Principal Investigator(s) of the project	Marlies Ostermann (United Kingdom)
Duration	12 months
Fellowship Grant	3.050,00 €
Start of the fellowship	Within 6 months after notification of the grant award to the fellow.

Receiving Institute

Name of receiving institute	Guy's & St Thomas' Hospital London, UK
Supervisor's name	Marlies Ostermann (United Kingdom)
Supervisor's e-mail address	Marlies.Ostermann@gstt.nhs.uk

Project's detailed description

Project description

During critical illness, 1 in 2 patients develop AKI during their stay in the Intensive Care Unit (ICU). AKI is associated with serious short and long-term complications, increases the risk of mortality, is associated with high healthcare costs, and has been recognised as a global health burden. The prevention of the development and progression of AKI is essential to reduce the downstream long-term complications. Despite the frequency and seriousness, there are currently no targeted pharmacotherapies to mitigate the harm from AKI. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors block the reabsorption of filtered glucose in the renal proximal tubule. Large cardiovascular trials and studies in patients with COVID-19 have shown a reduction in the risk of AKI in patients treated with SGLT-2 inhibitors. The hypotheses for the reno-protective effects of SGLT-2 inhibitors mainly focus on the reduction of renal hyperfiltration and improvement of renal cortical hypoxia. The latter effect is particularly relevant in AKI during critical illness. However, it is also known that SGLT-2 inhibitors can cause a temporary creatinine rise and euglycaemic ketoacidosis. In response to a trial of SGLT-2 inhibitors in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19 study), an editorial in the Clinical Journal of American Society of Nephrology emphasized the urgent need for a clinical trial to examine the effects of SGLT-2 inhibitors in acutely unwell patients with risk of AKI (PMID: 35483735). If such a trial was successful, it would have important health benefits for high-risk patients, including a reduced risk of chronic kidney disease, long-term dialysis dependency and cardiovascular complications and improved quality of life. Similarly, if the trial showed more harm than benefit, the medication would be routinely discontinued during critical illness.

Hypothesis: Among patients in the ICU who are at high risk of developing new AKI or progressive AKI, treatment with the SGLT-2 inhibitor dapagliflozin compared to placebo reduces the relative

risk of the occurrence of a major adverse kidney event (MAKE) at 30 days where MAKE is a composite end point of doubling of serum creatinine, requirement for renal replacement therapy (RRT) or death within 30 days of randomisation.

Primary Objective: To investigate whether it is feasible and safe to conduct a blinded randomised controlled trial (RCT) comparing treatment with SGLT-2 inhibitor versus placebo in critically ill patients at high risk of new or progressive AKI.

Study design: Prospective parallel group, double-blinded randomised controlled feasibility study

Patient population: Patients at high risk of AKI in the ICU

Sample size: 100 patients

Intervention: Dapagliflozin 10mg/day (oral or via nasogastric tube) while in ICU for up to 30 days

Comparator: placebo

Primary outcome: Proportion of eligible patients who are randomised

Secondary outcomes:

- proportion of randomised patients in whom the study drug is stopped due to safety concerns
- incidence of ketoacidosis or hypoglycaemia
- MAKE 30 (ie. composite endpoint of doubling of serum creatinine, requirement for RRT or death within 30 days of randomisation)
- doubling of serum creatinine within 30 days
- need for RRT within 30 days
- all-cause 30-day mortality
- AKI based on new biomarkers

Inclusion criteria:

- 18 years or older;
- admitted to ICU within last 7 days
- expected to be in ICU for at least 2 more days
- able to tolerate enteral intake
- high risk for AKI as defined by pre-morbid risk factor profile and need for fluid resuscitation or vasopressors to keep MAP >60mmHg

Exclusion criteria:

- all inclusion criteria were met >24 hours earlier
- type 1 diabetes mellitus
- already taking SGLT-2 inhibitor
- eGFR <20 mL/min/1.73m2
- AKI stage II or III
- need for RRT for any reason
- hypersensitivity to any SGLT-2 inhibitor
- imminent death

Randomisation: Following informed consent, patients will be randomised on a 1:1 ratio Intervention: Dapagliflozin tablets will be matched with a placebo, labelled, packaged and

distributed in accordance with Good Manufacturing Practice and applicable regulatory requirements. Study drug will be labelled in a manner that protects the blinding. If the treating clinician determines that the study participant has transient gastrointestinal dysfunction that requires a delay in study treatment initiation or the cessation of enteric feeding, the study drug may be withheld until it is considered safe to start/resume. If a serious adverse event occurs that is related to the study drug, the study drug will be permanently discontinued.

Evaluation: Daily clinical information and laboratory data will be recorded whilst the participant is in ICU for up to 30 days post randomisation or until death or discharge from ICU (whichever occurs first) to document response to study treatment and to monitor safety. Serum glucose and urinary ketones will be measured twice a day per protocol. In the first 7 days post-randomisation, a daily urine sample will be taken for measurement of kidney biomarkers to diagnose AKI before serum creatinine rises.

Other management: Aside from the study treatment, the treating clinicians will be free to provide whatever medical care is deemed best and necessary for the patient. Data sharing Fully anonymised results will be shared with Prof M Gallagher and the team at the George Institute in Australia who are conducting the same feasibility study at their institution.

Statistical analysis and sample size justification: We estimate that 50 patients per arm will be required to study the feasibility of the protocol in terms of recruitment target, compliance with protocol and safety. The analyses will be performed on the Intention-to-treat population using standard statistical methods for categorical and continuous variables.

Long-term plan: If the study confirms that the protocol is feasible and safe, we will use the data to develop the protocol and funding application for a larger appropriately powered clinical trial.

Additional commitment: In parallel to setting up this feasibility study, we will also conduct a systematic review of the existing literature on the role of SGLT-2 inhibitors in preventing AKI.

Goals of the project

The main goals of the project are:

- To investigate whether it is feasible and safe to conduct a blinded RCT comparing treatment with SGLT-2 inhibitor versus placebo in critically ill patients at high risk of new or progressive AKI. The results, together with the conclusions of a systematic review of the literature will inform the protocol and funding application of an adequately powered future multi-site RCT.
- To support the successful candidate in their research training
- To strengthen research collaboration with the George Institute in Australia and the home institution of the candidate.

The successful candidate will be fully involved in the conduct of the project, including regulatory approval, screening, randomisation, data collection, analysis and writing of the manuscript. The candidate will work closely with the local research team. In addition, they will have the opportunity to register for the national NIHR Associate Principal Investigator training scheme (Associate Principal Investigator Scheme | NIHR) which provides formal training in research within the NIHR framework. The candidate will also lead the systematic review of the existing literature and the preparation of a manuscript for publication. Expert guidance and support will be available throughout the process. Finally, the candidate will join a network of active researchers in kidney disease and will have ample opportunities to meet colleagues who are engaged in AKI research.

Qualifications and/or expertise required to the fellow

The fellow is expected to:

- be enthusiastic about AKI research;
- have good communication skills in English;
- have a high level of self-motivation, commitment, and strong work ethic to lead the project;
- be interested in interacting and collaborating with the local research team and collaborators;
- be motivated to present the results at national and international meetings.