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Efficacy and safety of Dapagliflozin vs. Canagliflozin in addition to metformin for treatment of type 2 diabetes, a randomized, double-blind, non-inferiority clinical trial

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Abstract:

Type 2 Diabetes is the plague of the 21st century; a chronic condition with complex pathogenetic mechanisms that require the use of multiple therapies to achieve optimal glycemic control. Although conventional therapies offer robust reduction in glycated hemoglobin (HbA1c), they are also associated with increased risks of hypoglycemia and weight gain over time.

SGLT-2 Inhibitors are the latest class in the diabetes armamentarium to emerge with the promise of minimal hypoglycemia risk and potential for weight loss based on their unique mechanism of action. They reduce hyperglycemia by promoting the excretion of glucose through the urine.

Several studies have demonstrated efficacy in HbA1c reduction of the SGLT-2 inhibitors dapagliflozin and canagliflozin, when compared with both placebos and other types of oral hypoglycemic agents. However, to date no head to head trials exist that have compared the efficacy of HbA1c reduction of these two agents.

We propose a randomized controlled double-blind non-inferiority trial that will examine the efficacy of HbA1c reduction of canagliflozin to dapagliflozin respectively in patients treated with metformin monotherapy with suboptimal glycemic control. We hypothesize that there will be no difference in efficacy of HbA1c reduction between these two agents.

Keywords: Type 2 Diabetes, HbA1c, SGLT-2 Inhibitors, dapagliflozin, canagliflozin, metformin.

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INTRODUCTION

Diabetes Mellitus is a chronic, progressive, debilitating condition that has reached epidemic proportions worldwide. The International Diabetes Federation (IDF) estimates that there are over 300 million diabetics worldwide, and projects that this figure will increase to over 500 million by 2050 (1). The complex pathogenetic mechanisms of type 2 diabetes mellitus (T2DM) necessitate the use of multiple agents to optimize glycemic control. Most of the conventional therapies are associated with adverse effects such as weight gain over time and hypoglycemia, leading to a constant quest for newer safer therapies (2, 3).

Selective sodium glucose cotransporter-2 (SGLT-2) inhibitors are the latest class of oral hypoglycemic agents which act in a non-insulin dependant pathway by promoting urinary glucose excretion. This novel mechanism of action has ushered in the promise of reduction in glycemia without the risk for hypoglycemia plus an additional bonus of potential weight and blood pressure reduction (4, 5). The U.S. Food and Drug Administration (FDA) has approved 3 of the SGLT-2 inhibitors, namely dapagliflozin, canagliflozin and empagliflozin. Due to their unique method of action, and reduced risk for side effects, the joint EASD-ADA guidelines has placed this class of oral hypoglycemic agents as adjunctive therapy to metformin in those not

achieving glycemic control or as initial therapy in those who have contraindications to metformin and where the concern for weight gain and hypoglycemia takes precedence (6). Studies of both dapagliflozin and canagliflozin report similar efficacy in glycated hemoglobin (HbA1c) reduction of approximately (0.5-0.8%) (7, 8, 9). Several studies have compared each drug with both placebo and active drugs such as sulfonylureas, DPP-IV Inhibitors and thiazolidindiones.

However, there are no head to head randomized controlled studies that examine the efficacy of dapagliflozin to canagliflozin in terms of HbA1c reduction and extent of weight loss. Therefore we propose to conduct the first of its kind head to head comparison between these two molecules to compare their efficacy in HbA1c reduction, weight loss and safety parameters. This study will have significant clinical implications allowing physicians to choose from either drug if both are found to be comparable in their efficacy. Our primary aim is to demonstrate non-inferiority of canagliflozin to dapagliflozin in HbA1c reduction when added to metformin in patients with suboptimal glycemic control. The secondary objectives include evaluation of differences in weight loss, blood pressure reduction and safety parameters.

METHODS

We will conduct a randomized, double-blind, non-inferiority trial in subjects with T2DM inadequately controlled with metformin monotherapy as defined by the glycated hemoglobin (HbA1c) in two large diabetes centers in the United States. The study consists of 52-weeks, divided into a 2-week run-in phase and a 50-week treatment phase. In the run-in phase patients will be selected based on eligibility criteria after signing the informed consent (Day 1, Visit 1). In the treatment phase, on day 14 (Visit 2), patients will be submitted to clinical and laboratorial exams, and receive the first round of medication.

Eligibility criteria: Inclusion

Our study will include adults of both gender aged 18 to 65 diagnosed with T2DM, treated with monotherapy according to the current ADA guidelines for at least 90 days and HbA1c > 7.0%.

Eligibility criteria: Exclusion

- Renal insufficiency grade III or above
- Mental incapacity defined as a difficulty of communication or cognitive problems because of intellectual disability, dementia and other organic brain

syndromes assessed by attending physician of the patients.

- HbA1c > 9%
 - Women who are pregnant or intend to become pregnant during the time of the trial
 - Use of investigational product during the last 3 months
 - Involvement in another clinical trial at the time of recruitment for this study
 - Metformin monotherapy of less than 90 days duration
- The study will have a multi-disciplinary team with specific roles to ensure smooth execution of all study procedures.

Recruitment strategy

T2DM patients will be screened according to the eligibility criteria specified above by attending staff through patient files, registries and interviews. Eligible patients will be contacted by a study nurse who will explain the study and, if agreeable, the patient will be referred to a research coordinator for enrollment. Screening will continue until target population is achieved.

Interventions

Patients will be randomly allocated to:

- Group 1 dapagliflozin plus metformin: Patients will receive dapagliflozin 10 mg orally once a day in the morning before breakfast, and metformin 850 mg 2 times per day after meals.
- Group 2 canagliflozin plus metformin: Patients will receive canagliflozin 300 mg orally once a day in the morning before breakfast, and metformin 850 mg 2 times per day after meals.

Modification or discontinuation will be performed in the following scenarios:

- Development of ketoacidosis
- Deterioration of renal function
- Urinary tract infections: more than two mild urinary tract infection or one severe urinary tract infection (requiring hospitalization)
- Non-compliance to taking the SGLT-2 Inhibitor
- Cognitively healthy older adults.

In three of the studies participants were right handed subjects (42- 44) while in one of the studies handedness was not reported (41).

Adherence

The investigator or his/her designated and qualified representative will dispense the study drug only to subjects enrolled in the study in accordance with the protocol.

During out-patient treatment, subjects will document the intake of the investigational product on a patient diary which they will receive on Visit 2. The patients will be instructed to return all blisters/bottles, unused study drugs and the patient diary on each visit in the 50-week treatment phase so that a compliance check can be performed.

At the start of the study, each subject will receive counseling by the investigator regarding the importance of dosing adherence with the treatment regimen.

At the week 2 (visit 2) patients will receive standard counseling on diet and exercise and avoid using the study drug for reasons other than the protocol.

Patients will also be provided with a glucose meter, testing supplies and testing instructions. They will be expected to perform fasting self-monitored blood glucose three times per week and record testing results in the patient diary, which will be reviewed by study research staff at each visit.

Adherence to the study drug within the Treatment Period will be assessed by the calculation of the percentage of tablets taken relative to the total tablets expected to be taken, and based on the analysis of the patient diary (which includes analysis of the compliance to the glucose meter test). In addition, the percentage of compliant subjects will be calculated per treatment group.

Drug accountability

All study drugs will be stored at the investigational site in accordance with Good Clinical practices (GCP) and Good Manufacturing Practices (GMP) requirements and in a place inaccessible to unauthorized personnel. An inventory of the study drugs, including record of all lot numbers, numbers of tablets dispensed, subject numbers and expiry dates, will be kept by the investigator in the sponsor study file. The monitor will review study drug accountability on an ongoing basis and final accountability will be performed at the end of study at each site.

Outcomes

The primary outcome is to assess the change of the HbA1c reduction at the 52 weeks follow up in both groups from the baseline HbA1c.

As secondary outcome we will examine the change in body weight at 52 weeks from baseline.

Safety parameters that we plan to assess include hypoglycemia, all events leading to discontinuation of study drug (ketoacidosis, urinary tract infection or deterioration of renal function) and other serious adverse events for safety reasons.

Study timeline (Figure 1)

First visit (Day 1):

Eligible patients will be invited to participate in the trial, and receive informed consent and further explanation of the purpose of our research.

Second visit (Week 1):

After the patient delivers the informed consent, they will be given specific instructions on medication dispensing and who will be performing the tests at each visit within the designated hospitals.

Third visit (Week 2)

Patients will be subjected to:

- 1) Blood collection for analysis
 - 2) Clinical exam (age, weight, height, BMI (defined as W (kg)/H (m)²), systolic arterial pressure, diastolic arterial pressure, abdominal and hip circumference, weight of fat and fat percentage, weight of lean mass, basal metabolic rate, total water in the body, bio-resistance and reactance)
 - 3) Anamnesis: adverse event reports (e.g. urinary tract infections, hypoglycemia events, severe hypoglycemia episodes that required the assistance of another person as in seizure or loss of consciousness),
 - 4) Cardiac exam: electrocardiogram
 - 5) Food diary: to record approximate daily consumption
- Patients will receive the first round of medication.

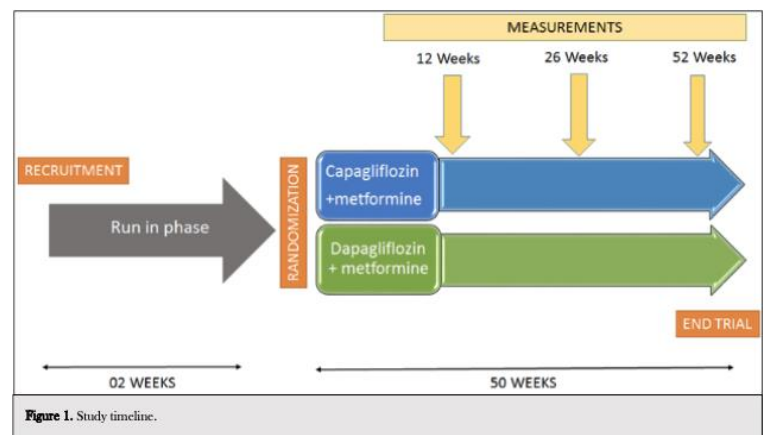


Figure 1. Study timeline.

Randomization

A computer-generated in block randomization sequence will be created for the patients to be included in both arms of the trial (10). The sequence sheet will be kept by a third party, a Data and Safety Monitoring Committee (DSMC), in a password-protected Microsoft Excel file, and only a trained pharmacist will receive the group selection for each patient as requested. We will be using a centralized off site computer allocation process.

The staff at the centralized off site center is responsible for consulting a previously web-based

randomized computer generated randomization sequence (<http://randomization.com>) which used set of block permutations to ensure approximately equal number of interventions in each group per site center without ability to predict assignment. The centralized office center is not involved in any other part of the trial. Physicians in charge will register only the participants who accept the informed consent through the computer system which is online and managed by only one computer in each center. Then the computer software will conduct randomization automatically and result of allocation will be informed to the center pharmacist in a list of group drugs as codes for each allocated subject.

The allocation will be informed only to the DSMC, the third party. Allocation concealment will be kept from the participants, the physician and the pharmacist, as the DSMC will not release the allocation code until the participant has completed the trial. The DSMC will only respond to the corresponding site center with the information of the drug administered, in cases of suspected adverse events that would jeopardize the patient's life and hence exclude the patient from the trial (11, 12).

Blinding

Participants, blinded study personnel and sponsor will not know the patient assignment to the group treatments.

1 - Trial participants: Each participant will get a sealed package with the daily tablet of the intervention - canagliflozin or dapagliflozin. Tablets of metformin will be delivered separately. The study medication will be delivered to participants weekly. The study medication will be given the same way to all participants. The sealed study medication envelopes will be separated by study staff not involved in the patient care neither the clinic staff.

2- Care providers: Clinicians, pharmacists, nurses and all study personnel will not know what medications the patients have been assigned.

Provision for emergency un-blinding has been included in cases of serious adverse events.

Those circumstances that allow for code breaking include:

- Occurrence of any serious adverse effects that endangers the patient's life.
- If it is the patient's own free will or if the patient makes contact with the site pharmacy department requesting for code breaking
- If any person that is not in the clinical trial, took the trial medication, example, the child of a participant.

System for emergency un-blinding:

- Patients will have access to a toll-free help line or a local emergency number, which to assist in situations that need code breaking

- Only the assistant responsible for this line (part of the DSMC), will know the code breaking.

- Report the drug administered to the trial site center for evaluation of drug discontinuation and exclusion of the patient from the trial, if confirmed.

Data management

Complete data management procedures will be documented in the Data Management Plan. Adverse events, medical history and co-morbidities will be registered using the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0 (13). Concomitant drugs will be registered using the WHO Drug Dictionary Enhanced (14).

The study will make use of electronic clinical research files (eCRFs) for each subject that will be identified by a unique number to be filled in English only. Each site center- level will be granted access to the eCRFs by a site coordinator. Periodic monitoring visits by the study coordinators will be scheduled at each site to guarantee precision and accuracy of eCRF information.

Sample size calculation

HbA1c reflects average plasma glucose over the previous 8 to 12 weeks. An HbA1c of 6.5% is recommended as the cut point for diagnosing diabetes and may indicate the presence of intermediate hyperglycaemia. Reduction of at least 0.5% is recommended for treating T2DM (15). Various studies on both dapagliflozin and canagliflozin have shown a reduction of Hba1c of 0.8% when compared to both placebos and active comparators (16, 17, 18, 19, 20).

Assuming no effect difference between canagliflozin and dapagliflozin treatment we based our sample size estimate on the most conservative estimates (i.e., largest) SD (1.0). Considering a reduction of at least 0.5% (15) as a clinically significant difference, but expecting a mean reduction of 0.75% based on previous studies, we set a non- inferiority margin at 0.25%. For a significance level of 5% and power of 80% and a proportion of 1:1 between the two arms of the study, our sample size required per arm is of 198. Assuming a 20% drop-out rate we planned a total of 495 patients to be randomized, as calculated by the online tool: www.sealedenvelope.com/power/ continuous- noninferior.

Statistical analysis

The efficacy and safety data analysis will be performed using intent-to-treat population. Descriptive statistics will be used for both exploratory and safety variables. The distribution of the data will be assessed using Shapiro-Wilk test. Student T test or Mann-Whitney will be performed in order to compare the difference of HbA1c mean percentages between the two groups as well as weight loss at the 26th and 52th week of follow up.

An analysis of covariance model will be performed afterwards in order to compare the difference of HbA1c percentage mean change. The baseline variable will be used as a covariate and the treatment as the effect. All tests will be performed under an alpha level of 0.05 and 95% confidence intervals (CI). Missing patent data will be handled with the multiple imputation method. Statistical analysis will be performed using Stata 13 software.

Data monitoring

A DSMC will be established independent of study organizers. The DSMC members will declare any competing interest. The primary role of the DSMC is to periodically review the accumulating data and determine if the study should be modified or discontinued. During the period of recruitment to the study, interim analysis will be supplied, in strict confidence, to the DSMC, together with other analyses that the committee may request. In the light of these interim analyses, the DSMC will advise the Trial Steering Committee if, in its view:

1) The procedures by which collected data will be verified should be provided.

2) Review of the rate of subject accrual and compliance with inclusion/exclusion criteria will occur monthly during the recruitment phase and then every 12 weeks to ensure that a sufficient number of participants are being enrolled and that they meet eligibility criteria and the targeted ethnic diversity goals outlined in the grant proposal.

Consent

The trial will be performed according to the guidelines of Good Clinical Practice and the Declaration of Helsinki and regulatory requirements, and approval will be obtained from an independent ethical committee and institutional review board of each Hospital (21). All the research team members will be required to have completed Good Clinical Practice training before involvement in the trial.

Confidentiality of data

To ensure privacy and confidentiality, patients' data will be stored in only one restricted computer. Nurses and

medical staff will have access to limited data through an encrypted computer application. Each patient would be assigned to a trial code that would be used as the identity of that patient in all aspects of the trial (assigning the medication, recording personal data, clinical information, HbA1c, secondary effects, etc) until its conclusion. During the trial or at the end of it, the identity of patients will only be revealed for health reasons unless express request of any patient. Data will be stored for 10 years after the end of the trial to assess possible long-term complications.

Budget and funding

Our primary source of funding will be through grants. We will be soliciting funds from the NIH, and will not approach commercial sources. We estimate that in order to successfully carry out this project, we would need US\$3,113,443.84.

DISCUSSION

Since we are embarking on a randomized, double-blind trial with a relatively large patient population, we envisage challenges in securing the estimated budget for the study. Furthermore, as we intend to conduct the study in only two centers in a single country, we will be limited in terms of generalizability of the study results, as other populations might have different responses to the medications studied.

We opted for a non-inferiority design as both drugs have demonstrated similar efficacy in HbA1c reduction of approximately 0.75%-0.8% in previous studies when compared against both placebo and other types of diabetes medications. In addition, the weight loss effects and blood pressure reduction of both drugs also appears to be similar. Given that both drugs belong to a relatively new class of oral hypoglycemic agents and the emerging safety data, it might be reasonable in the future to conduct a long-term comparative effectiveness trial that will better elucidate the differences in safety and efficacy of glycemic control.

Embedded within the design of our study is a robust randomization procedure that will maintain allocation concealment to ensure strong internal validity. Our patient eligibility criteria will allow rapid and effective patient recruitment in centers with a high volume of T2DM. The simplicity of the intervention will enhance patient adherence to the study procedures. The study period of 52 weeks is sufficient to determine both our primary and secondary objectives. A data safety monitoring board will be established that will be independent of the study organizers to ensure that patient safety is maintained throughout the trial.

CONCLUSION

Currently, there is a lack of evidence in head to head comparison between dapagliflozin and canagliflozin assessing the efficacy of HbA1c and weight reduction. Valuable information will emerge to assist physicians in their clinical choice to patient's benefit with this trial.

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Conflict of interest and financial disclosure

The authors followed the International Committee or Journal of Medical Journals Editors (ICMJE) form for disclosure of potential conflicts of interest. All listed authors concur with the submission of the manuscript, the final version has been approved by all authors. The authors have no financial or personal conflicts of interest.

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