Is the stepping-down approach a better option than multiple daily injections in patients with chronic poorly controlled diabetes on advanced insulin therapy?

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Study Protocol

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Methods and Materials:

This study is an interdepartmental collaborative study among the Department of Internal Medicine, Department of Family & Community Medicine (UCSF Fresno), Sierra Vista Family Medicine Residency Program and Division of Endocrinology.

The study will be conducted at the following multiple locations in order to maximize the patient recruitment:

(1) Internal medicine clinic at Derian Koligian ambulatory care center (ACC)
(2) Family practice medicine clinic at ACC
(3) Endocrine clinic at ACC
(4) Internal medicine clinic at University Medicine Associates in East medical Plaza
(5) Endocrine clinic at University Medicine Associates in East medical Plaza
(6) Sierra Vista clinics

The patients will be recruited during the first 12 months of the study or until the predetermined sample size is reached, whichever comes first.

Inclusion criteria

The patients with T2DM who met all of the following criteria were included in the study.

(1) > 21 years of age
(2) Body mass index (BMI) ≥30 kg/m2
(3) On insulin at least 2 times daily comprising both a basal and a prandial insulin or a pre-mix insulin with or without other non-insulin medications for a least past 3 months
(4) A1c >8%
(5) eGFR >45%

Exclusion criteria

The patients with any of the following criteria were excluded.

(1) Any patient who did not meet the above inclusion criteria.
(2) Pregnancy
(3) On a SGLT2i and a GLP1 RA or U-500 insulin at the time of enrollment.
(4) T1DM
(5) C-peptide below normal range if measured in the past.
(6) A history of diabetes ketoacidosis
(7) A history of recent and frequent (≥ 2 times within past 3 months) urinary tract infection or genito-urinary candidiasis requiring antibiotic and/or anti-fungal therapies within past 3 months
(8) A personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)
(9) eGFR <45%
(10) A history of acute pancreatitis

Design
This is the prospective, randomized, open-label, controlled, parallel-group study. Patients will be allocated 1:1 to either intervention (i.e. Step-Down) or control (MDI) group by using block randomization with computer-generated random sequence from http://www.randomization.com.

Procedures
All participants in both groups will make a total of 3 visits over a 16- week period. The 2nd visit is at week 4 and 3rd visit at week 16 after initial visit. At each visit, all patients will have a blood test for A1c, CMP, CBC, fasting lipid and measurements of body weight, height, blood pressure, and heart rate, answered adverse reaction questions and completed the Diabetes Medications Satisfaction (DM-SAT) Questionnaire form.

At first visit, the following changes will be made in intervention group:

(1) All prandial insulin injections (Humalog, Novolog, Apidra, Novolin R or Humulin R) will be discontinued.
(2) Basal insulin (NPH, Lantus, Levemir, Toujeo or Tresiba) will be continued at 80 % of the home dose. The dose will be gradually increased until the patient is back on the home dose (the dose that the patient has been taking at home prior to the enrollment) or fasting BG of 80-130mg/dl was achieved by using the self-titration regimen. (Attachement#1)
(3) If the patient is on pre-mixed insulin 2-3 times daily, it will be switched to a basal insulin alone and Glargine was given at 40% of total daily dose of pre-mixed insulin. The dose will be gradually increased until fasting BG of 80-130mg/dl is achieved by using the self-titration regimen. (Attachement#1)
(4) Metformin at home dose will be continued, but other non-insulin diabetes medications will be discontinued. If the patient is not on metformin, then Metformin ER will be started at 500mg daily with a meal for 2 weeks and then 1000mg daily as a maintenance dose if tolerated.
(5) Both SGLT2i, Empagliflozin 10 mg or 12.5mg once daily, and GLP1 RA, Dulaglutide 0.75mg subcutaneously once weekly, will be added to metformin and a basal insulin.

The patients will be trained on the injection technique of the once-weekly GLP1 RA and given information on potential side effects, risk and benefits of all new medications in detail, hypoglycemia management and the self-titration regimen for the basal insulin.
In the control group, the patients will be advised to remain on MDI and to have the usual and standard care through the primary care provider. They will also be advised to gradually increase the basal insulin until fasting BG of 80-130mg/dl is achieved by using the self-titration regimen as in the intervention group. (Attachement#1)
The patients in both groups will be advised to monitor FPGs daily at minimum.
A research coordinator will make a phone call to all participants in both groups at week 1, 2, 8, and 12 to review fasting glucose measurements, ask for possible adverse events, incidents of hypoglycemia, and any change in medication.
At each visit, the patients will be questioned for adverse events (nausea, vomiting, diarrhea, headache, acute pancreatitis, bacterial or fungal genito-urinary tract infection, severe hypoglycemia with blood glucose <40, mild hypoglycemia with BG 41-69, diabetes ketoacidosis, any hospitalization for hyper or hyper-glycaemia).
At 2nd visit, Empagliflozin and GLP1 RA, Dulaglutide will be increased to maximum doses of 25mg and 1.5mg respectively if the patient tolerated the starting dose and if the additional glycemic control is required.

Outcome measurements
The primary outcome is the change in A1c at the end of study period at week 16 and secondary outcomes are the changes in fasting blood glucose, weight, blood pressure, heart rate, fasting

lipids, serum sodium and potassium, serum creatinine, liver enzymes, CBC and Diabetes Medications Satisfaction (DM-SAT) scores at week 16.
Treatment satisfaction will be measured using the Diabetes Medication Satisfaction Tool (DM-SAT).[4] The DM-SAT measures satisfaction with the patient's diabetes medications regimen. The instrument consists of 16 items which create 4 subscales (3 items for wellbeing, 3 items for medic al control, 5 items for lifestyle, and 5 items for convenience) and a total score. Responses are summed and converted to a score from 0 to 100 for each subscale and overall, with higher scores representing moresatisfaction.

Statistical Analysis:

We will attempt to recruit and consent 20 patients in each arm that was calculated to provide an 80% statistical power at a 0.05 alpha in this continuous endpoint, two independent sample study.

The calculation was based on the following:

A mean Hemoglobin A1c of 8.5±1% at the initiation of the study period. In the treatment group we anticipate a decline in Hemoglobin A1c of 12-15% by the end of the study period. The standard deviation for the mean A1c was derived from the literature (Glucagon-Like Peptide 1 Receptor Agonist or Bolus Insulin With Optimized Basal Insulin in Type 2 Diabetes. Michaela Diamant Et al. Diabetes Care October 2014 vol. 37 no. 10. 2763-2773)

The data will be analyzed by using SPSS or similar software. Significance testing will be conducted at the two-sided 5% level. Continuous variables will be examined for normality and if assumption is met, differences in mean values will be tested using Student's t test an analysis of variance (ANOVA). If not normally distributed, non-parametric procedures will be used, including Wilcoxan rank Sum test. Categorical data will be analyzed using Fisher's exact test and Chi square analysis. Since before/after comparisons will also be performed on the same study patients, we will utilize paired t tests and McNemar's chi-square test.