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Final Study Report
GLYCEMIA-Heart
EudraCT code 2018-000832-82

Study drug: Emplagliflozin

Promoter: Fondazione Toscana Gabriele Monasterio

Study start: 31/10/2018 End of study: 07/04/2022

Principal investigator: Dr. Giuseppe Vergaro, UOC Medicina Cardiovascolare – FTGM, Pisa

The study hypothesis was that the drug empagliflozin, a sodium-glucose cotransporter inhibitor, ameliorates neuro-hormonal imbalance and promotes reverse cardiac remodeling in patients with type 2 diabetes mellitus and chronic heart failure with reduced ejection fraction. The GLYCEMIA-Heart was designed as a prospective, monocentric randomized, open-label, phase IV study. We planned to enroll 66 male and female patients aged ≥18 years old and diagnosed with type 2 diabetes mellitus and chronic heart failure with reduced ejection fraction. Patients had to be randomly allocated to one of the two following therapeutic strategies, both aimed at achieving a target HbA1c <7.0%:

(1) increase in the posology of the ongoing therapy, or introduction of new glucose-lowering agents (except for empagliflozin or other SGLT2 inhibitors);
(2) introduction of empagliflozin (10 mg/die with the possible titration up to 25 mg/die).
The primary end-point of the study was 1-year variation in NT-proBNP plasma concentrations.

By the day of study closure, only 5 patients had been enrolled, 2 randomized to conventional therapy, 3 randomized to empagliflozin. Due to the limited number of patients enrolled, no formal statistical analysis has been performed, and the original hypothesis of the study could not be tested.

ETHICAL ASPECTS

The study protocol was evaluated and approved by the local Ethics Committee (CEAVNO) and by the Competent Authority, or the Italian Medicines Agency (AIFA). The study was performed in accordance with the Helsinki Declaration. The willingness of each individual patient to participate in the study was respected and informed consent was requested from each patient at the time of enrollment. The study was performed in accordance with the rules of Good Clinical Practice (GCP). No discrimination was applied in the enrollment of patients in terms of ethnicity, sexual, religious or political orientation. Sensitive data relating to enrolled patients will be kept for 7 years and will be used anonymously according to an alphanumeric coding.

EXECUTIVE COMMITTEE

- Dr. Giuseppe Vergaro, Principal Investigator
- Dr.ssa Kyriazoula Chatzianagnostou
- Prof. Michele Emdin
- Prof. Claudio Passino
- Prof. Andrea Natali
- Dr. Domenico Tricò
- Dr. Graziano Di Cianni
- Dr. Roberto Andreini
- Dr. Plinio Fabiani

REPORT

Introduction

Sodium-glucose cotransporter inhibitors (SGLT2i) have been demonstrated to improve outcome of heart failure patients with and without diabetes, but the mechanism of this beneficial effect remain to be fully elucidated. The study hypothesis is that empagliflozin, a drug belonging to the SGLT2i class, ameliorates neuro-hormonal imbalance and promotes reverse cardiac remodeling in patients with type 2 diabetes mellitus and chronic heart failure with reduced ejection fraction.

Objectives

Primary goal:

Test the effects of empagliflozin on neuro-hormonal activation, as exstimated by 1-year variation in NT-proBNP plasma concentrations.

Secondary goals:

- Test the effects of empagliflozin on left ventricular remodeling, defined as variations in end-systolic and end-diastolic left ventricular volumes at 1-year transthoracic echocardiographic follow-up

- Test the effects of empagliflozin on adrenergic and renin-angiotensin-aldosterone systems activation

- Test the effects of empagliflozin on exercise capacity, measured as peak oxygen consumption at cardiopulmonary test.

Study design

Prospective, monocentric randomized, open-label, phase IV study.

Study drug

Empagliflozin, 10 mg/die per os, with the possible titration up to 25 mg/die

Study procedures

	Screening	Randomization (V1)	Month 1 (V2)	Month 3 (V3)	Month 6 (V4)	Month 12 (V5)
Informed consent	X					

Inclusion/Exclusion criteria	X					
Therapy and adverse events		X	X	X	X	X
Demographic data	X					
Medical therapy	X	X	X	X	X	X
Vital parameters		X	X	X	X	X
EKG		X			X	X
Cardiopulmonary exercise testing		X			X	X
Holter ECG		X			X	X
Cardiorespiratory monitoring		X			X	X
Laboratory examinations*	X	X	X	X	X	X
Ecocardiography		X		X	X	X
Cardiac magnetic resonance		X				X

* The following laboratory parameters were tested at screening: HbA1c, NT-proBNP, creatinine (for the calculation of estimated glomerular filtration rate), ALT, AST, total bilirubinemia.
The following parameters were evaluated at randomization and at subsequent visits (1, 3, 6, 12 months): complete blood count, sodium, potassium, chlorine, magnesium, ALT, AST, GGT, total bilirubinemia, NT-proBNP, TSH, fT3, fT4, sST2, high-sensitive troponin T, aldosterone, renin, serum catecholamine, glycaemia, HbA1c, insulin, C-peptide, glucagon, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, uricemia, creatinine, azotemia, ß- hydroxybutyrate; complete urine test, with urinary electrolytes and albuminuria/creatininuria ratio.

Study population

Inclusion criteria

- Diagnosis of type 2 diabetes mellitus with HbA1c ≥7.0% and ≤10.0%, on stable pharmacological therapy for at least one month;

- Heart failure (diagnosed according to Framingham criteria) with left ventricular dysfunction (defined as left ventricular ejection fraction - EF <50%), New York Heart Association

(NYHA) classes II-IV;

- Stable therapy with ACEi/ARBs, beta-blockers and, when indicated, with aldosterone receptor antagonist and sacubitril/valsartan (in patients not treated with ACEi/ARBs) for at least one month;

- Plasma levels of NT-proBNP ≥600 ng/L

- Age ≥ 18 years;

- Estimated Glomerular Filtration Rate (evaluated with MDRD formula) ≥60 ml/min/1,73m2;

- Informed Consent signature.

Exclusion criteria

- Patients with acute coronary syndromes, coronary revascularization, valvular surgery or resynchronization therapy in the previous 3 months;

- Patients with type 1 diabetes mellitus (with undetectable C-peptide serum levels) or diabetes secondary to pancreasectomy, history of diabetic ketoacidosis, at least one episode of severe hypoglycemia in the previous 6 months;

- Patients treated with pioglitazone or saxagliptin;

- Severe obesity (BMI >40kg/m2);

- Clinical history of recurrent or severe genitourinary infections;

- Active malignancies;

- Patients with estimated life expectancy <1 year;

- Patients with significant hepatic function abnormalities (defined as ALT/AST elevation of more than 3-fold the upper limit of reference values or elevation of total bilirubin more than 1,5-fold the upper limit of reference values, without diagnosis of Gilbert's Syndrome);

- Uncontrolled thyroid disease;

- Known or suspected allergy to the drugs subjected to investigation or to one or more of the excipients;

- Pregnant, breast-feeding women or fertile women who do not follow an adequate contraception (all women must consent to abstinence from heterosexual-intercourse, or adopt any two of the following contraceptive measures considered efficacious as: bilateral tube ligation, male sterilization, use of hormonal contraceptives that inhibit ovulation, copper intrauterine devices; every barrier device must be used together with a spermicide cream);

- current or past participation to clinical trials testing empaglifozin in heart failure, or current participation to another clinical trial;

- drug or alcool abuse, or any other condition potentially limiting, in the opinion of the testing physician, the patient's ability to correctly perform study procedures;

- patients who must or want to maintain therapy with drugs not allowed, or potentially limiting the proper conduction of the study;

- inability to sign the informed consent form.

Statistical aspects

Sample size calculation has been performed considering as significative a 10% reduction in NT-proBNP values, with an expected effect size of 0.8. Given the non-normal distribution of NT-proBNP, the Mann-Whitney test will be used for comparisons. With a power of 80% and alpha=0.05 each group was planned to be composed of 30 subjects. Considering a drop-out rate of 10%, 66 patients should have been enrolled for the study. Sample size has been calculated with G*Power software. According to the original statistical plan, in order to assess the distribution of the variables, Shapiro–Wilk test would have been performed. Continuous variables would have been described with the mean value and the standard deviation if normally distributed, with median value and interquartile range if non-normally distributed. Differences between the basal and follow-up evaluation in each group of treatments would have been tested with Wilcoxon test with paired samples. Differences between group of treatments would have been evaluated using Mann-Whitney test. $P < 0.05$ would have been considered as significative.

Given the limited number of subjects enrolled, the executive committee has agreed not to perform any formal statistical analysis on the data collected.

Results

As no formal statistical analysis could be performed, no relevant result can be provided from the GLYCEMIA-Heart study.

Protocol deviations

There were no unplanned excursions from the protocol.

Conclusions

The GLYCEMIA-Heart study has been prematurely interrupted given the very low enrollment rate, and no relevant results could be obtained. The main reasons for such a low recruitment have been identified in the stringent enrollment criteria and, at least in the last 2 years, to the COVID-19 pandemics. Moreover, recent international indications have supported the use of SGLT2i in patients with heart failure and reduced ejection fraction, thus limited the possible pool of eligible patients and raising an ethical issue related to the allocation of a subgroup of patients to the "no-empagliflozin arm".