Repurposing of Verapamil as a Beta Cell Survival Therapy in Type 1 Diabetes

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November 26, 2018

1. INTRODUCTION

Loss of pancreatic beta-cell mass is a key factor in Type 1 Diabetes (T1D), but therapies to halt this process are not available. The investigators have discovered thioredoxin-interacting protein (TXNIP), as a promising target in this regard and have now found that the commonly used anti-hypertensive drug and calcium channel-blocker, verapamil, effectively lowers beta-cell TXNIP expression in rodent beta-cells and human islets, promotes beta-cell survival and rescues mice from T1D. This makes verapamil a potentially attractive drug for T1D, but prospective clinical data are lacking. The investigators primary objective is therefore to conduct a randomized, placebo-controlled, double-blind study of the efficacy and safety of verapamil in adults with recent-onset T1D and to demonstrate that subjects on oral verapamil daily for 12 months will have improved insulin production (as an indirect measure of beta-cell mass).
Results will have major translational implications with potential immediate impact on clinical care, encourage large clinical follow-up trials, evaluate markers of beta cell health and ultimately help develop a novel therapy that enhances the patient's own beta-cell mass and function.

2. STUDY OBJECTIVES

The overall purpose of this trial is to assess the efficacy and safety of using oral verapamil in subjects with recent onset T1D in order to downregulate TXNIP and enhance the patients' endogenous beta cell mass and insulin production. The objectives are therefore to assess parameters of beta cell survival (including new biomarkers), insulin production and glucose control and the feasibility of this approach and thereby provide the basis for future, larger/expanded, longer-term verapamil studies and the off-label use of this approved drug for T1D.

3. STUDY DESGIN

3.1 General Design
The trial is designed as a double-blind placebo-controlled study. Participants will be randomized in a 1:1 ratio, through a simple randomization approach using computer-generated random numbers, to receive oral verapamil or match placebo in addition to standard care with continuous subcutaneous insulin infusion via an insulin pump.

3.2 Primary Outcome
Functional Beta Cell Mass as determined by the area under the curve (AUC) from a 2-hour mixed meal stimulated C-peptide after daily verapamil for 12 months. A greater improvement in insulin production (as an indirect measure of beta cell mass) in subjects receiving verapamil as compared to those receiving placebo would provide an indication of the efficacy of the intervention.

3.3 Secondary Outcomes
1. Exogenous Insulin Requirements at 3 and 12 months
   Exogenous insulin requirements as assessed by mean daily insulin use over 7-14 consecutive days. The percent change from baseline will be assessed as a surrogate inverse marker of residual beta cell function.
2. Glycemic Control at 3 and 12 months

Glycemic control, as measured by HbA1c and hypoglycemic events. In addition to being an important determinant of residual beta cell function/survival, it also helps reveal a more complete picture of beta cell function.

3.4 Other Outcome Measures
Beta cell markers at 3 and 12 months
We will collect serum at baseline and Months 3, 6, 9, 12 for future assessment of putative beta cell markers.

4. SUBJECT SELECTION AND WITHDRAWAL

4.1 Inclusion Criteria
Subjects must meet all of the following criteria:
A. Diagnosis of Type 1a Diabetes Mellitus based on ADA Criteria
B. Written informed consent obtained from the subject including consent for the use of research-related health information
C. ≥ 18 years of age and ≤ 45 years of age
D. < 3 months since T1DM was diagnosed
E. BMI < 30
F. Baseline A1c <10%
G. Detectable fasting or stimulated C-peptide level (above the lower limit of detection of the assay)
H. C-peptide increase during screening mixed meal tolerance test with a minimal stimulated value of ≥ 0.2 pmol/mL
I. Presence of antibodies to at least one of the following antigens: insulin, GAD-65, IA-2, or Znt8
J. Agree to intensive management of diabetes with an HgbA1c goal of < 7.0% and willing to wear and insulin pump and CGMS
K. If female, (a) surgically sterile or (b) postmenopausal or (c) if of reproductive potential, willing to use medically acceptable birth control (e.g. female hormonal contraception, barrier methods or sterilization) until 3 months after completion of any Treatment Period
L. Serum creatinine ≤ 1.5 x upper limit of normal (ULN)
M. Currently receiving insulin therapy
N. Willing to forego other forms of experimental treatment during the study

4.2 Exclusion Criteria
Subjects must have none of the following:
A. Any medical condition that, in the opinion of the investigator, would interfere with safe completion of the trial
B. Pregnant females or lactating females who intend to provide their own breast milk to the baby during the study
C. Current therapy with GLP-1 receptor agonists, pramlintide, or any other agents that might be thought to potentially stimulate pancreatic beta cell regeneration or insulin secretion
D. Current treatment with oral antidiabetic agents
E. Uncompensated heart failure, fluid overload, myocardial infarction or evidence of ischemic heart disease or other serious cardiac disease as described in New York Heart Association (NYHA) Class III or IV criteria within the 12 weeks before randomization

F. History of epilepsy, cancer, cystic fibrosis, sickle cell anemia, neuropathy, peripheral vascular disease or cerebrovascular disease

G. Untreated hypothyroidism or active Graves' disease with hyperthyroidism

H. Treatment with systemic glucocorticoid therapy by oral, intravenous (IV), or intramuscular (IM) route within 12 weeks before randomization; patients who are likely to require treatment with corticosteroids during the trial are also excluded

I. Evidence of active infection

J. Total bilirubin > 1.5 x upper limit of normal (ULN)

K. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 1.5 x ULN

L. A psychiatric or medical disorder that would prevent giving informed consent

M. Hypersensitivity to verapamil or any component of the formulation; known left ventricular dysfunction; hypotension (systolic pressure <90 mm Hg); PR interval prolongation on EKG or any bradydysrhythmia (e.g. sick sinus syndrome, AV block); atrial flutter or fibrillation, and an accessory bypass tract (Wolff-Parkinson-White [WPW] syndrome, Lown-Ganong-Levine syndrome)

4.3 Recruitment and Screening

Subjects who are 18-44 years of ages and diagnosed with T1D within the previous 3 months will be screened with mixed-meal tolerance test (MMTT) for the presence of a minimal stimulated C-peptide value of ≥ 0.2 nmol/L and at least one positive T1D associated antibody.

4.4 Early Withdrawal of Subjects

Subjects will be considered withdrawn if they stop participating in the study or withdraw consent. Subjects are not required to state their reasons for withdrawing consent. Subjects will be withdrawn if, in the investigator's opinion, continuation in the study would be detrimental to their well-being.

5. STUDY DRUG

Verapamil SR or Placebo
1st month 120mg daily, 2nd month 240mg daily, 3rd-12th month 360mg daily

6. STUDY PROCEDURES

To assess the primary endpoint of beta cell function as determined by the stimulated C-peptide AUC, mixed meal tolerance tests (MMTT) will be performed at 0, 3 and 12 months as previously described (Diabetes Care 31, 1966–1971, 2008). The MMTT will only be performed when fasting blood glucose levels are within the range of 3.9-11.1 mmol/L, otherwise the test will be rescheduled. Blood samples will be collected at -10, 0, 15, 30, 60, 90 and 120 min for serum C-peptide analysis. The C-peptide AUC (0-120min) will be divided by the time of the test to obtain the mean AUC (in nmol/L).

7. STATISTICAL PLAN

Participants' demographic characteristics and outcomes will be summarized as mean and standard errors for continuous variables, and frequency and proportion for categorical variables. The group comparison of baseline measures will be conducted with chi-square test, Fisher's exact test or Student's *t* test where appropriate. The normal distribution assumption will be checked with Q–Q plots. All tests will be two sided. For the primary and secondary outcomes, a repeated-measures two-way ANOVA will be

conducted first; then, where appropriate, the ANCOVA model controlling for the baseline will be conducted to compare group means at the 3- or 12-month time points. Sample-size estimates are based on the primary outcome of endogenous beta cell function according to stimulated C-peptide AUC, on previously reported sample-size considerations for studying treatment effects on beta cell function at 12 months in newly diagnosed patients with T1D who were older than 18 years in the T1D Trial Network (PLoS One 6, e26471, 2011), and on recommendations for planning pilot studies in clinical and translational research (Clin. Transl. Sci. 4, 332–337, 2011).

8. SAFETY

Participants will be seen monthly during the first three months and then every 3 months until the end of the study, and will be carefully monitored for any occurrence of hypotension, bradycardia, or EKG changes (PR- or QT- interval prolongation).

9. CONFIDENTIALITY

All data will remain confidential and securely stored electronically, under digital encryption, in the Principal Investigators office, behind two separately locked doors.

10. ETHICAL CONSIDERATIONS

The trial protocol will be approved by the Institutional Review Board of the University of Alabama at Birmingham (UAB) and will comply with all ethical regulations. All subjects will provide written informed consent.

11. STUDY FINANCES

The study is funded by JDRF. Study participants will be paid $80 for completing the Mixed Meal Tolerance Test. In addition, participants who live greater than or equal to 250 miles from UAB will be reimbursed $250 for their travel expenses. Payments will be made every 3 months. None of the investigators have a conflict of interest.

12. PUBLICATION PLAN

Once the study is complete and fully analyzed, we plan to publish the results in a peer-reviewed journal.