Diabetes, Metabolic Syndrome and Obesity

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STUDY PROTOCOL

PRE1BRAZIL Protocol: A Randomized Controlled Trial to Evaluate the Effectiveness and Safety of the DPP-4 Inhibitor Alogliptin in Delaying the Progression of Stage 2 Type 1 Diabetes

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Background: The incidence of Type 1 Diabetes Mellitus (T1DM) is on the rise. Since there is no curative treatment, it is urgent to look for therapies that can delay disease progression and protect pancreatic β-cells. Dipeptidyl peptidase-4 inhibitors (DPP-4i) have shown potential in modulating inflammation and preventing β-cell destruction. This protocol describes an upcoming trial to evaluate the effectiveness of the DPP-4i alogliptin in delaying the progression of stage 2 (presymptomatic) to stage 3 (symptomatic) T1DM.

Patients and Methods: We propose a two-year, two-arm, multicenter, randomized, open-label clinical trial targeting Brazilian patients aged 18 to 35 with stage 2 T1DM. The study, facilitated by the custom-developed "PRE1BRAZIL" web application, aims to enroll 130 participants. They will be randomly assigned in a 1:1 ratio to either a treatment group (alogliptin 25 mg daily plus regular clinical and laboratory assessments) or a control group (regular assessments only). The primary outcome is the rate of progression to stage 3 T1DM. Secondary outcomes include changes in A1c levels, glucose levels during a 2-hour oral glucose tolerance test (OGTT), C-peptide levels, exogenous insulin requirements, Insulin-Dose Adjusted A1c (IDAA1c), and the incidence of diabetic ketoacidosis (DKA) in those advancing to stage 3.

Discussion: This protocol outlines the first randomized clinical trial (RCT) to investigate the impact of a DPP-4i in the presymptomatic stage of T1DM. The trial is designed to provide critical insights into the role of DPP-4i in the secondary prevention of T1DM. Utilizing the "PRE1BRAZIL" web application is expected to enhance participant enrollment and reduce operational costs.

Registration: Brazilian Registry of Clinical Trials.

Keywords: type 1 diabetes, web applications, DPP-4i, stage 2 T1DM, clinical trial protocol

Introduction

The incidence of Type 1 Diabetes Mellitus (T1DM) is rising at an alarming rate globally. Currently, over 1.2 million children and adolescents are living with T1DM[1] and the worldwide prevalence is estimated at over 46 million.[2] In Brazil, it is projected that the prevalence of diabetes will rise from 8.5% to 9.9% within the next three decades; and T1DM

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represents 10–15% of all Diabetes Mellitus (DM) etiologies.[1] The economic burden per case of DM is greater for T1DM than for type 2 diabetes (T2DM) and data suggest that the annual direct and indirect costs secondary to T1DM amount to US$ 14.4 billion.[3]

T1DM develops due to a combination of genetic susceptibility and environmental factors, leading to autoimmunity, inflammation, and destruction of insulin-producing pancreatic β-cells.[4] The presence of one or more specific autoantibodies, such as insulin autoantibodies (IAA), glutamic acid decarboxylase antibodies (GAD), protein tyrosine phosphatase islet antigen-2 (IA2), and zinc transporter 8 (ZnT8) is a hallmark of T1DM. These autoantibodies serve as early indicators of β-cell autoimmunity and are crucial in identifying individuals at risk of progressing from presymptomatic stages to overt DM.[5]

The progression of T1DM can be categorized into three stages. Stage 1 is marked by the presence of autoantibodies without dysglycemia. Stage 2 involves both autoimmunity and glucose intolerance, defined by a fasting plasma glucose ≥100 mg/dL; plasma glucose two hours after a 75-g oral glucose tolerance test (OGTT) ≥140 mg/dL or ≥200 mg/dL at intermediate time points of 30, 60, 90 min; or A1c ≥5.7%). Stage 3 is characterized by the onset of symptomatic disease, including fatigue, weight loss, polyuria, polydipsia, and diabetic ketoacidosis; along with dysglycemia. Dysglycemia is defined by fasting plasma glucose > 126 mg/dL; random plasma glucose > 199 mg/dL with symptoms of hyperglycemia; plasma glucose two hours after an OGTT> 199 mg/dL; or a hemoglobin A1C ≥6.5.[6,7]

While no curative therapy exists for T1DM, delaying the autoimmune destruction of β-cells and protecting still active cells are more likely achievable goals in the near future.[8] The Diabetes Prevention Trial-Type 1 (DPT-1) was the first prevention trial to be widely reported. It was started in the 90s in the form of an international consortium and comprised multiple study arms that have been concluded.[9] Most of them evaluated the use of insulin preparations for secondary prevention, rationalizing that specific therapies could improve the function of T regulatory cells.[10] Initially, subcutaneous and oral insulins were tested in individuals with high-risk HLA (HLA-DR3-DQ2 E HLA-DR4-DQ8) with stage 1 or 2 T1DM. Post-hoc analysis showed a delay in progression to stage 3 in patients with insulin autoantibody (IAA) levels ≥80 U/mL.[11] Subsequent studies have further explored strategies evaluating the use of insulin but with limited success.[12,13]

In the context of these prevention efforts, Dipeptidyl peptidase-4 inhibitors (DPP-4i), a widely used group of medications in patients with T2DM, have emerged as a promising therapeutic option for T1DM.[14] An increasing number of studies, both in animal and human models, have shown mutual characteristics of DPP-4 in modulating inflammation and autoimmune β-cell destruction.[15–19] CD26 is a surface T cell activation antigen with DPP4 enzymatic activity that plays a central role in thymic maturation and co-stimulation, migration, and memory development of T cells.[20] It has been shown that CD26 inhibition suppresses T cell proliferation and Th1 cytokine production besides stimulating the secretion of tumor growth factor beta-1 (TGF-β1), which is important for autoimmunity regulation in patients with T1DM.[21] In addition, diverse trials have demonstrated upregulated DPP-4 activity in patients with T1DM.[22–25]

However, to the best of our knowledge, most studies with DPP-4i in patients with T1DM to date have involved a small number of participants and have not specifically targeted the early stages of the disease. Therefore, RCTs are needed to further explore their potential role in slowing the progression to more advanced stages of T1DM.

The PRE1BRAZIL trial represents a pivotal step in understanding the role of DPP-4i in delaying the progression of T1DM. This present article aims to delineate the protocol of PRE1BRAZIL, an RCT designed to assess the efficacy and safety of Alogliptin, a synthetic DPP-4i with a well-established safety profile,[26] in delaying the progression from Stage 2 to Stage 3 T1DM in Brazilian patients. We will compare the rate of disease progression over a two-year follow-up period between the treatment (alogliptin 25 mg daily) and control groups (no pharmacological intervention).

Material and Methods

Study Design

PRE1Brazil is designed as a randomized, two-arm, multicenter, and open-label digital clinical trial (DCT). Participants will be evenly randomized into two groups: the treatment group, receiving a daily dose of 25 mg Alogliptin plus regular quarterly clinical and laboratory evaluations, and the control group, which will undergo the same frequency of evaluations without the drug intervention. In the event of any protocol modifications that might affect the study's conduct or design, such changes will require consensus among the authors and subsequent approval from the ethics

committee before implementation. All stakeholders, including trial participants, academic journals, and regulatory bodies, will be duly informed of any such alterations.

DCT is the term used to describe clinical trials that utilize digital technology to improve the implementation of clinical trials.[27] For the PRE1BRAZIL DCT, we developed a web application that enables the remote execution of all trial-related processes, which is detailed below.

"PRE1BRAZIL" Web Application

The PRE1BRAZIL web application (APP) was designed to support all RCT steps, from enrollment, randomization, and data collection to adverse event reporting. Its design and requirements were guided by RCT protocols. The APP's homepage functions as the registration form for the researcher. The patient's record will be completed by filling in the demographic data and clinical and laboratory exams. The APP will then validate the exclusion and inclusion criteria and randomize the patient. At the end of each session, it will provide the researcher with the appropriate tests to be ordered for the follow-up. This process is expected to optimize patient allocation and data analysis, meanwhile reducing costs. This APP will allow PRE1BRAZIL to be the first fully automated T1DM prevention trial.

Study Population

The study population consists of female and male patients aged 18 to 35 years diagnosed with stage 2 T1DM. Stage 2 T1DM is characterized by the presence of at least one autoantibody against pancreatic islets, dysglycemia (fasting blood glucose levels between 100–124 mg/dL and/or A1c between 5.7–6.4%), and the absence of symptomatic disease. Exclusion criteria include pregnant or lactating women, individuals with chronic kidney disease (glomerular filtration rate <60 mL/min/1.73m²), and patients currently receiving steroids or any hypoglycemic therapy.

Prior to participating in any study procedures, patients are required to provide a written informed consent form (ICF). The process involves the researcher logging into the PRE1BRAZIL APP and selecting the option "send the ICF" to receive a digital copy of the ICF via email for printing. The researcher will then thoroughly explain the trial and the ICF to the patient. All patients who provide consent and meet the inclusion criteria will be subsequently randomized.

Recruitment Phase

Participant recruitment for the trial will be conducted by physicians. Eligibility for recruitment requires physicians to be either practicing endocrinologists or residents in an endocrinology and metabolism program. To enhance physician participation, the research will be promoted at medical conferences, through household mailings, and on medical media websites. We anticipate that the use of the "PRE1BRAZIL" APP will further facilitate physician involvement. A survey of 16 Brazilian endocrinologists indicated that 81% believe the "PRE1BRAZIL" APP is a positive factor in encouraging their participation in this trial (data pending publication). Eligible physicians will be granted access to the "PRE1BRAZIL" APP.

Our target is to recruit approximately 130 patients (n = 65 per treatment arm) over the 3-year enrollment period, which commenced in July 2022 (Figure 1). The sample size was determined using G*Power 3.1.9.2 software, aiming for a minimum of 80% power (alpha = 0.05) to detect a significant difference in the progression rate to stage 3 T1DM between the intervention and control groups. This calculation is based on the assumption that there is a 60% risk of progressing to symptomatic T1DM within two years at stage 2.[28,29]

Randomization

Eligible patients will be randomized in a 1:1 ratio to a treatment group or a control group in a fully automated way through an algorithm generated by the APP PRE1BRAZIL, minimizing the possibility of bias in allocating the intervention.[30] Recognizing that time is a determining factor for progression to symptomatic disease,[28,29] the algorithm will consider the time between the first known glycemic alteration and the study start date for randomization to keep this data paired between groups.

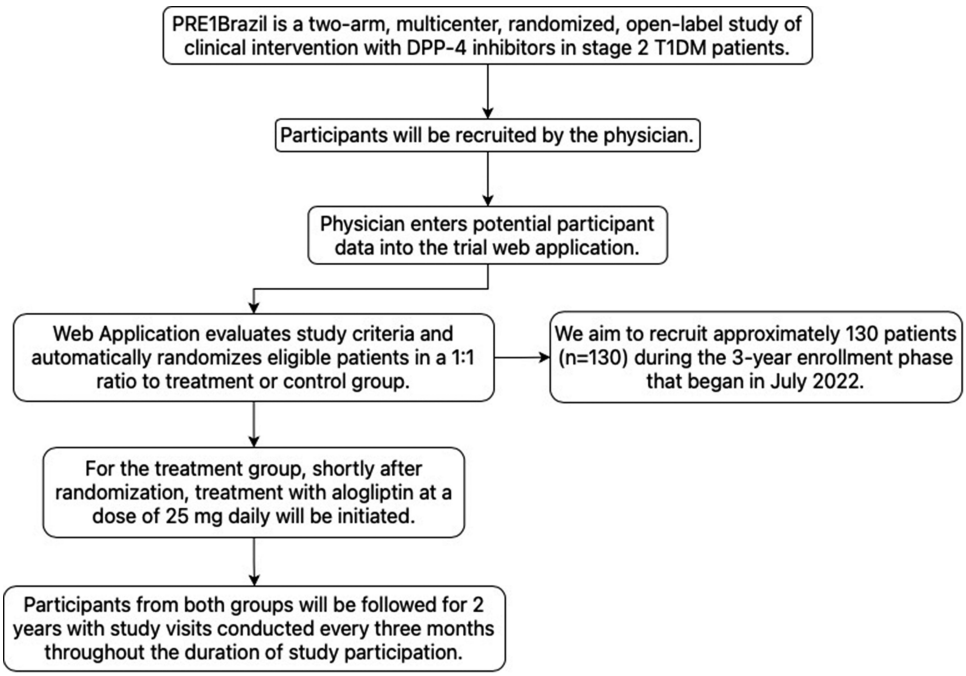

Figure 1 Participant recruitment diagram.

Interventions

After randomization, participants in the treatment group will receive a daily dose of 25 mg of the study drug. This dosage aligns with the drug's approval study for patients with normal GFR.[26] Both groups, comprising female and male patients, will be monitored for two years by an endocrinologist and a multidisciplinary team of nutritionists and nurses, with visits scheduled every three months.

In each consultation, we will emphasize the importance of regular follow-up during the presymptomatic phase to mitigate short- and long-term T1DM-associated complications.[31–35] For the treatment group, medication adherence will be assessed and reinforced at each visit. Patients exhibiting adherence rates below 80% will be discontinued from the study.

The Cardiovascular Outcomes Study of Alogliptin (EXAMINE) reported that the safety profile of alogliptin was comparable to placebo, with no significant differences in rates of serious adverse events, including hypoglycemia, angioedema, malignancy, changes in GFR, and increases in serum aminotransferases.[26] Any adverse events will lead to the patient's discontinuation from the study and will be reported to the Brazilian Health Surveillance Notification System (NOTIVISA).[36]

The primary endpoint is to evaluate whether alogliptin at 25 mg daily can reduce the progression to stage 3 T1DM after 24 months, compared to a control group. T1DM progresses predictably from the onset of asymptomatic dysglycemia to stage 3. Thus intermediate outcomes can also evaluate the therapeutic response to a proposed intervention.[28] Secondary outcomes to be compared include changes in A1c, fasting glucose, and C-peptide levels during a 2-hour OGTT. These will be monitored every three months for A1c and fasting blood glucose, and every six months for 75mg OGTT glucose, stimulated C-peptide, and 25-hydroxyvitamin D levels (Table 1).

For patients advancing to stage 3, we will evaluate the required dose of exogenous insulin, the Insulin-Dose Adjusted A1c (IDAA1c), the incidence of diabetic ketoacidosis (DKA), and the time to event. Increasing A1c values are indicative of T1DM progression,[25,37,38] with a 20% increase in baseline A1c correlating with an almost certain progression to stage 3 within 3–5 years.[28] Similarly, 2-hour OGTT glucose levels are effective predictors, typically starting to change 0.8 years before diagnosis.[26–37] Reductions in C-peptide values generally follow changes in OGTT, with a notable decline in stimulated C-peptide levels occurring six months before symptom onset.[29,39]

Table 1 Tests to Be Ordered at Each Phase

Run-In Phase	Quarterly	Half-Yearly
Fasting blood glucose	Fasting blood glucose	Fasting blood glucose
A1C (HPLC or immunoturbidimetry)	A1C (HPLC or immunoturbidimetry)	A1C (HPLC or immunoturbidimetry)
Lipid profile	Fasting C-peptide levels	Fasting C-peptide levels
Fasting and 2-hour OGTT stimulated C-peptide levels		2-hour OGTT stimulated C-peptide levels
2-hour OGTT glucose levels		2-hour OGTT glucose levels
Fasting insulin		Thyroid-stimulating hormone (TSH)
Thyroid-stimulating hormone (TSH)		25-Hydroxyvitamin D
Anti-thyroid peroxidase (Anti-TPO)		2-hour OGTT stimulated C-peptide levels
HOMA-IR		Creatinine
Serum Creatinine		Urine albumin-creatinine ratio
25-hydroxyvitamin D		Serum creatinine phosphokinase
Islet autoantibodies (GADA, IAA, IA-2, ICA, Anti-Zinc transporter 8 A).		Complete blood count
Urine albumin-creatinine ratio		Serum potassium
Serum creatinine phosphokinase		
Complete blood count		
Serum potassium		

Several studies have linked low levels of 25-hydroxyvitamin D with an increased risk of developing T1DM.[40–43] Therefore, these levels will be periodically evaluated, and supplementation will be administered as per current Brazilian guidelines to maintain levels above 30 in all patients.[44]

In addition to laboratory tests, weight, blood pressure, and abdominal circumference will be assessed at every visit. The PRE1BRAZIL APP will facilitate clinical anamnesis by inquiring about any adverse effects or clinical or infectious complications since the last consultation. Close-ended questions within the app will guide all consultations, thereby enhancing the standardization of follow-up procedures.

Data entered into the APP will be automatically exported to its database, accessible only to the lead investigators via login credentials. No data will be stored on personal devices. Once entered and verified, data cannot be altered in subsequent visits. The authors will conduct periodic interim analyses of the data and adverse event notifications. Decisions regarding the trial's continuation or termination will be made based on these analyses and communicated to the central ethics committee and other stakeholders.

Participants who discontinue the study, except those withdrawing consent, will have their data included for intermediate outcome assessment.

This trial will not have a formal Data Monitoring Committee (DMC), as their use is typically reserved for larger, longer trials,[45] and considering the minimal risks associated with DPP-4i.[14,46]

Upon completion, the authors will disseminate the results through scientific journals and directly to the participants.

Statistical Analysis

Statistical analyses will be conducted using SPSS software, version 22.0. Results will be deemed statistically significant at a p-value less than 0.05. Continuous variables will be expressed as median and standard deviation (SD), while categorical variables will be presented as absolute frequencies and percentages. To compare secondary outcomes between the treatment and control groups, the unpaired Student's *t*-test or Mann–Whitney *U*-test will be employed, depending on the distribution of the data. For patients who progress to stage 3, the chi-square test will be utilized to analyze the Insulin-Dose Adjusted A1c (IDAA1c) and the requirements for exogenous insulin doses. The progression to stage 3 T1DM between groups will be compared using Fisher's exact test. Upon the completion of data collection, the trial statistician will review this statistical analysis plan. The study findings will be disseminated in an indexed journal, adhering to the guidelines of the CONSORT 2010 Statement for reporting parallel group randomized trials.[47]

Discussion

T1DM is a chronic disease with progressive incidence and is associated with a reduction in life expectancy and an increase in hospitalization rates.[1] Despite the significant advancements in predicting T1DM, there have not yet been safe and effective programs for preventing the disease.[48] Challenges related to underdiagnosis, high costs, and low recruitment rates reduce the reach of prevention research in this area and hinder the advancement of science.[49] On the other hand, recent studies have demonstrated that the utilization of DCTs is effective in overcoming these obstacles.[50]

In light of this, the PRE1BRAZIL DCT aims to assess the impact of alogliptin, a DPP-4 inhibitor, in slowing the progression from stage 2 to stage 3 Type 1 T1DM. We believe that the specially designed PRE1BRAZIL web application, with its accessibility and intuitive design, will significantly enhance the reach and efficiency of T1DM prevention research. This innovative application is expected to seamlessly integrate patient follow-up processes, ensure standardized medical practices, and enable remote and automated recording of clinical research data.

The DPP-4i are safe drugs with potential benefits in the early stages of T1DM.[14,46] To our knowledge, this is the first RCT assessing the impact of alogliptin in the pre-symptomatic stage of T1DM. This RCT will provide evidence on the effectiveness of DPP-4i in the secondary prevention of T1DM.

Abbreviations

APP, Application; CONSORT, Consolidated Standards of Reporting Trials; DCT, Digital Clinical Trial; DKA, Diabetic Ketoacidosis; DM, Diabetes Mellitus; DPP-4i, Dipeptidyl Peptidase-4 Inhibitor; DPT-1, Diabetes Prevention Trial-Type 1; GAD, Glutamic Acid Decarboxylase Antibodies; GFR, Glomerular Filtration Rate; HLA, Human Leukocyte Antigen; IAA, Insulin Autoantibodies; IDAA1c, Insulin-Dose Adjusted A1c; OGTT, Oral Glucose Tolerance Test; RCT, Randomized Clinical Trial; SD, Standard Deviation; T1DM, Type 1 Diabetes Mellitus; T2DM, Type 2 Diabetes Mellitus; TGF-β1, Tumor Growth Factor Beta-1; ZnT8, Zinc Transporter 8.

Ethics Approval and Informed Consent

Prior approval for this study was obtained from the University of Ceará Hospital Research Ethics Board (Protocol number: 29728319.5.0000.5054). The PRE1BRAZIL trial was submitted to the Brazilian Registry of Clinical Trials (ReBEC) RBR-723bk5p. This study will be conducted in accordance with the recommendations of the Declaration of Helsinki, with written informed consent obtained from all subjects.

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Disclosure

Prof. Dr. Renan Montenegro Júnior reports personal fees from NovoNordisk, Amryt Pharma, PTC therapeutics, and Hypera Mantecorp, outside the submitted work. The authors declare no other conflicts of interest in this work.

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