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Therapy of type 1 diabetes with T regulatory cells and anti-CD20 monoclonal antibody

Submission date
19/01/2021

Recruitment status
No longer recruiting

Registration date
22/01/2021

Overall study status
Completed

Last Edited
05/05/2022

Condition category
Nutritional, Metabolic, Endocrine

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Type 1 diabetes is a disease which usually develops in patients as a result of the destruction of the pancreas – the internal organ producing insulin. No insulin in the body results in high levels of sugar glucose in the blood. This can lead to impaired consciousness leading to coma, excessive drinking and urination, and weight loss. In the long term, diabetes is responsible for damage to the kidneys, eyes and heart. Current medicine is able to find early symptoms suggesting the beginning of diabetes or increased risk of the onset. The level of anti-islet antibodies and HLA antigens can be used for such a purpose. Usually, those anti-islet antibodies and some specific forms of HLA antigens can be found in patients with diabetes.
Currently, it is known that the disease is triggered by cells called lymphocytes, which attack and kill pancreatic insulin-producing cells. It is also known that the destruction of the pancreas is facilitated by the lack of some other cells, T regulatory cells. T regulatory cells are able to stop lymphocytes from killing pancreatic cells but this effect requires a high number of the former cells. Unfortunately, the number of T regulatory cells in blood is very low. It is estimated that one T regulatory cell can be found in a million of other blood cells and that they are even rarer in patients with diabetes.
The study aims to assess the safety and effectiveness of treatment with T regulatory cells and anti-CD20 monoclonal antibodies and to address the questions: 'how safe is the treatment?', 'how far we can delay the onset of full onset type 1 diabetes?', 'how much of the insulin secretion can be saved from type 1 diabetes?'.

Who can participate?
Patients aged 8-16, up to 2 months after being diagnosed with type 1 diabetes

What does the study involve?
Patients are randomly allocated to receive doses of T regulatory cells with or without the anti-CD20 antibody rituximab, or to a treatment-free control group.
A sample of blood is taken from the patients and T regulatory cells are separated from it. Then, the number of these cells will be increased in the laboratory. If the number of T regulatory cells is increased sufficiently, they are administered as an accessory treatment of diabetes. Before the administration, the cells are carefully checked for safety and quality. This is experimental therapy which was previously used from 2008 and for treating patients with type 1 diabetes

from 2010. Up to now, the researchers have not seen any health problems in patients treated with these cells. Nevertheless, for safety the patients will be under special medical care during the blood drawing and infusion of T regulatory cells and will be regularly examined.
In addition to the preparation of regulatory cells, patients will also receive a drug (at intervals of several days) containing antibodies. The aim of this medicine is to destroy some of the white blood cells that are involved in pancreatic damage and the development of diabetes. Administration of this drug is intended to enhance the function of regulatory cells. This drug has already been successfully used in the treatment of type 1 diabetes. Administration of the drug will be performed in the operating room under medical supervision. The drug will be administered into a vein.
Then, the patients will be followed up for 2 years in order to assess the safety and effectiveness of the treatment.

What are the possible benefits and risks of participating?
In previous studies, patients receiving the treatment had a significantly longer time without the need to receive insulin, and in cases where they needed insulin the doses of the drug were lower. However, it should be emphasized that the proposed treatment is experimental and the patient's health condition may not improve or even deteriorate as a result of adverse effects. Treatment with T regulatory cells has been used since 2008 and in the treatment of diabetes since 2010. So far, among the side effects of the treatment, the researchers have observed only a few viral infections lasting less than 7 days, which gave way without any consequences.
The blood donation and the administration of T regulatory cells may be theoretically associated with the occurrence of adverse effects typical of peripheral vascular punctures and transfusions. These are mainly excessive bleeding, reactions related to the site of injection, fever, chills, petechiae and other skin changes. Diagnosis and treatment of these reactions will belong to the physician assisting with the procedures.
Regulatory lymphocytes suppress immune reactions and therefore potentially can increase sensitivity to serious infections and promote the growth of cancer cells present in the patient's body. These symptoms after administration of regulatory lymphocytes have never been described (the longest observation of the patient after administration of these cells is more than 5 years), but because of their theoretically possible occurrence, this statement must be included in this information.
The manufacturer of the anti-CD20 antibody lists the following adverse effects: bacterial and viral infections, upper respiratory tract infections, bronchitis, urinary tract infections, neutropenia, leukopenia, febrile neutropenia, thrombocytopenia, infusion reactions (mainly fever, chills and cold feeling), angioedema edema, nausea, pruritus, rash, alopecia, fever, chills, asthenia, headache and lowered IgG antibodies.
During the first 2 hours during the first infusion the following may occur: fever, chills and a feeling of cold. There is less frequent: pain at the injection site, blisters on the skin, pruritus, nausea, tiredness, headache, difficulty in breathing, swelling of the tongue or throat, runny nose or itching, vomiting, hot flush or palpitations, heart attack or lowering the number of platelets. People who have had heart disease or angina before treatment may get worse. There is a reduced probability occurring of these reactions after the second infusion
Exceptionally, rare neurological complications called progressive multifocal leukoencephalopathy may occur. Due to the mechanism of action, rituximab may increase the risk of cancer. Based on the limited experience of using rituximab in rheumatoid arthritis (an autoimmune disease with a similar mechanism to type 1 diabetes), it seems that the data currently available do not support the increased risk of cancer, but theoretically there is a risk cannot be excluded.
Each patient undergoing treatment will be subject to constant medical supervision in order to minimize/avoid the effects of potential adverse effects. The basic monitoring will be carried out during control visits resulting from the study schedule. In urgent cases, parents, carers or

patients will have the opportunity to telephone and have personal contact with the attending physician/researcher.

Where is the study run from?
Medical University of Gdańsk (Poland)

When is the study starting and how long is it expected to run for?
February 2013 to December 2019

Who is funding the study?
1. National Centre for Research and Development (Poland)
2. EU Framework Programme Horizon 2020

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2014-004319-35

Protocol serial number
NKBBN/374/2012-NKBBN/374- 7/2014, version 09_2-14, dated 30-Sep-2014

Study information

Scientific Title

Therapy of type 1 diabetes with ex-vivo expanded CD4+CD25+CD127- T regulatory cells (Tregs) and anti-CD20 monoclonal antibody – a randomized trial

Acronym
TregVAC 2.0

Study objectives
Rationale: Type 1 diabetes is a condition in which pancreatic islets are destroyed by self-reactive effector T cells. The process is facilitated by deficits in the number and suppressive activity of T regulatory cells (Tregs). The administration of expanded autologous CD4+CD25+FoxP3+ Tregs in children and adolescents with recently diagnosed type 1 diabetes can delay the process of pancreatic islets destruction by suppressing self-reactive effector T cells. Early administration and repetitive doses of Tregs seem to positively affect this suppressive effect.
B lymphocytes seem also contribute to the pathogenesis of the disease as their selective depletion with the anti-CD20 antibody rituximab results in preserved beta-cell function in patients with type 1 diabetes of recent onset. Although clinically significant, the therapeutic effect of these two therapies is only transient, and patients eventually develop diabetes.
In this study, these two therapeutic approaches are combined. Patients are recruited in earlier phases of the disease and treated by repetitive administration of Tregs and anti-CD20 antibody rituximab with the aim of significantly prolonging insulin independence and further delaying disease onset.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 21/01/2014, Independent Bioethics Committee for Scientific Research at the Medical University of Gdańsk (Dębinki 7, 80-211, Gdańsk, Poland; +48 (0)58 349 25 05, +48 (0)58 349 10 11; irmez@gumed.edu.pl), ref: NKBBN / 374 / 2012 with correction NKBBN / 374-7 / 2014

Primary study design
Interventional

Study design
Prospective multicenter randomized open-label single-blinded placebo-controlled parallel-group study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Type 1 diabetes

Interventions
Randomization:
The patient receives a sequential number (1 to 45) and is randomized to one of the groups prior to blood collection for expansion according to a predefined bloc of numbers assigned to particular groups. Due to the specificity of study, the randomization is performed by the team

separated from clinical investigators. For the same reason, the person responsible for randomization will not have access to the clinical and laboratory results collected by the team responsible for the clinical part of the study until the end of the study.

Two parallel groups and a treatment-free control arm (total N=45, Tregs group N=15, Tregs+anti-CD20 rituximab group N=15, treatment-free control group N=15).

Patients are randomized to receive doses of Tregs between 10 and 30 x 10^6/kg (up to not more than 60 x 10^6 cells/kg in total) on day 0 and day 90. Those randomized to treatment with both Tregs and anti-CD20 antibody receive anti-CD20 antibody rituximab at 375 mg/m^2 on study days 14, 22, 29 and 36.

Duration of follow up: 24 months

Intervention Type
Biological/Vaccine

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
CD4+CD25+CD127- T regulatory cells (Tregs) preparation, rituximab

Primary outcome(s)
1. Number of adverse effects assessed from histories taken from patients, obtained during physical examination and laboratory tests at 2 years (week 104) after the first dose of Tregs
2. C-peptide level measured as fasted, post-MMTT stimulation and after glucagon test from peripheral blood at 2 years after the first dose of Tregs
3. Daily insulin dose per kg of body weight (DDI) assessed using patient records at 2 years after the first dose of Tregs
4. Number of treated patients in remission (the number of patients with daily insulin dose lower than 0.5U/kg/day and HbA1c lower than 6.5%) at 1 and 2 years after the first dose of Tregs

Key secondary outcome(s)
1. The following four secondary safety endpoints are documented as AEs of special interest (AESI) and related treatment-emergent AEs (TEAEs), where appropriate, throughout 24 months follow-up:
1.1. Assessment of the occurrence and severity of side effects directly related to Tregs (hypersensitivity reactions, injection-site thromboembolic events) and blood sampling (>2 g/dl drop in hemoglobin levels)
1.2. Assessment of the occurrence and severity of effects directly related to anti-CD20 antibody rituximab administration (hypersensitivity reactions)
1.3. Assessment of the occurrence and severity of side effects associated with administration of Tregs or anti-CD20 rituximab antibodies, primarily immunosuppressive effects: occurrence of infections of any etiology and de novo tumors detected
1.4. Any serious AE (SAE) in two or more patients with a confirmed association with the administration of therapy
2. The efficacy is documented as:
2.1. C-peptide level measured as fasted level from peripheral blood at weeks 2, 5, 12, 26, 39, 52, 65, 78, 92, and 104
2.2. C-peptide level measured post MMTT stimulation and after glucagon test from peripheral

blood at weeks 12, 26, 52, 78, and 104
2.3. Exogenous insulin dose per kg of body weight assessed using patient records at weeks 2, 3, 4, 5, 12, 14, 26, 39, 52, 65, 78, 92, and 104
2.4. The proportion of insulin-independent patients (DDI = 0 UI/kg body weight [b.w.]) assessed using patient records at weeks 52 and 104
2.5. The proportion of patients in remission (DDI ≤0.5 UI/kg b.w. and HbA1c lower than 6.5%) assessed using patient records and laboratory tests at weeks 52 and 104
2.6. HbA1c level (%) measured using patient records and laboratory tests at week 2, 5, 12, 26, 39, 52, 65, 78, 92, and 104
2.7. Glycemic control (fasting average of 7 days) measured using patient records and laboratory tests at week 2, 5, 12, 26, 39, 52, 65, 78, 92, and 104
2.8. The amount and intensity of side effects of therapy assessed from histories taken from patients, obtained during physical examination and laboratory tests at weeks 52 and 104
2.9. Peripheral blood lymphocyte immunophenotype measured using flow cytometry tests at weeks 2, 5, 12, 14, 26, 39, 52, 65, 78, 92, and 104 with basic phenotype results

Completion date
31/12/2019

Eligibility

Key inclusion criteria
1. 8 to 16 years of age
2. BMI in the range of 25-75 percentiles (according to OLAF)
3. Fasting plasma C-peptide more than 0.7 ng/ml and in a stimulation test the increase is ≥100%
4. The presence of anti-islet autoantibody (ICA, IAA, GAD) - high titer one of the antibodies (≥4 times the norm, not applicable ICA) or low titer of two or three antibodies (2-4 times the norm)
5. Ability to provide written informed consent by parents (and patients if above 16 years old)
6. Involvement of the patients and parents in the intensive diabetes management defined as self-monitoring of glucose values no less than three times per day and by the administration of insulin
7. Appropriate venous access for blood drawing

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
8 Years

Upper age limit
16 Years

Sex
All

Total final enrolment
45

Key exclusion criteria
1. No agreement for participation in the study and no informed consent signed
2. Other than autoimmune type 1 diabetes
3. Age below 8 and above 16 years
4. IgA deficiency or other genetic defect present
5. BMI <25 or >75 percentiles for a particular age
6. Hypersensitivity to anti-CD20 or other components of the preparation
7. Presence or history of active infection including hepatitis B, hepatitis C, HIV, tuberculosis (TB) or syphilis. Subjects with laboratory evidence of active infection are excluded even in the absence of clinical evidence of active infection
8. Presence of active EBV virus infection (positive IgM)
9. Presence or history of active systemic fungal infection
10. Any history of malignancy
11. Anemia, lymphopenia, neutropenia or thrombocytopenia below the lower limits of the reference range during the 6 weeks before study
12. Known hypercoagulative state
13. Medical treatment requiring chronic use of drugs other than insulin longer than 3 months
14. Treatment with any anti-diabetic medication other than insulin within 4 weeks of enrolment
15. Diabetic retinopathy
16. Arterial hypertension
17. Presence or history of macroalbuminuria
18. For female subjects older than 15 years positive pregnancy test, unwillingness to use effective contraceptive measures for the duration of the study and 4 months after discontinuation, when appropriate
19. For male subjects: intent to procreate during the duration of the study or within 4 months after discontinuation when appropriate
20. Excessive anxiety of the patient or parents related to the procedures
21. Any medical condition that, in the opinion of the investigator, will interfere with safe participation in the trial
22. For parents and children older than 15 years: known active alcohol or substance abuse

Date of first enrolment
02/06/2015

Date of final enrolment
20/09/2017

Locations

Countries of recruitment
Poland

Study participating centre
Klinika Pediatrii, Diabetologii i Endokrynologii, Uniwersyteckie Centrum Kliniczne w Gdańsku
ul. Dębinki 7
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Study participating centre
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Study participating centre
Klinika Pediatrii, Onkologii, Hematologii i Diabetologii Uniwersytet Medyczny w Łodzi
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Poland
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Study participating centre
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Sponsor information

Organisation
Gdańsk Medical University

ROR
https://ror.org/019sbgd69

Organisation
Poltreg S.A.

Funder(s)

Funder type
Government

Funder Name
Narodowe Centrum Badań i Rozwoju

Alternative Name(s)
National Centre for Research and Development, The National Centre for Research and Development, Polish National Center for Research and Development, National Center for Research & Development, NCBR, NCBiR, NCRD

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Poland

Funder Name
Horizon 2020 Framework Programme

Alternative Name(s)
EU Framework Programme for Research and Innovation H2020, Horizon 2020, Horizon 2020 Framework Programme (H2020), Rahmenprogramm Horizont 2020, Horizont 2020, Programa Marco Horizonte 2020, Horizonte 2020, Programme-cadre Horizon 2020, Orizzonte 2020, Programma quadro Orizzonte 2020, H2020

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in the NIDDK Central Repository website. The data will be fully anonymized and access will be available according to the rules of the NIDDK Central Repository.

IPD sharing plan summary

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Abstract results		19/04/2022	21/04/2022	No	No
Other unpublished results	version 1.0	18/11/2020	05/05/2022	No	No
Other unpublished results	Integrated data analysis	18/11/2020	05/05/2022	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file			04/02/2021	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes