ISRCTN06128462 https://doi.org/10.1186/ISRCTN06128462

Cellular therapy of type 1 diabetes with T regulatory cells

Submission date
24/08/2013

Recruitment status
No longer recruiting

Registration date
04/09/2013

Overall study status
Completed

Last Edited
05/12/2016

Condition category
Nutritional, Metabolic, Endocrine

[_] Prospectively registered
[_] 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 children as a result of destruction of pancreas the internal organ producing insulin. No insulin in the body results in high levels of sugar (glucose) in the blood. This is manifested as disease symptoms such as impaired consciousness leading to complete loss of consciousness called coma; excessive drinking and urination, and weight loss. In the long term, diabetes is responsible for damage to the kidneys, eyes and heart. Doctors can find early symptoms suggesting the beginning of diabetes or increased risk of the onset. The level of anti-islet antibodies and some features of our cells, 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 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 high numbers of the former cells. Unfortunately, the number of T regulatory cells in the blood is very low. It is estimated that one T regulatory cell can be found in a million of other blood cells and it is even more rare in patients with diabetes.
This study aims to evaluate for the first time the effect of infusion of T regulatory cells in children recently diagnosed with type 1 diabetes . We expect that this procedure will be sufficient to stop or at least delay the progress of diabetes.

Who can participate?
Male and female patients 5 to 18 years of age with recently diagnosed diabetes type 1.

What does the study involve?
We will take blood samples from children recently diagnosed with diabetes type 1 and separate T regulatory cells from the samples. Then, the number of these cells will be increased in the laboratory. If the number of T regulatory cells increases sufficiently, we will administer them back to the child as an treatment for diabetes. Before the administration, the cells will be carefully checked for safety and quality and the doctor will consult parents again about their decision about infusion. This is experimental therapy which was previously used in our hospital in healthy volunteers and in some other diseases. Up to now, we do not see any health problems in

patients treated with these cells. Nevertheless, for the safety of children, patients will be under special medical care during the blood drawing and infusion of T regulatory cells. We will also ask children and their parents to visit the hospital two weeks later, every two months for the first half a year, then every 3 months for the duration of the study (2 years) in order to assess the health status of the child. Whenever possible, these visits will be together with normal visits to the outpatient clinic. During these visits after T regulatory cell infusion, we will draw a small amount of blood in order to perform necessary laboratory tests.

What are the possible benefits and risks of participating?
Patients will receive therapy which may stop or delay the onset of type 1 diabetes. Like in all medical procedures there is a risk that the procedures of blood drawing and T regulatory cell production fail and the child is then disqualified from further trial. The risks of blood drawing and administration of Tregs are mainly associated with the bleeding and bruises around the site of injection, fainting and febrile reactions. Administration of Tregs is a therapy that reduces the immune response and theoretically in the long term it carries the risk of increased susceptibility to infections and promotion of tumours. These reactions have been never noticed after infusion of Tregs but they cannot be excluded.
At any time, patients are allowed to stop their participation in the study. The wish will be fully respected and will not affect routine treatment .
All information obtained by the investigators during this study are kept confidential. All information on patients and families will only be used for the purpose of this study and will be not used in any other purpose. In particular, the information will not be shared with other people and institutions unless written consent is given for that. The exceptions for that are representatives of the approved government agencies, the Ethics Committee, and other regulatory agencies when approval is given by appropriate court.
There is an option for blood storing for future analysis in this study. It will be only performed if patients and parents agree in a separate document.

Where is the study run from?
The experiment will be performed in the Department of Pediatrics, Hematology and Oncology Medical University of Gdańsk, Poland.

When is the study starting and how long is it expected to run for?
The study started in March 2011 and it is expected to run until October 2014.

Who is funding the study?
The study is funded by the National Centre for Research and Development Poland.

Who is the main contact?
Piotr Trzonkowski MD PhD
ptrzon@gumed.edu.pl

Contact information

Type(s)
Scientific

Contact name
Dr Piotr Trzonkowski

Contact details

Medical University of Gdansk
Department of Clinical Immunology and Transplantology
Debinki 7
Gdansk
Poland
80-952
+48 (0)58 349 15 93
ptrzon@gumed.edu.pl

Additional identifiers

Protocol serial number
NKEBN/8/2010

Study information

Scientific Title
Cellular therapy of type 1 diabetes with ex vivo expanded CD4+CD25+CD127- T regulatory cells

Acronym
TregVac

Study objectives
Type 1 diabetes is a condition in which pancreatic islets are destroyed by self-reactive T cells. The process is facilitated by deficits in the number and suppressive activity of T regulatory cells (Tregs). Here, we evaluate for the first time the effect of infusion of autologous Tregs in recently diagnosed type 1 diabetes in children. We expect that this procedure will be sufficient to stop or at least delay the progress of diabetes.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Independent Ethics Committee Medical University of Gdansk, last amendment 01/05/2012, agreement no NKEBN/8/2010

Study design
Prospective non-randomised pilot non-commercial study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Diabetes type 1

Interventions

Patients will receive a single or double intravenous infusions of ex vivo expanded autologous CD4+CD25+CD127- T regulatory cells (Tregs) in a total dose of up to 30x106cells/kg b.w. All the patients will be on standard insulin therapy.
Control group will consist of patients fulfilling the inclusion criteria whose blood cannot be drawn due to inappropriate venous access.

Intervention Type
Biological/Vaccine

Primary outcome(s)
1. The proportion of subjects with no reported adverse effects of the treatment from day 0 to two years after administration of Tregs. The day of Tregs infusion is designated Day 0 (as recommended by the Ethics Committee).
2. The proportion of subjects with daily insulin dose (DDI) ≤ 0.5UI/kg b.w. and plasma fasting C-peptide levels more than 0.5ng/mL present without any stimulation at Day 365. The day of Tregs infusion is designated Day 0.

Key secondary outcome(s))
1. The proportion of subjects with daily insulin dose (DDI) ≤ 0.5UI/kg b.w. and plasma fasting C-peptide levels >0.5ng/mL present without any stimulation at 120days after the administration of Tregs. The day of Tregs infusion is designated Day 0.
2. The proportion of subjects with daily insulin dose (DDI) ≤ 0.5UI/kg b.w. and plasma fasting C-peptide levels >0.5ng/mL present without any stimulation from Day 0 to two years after the administration of Tregs. The day of Tregs infusion is designated Day 0.
3. The proportion of subjects with ≥15% reduction of DDI/kg b.w. from baseline at 120days after the administration of Tregs. The day of Tregs infusion is designated Day 0.
4. The proportion of subjects with ≥15% reduction of DDI/kg b.w. from baseline at 2 years after the administration of Tregs. The day of Tregs infusion is designated Day 0.
5. The proportion of subjects with ≥2% reduction of HbA1c from baseline at 120days after the administration of Tregs. The day of Tregs infusion is designated Day 0.
6. The proportion of subjects with HbAlc ≤6.5% at 120days after the administration of Tregs. The day of Tregs infusion is designated Day 0.
7. The proportion of subjects with HbAlc ≤7.0% at 120days after the administration of Tregs. The day of Tregs infusion is designated Day 0.
8. The proportion of subjects with HbAlc ≤6.5% at Day 365. The day of Tregs infusion is designated Day 0.
9. The proportion of subjects with HbAlc ≤7.0% at Day 365. The day of Tregs infusion is designated Day 0.
10. The proportion of subjects with HbAlc ≤6.5% from Day 0 to two years after the administration of Tregs. The day of Tregs infusion is designated Day 0.
11. The proportion of subjects with HbAlc ≤7.0% from Day 0 to two years after the administration of Tregs. The day of Tregs infusion is designated Day 0.

Completion date
01/10/2014

Eligibility

Key inclusion criteria

TREGS STUDY ARM
1. Male and female patients 5 to 18 years of age.
2. Ability to provide written informed consent by parents (and patients if above 16years old)
3. Clinical history of autoimmune type 1 diabetes diagnosed within recent 2 months and presence of at least one type of anti-islet autoantibody: antiGAD, antiIA2, IAA, ICA (high titer).
4. Fasting plasma C-peptide more than 0.4ng/mL
5. Involvement of the patients and parents in the intensive diabetes management defined as self monitoring of glucose values no less than three times/ day and by the administration of insulin injections each day or insulin pump therapy.
6. Patient and parents mentally stable and able to comply with the procedures of the study protocol.
7. Appropriate venous access for blood drawing.

CONTROL GROUP ARM :
1. Patients fulfilling the inclusion criteria from 1 to 6 but
2. EXCLUDED from blood drawing due to inappropriate venous access.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
5 years

Upper age limit
18 years

Sex
All

Key exclusion criteria
1. No agreement for participation in the study and no inform consent singed
2. Other than autoimmune type 1 diabetes
3. Age below 5 and above 18 years at the time of recruitment
4. Carriage of HLA-DQB1*0602 allele
5. IgA deficiency or other genetic defect present
6. Body mass index (BMI) outside the range of 25-75 percentiles for a particular age.
7. Presence or history of active infection including hepatitis B, hepatitis C, HIV, syphilis or tuberculosis (TB). Subjects with laboratory evidence of active infection are excluded even in the absence of clinical evidence of active infection.
8. Invasive aspergillus, histoplasmosis, or coccidioidomycosis infection within one year prior to study enrollment.
9. Any history of malignancy
10. Baseline Hb below the lower limits of the reference range ; lymphopenia (<l,000/uL), neutropenia (<l,500/uL), or thrombocytopenia (platelets <100,000/uL).
11. Known hypercoagulative state.

12. Medical treatment requiring chronic use of drugs other than insulin
13. Treatment with any anti-diabetic medication other than insulin within 4 weeks of enrolment (special attention to exclude anti-CD3 treated patients).
14. Diabetic retinopathy.
15. Arterial hypertension.
16. Presence or history of macroalbuminuria (>300 mg/g creatinine).
17. 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. For male subjects: intent to procreate during the duration of the study or within 4 months after discontinuation or unwillingness to use effective measures of contraception when appropriate.
18. Excessive anxiety of the patient or parents related to the procedures.
19. Any medical condition that, in the opinion of the investigator, will interfere with safe participation in the trial.
20. For parents and children older than 15 years: known active alcohol or substance abuse.

Date of first enrolment
01/03/2011

Date of final enrolment
01/10/2014

Locations

Countries of recruitment
Poland

Study participating centre
Medical University of Gdansk
Gdansk
Poland
80-952

Sponsor information

Organisation
Medical University of Gdansk (Poland)

ROR
https://ror.org/019sbgd69

Funder(s)

Funder type

Government

Funder Name
Narodowe Centrum Badań i Rozwoju (ref: Grant no NR13-0126-10)

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

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/09/2012		Yes	No
Results article	results	01/07/2014		Yes	No
Results article	results	01/12/2016		Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes