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Balancing "bad" and "good" immune cells: testing a novel method for monitoring an immunosuppression strategy in people with Type 1 diabetes

Submission date
14/01/2025

Recruitment status
Recruiting

Registration date
07/03/2025

Overall study status
Ongoing

Last Edited
07/03/2025

Condition category
Nutritional, Metabolic, Endocrine

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Type 1 diabetes (T1D) is caused by autoimmunity when the body's own white blood cells damage the insulin-producing cells (beta-cells). Researchers are trying to develop treatments (immunotherapies) that can stop autoimmunity by switching off these damaging white cells that work in silence until it is too late to intervene. We currently have no way of measuring the activity of the autoimmune process in T1D, so we have to design research studies by measuring the individual's insulin production. These effects change slowly requiring long studies that are often found to be unsuccessful after lots of money and time had been spent. We want to develop a way to identify potentially effective drugs based on their effect on autoimmunity in smaller and quicker studies. This study aims to establish a robust and quick method to test the impact of immunotherapies on the autoimmune process.

Who can participate?
Patients aged 18 to 50 years who have been diagnosed with Type 1 diabetes 3 months to 5 years before entering the study

What does the study involve?
We will give participants two drugs: abatacept and interleukin-2, which have been shown to slow autoimmune processes in other diseases. Both drugs are licensed for use in other diseases and have been used in T1D research. They have a very good safety profile but when used separately they showed a modest effect on preserving insulin-producing cells. We think that combination will work better because abatacept will deal with "bad" cells (drivers of the autoimmunity) whilst IL-2 will protect "good" cells (controllers of autoimmunity). These interventions will elicit predictable changes in immune cells that will allow us to test our sampling method.
We will use state-of-the-art cell-tracking techniques ("heavy water" labelling and flow cytometry) to isolate and analyse individual cells and perform mathematical modelling of trajectories of immune cells. We will look into blood and lymph nodes. Lymph nodes are little glands throughout the body that are full of white blood cells that are relevant for the

autoimmune process.
Once proven, our method can be used to triage promising drugs before proceeding with the assessment of their metabolic effect in a large clinical trial.

What are the possible benefits and risks of participating?
This study demands substantial patient commitment due to its complexity and frequency of visits. The researchers consulted their Patient and Public Involvement (PPI) panel through our Type 1 UK Immunotherapy Consortium. PPI members were very supportive of the study and acknowledged the importance of making a paradigm change in the treatment approach to T1D i. e., preventing rather than replacing the loss of insulin. They emphasised the importance of the balance between altruistic motives for participation and potential individual benefit from the study intervention in this complex study. Based on the PPI panel, the researchers made the following changes in the study design to make the study more acceptable for the potential participants:
1. The researchers will recruit patients with residual insulin production/C peptide (who have a prospect of benefit and active autoimmune response), which was particularly welcomed by the PPI panel.
2. The researchers will offer home visits to reduce the number of hospital-based study visits.
3. The researchers will tailor the timing of study visits to the participant's schedule (evenings, early mornings, weekends, school holidays) as long as it can be coordinated and supported by laboratories and research centres.
4. The researchers will use local databases to recruit local people to reduce the burden of long commutes to the study centre.
5. The researchers will make sure that the study is presented and explained to the potential participants by a consultant or other senior health care professional as the PPI panel emphasised that this procedure-heavy study needs to be explained to them by a knowledgeable person who they trust.
The researchers will make sure that participants are immunocompetent before entering the trial and have no evidence of latent tuberculosis or infections such as hepatitis or HIV. They will be regularly monitored during the study by a medical doctor and by doing safety blood tests.
Lymph node aspiration is routine, safe, short (less than 30 minutes including preparation) and minimally invasive technique widely used in clinical practice that will be performed by experienced consultant radiologists. The researchers' experience in using it in the research setting with over 50 patients is that it is very well tolerated and accepted by participants. Participants will be explained the procedure in detail including that it is done under local anaesthetic, which may feel as a light sting when administered.
Participants will have bottles of heavy water in their homes. They will be reassured that this is not toxic or radioactive material. They will receive instructions for the storage and disposal of the heavy water.
As they aim to test different methods (such as "heavy water" labelling, cytometry - method to sort, isolate and analyse cells on an individual basis and immune assays) the researchers require large blood volumes. Importantly no more than 470 ml will be taken over the course of 16 weeks, which is in concordance with guidance for blood donors. 470 ml is the volume normally taken during a single blood donation session. The researchers will make sure that participants way more than 50 kg (as per blood donation guidelines) and that they have normal red cell count, which will be regularly monitored during the study.

Where is the study run from?
It will be conducted in NHS sites affiliated with Cardiff University (University Hospital of Wales) and University College London (Royal Free Hospital London) (UK)

When is the study starting and how long is it expected to run for?
October 2024 to January 2027

Who is funding the study?
1. Steve Morgan Foundation
2. Breakthrough T1D
3. Diabetes UK

Who is the main contact?
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Contact information

Type(s)
Public, Scientific, Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
336032

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
24/WA/0283

Study information

Scientific Title
Treg-sparing co-stimulation blockade: testing a novel method for monitoring an immunosuppression strategy in people with Type 1 diabetes

Acronym
SMART

Study objectives
Immunotherapy in Type 1 diabetes (T1D) aims to stop beta-cell destruction in order to preserve the individual's ability to make their own insulin. This could lead to better control or even disease prevention. Recent FDA approval of teplizumab, the first-ever immunotherapy for T1D highlights the promise of this approach. However, new and better immunotherapies are needed, and we currently lack a good way to measure their effectiveness. Clinical trial endpoints are measured only through metabolic outcomes (stimulated C-peptide production), which change slowly, requiring long, large and expensive trials. Combination treatments that have revolutionised cancer immunotherapy, may bring breakthroughs in T1D too, but predicting which therapies will work best together presents a challenge. A logical approach would be to triage potentially effective therapies based on their immune effect in smaller and quicker mechanistic studies followed by larger clinical trials designed to assess metabolic efficacy.

This mechanistic study aims to establish a quick, effective, state-of-the-art method of identifying agents with favourable immunomodulatory profiles. Once identified, these can be tested for their impact on metabolic outcomes i.e., preservation of endogenous insulin production in early stages of T1D.

The researchers have chosen to use the combination of two drugs, abatacept and interleukin 2 (IL-2) because of their established safety profiles and the suggestion that in combination they will induce predictable changes to immune cells that would be suitable to test our methodology.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 23/10/2024, Wales REC 1 (Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, United Kingdom; +44 (0)292078738; wales.rec1@wales.nhs.uk), ref: 24/WA/0283

Study design
Two-centre open-label mechanistic feasibility study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Other

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

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

Interventions
Group 1: Abatacept at weeks 0, 2, 4 and 8 in combination with Interleukin-2 only for 16 weeks starting at week 0
Group 2: Abatacept only at week 0, 2, 4 and 8

Abatacept
Participants will receive 10 mg/kg intravenously (maximum 1000 mg per dose) at 0, 2, 4 and 8 weeks.

Interleukin-2
0.45 x 10e6 IU/m2 of body surface will be given twice weekly (every 3+/-1 days) subcutaneously.

Intervention Type
Other

Primary outcome measure
The feasibility of detecting that the decrease in Treg frequency associated with abatacept treatment in T1D is inhibited by appropriately dosed IL-2 therapy, measured using flow cytometry at Week 20 in comparison to baseline.

Secondary outcome measures
There are no secondary outcome measures

Overall study start date
01/10/2024

Completion date
21/01/2027

Eligibility

Key inclusion criteria
1. Aged 18-50 years
2. Diagnosis of Type 1 diabetes in the last 5 years, but not earlier than 3 months
3. Written and witnessed informed consent to participate
4. Detectable non-fasting C-peptide in the blood at screening

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit

50 Years

Sex
Both

Target number of participants
24

Key exclusion criteria
1. Females who are pregnant, breastfeeding, anticipating being pregnant within 14 weeks of the last study drug administration or not using adequate forms of contraception. Males whose partners are WOCBP and not using an adequate form of contraception. The following birth control methods should be used (considered highly effective with a failure rate of less than 1% per year when used consistently and correctly):
1.1. Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, transdermal
1.2. Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, implantable
1.3. Intrauterine device (IUD)
1.4. Intrauterine hormone-releasing system (IUS)
1.5. Bilateral tubal occlusion
1.6. Vasectomised partner (provided that the partner is the sole sexual partner of the trial participant, and that medical assessment of azoospermia has been confirmed)
1.7. Sexual abstinence (defined as refraining from heterosexual intercourse during the duration of the trial)
2. Use of immunosuppressive or immunomodulatory therapies, including systemic steroids within 1 month prior to randomisation and any monoclonal antibody therapy given for any indication
3. Immunisations with live vaccines within 1 month from screening
4. Immunodeficient or have clinically significant lymphopaenia
5. Patients with White Blood Count (WBC) <4.000/mm3; platelets < 100.000/mm3; haematocrit (HCT) <30%.
6. Have an active infection at the time of randomisation
7. Have positive Purified Protein Derivative (PPD) or IGRA (interferon-gamma release assay) result or history of previously treated tuberculosis
8. Have serological evidence of current or past HIV, Hepatitis B (positive for Hepatitis B core antibody or surface antigen), or Hepatitis C infection
9. Have a history of malignancies
10. Have multiple sclerosis
11. Patients with a significant history or current evidence of severe cardiac disease
12. Patients with pre-existing severe major organ dysfunction
13. Patients with seizure disorders
14. Patients with organ allografts
15. Patients with pre-existing auto-immune disease except for Type 1 diabetes and primary hypothyroidism
16. Patients with serum bilirubin (except for Gilbert’s syndrome) and creatinine outside normal range
17. Weight <50 kg
18. Any other medical condition, which, in the opinion of investigators, could affect the safety of the subject’s participation
19. Recent subject’s involvement in other research studies which, in the opinion of investigators,

may adversely affect the safety of the subjects or the results of the study
20 .HbA1c >90 mmol/mol measured in the last 3 months

Date of first enrolment
21/01/2025

Date of final enrolment
21/01/2026

Locations

Countries of recruitment
England

United Kingdom

Wales

Study participating centre
Cardiff ECMC
Cardiff University
University Hospital of Wales
Heath Park
Cardiff
United Kingdom
CF14 4XN

Study participating centre
Royal Free London NHS Foundation Trust
Royal Free Hospital
Pond Street
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United Kingdom
NW3 2QG

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Sponsor type
University/education

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ROR
https://ror.org/03kk7td41

Funder(s)

Funder type
Charity

Funder Name
Steve Morgan Foundation

Funder Name
Breakthrough T1D

Funder Name
Diabetes UK

Results and Publications

Publication and dissemination plan
Planned publication in peer-reviewed journal.

Intention to publish date
21/01/2028

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary

Data sharing statement to be made available at a later date