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Plasma cell depletion for Graves’ disease trial

Submission date
14/06/2021

Recruitment status
No longer recruiting

Registration date
01/07/2021

Overall study status
Completed

Last Edited
18/03/2025

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered

[X] Protocol

[X] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
Graves' disease gives symptoms such as heart palpitations, heat intolerance, unintended weight loss, enlarged thyroid, red and swollen eyelids, protuberant eyeballs and double vision. Patients with severe Graves' disease frequently have disabling eye disease and occasionally loss of vision. Treatment with antithyroid drugs lead to remission in only around 50% of people, which falls to around 20% for people with severe Graves' disease, and does not improve the eye problems. Patients with severe Graves' disease often have their thyroid gland removed surgically, followed by several eye operations to correct the visual function and appearance of the eyes. These are expensive operations with low overall patient satisfaction. Better treatments are needed.

This Medical Research Council funded trial will find out whether a new treatment called daratumumab that has been developed to treat plasma cell cancer, could also be used to target the benign (non-cancerous) plasma cells in patients with severe Graves' disease.

Who can participate?
Patients who are 18 or over and have been diagnosed with a severe Graves’ disease episode within the last 12 months.

What does the study involve?
This study will perform a two-stage randomised trial of daratumumab in 30 patients with severe Graves' disease. Because daratumumab has not been used in Graves' disease before, the first part of our study will administer 4 different doses or a placebo “dummy drug” to small groups of participants to see which of the doses works best. In stage 2 of the study, 1 or 2 of the best daratumumab doses or a placebo will be used to treat larger groups of patients. The daratumumab or placebo is given twice by intravenous infusion to each participant, and participants will be followed up in a further 4 clinic appointments across 6 months.

What are the possible benefits and risks of participating?
The reason this is a trial is that we do not know whether the treatment will work, so we cannot promise that it will benefit participants directly. However, the information we get from this study may help to improve treatment for people with severe Graves’ disease in the future.

All participants will receive background treatment with anti-thyroid medication, which is the same as standard-of-care treatment outside of the trial. The safety profile of daratumumab

when used for myeloma is well understood and there are no specific risks in the Graves' disease population who in general will be younger and in better overall health than myeloma patients. The most common side-effect of daratumumab is infusion-related reactions which are normally short-lived feelings like the flu (temperature, aches, blocked nose). Therefore, before each treatment session participants will be given medication to help to lower the chance of this type of reaction, and will be monitored closely throughout the treatment. The safety of patients will be closely monitored throughout the trial through clinical exams and blood tests.

Where is the study run from?
The Newcastle upon Tyne Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
February 2021 to October 2024

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Graves-PCD Trial Manager
graves.pcd@newcastle.ac.uk

Contact information

Type(s)
Scientific

Contact name
Dr Faye Wolstenhulme

Contact details
Graves-PCD Trial Manager
Newcastle Clinical Trials Unit
Newcastle University
1-4 Claremont Terrace
Newcastle upon Tyne
United Kingdom
NE2 4AE
-
graves.pcd@newcastle.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2020-005635-78

Integrated Research Application System (IRAS)
1003652

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 49543, Grant Codes: MR/V005898/1, IRAS 1003652

Study information

Scientific Title
Randomised controlled trial of plasma cell depletion for severe Graves' disease

Acronym
Graves-PCD

Study objectives
This trial will determine proof of concept that the plasma cell depleting antibody daratumumab can ameliorate severe Graves' disease and determine an optimal dose for this therapeutic use.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 08/07/2021, London – Hampstead REC (Health Research Authority, Skipton House, 80 London Road, London, SE1 6LH, UK; +44 (0)207 104 8328; hampstead.rec@hra.nhs.uk), ref: 21/LO/0449

Study design
Interventional randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Graves' disease

Interventions
Stage 1 is a dose-response study using 4 doses of daratumumab (9 mg/kg, 3 mg/kg, 1 mg/kg, 0.5 mg/kg) and a colourless, volume-matched placebo infusion in approximately 15 patients (i.e. five groups of n = 3). Participants will be randomised between arms using an online tool. Following Stage 1, an interim analysis will be performed in order to select an optimal dose(s) of daratumumab for Stage 2.

In stage 2, the remaining patients will be randomised between placebo and one or two chosen doses of daratumumab depending on the results of the interim analysis. The daratumumab or placebo will be given twice by intravenous infusion to each participant and all participants will receive paracetamol (1 g po), methylprednisolone (100 mg IV) and chlorphenamine (10 mg IV) directly prior to each treatment to lower the chance of infusion-related reactions. Patients will continue their regular medications, including antithyroid drugs and beta blockers throughout the study, as deemed appropriate by the clinical team. Participants will be followed up in a further 4 clinic appointments across 6 months.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Daratumumab (Darzalex)

Primary outcome(s)
Serum TRAb antibodies measured using blood samples at baseline and 12 weeks

Key secondary outcome(s))
1. Serum TRAb antibodies measured using blood samples at baseline and 2, 4, 6, 12 and 24 weeks
2. Dose-response curve for daratumumab against serum TRAb antibodies measured using blood samples at baseline and 6 and 12 weeks
3. Serum FT3 & FT4 measured using blood samples at baseline and 2, 4, 6, 12 and 24 weeks
4. Serum TSH measured using blood samples at baseline and 2, 4, 6, 12 and 24 weeks
5. Thyroid volume measured by ultrasound at baseline and 24 weeks
6. Serum ATPO and thyroglobulin antibodies measured using blood samples at baseline and 6, 12 and 24 weeks
7. CAS, composite eye index and GOQoL score measured using an eye exam and a patient completed questionnaire at baseline and 6, 12 and 24 weeks
8. ThyPRO39 score measured using a patient completed questionnaire at baseline and 6, 12 and 24 weeks
9. Serum immunoglobulins, specific antibodies including (SARS-CoV2) and blood count parameters measured using blood samples from baseline and 6, 12 and 24 weeks
10. Adverse Reactions to 24 weeks measured using patient and clinician reported adverse events

Exploratory outcome measures
1. Analysis of blood plasma cell markers and mRNA signature measured using blood samples at baseline and 6, 12 and 24 weeks
2. Lymphocyte subsets (by FACS) measured using blood samples at baseline and 6, 12 and 24 weeks

Completion date
31/10/2024

Eligibility

Key inclusion criteria
Current inclusion criteria as of 23/02/2024:

1. Patients ≥18 years old
2. Recent-onset Graves' disease (within 12 months) (defined as the date of first thyroid function test showing hyperthyroidism (FT4 and TSH) in the current episode)
3. TRAb antibody concentrations above 10 U/L (on Roche or Brahms TBII assays)
4. One or more of:
4.1. Pre-treatment severe hyperthyroidism (FT4 ≥50 pmol/L; or FT3 ≥15 pmol/l)
4.2. Persisting hyperthyroidism despite more than 12 weeks of antithyroid drug therapy (defined

as FT3 above the upper limit of the reference range following 12 weeks of carbimazole treatment at a dose of 40mg or more daily (or equivalent dose of PTU))
4.3. Inflammatory thyroid eye disease (defined as clinical activity score, CAS ≥3), or thyroid dermopathy
4.4. Large (visible) goitre (WHO grade III)
4.5 2 or more relapses (3 episodes in total) despite completing 12 months or more of medical treatment on each occasion. Relapse is defined as FT3 above the upper limit of the local reference range.
5. For women of childbearing potential, willing to use a highly effective contraceptive method during their participation in the trial.
6. Able to understand and speak sufficient English to complete trial procedures
7. Willing and able to provide informed consent prior to any trial procedures taking place

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1. Patients ≥18 years old
2. Recent-onset Graves' disease (within 12 months) (defined as the date of first thyroid function test showing hyperthyroidism (FT4 and TSH))
3. TRAb antibody concentrations above 10 U/L (on Roche or Brahms TBII assays)
4. One or more of:
4.1. Pre-treatment severe hyperthyroidism (FT4 ≥50 pmol/L; or FT3 ≥15 pmol/l)
4.2. Persisting hyperthyroidism despite more than 12 weeks of antithyroid drug therapy (defined as FT3 above the upper limit of the reference range following 12 weeks of carbimazole treatment at a dose of 40 mg or more daily (or equivalent dose of PTU))
4.3. Inflammatory thyroid eye disease (defined as clinical activity score, CAS ≥ 3), or thyroid dermopathy
4.4. Large (visible) goitre (WHO grade III)
5. For women of childbearing potential, willing to use a highly effective contraceptive method during their participation in the trial.
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Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
30

Key exclusion criteria
1. Previous thyroidectomy, or radioiodine treatment within 2 years
2. Pregnant or breastfeeding, or with a plan for pregnancy within 6 months
3. Previous shingles, known untreated cervical dysplasia, hepatitis B & C, or HIV infection
4. Anaemia (Hb ≤100g/l),thrombocytopenia (≤75 x10^9/L) or neutropenia (≤1.0 x10^9/L)
5. Known chronic obstructive pulmonary disease (COPD) (defined as a forced expiratory volume [FEV] in 1 second <60% of predicted normal), persistent asthma, or a history of asthma within the last 2 years (intermittent asthma without hospitalisation is allowed)
6. Any other significant physical or mental health conditions, e.g. major cardiorespiratory disease, renal or hepatic failure, pancreatitis, cancer undergoing active treatment (excluding non-melanoma skin cancer), untreated chronic infection including TB, psychosis, depression impairing Activities of Daily Living
7. Current use of immunosuppressive therapy for thyroid eye disease or other conditions (within 3 months)
8. Current or previous participation in a CTIMP research study within 4 months
9. Hypersensitivity or anaphylactic reaction to previous monoclonal antibody treatments or methylprednisolone
10. Inability, in the opinion of the investigator, to be able to complete the clinical trial visits or procedures.

Date of first enrolment
29/09/2021

Date of final enrolment
31/10/2023

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Royal Victoria Infirmary
The Newcastle upon Tyne Hospitals NHS Foundation Trust
Queen Victoria Road
Newcastle upon Tyne
United Kingdom
NE1 4LP

Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request from graves.pcd@newcastle.ac.uk

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		12/06/2024	13/06/2024	Yes	No
Basic results	version 1.0		18/03/2025	No	No
HRA research summary			28/06/2023	No	No
Statistical Analysis Plan	version 1.0	13/10/2022	08/11/2024	No	No
Statistical Analysis Plan	version 2.0	01/07/2024	08/11/2024	No	No