ISRCTN20381716 https://doi.org/10.1186/ISRCTN20381716

Rituximab in Graves' disease (RIGD)

Submission date 02/11/2016	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 03/11/2016	**Overall study status** Completed	
Last Edited 03/03/2022	**Condition category** Nutritional, Metabolic, Endocrine	

Plain English summary of protocol

Background and study aims
Graves' disease, also known as Graves' hyperthyroidism, is one of the most common conditions affecting the thyroid gland. The thyroid gland, located in the neck, is responsible for making thyroid hormones which play an important role in the regulation of brain activity, heart rate and gut function. In Graves' disease, the immune system mistakenly attacks the thyroid gland, causing it to become overactive and produce too much thyroid hormone. Treating Graves' disease is much more difficult in young people because the available drugs are less likely to cure the condition and are more likely to be associated with side-effects. Only 1 in 4 affected young people will be cured after a 2 year course of standard therapy, usually with the drug Carbimazole, (CBZ). The other treatments used to treat Graves' disease (surgery and treatment with radioactive iodine) are associated with additional risks in the young and could make the person dependent on life-long thyroid hormone replacement. Rituximab (RTX) is a medication used in the treatment of many immune disorders and works by targeting certain types of white blood cell, which are responsible for attacking the healthy parts of the body. The aim of this study is to find out whether the effects of RTX increase the likelihood of curing Graves' disease in young people when given with a shortened course of standard CBZ treatment.

Who can participate?
Graves' disease patients aged between 12-20 years who are at the beginning (first six weeks) of receiving treatment.

What does the study involve?
All participants receive a single dose of Rituximab through a drip at the start of the study. A relatively low dose of RTX is used (500mg) because it has recently been shown that this amount has the desired effect on the immune system in adults. Patients also receive a 12 month course of standard treatment with a drug such as Carbimazole. Over a period of two years, participants provide around 15 blood samples so that the effectiveness of the RTX treatment with the short course of standard therapy can be assessed.

What are the possible benefits and risks of participating?
The potential benefit of taking part is that treatment with RTX will reduce the likelihood of the thyroid gland over-activity returning when ATD is stopped. Around half of the people receiving a Rituximab infusion have a risk of experiencing some side effects. These can include, feeling hot or cold, shivering, feeling sick, or itchiness. Paracetamol, piriton and methylprednisolone (a

steroid medicine) are used to help prevent this. If symptoms do develop then the treatment will be stopped for a few minutes and then restarted at a slower rate when the patient feels better. In addition, because RTX is acting on the immune system, there is a small risk (1 in 50) that patients will develop an infection, such as pneumonia, after the they are given the drug through a drip (infusion). If this happens then subjects will receive antibiotic treatment. Most people have RTX without any infection occurring as a result.

Where is the study run from?
Department of Paediatric Endocrinology, Royal Victoria Infirmary (Lead centre) and nine other NHS hospitals in England and Scotland (UK)

When is the study starting and how long is it expected to run for?
September 2016 to February 2021

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

Who is the main contact?
Gillian Watson, gillian.watson@ncl.ac.uk
(updated 28/06/2021, previously: Dr Faye Wolstenhulme, faye.wolstenhulme@ncl.ac.uk)

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number
2016-000209-35

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers

32511

Study information

Scientific Title
Adjuvant rituximab – a potential treatment for the young patient with Graves' hyperthyroidism

Acronym
RIGD

Study objectives
This aim of this study is to examine whether the effects of rituximab (RTX) increase the likelihood of Graves' hyperthyroidism resolving in young people when administered in association with an abbreviated course of standard Carbimazole (CBZ) treatment.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Tyne and Wear South, 15/08/2016, ref: 16/NE/0253

Study design
Non-randomised; Both; Design type: Treatment, Drug, Cohort study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Treatment

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

Health condition(s) or problem(s) studied
Specialty: Children, Primary sub-specialty: Diabetes and endocrinology; UKCRC code/ Disease: Metabolic and Endocrine/ Disorders of thyroid gland

Interventions
The trial involves administering a 500mg dose of Rituximab (RTX) together with a 12 month course of anti-thyroid drug (Carbimazole [CBZ] or Propylthiouracil [PTU]) to each participant with Graves' hyperthyroidism. The trial team will follow the subjects for 2 years and the outcome will be whether or not they are in remission and hence no longer hyperthyroid at the end of this period. Typically 20 to 30 % of young patients with Graves' hyperthyroidism enter remission

after a 2 year course of anti-thyroid drug (ATD). If this pilot trial provides evidence that the remission rate is plausibly 40% or more, 2 years after a single dose of RTX and a 12 month course of ATD, then this will indicate a likely effect of RTX on disease outcome and justify a randomised efficacy evaluation of this adjuvant RTX regimen.

Only participants who have consented and who have then screened negative for hepatitis and who have submitted a negative pregnancy test will be recruited to this trial. All participants will receive the RTX infusion during the course of a day-case admission that will last around 6 hours. Participants will then be seen in clinic every 4 weeks for the first 6 months, every 8 weeks for the following 6 months and then every 3 months in the second year of the trial. The final trial visit will be 2 years after the RTX infusion. Subjects will undergo a routine clinical examination at each clinic visit and they will be asked about possible adverse events. A blood sample will be taken at each visit so that a range of parameters including thyroid status and markers of immune function can be assessed. There will be phone contact after each clinic visit so that participants can be informed of their blood results with advice regarding the potential need for a revised ATD regimen during the first 12 months.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
1. Rituximab 2. Carbimazole 3. Propylthiouracil

Primary outcome measure
Remission as assessed through measuring serum FT3 levels and serum thyroid stimulating hormone (TSH) concentrations in blood samples or the need for alternative treatment at 2 years.

Secondary outcome measures
1. TRAb titre and related thyroid hormone status measured in blood samples taken at the time of RTX administration, 1 year after RTX and then at 2 years post RTX at the final trial visit
2. Time to recovery of B cell lymphocyte numbers (CD 19+ cells) to the normal local lab reference range in relation to thyroid hormone status. The B cell lymphocyte numbers will be measured in a blood sample taken at baseline, then 4, 12, 28, 36, 52 weeks and then 2 years after the RTX infusion
3. Cumulative dose of ATD (mg/kg) in relation to thyroid hormone status 2 years post RTX treatment. The cumulative ATD dose will be calculated from information collected at each clinic visit. This information will be collected at the clinic visits that take place every 4 weeks for the first 6 months, every 8 weeks for the next 6 months and then every 3 months in the second year post RTX treatment
4. The time taken for TSH and thyroid hormone concentrations to normalise to within the local laboratory reference range post RTX and thyroid status in the period between cessation of ATD and the final trial visit 2 years post RTX. The TSH and thyroid hormone concentrations will be measured in blood samples taken every 4 weeks for the first 6 months, every 8 weeks for the next 6 months and then every 3 months in the second year post RTX treatment
5. The frequency and nature of adverse events. The information will be collected throughout the trial with subjects asked specifically about potential adverse events at clinic visits that take place

every 4 weeks for the first 6 months, every 8 weeks for the next 6 months and then every 3 months in the second year post RTX treatment. They will also be encouraged to contact the trial team between clinic visits if they are unwell

Overall study start date
30/09/2016

Completion date
28/02/2021

Eligibility

Key inclusion criteria
1. Excess thyroid hormone concentrations at diagnosis: elevated free tri-iodothyronine (FT3) and / or free thyroxine (based on local assay)
2. Suppressed (un-recordable) TSH (based on local assay)
3. Patients between the ages of 12-20 years inclusive who are less than 6 weeks from the initiation of anti-thyroid drug treatment (carbimazole or propylthiouracil) for the first time
4. Elevated thyroid binding inhibitory immunoglobulin or thyroid receptor antibodies (TRAb including TBII) based on local assay. Patients may or may not have a raised TPO antibody titre
5. All patients must be willing to use effective forms of contraception for 12 months post-treatment with Rituximab
6. If females are of childbearing potential, they must have a negative pregnancy test at screening. This will need to be repeated on the day of RTX administration if more than 7 days has elapsed since the screening visit or a negative pregnancy test.
7. Able and willing to adhere to a 2 year study period

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
Planned Sample Size: 27; UK Sample Size: 27

Total final enrolment
27

Key exclusion criteria
1. Previous episodes of autoimmune thyroid disease
2. Patients with an active, severe infection (e.g. tuberculosis, sepsis and opportunistic infections) or severely immunocompromised patients
3. Patients with known allergy or contraindication to carbimazole and propylthiouracil
4. Participants with previous use of immunosuppressive or cytotoxic drugs (including Rituximab and methylprednisolone but excluding inhaled glucocorticoid and oral glucocorticoid for asthma or topical glucocorticoid for eczema)

5. Chromosomal disorders known to be associated with an increased risk of autoimmune thyroid disease including Downs' syndrome and Turners' syndrome
6. Pregnancy, planned pregnancy during the study period or current breast-feeding
7. Absence of informed consent from parent/legal guardian for participants age < 16 years
8. Participants with previous use of immunosuppressive or cytotoxic drugs (including Rituximab and methylprednisolone but excluding inhaled glucocorticoid and oral glucocorticoid for asthma or topical glucocorticoid for eczema)
9. Participants with significant chronic cardiac, respiratory or renal disorder or non-autoimmune liver disease. • Participants with known allergy or contraindication to Rituximab or methylprednisolone
10. Participants with evidence of Hepatitis B/C infection, assessed by determining hepatitis 'B' surface antigen (HBsAg) status, hepatitis 'B' Core antibody (HB Core antibody) status and hepatitis 'C' virus antibody (HCV antibody) status
11. Participants in families who know they will be moving out of the catchment areas during the 2 years following RTX treatment
12. Participants currently involved in any other clinical trial of an IMP or who have taken an IMP within 30 days prior to trial entry

Date of first enrolment
04/11/2016

Date of final enrolment
08/08/2018

Locations

Countries of recruitment
England

Scotland

United Kingdom

Study participating centre
Royal Victoria Infirmary
Department of Paediatric Endocrinology
Newcastle upon Tyne
United Kingdom
NE1 4LP

Study participating centre
Royal Hospital for Sick Children
9 Sciennes Road
Edinburgh
United Kingdom
EH9 1LF

Study participating centre
Royal Infirmary of Edinburgh
51 Little France Crescent
Edinburgh
United Kingdom
EH16 4SA

Study participating centre
Birmingham Children's Hospital
Steelhouse Lane
Birmingham
United Kingdom
B4 6NH

Study participating centre
Queen Elizabeth Medical Centre
Mindelsohn Way
Birmingham
United Kingdom
B15 2TH

Study participating centre
Sheffield Children's Hospital
Western Bank
Sheffield
United Kingdom
S10 2TH

Study participating centre
Royal Hallamshire Hospital
Glossop Road
Sheffield
United Kingdom
S10 2JF

Study participating centre
Children & Young People's Diabetes Centre
Level 1, Multi-Speciality Outpatient Department
St. James's University Hospital

Leeds
United Kingdom
LS9 7TF

Study participating centre
St James's University Hospital
Leeds Centre for Diabetes & Endocrinology
Beckett Street
Leeds
United Kingdom
LS14 3AR

Study participating centre
Doncaster Royal Infirmary
Armthorpe Road
Doncaster
United Kingdom
DN2 5LT

Sponsor information

Organisation
Newcastle Upon Tyne Hospitals NHS Foundation Trust

Sponsor details
Freeman Hospital
Freeman Road
High Heaton
Newcastle Upon Tyne
England
United Kingdom
NE7 7DN

Sponsor type
Hospital/treatment centre

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, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal

Intention to publish date
28/02/2022

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a non-publically available repository EudraCT (https://eudract.ema.europa.eu/) and are available upon request from Dr Tim Cheetham (Chief Investigator, Tim.Cheetham@nuth.nhs.uk)

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	21/01/2019	12/02/2020	Yes	No
Results article		17/02/2022	03/03/2022	Yes	No
HRA research summary			28/06/2023	No	No