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Does rituximab added to usual treatment reduce kidney transplant failure following rejection?

Submission date
12/11/2018

Recruitment status
Stopped

Registration date
11/03/2019

Overall study status
Stopped

Last Edited
12/09/2023

Condition category
Injury, Occupational Diseases, Poisoning

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

Plain English summary of protocol

Background and study aims
Antibody-mediated rejection (AMR) is when the immune system of the person who has received a transplanted organ, known as the recipient, produces antibodies against the organ. This can lead to damage to the organ so that it does not function well. AMR is the leading cause of kidney transplant failure. How to best treat AMR is not known. Different treatment combinations are used across the world. This study aims to investigate whether a drug called rituximab, when added to the usual treatment for AMR, can improves transplant survival. Rituximab works by reducing the numbers of B cells, the white blood cells that produce antibodies. This drug is widely used in transplantation and in other diseases involving B cells.

Who can participate?
Patients aged 5 years or older with AMR of their kidney transplant

What does the study involve?
All patients will receive treatment accepted as standard of care for AMR. This involves the use of plasma exchange (a process that removes antibodies from a patient's body), together with steroids (to suppress immune system activity) and immunoglobulins (which inactivate antibodies). This treatment is given over approximately 2-3 weeks. One half of the patients will be allocated at random to receive rituximab. Rituximab is given through a patient's vein, and is administered in 2 separate doses, 2 weeks apart. After treatment, all patients will be followed up for a period of 4 years and have their transplant function monitored. Study visits will coincide with the usual hospital appointments.

What are the possible benefits and risks of participating?
There are no guaranteed benefits of taking part in the study. Use of immunosuppressants (drugs that reduce the activity of the immune system) leads to an increased risk of infection and cancer compared with the general population. All patients, regardless of whether they participate in the trial or not, will require immunosuppression to treat AMR. The side effects of rituximab include that in patients who have previously had hepatitis B, the infection might be reactivated. Patients with active hepatitis will be excluded and patients who have previously had hepatitis B

will be included or excluded from the trial on the decision of the researchers. There is also a very small chance of the brain condition progressive multifocal leukoencephalopathy (PML) with rituximab, but research suggests that this occurs in less than one in 25,000 people taking rituximab.

Where is the study run from?
The study is planned to take place across approximately 24 different hospitals, with Imperial College Healthcare NHS Trust being the lead centre.

When is the study starting and how long is it expected to run for?
November 2018 to February 2026

Who is funding the study?
The study is funded jointly by Kidney Research UK and the National Institute for Health Research.

Who is the main contact?
The chief investigator is Dr Michelle Willicombe
The trial contact is Dr Graham Armstrong, graham.armstrong@addenbrookes.nhs.uk

Contact information

Type(s)
Public

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Dr Graham Armstrong

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Additional identifiers

EudraCT/CTIS number
2018-002882-20

IRAS number

ClinicalTrials.gov number
NCT03994783

Secondary identifying numbers
1.0; CPMS 40785

Study information

Scientific Title
Transplant Antibody Mediated Rejection: Guiding Effective Treatments (TAR:GET-1): A multicentre randomised controlled trial to assess the safety and efficacy of rituximab compared with control in treating acute antibody-mediated rejection in kidney transplantation

Acronym
TAR:GET-1

Study objectives
The study aims to test the hypothesis of whether rituximab in addition to standard of care treatment (plasma exchange, IVIG and corticosteroids) is more effective than standard of care alone in treating antibody-mediated rejection of kidney transplants.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 17/04/2019, London – West London & GTAC REC (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, United Kingdom; +44 (0)2071048007; NRESCommitte.London-WestLondon@nhs.net), ref: 19/LO/0180

Study design
Multicentre phase 3 open-label randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format at this time.

Health condition(s) or problem(s) studied
Antibody-mediated kidney transplant rejection

Interventions
Patients will be stratified by age and kidney transplant function and randomised at a 1:1 ratio to receive standard of care treatment alone or standard of care plus rituximab. All patients will

receive standard of care treatment, which involves 7 plasma exchanges, intravenous immunoglobulins and corticosteroids (3 doses intravenous methylprednisolone followed by oral corticosteroids). This treatment will occur over a 2- to 3-week period. Those in the rituximab group will also receive rituximab dosed at 2 x 375 mg/m2, given 2 weeks apart. Each patient will be followed up for a period of 48 months following randomisation.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Rituximab

Primary outcome measure
Allograft survival, defined as the duration from the date of randomisation to the date of starting dialysis dependency or date of eGFR <15 mL/min/1.73 m2, with follow-up of 48 months.

Secondary outcome measures
1. Serum creatinine) at 1, 3, 6, and 12 months post-randomisation and then annually until 4 years
2. Estimated GFR (CKD-EPI)) at 1, 3, 6, and 12 months post-randomisation and then annually until 4 years
3. Proteinuria (urinary protein:creatinine ratio)) at 1, 3, 6, and 12 months post-randomisation and then annually until 4 years
4. Donor-specific antibody (DSA) positivity at 3 and 12 months
5. Number of different DSA at at 3 and 12 months
6. Level of the immunodominant DSA assessed using mean fluorescence index at 3 and 12 months
7. Adverse event rate assessed by reviewing patient medical records
8. Patient-reported health-related quality of life , assessed using EQ-5D-5L/EQ-5D-Y questionnaires at baseline, 3 months, and 1, 2, 3 and 4 years following transplantation
9. Economic analysis of cost per quality-adjusted life year (QALY) gained from the perspective of the NHS

Overall study start date
01/11/2018

Completion date
01/02/2026

Reason abandoned (if study stopped)
Objectives no longer viable

Eligibility

Key inclusion criteria
1. Informed consent provided by patient or by a parent or legal guardian for patients aged <16 years
2. Aged 5 years or older

3. Diagnosis of acute antibody-mediated rejection (AMR) as defined by:
3.1. The presence of ≥1 donor-specific antibodies (DSA)
3.2. An adequate transplant biopsy (≥7 glomeruli and ≥1 artery) with histological features consistent with active AMR with no evidence of chronicity as defined by the Banff histological classification of allograft pathology:
3.2.1. If C4d positive (2 or 3): v score (for arteritis) ≥1 and/or thrombotic microangiopathy and/or g score (for glomerulitis) ≥1 and/or ptc score (for peritubular capillaritis) ≥1, or if co-existing cellular rejection, a g score ≥1
3.2.2. If C4d negative (0 or 1): microcirculation inflammatory score (g + ptc) ≥2, or if co-existing cellular rejection, a g score ≥1 and (g + ptc) ≥2 plus chronic glomerulopathy (cg) score 0 or 1a, or tubulo-interstitial fibrosis <50% and glomerular obsolescence <50%

Participant type(s)
Patient

Age group
Mixed

Sex
Both

Target number of participants
170

Key exclusion criteria
1. ABO-incompatible transplant
2. Received rituximab as part of induction or post-transplant for any other indications within the preceding 12 months (eg. recurrent focal and segmental glomerular sclerosis)
3. Received complete plasma exchange (PEX) treatment prior to the index biopsy on the suspicion of acute AMR in the absence of histology
4. Active infection including bacterial, viral (including CMV and EBV) or fungal infection or tuberculosis, which in the investigator's opinion could affect the conduct of the study
5. Co-existing BK nephropathy
6. Active hepatitis B or hepatitis C (patients with prior exposure to hepatitis B may be enrolled at the discretion of the PI; patients may be included if a negative hepatitis C recombinant immunoblot assay is confirmed or have a negative hepatitis C virus RNA [qualitative] test), or subjects with suspected human immunodeficiency virus (HIV) infection
7. Active malignancy
8. Known allergy, intolerance or contraindication to the treatments in the standard of care arm or rituximab as outlined in the Summaries of Product Characteristics (SmPCs)
9. Clinically significant comorbidity
10. Females must be either post-menopausal for at least 1 year, surgically sterile or, if of child-bearing potential, must not be pregnant or lactating. If sexually active, must agree to use an acceptable method of birth control for the first year post-randomisation.

Date of first enrolment
01/02/2019

Date of final enrolment
01/08/2022

Locations

Countries of recruitment
England

Northern Ireland

Scotland

United Kingdom

Wales

Study participating centre
Imperial College Healthcare NHS Trust
Hammersmith Hospital, Du Cane Road, Acton. W12 0HS
London
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W12 0HS

Study participating centre
Cambridge University Hosptials NHS Foundation Trust
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Study participating centre
OXFORD UNIVERSITY HOSPITALS NHS FOUNDATION TRUST
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Study participating centre
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Study participating centre
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Study participating centre
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Study participating centre
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Study participating centre
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Study participating centre
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Sponsor information

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Sponsor type
University/education

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Charity

Funder Name
Kidney Research UK

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan

Study results will be presented at national and international transplant conferences and published in a high-impact peer reviewed journal.

Intention to publish date
01/02/2027

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