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Stopping Eculizumab Treatment Safely in atypical Haemolytic Uraemic Syndrome (SETS aHUS)

Submission date
04/04/2018

Recruitment status
No longer recruiting

Registration date
20/04/2018

Overall study status
Completed

Last Edited
13/12/2022

Condition category
Urological and Genital Diseases

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

Plain English summary of protocol

Background and study aims
Atypical hemolytic uremic syndrome (aHUS) is a disease that causes abnormal blood clots to form in small blood vessels in the kidneys. Lifelong treatment with the drug Eculizumab is currently recommended for aHUS due to risk of relapse. Many physicians are now questioning the recommendation for indefinite treatment and feel alternative treatment strategies should be considered. Data from before the availability of Eculizumab suggests that if patients survive the initial episode of aHUS with intact kidney function, less than 50% of patients will subsequently relapse, so over half of patients receiving maintenance Eculizumab treatment could be doing so unnecessarily. Withdrawal of drug would lead to a reduction in the burden of treatment (intravenous Eculizumab injections every 2 weeks and use of prophylactic antibiotics), replacing it with reduced monitoring after a period of intense monitoring. Patients will also avoid potentially fatal complications associated with Eculizumab use (6 of approximately 100 patients treated have suffered severe complications – death, meningococcal or other unexpected, severe infection). There would be cost savings for the NHS of over £10.6 million if 50% of study participants withdraw for the 2 years of the study. Of 10 UK patients identified who have withdrawn from Eculizumab because of patient/physician choice, only 1 patient has required re-initiation of treatment. Relapse may occur after withdrawal of treatment but early re-initiation of treatment should avoid harm to patients. As the number of patients on Eculizumab increases, so does potentially unnecessary treatment, cost to the NHS, and burden of treatment to patients and their families. Therefore, a tested method of safe withdrawal and monitoring will be vital for efficient delivery of this high-cost treatment. The aim of this study is to establish an evidence-based treatment strategy for patients with aHUS that includes safe withdrawal of treatment and the reintroduction of Eculizumab in those patients who relapse.

Who can participate?
Patients aged 2 and over with aHUS who have been on Eculizumab treatment for at least 6 months

What does the study involve?
Patients who consent to withdraw from Eculizumab receive their last dose of Eculizumab at their

screening/consent visit. Any patient with a suspected relapse should be reported to the PI at the local site and the aHUS National Service. When a relapse is diagnosed patients restart Eculizumab treatment within 24 hours of presentation. They continue to be followed up for the remainder of their 24-month follow-up period. Patients who are not withdrawing from their Eculizumab treatment continue to receive their standard care and complete questions at the eight specified time points only in the 24-month follow-up period.

What are the possible benefits and risks of participating?
Patients will no longer need to take the Eculizumab treatment and face any potential risks or side effects associated with treatment. Patients are about a thousand times more likely to develop a serious, potentially life threatening infection with meningococcus, a bug that causes meningitis or sepsis. Vaccination, and even antibiotics, do not give complete protection from this. Being in the study will mean that patients will no longer need bi-weekly infusions and will not have to continue taking additional antibiotics to prevent infection. However, it is possible that they may need to restart and continue Eculizumab if a relapse was to occur. The withdrawal of Eculizumab treatment could lead to a relapse of aHUS and relapse-associated complications. When a relapse is diagnosed, the Eculizumab treatment will be restarted within 24 hours of presentation. Patients are told to present to a hospital with their patient card as soon as they begin to feel unwell or the home urine test shows an increase in the level of blood. This is to ensure that the Eculizumab is re-started as soon as possible to reduce the likelihood of kidney damage and associated complications.

Where is the study run from?
1. Freeman Hospital (UK)
2. Royal Devon & Exeter Hospital (UK)
3. Royal Liverpool University Hospital (UK)
4. University College Hospital (UK)
5. Queen Alexandra Hospital (UK)
6. Guy's Hospital (UK)
7. The Royal London Hospital (UK)
8. St James's University (UK)

When is the study starting and how long is it expected to run for?
September 2017 to November 2023

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
Dr Ciara Kennedy
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Study website
http://www.atypicalhus.co.uk/sets-ahus/

Contact information

Type(s)
Scientific

Contact name

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Additional identifiers

EudraCT/CTIS number
2017-003916-37

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
36901

Study information

Scientific Title
Multicentre, open label, prospective, single arm study of the safety and impact of eculizumab withdrawal in patients with atypical haemolytic uraemic syndrome

Acronym
SETS aHUS

Study objectives
The aim of the current trial is to establish an evidence based treatment strategy for patients with atypical Haemolytic Uraemic Syndrome (aHUS) that includes safe withdrawal of treatment and the reintroduction of Eculizumab in those patients who relapse.

Ethics approval required
Old ethics approval format

Ethics approval(s)
North East – Tyne & Wear South Research Ethics Committee, ref: 18/NE/0078

Study design
Non-randomised; Both; Design type: Treatment, Drug, Management of Care, Active Monitoring, Health Economic

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 to request a patient information sheet

Health condition(s) or problem(s) studied
Atypical hemolytic uremic syndrome

Interventions
Patients who consent to withdraw from Eculizumab will receive their last dose of Eculizumab at their screening/consent visit (day -14). Any patient with a suspected relapse should be reported to the PI at the local site and the aHUS National Service. When a relapse is diagnosed patients will restart Eculizumab treatment within 24 hours of presentation. They will continue to be followed up for the remainder of their 24-month follow-up period.

Patients who are not withdrawing from their Eculizumab treatment will continue to receive their standard care and complete the health economic questions at the 8 specified time points only in the 24-month follow-up period.

Intervention Type
Other

Phase
Phase II

Primary outcome measure
Number of patients with a Thrombotic Microangiopathy (TMA) related Serious Adverse Event (SAE) defined as any of the following:
1. Irreversible (>3 months) reduction in estimated glomerular filtration rate (eGFR) by ≥20%, not attributable to another cause
2. An episode of AKI attributed to a TMA that requires renal replacement therapy
3. A non-renal manifestation of a TMA that require hospitalisation, cause irreversible organ damage or death
Timepoint(s): Only if/when a patient relapses

Secondary outcome measures
1. The effectiveness of a monitoring protocol to detect disease relapse following withdrawal of Eculizumab assessed by:
1.1. The proportion of patients who relapse and restart Eculizumab without the development of

a TMA-related SAE (section 3.3)
1.2. The time from the first clinical feature (symptom, positive urinalysis or laboratory result) of a relapse of TMA and the re-introduction of Eculizumab
This outcome is ongoing and not measured at any particular timepoint
2. The relapse rate after withdrawal of Eculizumab as determined by the proportion of patients who relapse after Eculizumab is withdrawn. This outcome is ongoing and not measured at any particular time point. A patient could relapse at any point in the 2 years participation period.
3. The proportion of patients, currently on long-term treatment with Eculizumab, who can be maintained off treatment. This outcome is measured at the end of the trial when all relapse data is collected. A patient could relapse at any point in the 2 years participation period.
4. The period from withdrawal to relapse in those patients who restart treatment. This outcome is measured at the end of the trial when all relapse data is collected.
5. The change in estimated GFR as calculated by the CKD-EPI or modified Schwartz equations over the course of the study from baseline (day 0) to end of the study. This outcome is calculated at the end of the trial when all GFR data is collected. GFR data is collected at all 34 visits
6. Important clinical and laboratory indicators of imminent relapse by review of reported symptoms, physical signs, urinalysis and laboratory results prior to the diagnosis of a relapse. This outcome will be assessed at the end of the trial when all relapse data is collected. Those who have relapsed will have all data preceding relapse reviewed to establish a relapse profile
7. The costs and health outcomes (measured in terms of adverse events and quality-adjusted life years [QALYs]) for patients on standard care (not withdrawing from Eculizumab treatment) over the two-year trial duration:
7.1. Healthcare Utilisation Questionnaires for non-withdrawal participants at Day 0, 14, 70,154, 252, 336, 504 and 672
7.2. Adverse Event Assessment at every visit from Day 7 (32 visits) for withdrawal participants
8. QALYs estimated from responses to the EQ-5D-5L, and SF-36 and determinants of QALYs /utilities over the 24-month follow-up period. at Day 0, 14, 70,154, 252, 336, 504 and 672
9. Model-based estimate of the costs and health consequences, with results presented in terms of cost per QALY gained, over the estimated lifetime of patients withdrawing from treatment compared with standard care

Overall study start date
01/09/2017

Completion date
30/11/2023

Eligibility

Key inclusion criteria
All patients must fulfil the following criteria in order to be eligible for the trial:
1. Age ≥2+ years of age
2. On Eculizumab treatment for at least 6 months
3. In remission with no evidence of ongoing microangiopathic haemolytic anaemia (MAHA) activity at screening defined by:
3.1. Platelet count > lower limit of normal as determined by local reference range
3.2. Lactate Dehydrogenase (LDH) <x2 upper limit of normal as determined by local lab reference ranges
4. Normal renal function or Chronic Kidney Disease (CKD) stages 1-3
5. Absence of decline of renal function confirmed by review of available assessments of renal

function for the preceding 6 months by the Chief Investigator and clinical members of the Trial Management Group (TMG)
6. Willing to attend for safety monitoring assessments
7. Willing to travel only to countries that can supply Eculizumab (to be confirmed with co-ordinating centre prior to travel).

The following criteria must be met by those only wishing to be enrolled in the withdrawal component of the trial:
8. Able to perform or parent/guardian to perform and record self-monitoring urinalysis
9. Sexually active female patients must have a negative pregnancy test at screening and be using an effective contraception for the duration of the study (implant, injectable [combined hormone], intrauterine device, intrauterine system, male sterilisation,
injectable (single hormone), combined oral, progesterone only)
OR
10. Fulfil one of the following criteria:
10.1. Be postmenopausal
10.2. Have undergone surgical sterilisation

Participant type(s)
Patient

Age group
Mixed

Sex
Both

Target number of participants
Planned Sample Size: 50; UK Sample Size: 50

Total final enrolment
39

Key exclusion criteria
1. Severe non-renal disease manifestations at initial presentation with aHUS, which in the opinion of the Chief Investigator and/or the clinical members of the TMG makes the risk of treatment withdrawal unacceptable
2. Loss of a previous transplant kidney to recurrent aHUS
3. Transplant recipient with a pathogenic mutation in C3, CFH or CFB
4. Current or planned pregnancy
5. Unable to give informed consent or assent, or unable to obtain parent/guardian consent if under 16 years of age
6. Unable to comply with monitoring protocol
7. Current participation in another clinical trial
8. Haematuria rating of 3+
9. Severe, uncontrolled hypertension (systolic blood pressure > 160 mmHg) that is likely to induce at TMA

Date of first enrolment
01/05/2018

Date of final enrolment
30/11/2021

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
The Newcastle Upon Tyne Hospitals NHS Foundation Trust
Freeman Hospital
Freeman Road
United Kingdom
NE7 7DN

Study participating centre
Royal Devon & Exeter Hospital
United Kingdom
EX2 5DW

Study participating centre
Royal Liverpool University Hospital
United Kingdom
L7 8XP

Study participating centre
University College Hospital
250 Euston Road
United Kingdom
NW1 2PG

Study participating centre
Queen Alexandra Hospital
United Kingdom
PO6 3LY

Study participating centre

Guy's Hospital
United Kingdom
SE1 9RT

Study participating centre
The Royal London Hospital
United Kingdom
E1 1BB

Study participating centre
St James's University
United Kingdom
LS9 7TF

Sponsor information

Organisation
The Newcastle Upon Tyne Hospitals NHS Foundation Trust

Sponsor details
Freeman Hospital
Freeman Road
High Heaton
Newcastle-Upon-Tyne
England
United Kingdom
NE7 7DN
+44 (0)191 2824454
Tnu-tr.sponsormanagement@nhs.net

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: 15/130/94

Results and Publications

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

Intention to publish date
31/03/2024

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		19/09/2022	20/09/2022	Yes	No
HRA research summary			28/06/2023	No	No