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A study of the benefit of a medicine called eculizumab in Shiga-Toxin producing E. Coli Haemolytic Syndrome

Submission date
15/12/2016

Recruitment status
No longer recruiting

Registration date
15/12/2016

Overall study status
Completed

Last Edited
14/03/2022

Condition category
Infections and Infestations

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Shiga-toxin producing E. coli Haemolytic Uraemic Syndrome (STEC HUS) follows a gut infection with Shiga-toxin producing E. coli (STEC), which causes severe (often bloody) diarrhoea. Around 1000 UK children are infected with STEC each year and approximately 100 of these develop STEC HUS when a toxin from STEC causes damage to small blood vessels, especially in the kidneys. About 50-60% of children with STEC HUS need artificial kidney support (dialysis), which may last several weeks. About 2-3% of children with STEC HUS die, and about 20-25% get HUS in their brain, causing fits or a stroke. Many make a full recovery, but about 25-30% will have permanent kidney damage or more rarely brain damage. Previous studies have investigated a number of different treatments for STEC HUS, but have failed to show significant benefit. Eculizumab is a medicine that blocks part of the immune system called complement. Evidence suggests complement plays a role in STEC HUS. Eculizumab is very effective in a related condition called atypical HUS. Some doctors have given it to children with severe STEC HUS and seen a very good recovery, but this may have been just chance because others have tried it and didn't see much effect. The aim of this study is to investigate the benefit of eculizumab in patients with STEC HUS.

Who can participate?
Children aged between 6 months and 19 years old with STEC HUS who have had diarrhoea within the two weeks before they were diagnosed.

What does the study involve?
Participants are randomly allocated to one of two groups. Those in the first group are treated with eculizumab and those in the second group are treated with placebo (inactive medicine) soon after arriving at the unit and a second dose of the same medicine a week later. Before starting treatment, children in both groups are given a meningococcal vaccination (meningitis vaccine). All participants are followed-up for 12 months from randomisation, with daily trial assessments until hospital discharge, then at 30 and 60 days and 6 and 12 months. This is in keeping with the normal frequency of follow up in clinical practice.

What are the possible benefits and risks of participating?
Participants may benefit from a reduction in both the acute (sudden) severity of STEC HUS, and in long term complications. The main risk for study participants is a short term, small increase in the risk of meningococcal disease. This risk will be reduced by the use of vaccination and antibiotics.

Where is the study run from?
Birmingham Clinical Trials Unit (UK)

When is the study starting and how long is it expected to run for?
April 2009 to February 2021

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

Who is the main contact?
Dr Raquel Fernández del Río
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Study website
www.birmingham.ac.uk/ecustec

Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
2016-000997-39

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
32199

Study information

Scientific Title
Eculizumab in Shiga-Toxin producing E. Coli Haemolytic Uraemic Syndrome (ECUSTEC): a randomised, double-blind, placebo-controlled trial

Acronym
ECUSTEC

Study objectives
The aim of this study is to determine if the severity of Shiga-Toxin producing E. Coli Haemolytic Uraemic Syndrome (STEC HUS) is less in those given Eculizumab (Ecu) versus those given placebo therapy.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration

Study design
Randomised; Interventional; Design type: Treatment, Drug, Immunotherapy

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, please contact Ecustec@Trials.bham.ac.uk to request a patient information sheet

Health condition(s) or problem(s) studied
Shiga-toxin producing Escherichia coli Haemolytic Uraemic Syndrome (STEC HUS)

Interventions
Prior to entering the trial, all potential patients will commence an 8 week course of antibiotics (either phenoxymethylpenicillin or erythromycin if allergic to penicillin). Once they have been entered into the trial, but before receiving their randomised treatment, all participants will be given meningococcal vaccinations. Following this, participants will receive two doses of their study treatment; one dose soon after arriving at the children's kidney unit (day 1), and a second dose of the same medicine a week later (day 8).

Participants will be randomised to either of the following trial arms:

Active arm: Standard therapy + 1st dose eculizumab on day 1 and 2nd dose eculizumab on day 8

Control arm: Standard therapy + 1st dose placebo on day 1 and 2nd dose placebo on day 8

All participants will be followed-up for 12 months from randomisation, with daily trial assessments until hospital discharge, then at 30 and 60 days and 6 and 12 months post randomisation. This is in keeping with the normal frequency of follow up in clinical practice.

Intervention Type
Drug

Phase
Phase II

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

Primary outcome measure
Severity of acute kidney injury and extra-renal events is assessed using the purpose-developed STEC HUS clinical severity score at day 60.

Secondary outcome measures
1. Overall survival is measured by survival status at 52 weeks
2. Duration of dialysis, measured by the number of days on dialysis over 52 weeks

3. Duration of thrombocytopenia, measured by the number of consecutive days until platelet count >150x109/l up until 52 weeks. Participants enter the trial with a platelet count <150x109 and this is measured daily up until discharge or 28 days (whichever is soonest) then at 30 days, 60 days, 26 weeks and 52 weeks
4. Duration of haemolysis, measured by the number of days until lactate dehydrogenase is within normal reference range up until 52 weeks this is measured daily up until discharge or 28 days (whichever is soonest) then at 30 days, 60 days, 26 weeks and 52 weeks
5. Number of packed red blood cell transfusions required, measured by volume (ml/kg) over 52 weeks this data is collected at discharge, day 30, day 60, week 26 and week 52
6. Markers of inflammation, measured by the number of days until normal total white count and CRP over 52 weeks this is measured daily up until discharge or 28 days (whichever is soonest) then at 30 days, 60 days, 26 weeks and 52 weeks
7. Chronic Kidney Disease at 52 weeks which is measured by a composite endpoint of the presence of hypertension [average of 3 readings by manual method using centile charts* for age /sex/height], albuminuria [urine albumin-creatinine ratio >2.5mg/mmol on early morning urine] or eGFR<90ml/min/1.73m2 at 52 weeks) collected at week 52 only
8. eGFR measured using a centralised cystatin C assay at 52 weeks collected at baseline, discharge, day 30, day 60, week 26 and week 52
9. Persistent neurological defect rate, measured by a structured expert assessment to include CNS examination, vision, hearing and neuropsychological assessment measured at 60 days based on the CRFs we measure this at baseline, discharge, day 30 and day 60
10. Economic evaluation of cost per clinical severity score point measured at day 60, and cost per QALY gained, measured by PedsQL and CHU-9D assessments which are collected at baseline, day 8, day 30, day 60, week 26 and week 52

Overall study start date
01/04/2016

Completion date
23/02/2021

Eligibility

Key inclusion criteria
1. Children aged 6 months to <19 years
2. Weight of ≥5kg
3. A diagnosis of HUS:
3.1. Micro-angiopathic haemolytic anaemia (indicated by fragmented red cells on blood film or plasma lactate dehydrogenase above local centre reference range)
3.2. AND Thrombocytopenia (platelets <150x109/l)
3.3. AND AKI of “injury” or "failure" category of pRIFLE criteria (despite correction of hypovolaemia)
4. Reported diarrhoea within 14 days prior to diagnosis of HUS (defined according to World Health Organisation as "the passage of three or more loose or liquid stools per day - or more frequent passage than is normal for the individual")
OR
A stool culture/shiga toxin PCR/STEC result indicating STEC in the patient or household contact within 14 days prior to diagnosis of HUS.
Patient intended to be able to receive trial drug within 36 hours of arrival at renal unit, or within 24 hours of eligibility if already at renal unit
5. Patient intended to be able to receive trial drug within 36 hours of arrival at the renal unit, or

within 24 hours of eligibility if already at renal unit
6. Sexually active male or female patients must agree to practice an effective, reliable and medically approved contraceptive regimen for 6 months after enrollment
7. Written informed consent obtained from the participant's parents/guardians and written assent obtained from participant (where age appropriate). Participants aged 16 years and above will provide their own written informed consent

Participant type(s)
Patient

Age group
Child

Lower age limit
6 Months

Upper age limit
19 Years

Sex
Both

Target number of participants
Planned Sample Size: 134; UK Sample Size: 134

Total final enrolment
36

Key exclusion criteria
1. Family history of atypical HUS (aHUS)
2. Previous episode of HUS
3. Known pre-existing eGFR < 90ml/min / 1.73m2
4. Known or suspected pneumococcal infection
5. Known or suspected meningococcal infection
6. Patient taking a drug known to be associated with HUS, e.g. calcineurin inhibitors, chemotherapy, quinine, oral contracaptive pill
7. Hypersensitivity to eculizumab, murine proteins or any of the excipients listed in the Summary of Product Characteristics
8. Pregnancy or lactation
9. Malignancy
10. Known Disseminated Intravascular Coagulopathy (testing of coagulation is not mandatory for inclusion in trial)
11. Refusal of consent, including consent for meningococcal vaccination or antibiotic prophylaxis
12. Currently participating in another CTIMP

Date of first enrolment
11/08/2017

Date of final enrolment
06/02/2021

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Birmingham Clinical Trials Unit
The University of Birmingham
Edgbaston
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B15 2TT

Sponsor information

Organisation
The Newcastle upon Tyne Hospitals NHS Foundation Trust

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Sponsor type
Hospital/treatment centre

Website
http://www.newcastle-hospitals.org.uk/

ROR
https://ror.org/05p40t847

Funder(s)

Funder type

Government

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
The initial plan is that the study will be complete in early 2022 once the trial and final report are complete. The conclusions will be presented at national and international meetings and conferences and be submitted for publication in peer-reviewed journals. Findings will be disseminated to key stakeholders including paediatric nephrologists in all UK specialist renal units.

Intention to publish date
30/04/2022

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?
Basic results		25/11/2021	14/03/2022	No	No