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Biologics in refractory vasculitis

Submission date
25/06/2020

Recruitment status
Stopped

Registration date
02/07/2020

Overall study status
Stopped

Last Edited
18/02/2025

Condition category
Circulatory System

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

Plain English summary of protocol

Background and study aims
Vasculitis means inflammation of the blood vessels. There are many types of rare vasculitis that are treated with steroids and drugs to damp down the activity of the immune system but they often cause side effects. Some patients do not improve with this treatment and their vasculitis worsens (refractory vasculitis). These patients need newer more effective treatments with fewer side effects, such as biologic drugs. Although these treatments have been used for several years to treat vasculitis researchers do not have good data for many of the rarer types of vasculitis to guide the optimal choice of biologic. This study will compare three different biologics to a placebo (dummy) to understand which treatment works best.

Who can participate?
Adults and children (aged 5+ years) who have been diagnosed with a non-ANCA-associated vasculitis (GCA, Takayasu's arteritis, polyangiitis nodosa, relapsing polychondritis, IgA vasculitis of adults, IgA vasculitis of children, cryoglobulinaemia, Cogan's syndrome, primary angiitis of the central nervous system), and have relapsing or refractory disease

What does the study involve?
Patients who are experiencing a flare of vasculitis will be randomly allocated to a sequence of the three treatments: infliximab, rituximab and tocilizumab plus a placebo (dummy) treatment. Everyone will be allocated to receive these treatments, one at a time, but in a different order. Each treatment will be given as an infusion or a ‘drip’. Patients start on the first treatment in their allocated sequence, and continue until the treatment is no longer showing clinical benefit or the patient is not responding to treatment. The next treatment in the sequence will then be started. Patients will receive treatment for up to 2 years.
Patients would receive their treatments in a hospital setting, according to the treatment's standard clinical regimen. Study assessments will take place every 4 months (approx every 120 days), and involve clinical blood tests and evaluation by the study doctor to assess clinical response, and patient questionnaires to assess how they feel and what impact their disease is having on daily life.

What are the possible benefits and risks of participating?
The study provides access to treatments that may not otherwise be available to patients with relapsing and refractory non-ANCA-associated vasculitis. It is hoped that treatment with biologics will help alleviate symptoms and prevent long-term organ damage in these patients.

Treatment with biologic drugs may also result in a reduced need for steroid treatment. Treatments with biologic agents intravenously have a number of risks including infusion reactions, increased risk of infection, dizziness, stomach and liver problems. Patients may have to visit the hospital more often for their treatments. Taking blood samples can cause pain /bruising, but the study is designed so that these are taken alongside all routine clinical bloods.

Where is the study run from?
Cambridge University Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
September 2019 to February 2025

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

Who is the main contact?
1. Ms Kim Maynard (public contact), add-tr.biovas@nhs.net
2. Prof. David Jayne (scientific contact), dj106@cam.ac.uk

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2019-003964-30

IRAS number

ClinicalTrials.gov number
NCT05168475

Secondary identifying numbers
HTA - 17/83/01

Study information

Scientific Title
Biologics in refractory vasculitis (BIOVAS): a pragmatic, randomized, double-blind, placebo-controlled, modified-crossover trial of biologic therapy for refractory primary non-ANCA associated vasculitis in adults and children

Acronym
BIOVAS

Study objectives
BIOVAS will test the hypothesis that biologics are superior to placebo in the control of refractory NAAV. Each of the three trial biologics (infliximab, rituximab and tocilizumab) will be compared to placebo in a sequential modified crossover, placebo-controlled design

Ethics approval required
Old ethics approval format

Ethics approval(s)
Submission pending

Study design
Multi-centre pragmatic randomized double-blind placebo-controlled modified-crossover phase 2B trial

Primary study design
Interventional

Secondary study design
Randomized modified crossover trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not yet approved for use, and will not be available in web format. Please use contact details to request a participant information sheet.

Health condition(s) or problem(s) studied
Patients with relapsing or refractory non-ANCA-associated vasculitis (NAAV). Specific diseases to be included in this trial are: giant cell arteritis (GCA), Takayasu's arteritis (TA), polyarteritis nodosa (PAN), relapsing polychondritis, IgA vasculitis (of adults and children), cryoglobulinaemia, Cogan's syndrome and primary central nervous system (CNS) vasculitis

Interventions
The treatments to be studied are rituximab, tocilizumab and infliximab. Eligible patients will be randomized to a sequence of the three biologics plus a placebo to one of the biologics in a blinded manner. There are 72 possible sequences; however, 36 sequences enable unblinding. Therefore there are 24 possible permutations that patients may be randomized to. An example is: rituximab-infliximab-tociluzumab placebo-tocilizumab.

Patients begin on the first IMP in their allocated sequence. If a patient is responding by day 120, they remain on this IMP, and continue to do so until they are no longer responding or experience a major relapse which meets the criteria for treatment failure. If a participant experiences an adverse reaction to an IMP, this is also considered a treatment failure. Then a participant meets the criteria for treatment failure, they would discontinue the IMP and move to the next IMP in their allocated sequence. Participants continue on treatment for 2 years, or until failure on all IMPs in sequence if sooner.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Rituximab, infliximab, tocilizumab

Primary outcome measure
Time to treatment failure (TTF): the time from the start of IMP treatment, to treatment failure.

Primary treatment failure is:
1. Progressive disease (defined by appearance of ≥1 new/worse severe or ≥3 new/worse non-severe items) on Birmingham vasculitis activity score (BVAS) v3 or paediatric vasculitis activity

score (PVAS) within 120 days from the time of IMP commencement
OR
2. Failure to achieve clinical response by 120 days from the time of IMP commencement

Clinical response is defined as:
1. Absence of new/worse BVAS V3 (adults)/PVAS (children) items assessed at each 120 evaluation time point after commencing IMP AND
2. Prednisolone ≤10 mg/day or ≤0.2 mg/kg for children (whichever is lower), unless the baseline dose is ≤10 mg/day or ≤0.2 mg/kg for children (whichever is lower), in which case it should not be more than the baseline dose*
*baseline dose is the dose of oral prednisolone, mg/day, or equivalent oral steroid, averaged over the 7 days prior to the start of each new IMP.

Secondary treatment failure is relapse having achieved a clinical response by 120 days of commencing IMP.

Relapse is defined as:
1. Appearance of ≥ 1 severe (new/worse) or ≥ 3 non-severe (new/worse) BVAS v3/PVAS items from the time of BVAS response (as defined above) assessed at the 120 day evaluation time points OR
2. The need to increase the dose of prednisolone to > 20 mg/day to treat vasculitis OR
3. The need to increase the dose of an immunomodulator or immune-suppressive therapy in order to treat vasculitis

Secondary outcome measures
1. Treatment effects of each of the IMPs compared to placebo and each IMP against other IMPs in two NAAV sub-groups: large vessel vasculitis (GCA/TA) and all other NAAV subgroups enrolled in the trial; measured by Bayesian priors meeting followed by statistical analysis of final dataset
2. Proportion of participants achieving response at 120 days evaluation after the start of each IMP, as measured by the response definitions provided in primary outcome measure
3. Proportion of participants achieving response at every 120-day evaluation timepoint defined by a BVAS v3/ PVAS of ≤ one non-severe (no new/worse) item, prednisolone dose ≤ 50% of the dose at the start of the IMP treatment and ≤ 10 mg/day (0.2 mg/kg/day for children, whichever is lower) and an ESR < 30 mm/h or CRP <10 mg/l assessed by BVAS v3/PVAS, review of participant daily steroid diary and standard of care clinical blood test review of ESR and CRP results at each 120-day trial visit
4. Disease-related damage measured by VDI/PVDI from start to end of an IMP treatment, recorded at each 120-day trial visit and at any relapse unscheduled visit
5. Disease activity measured using Physician's global assessment (PGA) (Likert scale 0-10) at every 120-day evaluation timepoint from the time of IMP commencement
6. Serious adverse events/adverse events of special interests; SAEs/AESI review throughout the trial
7. Patient-reported health and wellbeing measured using EQ-5D-5L or Child Health Utility (CHU9D) assessments at every 120-day evaluation timepoint
8. NHS resource use and out of pocket costs and lost productivity, measured using health resource use questionnaire for adults and children/parent/guardian, recorded at each 120-day trial visit

Overall study start date
01/09/2019

Completion date
28/02/2025

Reason abandoned (if study stopped)
Participant recruitment issue

Eligibility

Key inclusion criteria
1. Aged at least 5 years
2. Have given, or their parent/legal guardian aged ≥16 years old has given, written informed consent
3. Diagnosis of NAAV
4. Refractory disease defined by:
4.1. Active disease, BVAS v3/ PVAS with ≥ 1 severe (new/worse) or ≥ 3 non-severe (new/worse) items despite 12 weeks of conventional therapy prior to screening visit OR
4.2. Inability to reduce prednisolone below 15 mg/day or (0.2 mg/kg/day in case of children) without relapse in the 12 weeks prior to screening visit

Participant type(s)
Patient

Age group
Mixed

Lower age limit
5 Years

Sex
Both

Target number of participants
140

Total final enrolment
18

Key exclusion criteria
1. Previous treatment failure/contraindication to ≥2 trial IMPs
2. Increase in the dose or frequency of background immunosuppressive (e.g. methotrexate) or anti-cytokine therapy within 30 days of screening visit
3. Use of intravenous immunoglobulins within 30 days, or cyclophosphamide or lymphocyte depleting biologic (e.g. rituximab) within 6 months of screening visit
4. Have an active systemic bacterial, viral or fungal infection, or tuberculosis
5. Hepatitis B (HB) core antibody (Ab) or HB surface antigen-positive or hepatitis C antibody positive or human immunodeficiency virus (HIV) antibody test positive
6. History of malignancy within five years prior to screening visit or any evidence of persistent malignancy, except fully excised basal cell or squamous cell carcinomas of the skin, or cervical carcinoma in situ which has been treated or excised in a curative procedure
7. Pregnant or breastfeeding (Section 11.9)

8. Severe disease, which in the opinion of the physician prevents randomization to placebo
9. Recent or upcoming major surgery within 45 days of screening visit
10. Leukocyte count < 3.5 x 109 cells/l, platelet count < 100 x 109 cells/l, neutrophil count of < 1 x 109 cells/l
11. ALT or ALP > 3 times the upper limit of normal
12. Symptomatic congestive heart failure (NYHA class III/IV) requiring prescription medication within 90 days of screening visit
13. Demyelinating disorders
14. History or presence of any medical condition or disease which, in the opinion of the Investigator, may place the participant at unacceptable risk because of trial participation
15. Administration of live or live-attenuated vaccines within 45 days of screening
16. Have received an investigational medicinal product (IMP) within 5 half-lives or 30 days prior to screening
17. Diagnosis of adenosine deaminase type 2 (DADA2)
18. Hypersensitivity to the active IMP substance or to any of the formulation excipients

Date of first enrolment
09/06/2021

Date of final enrolment
31/07/2023

Locations

Countries of recruitment
England

Scotland

United Kingdom

Study participating centre
Queens Medical Centre
Nottingham University Hospitals NHS Trust
Nottingham
United Kingdom
NG7 2UH

Study participating centre
Queen Elizabeth Medical Centre
University Hospitals Birmingham NHS Foundation Trust
Birmingham
United Kingdom
B15 2TH

Study participating centre
Gartnavel Royal Hospital
NHS Greater Glasgow and Clyde
Glasgow
United Kingdom
G12 0XH

Study participating centre
Great Ormond Street Hospital for Children NHS Foundation Trust
Great Ormond Street
London
United Kingdom
WC1N 3JH

Study participating centre
Guy's Hospital
Guys & St Thomas NHS Foundation Trust
London
United Kingdom
SE1 9RT

Study participating centre
Kent & Canterbury Hospital
East Kent Hospitals University NHS Trust
Canterbury
United Kingdom
CT1 3NG

Study participating centre
Royal Preston Hospital
Lancashire Teaching Hospitals NHS Foundation Trust
Preston
United Kingdom
PR2 9HT

Study participating centre
Royal Cornwall Hospital
Royal Cornwall Hospitals NHS Trust
Truro
United Kingdom
TR1 3LJ

Study participating centre
Royal Berkshire Hospital
Royal Berkshire NHS Foundation Trust
Reading
United Kingdom
RG1 5AN

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

Study participating centre
Royal Liverpool University Hospital
Royal Liverpool and Broadgreen University Hospitals NHS Trust
Liverpool
United Kingdom
L7 8XP

Study participating centre
John Radcliffe Hospital
Oxford University Hospitals NHS Foundation Trust
Oxford
United Kingdom
OX3 9DU

Study participating centre
St Marys Hospital
Imperial College Healthcare NHS Trust
London
United Kingdom
W2 1NY

Study participating centre
St James University Hospital
Leeds Teaching Hospitals NHS Foundation Trust

Leeds
United Kingdom
LS9 7TF

Study participating centre
Bristol Royal Infirmary
University Hospitals Bristol and Weston NHS Trust
Bristol
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BS1 3NU

Study participating centre
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Sponsor information

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Sponsor type
Hospital/treatment centre

Website
http://www.cuh.org.uk/

ROR
https://ror.org/04v54gj93

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
1. Planned publication of protocol
2. Planned publication of results in a high-impact peer-reviewed journal. Only anonymised data will be published

Intention to publish date
31/12/2026

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