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Treatment of autoimmune encephalitis in adults with intravenous immunoglobulin

Submission date
29/09/2020

Recruitment status
No longer recruiting

Registration date
18/03/2021

Overall study status
Ongoing

Last Edited
12/12/2024

Condition category
Nervous System Diseases

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

Plain English summary of protocol

Background and study aims
Autoimmune encephalitis is inflammation and swelling of the brain caused by the body's own immune defence system. It affects about 1 in 100,000 people per year in the UK. The symptoms can include abnormal behaviour, memory problems and seizures. Some patients recover completely, but in others it can cause death or severe disability.
Autoimmune encephalitis is treated with steroids, which reduce inflammation and swelling. If patients are not improving, intravenous immunoglobulin (IVIG) is often also given, usually after a couple of weeks. IVIG is a protein product extracted from the blood of healthy donors. It is given through a drip into a vein each day for 5 days and is used for other diseases that affect the nervous system.
Some doctors think that if IVIG is used from the start of treatment, patients may recover more quickly and have fewer side effects from the illness. While IVIG may help patients it can have side effects, including blood clots or allergic reactions, is expensive and may not help recovery. Currently it is used in about 50% of patients with autoimmune encephalitis. This study is looking at whether or not early treatment with IVIG improves recovery. The aims of the trial are to:
1. To work out whether, in adults with autoimmune encephalitis, early treatment with IVIG leads to a different time to recovery and improves the outcome.
2. To carry out scientific studies to better understand the disease processes in autoimmune encephalitis and see how IVIG affects them.

Who can participate?
Patients aged 16 age or older admitted to hospital with suspected autoimmune encephalitis

What does the study involve?
All patients in the study will receive steroid treatment. This is the standard treatment for autoimmune encephalitis. In addition, participants may be given a short course of IVIG or a product which looks identical (a placebo), but which does not contain the active protein. All participants will undergo regular clinical assessments at the hospital and be asked to complete a series of questionnaires to assess their recovery, and general health and wellbeing.

What are the possible benefits and risks of participating?
There are no guarantees that participating in the study will have any benefits. It is possible

patients will benefit from the IVIG treatment and additional monitoring and assessments. The disadvantage in taking part in this study may be the risk of having the side-effects of IVIG (this will not be the case in the group that does not take IVIG). There is also the discomfort of receiving the IVIG through a drip and having a lumbar puncture. There are also risks associated with receiving steroids while pregnant or breastfeeding.

Where is the study run from?
The University of Liverpool and the Centre for Trials Research, Cardiff University (UK)

When is the study starting and how long is it expected to run for?
April 2020 to April 2026

Who is funding the study?
National Institute for Health Research Efficacy and Mechanism Evaluation Programme (UK)

Who is the main contact?
Paula Foscarini-Craggs
EncephIG@Cardiff.ac.uk

Study website
https://www.cardiff.ac.uk/centre-for-trials-research/research/studies-and-trials/view/enceph-ig

Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
2020-004428-40

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers

CPMS 47478, UoL001570

Study information

Scientific Title
Intravenous immunoglobulin in autoimmune encephalitis in adults – a randomised double-blind placebo-controlled trial

Acronym
Enceph-IG

Study objectives
To determine if early treatment with intravenous immunoglobulin (IVIG) changes the time to recovery as measured on the Glasgow Outcome Scale-Extended.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 25/03/2021, Wales REC 3 (15-19 Cowbridge Road East, Cardiff, CF11 9AB, United Kingdom; +44 (0)29 2078 5741; Wales.REC3@wales.nhs.uk), ref: 21/WA/0050

Study design
Multicentre double-blind two-arm placebo-controlled randomized superiority trial, incorporating an internal pilot study

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 use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Autoimmune encephalitis

Interventions
Patients will be randomized 1:1 to IVIG or placebo using random permuted blocks stratified by site, and time from symptom onset. Patients will receive 2 g/kg IVIG or placebo over 5 days. All patients will also receive methylprednisolone 1 g daily intravenously for 5 days, followed by 1 mg /kg bodyweight (maximum dose 60 mg) oral prednisolone daily for 2 weeks. This is followed by a

reduction of 10 mg per week until the patient is taking 10 mg daily, and then a further reduction of 1 mg per week until it is stopped.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
IVIG, methylprednisolone, prednisolone

Primary outcome measure
Recovery measured using the Glasgow Outcome Scale-Extended (GOSE) every 2 weeks for the first 3 months and then monthly until 12 months post-randomization

Secondary outcome measures
1. Recovery measured using the Glasgow Outcome Scale-Extended (GOSE) at 3 months (all patients), then at 12 months and annually for the duration of the trial for patients who reach those timepoints
2. Neuropsychological outcomes measured using a standard battery of tests (Addenbrooke's Cognitive Examination III, Weschsler Memory Scale version IV, Wechsler Adult Intelligence (WAIS) test version IV, Confrontational Naming Task, Trail Making Test Parts A and B, Test of Premorbid Functioning, Beck Depression Inventory, Beck Anxiety Inventory, and Perceived Deficits Questionnaire) as well as the Modified Rankin Scale, and The Liverpool Outcome Score. This will be administered at 12 months post-randomization.
3. Health utility and self-rated health measured using EuroQoL five dimension Scale (EQ5D5L) and European Brain Injury Questionnaire (EBIQ) at 3 months, then at 12 months and annually for patients who reach those timepoints
4. Clinical outcomes including adverse events, time to hospital discharge, use of additional immunotherapy rescue treatments, relapse, HDU/ITU admission, seizures, use of ventilator support, and mortality, measured using medical notes and assessment at clinical follow-up appointments at 2 weeks, 3 months and 12 months

Overall study start date
01/04/2020

Completion date
30/04/2026

Eligibility

Key inclusion criteria
Current inclusion criteria as of 05/03/2024:
1. Adults (≥16 years) with altered consciousness level AND/OR behavioural change AND/OR working memory deficit AND/OR psychiatric symptoms
2. Persisting for >24 hours and <12 months but no more than 3 months since diagnosis
3. In whom clinician thinks autoimmune encephalitis is the most likely diagnosis
4. CSF polymerase chain reaction (PCR) negative for HSV 1 and 2, and varicella zoster virus
5. CSF microscopy and culture-negative at 48 hours for organisms

PLUS two or more of:
1. Seizures (not explained by previously known seizure disorder) OR new movement disorder
2. Cerebrospinal fluid (CSF) white blood cell count 6-1000/mm³
3. Electroencephalogram consistent with encephalitis
4. Brain magnetic resonance imaging (MRI) or computer tomography (CT) changes consistent with encephalitis (including normal scan)

Previous inclusion criteria:
1. Adults (≥16 years) with altered consciousness level AND/OR behavioural change AND/OR working memory deficit AND/OR psychiatric symptoms
2. Persisting for >24 hours and <3 months
3. In whom clinician thinks autoimmune encephalitis is the most likely diagnosis
4. CSF polymerase chain reaction (PCR) negative for HSV 1 and 2, and varicella zoster virus
5. CSF microscopy and culture-negative at 48 hours for organisms

PLUS two or more of:
1. Seizures (not explained by previously known seizure disorder) OR new movement disorder
2. Cerebrospinal fluid (CSF) white blood cell count 6-1000/mm³
3. Electroencephalogram consistent with encephalitis
4. Brain magnetic resonance imaging (MRI) or computer tomography (CT) changes consistent with encephalitis

Participant type(s)
Patient

Age group
Adult

Lower age limit
16 Years

Sex
Both

Target number of participants
356

Key exclusion criteria
1. No other likely diagnosis
2. Current or recent (within last 6 months) treatment with IVIG
3. Contraindication to IVIG
4. Intolerance of corticosteroids
5. Recent history of gastric ulcers
6. CSF analysis not performed
7. CSF polymerase chain reaction (PCR) positive for any viruses
8. Brain imaging not performed
9. Alternative diagnosis on brain imaging (CT or MRI)
10. Known HIV infection
11. On steroids or other disease-modifying anti-inflammatory therapies
12. Not able to live independently prior to onset of condition

Date of first enrolment
11/11/2021

Date of final enrolment
31/10/2024

Locations

Countries of recruitment
England

Scotland

United Kingdom

Study participating centre
Walton Centre
Lower Ln
Liverpool
United Kingdom
L9 7LJ

Study participating centre
University College London
235 Euston Rd
Bloomsbury
London
United Kingdom
NW1 2BU

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

Study participating centre
Royal Hallamshire Hospital
Sheffield Teaching Hospitals NHS Foundation Trust
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United Kingdom
S10 2JF

Study participating centre
John Radcliffe Hopsital
Headley Way
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United Kingdom
OX3 9DU

Study participating centre
University Hospital Coventry
Clifford Bridge Road
Coventry
United Kingdom
CV2 2DX

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

Study participating centre
Royal Devon and Exeter Hospital
Royal Devon and Exeter NHS Hospital Foundation Trust
Barrack Road
Exeter
United Kingdom
EX2 5DW

Study participating centre
Royal Stoke University Hospital
Newcastle Road
Stoke-on-Trent
United Kingdom
ST4 6QG

Study participating centre
Addenbrooke's Hospital
Cambridge University Hospitals NHS Foundation Trust
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
Ashford and St Peter’s Hospital NHS Foundation Trust
London Road
Ashford
United Kingdom
TW15 3AA

Study participating centre
Aberdeen Royal Infirmary
NHS Grampian
Aberdeen
United Kingdom
AB25 2ZN

Study participating centre
Royal Preston Hospital
Sharoe Green Lane North
Fulwood
Preston
United Kingdom
PR2 9HT

Study participating centre
Leicester Royal Infirmary
University Hospitals of Leicester NHS Trust
Infirmary Square
Leicester
United Kingdom
LE1 5WW

Study participating centre

Salford Royal Hospital
Stott Lane
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Sponsor information

Organisation
University of Liverpool

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Sponsor type
University/education

Website
http://www.liv.ac.uk/

ROR
https://ror.org/04xs57h96

Funder(s)

Funder type
Government

Funder Name
Efficacy and Mechanism Evaluation Programme

Alternative Name(s)
NIHR Efficacy and Mechanism Evaluation Programme, EME

Funding Body Type
Government organisation

Funding Body Subtype

National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
All publications and presentations relating to the study will be authorised by the TMG and will be in accordance with the trial's publication policy. In addition to the required final report and monograph for the NIHR EME Programme, we will publish the main study results in international peer-reviewed journals and present at national and international scientific meetings. With the assistance of their collaborators and lay representatives the researchers will disseminate the trial findings to a wide NHS and general audience and vigorously promote uptake of the trial results into clinical care. Any outputs that include data collected through NHS digital or equivalent data provider will include an acknowledgement of the role of the data provider. The aim will be for the results to be revealed initially at the annual Encephalitis Conference, organised by the Encephalitis Society. The results of the study will then be used to inform national and international guidelines on the management of encephalitis. The Liverpool team led the development of the UK national encephalitis guidelines (Solomon et al., 2012), and is currently leading the production of European Guidelines, on behalf of the European Academy of Neurology and the European Society of Clinical Microbiology and Infectious Diseases to be published in 2020. The researchers expect the results of the Enceph-IG study to be available towards the end of 2025 in time for the revision of these guidelines.

Intention to publish date
01/04/2027

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from the research team by email to the trial email address, EncephIG@cardiff.ac.uk, and follow the standard CTR data sharing assessment process.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 5.1	04/05/2022	23/02/2023	No	No
HRA research summary			28/06/2023	No	No