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Obinutuzumab compared with rituximab for treating ANCA-associated vasculitis

Submission date
20/09/2022

Recruitment status
No longer recruiting

Registration date
24/10/2022

Overall study status
Completed

Last Edited
10/07/2026

Condition category
Circulatory System

[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
This trial will test if a drug called obinutuzumab works better than rituximab in treating ANCA (Anti-neutrophil cytoplasmic antibody) associated vasculitis, a disease in which the immune system (the system that fights infection) attacks your own cells and tissues, causing inflammation of the blood vessels. The drugs being tested, remove a type of white blood cell called 'B cells' which make the antibodies that are associated with the disease being active. Only rituximab is currently approved to treat vasculitis patients but data suggests that obinutuzumab (approved as a treatment for certain types of blood cancer) is better than rituximab at removing B cells.

Who can participate?
Adults with ANCA-associated vasculitis

What does the study involve?
Following consent, screening assessments will be performed such as taking blood, to check the participant is eligible for the trial. The trial will last for just over 18 months. Participants will receive 2 infusions of one of the medicines, 2 weeks apart at the very beginning of the trial. Which medicine a patient received will be determined randomly i.e. by chance using a computer and neither the participant nor trial doctors will know which drug has been assigned. On Day 1 and then again after 12 weeks, a nasal biopsy will be performed. This involves taking some tissue from inside the nose using a local anaesthetic. These small samples from the lining of the nose will be used to assess how well B cells are removed from tissues by obinutuzumab compared to rituximab. There will be 11 visits in total to the hospital, plus four telephone visits, where assessments e.g. blood and urine tests will be performed. Tests on these samples will help to understand how well the two treatments are working.

What are the possible benefits and risks of participating?
The benefits of participating in the trial are that the new drug obinutuzumab might work better and prevent relapses more than rituximab which is currently given as the standard of care.
A full medical history will be taken to exclude participants who might be at additional risk. The stringent exclusion criteria will mitigate significant risk. There is the risk of a reaction to the test and control IMPs (obinutuzumab and rituximab) but pre-medication therapy (IV corticosteroids,

paracetamol, antihistamine) is given to prevent this. The most common side-effects of both IMPs are bacterial or viral infections; lower white blood cells; lower immunity during the infusions; nausea; chills; and headache. Very rarely, potentially fatal side effects such as reactivation of viruses including hepatitis B causing liver failure and reactivation of JC virus causing progressive multifocal leucoencephalopathy can occur. All the common and important side effects will be clearly described in the Patient Information Sheet and discussed with the potential participant prior to signature. Patients will be excluded based on significant infection history, HBV or Hepatitis C virus (HCV) infection and immunoglobulin deficiency. There are small risks with taking blood such as possible fainting, bruising/bleeding, mild pain or irritation and rarely infection. Participants will be closely monitored for signs of infection. In addition to routine clinical tests, participants will have two nasal biopsies and give blood a little more often than if they were not in a trial. There are small risks associated with having a local anaesthetic nasal biopsy such as minor bleeding or infection. Any bleeding is easily stopped using packing gauze. Infection risks are minimised by using sterile equipment. The most common risk of local anaesthetic is minor discomfort when injecting the inside of the nose. There is a small risk of an allergic response to the local anaesthetic. Other possible side effects include dizziness, nausea, vomiting, accelerated heart rate, slow heart rate and prolonged numbness.
Participants should also consider the burden of having to attend hospital visits more regularly than if they were not taking part in a trial. Wherever possible, we will try to arrange study visits to coincide with routine standard-of-care appointments. Some appointments will be quite lengthy, especially on the days of the two infusions and two biopsies. If the patient works full-time, some time off will be required. Reasonable travel costs will be offered for additional trial appointments. There is a risk associated with the participant completing the prednisolone taper schedule daily at home, i.e. a small risk of the participant taking too much or too little of their scheduled dose. To mitigate this a taper schedule is provided to the participant with clear instructions on how much to take each day (with dates added). The trial nurse will spend time with each participant explaining how to complete this schedule and will be encouraged to contact the trial team with any queries.

Where is the study run from?
Cambridge Clinical Trials Unit, Addenbrooke's Hospital (UK)

When is the study starting and how long is it expected to run for?
July 2022 to July 2026

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Dr Rachel Jones (UK)
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2021-005218-32

Integrated Research Application System (IRAS)
1004254

Central Portfolio Management System (CPMS)
51946

Protocol serial number
A096175

Study information

Scientific Title
A randomised, phase II, double-blind, controlled mechanistic study of obinutuzumab versus rituximab in ANCA-associated vasculitis (ObiVas)

Acronym
ObiVas

Study objectives
To compare the effect of a new drug obinutuzumab against rituximab which is the drug currently approved to treat ANCA-associated Vasculitis. It is thought that obinutuzumab might be better at depleting B cells (the cells that release antibodies and attack the immune system in this disease). It is licensed in cancer treatment and has recently shown success in the treatment of lupus nephritis but is not currently approved for doctors to treat patients with vasculitis. By giving some participants rituximab and some obinutuzumab it will be possible to compare the results and determine which one is better at depleting B cells and potentially more effective at treating the disease.

To see how well obinutuzumab works compared with rituximab by:
1. Comparing the effects on B and T cells (another cell involved in immunity) in tissues (e.g. nasal tissue)
2. Comparing the effects on B and T cells in the blood
3. Comparing the effects on the time it takes for B cells to reappear in the blood after the drugs have depleted them
4. Comparing the effects on changes in PR3 ANCA (a particular protein that ANCA antibodies bind to)

To compare the safety of obinutuzumab by:
5. Comparing how well obinutuzumab versus rituximab in treating the disease
6. Comparing the safety of obinutuzumab versus rituximab e.g. by assessing how many infections occur during the trial

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 05/10/2022, West Midlands - Edgbaston Research Ethics Committee (3rd Floor Barlow House, Minshull Street, Manchester, M1 3DZ, UK; no telephone available; edgbaston.rec@hra.nhs.uk), ref: 22/WM/0174

Primary study design
Interventional

Study design
Randomized phase II double-blind controlled study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
ANCA-associated vasculitis

Interventions
ObiVas is a randomised, phase II, double-blind controlled trial. Participants will be randomised to one of two treatment groups in a 1:1 ratio and receive obinutuzumab (2 x 1000 mg iv infusions,

two weeks apart) plus prednisolone or rituximab (2 x 1000 mg iv infusions, two weeks apart) plus prednisolone. Follow-up will last for 18 months following entry into the study.
Randomisation is via a sealed envelope.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Obinutuzumab, rituximab, prednisolone

Primary outcome(s)
Current primary outcome measure as of 21/06/2024:
Relative percentage change in live single nasal CD19+ B cells in the nasal lymphoid compartment measured using spectral flow cytometry between baseline and week 26

Previous primary outcome measure:
Relative percentage change in nasal CD19+ B cell number measured using flow cytometry at baseline and at week 12

Key secondary outcome(s)
Current secondary outcome measures as of 21/06/2024:
1. Relative percentage change in nasal B and T cell subsets measured using spectral flow cytometry between baseline and week 26
2. Relative percentage change from baseline in blood B, T, NK cells and subsets of interest measured using spectral flow cytometry at weeks 12, 26, 39, 52, 65 and 78
3. Incidence of participants with detectable peripheral B cells measured using spectral flow cytometry at weeks 12, 26, 39, 52, 65 and 78
4. Incidence of participants with PR3-ANCA negativity measured using ELISA at weeks 12, 26, 39, 52, 65 and 78
5. Time to PR3-ANCA rise measured using ELISA
6. Incidence of participants in sustained remission (relapse-free) at weeks 12, 26, 39, 52, 65 and 78 (remission defined as a Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS-WG) ≤1 with daily prednisone dose ≤7.5 mg)
7. Time to remission defined using BVAS-WG
8. Time to first relapse in those who have achieved remission defined using BVAS-WG
9. Time to first major or second minor relapse in those who have achieved remission defined using BVAS-WG
10. Cumulative exposure to corticosteroids between groups (steroid dose calculations) from baseline to week 78
11. Incidence of participants with serious adverse events (SAEs) reported at week 78
12. Incidence of SAEs reported from consent to week 78
13. Incidence and severity of AEs of special interest (AESIs) reported from consent to week 78

Previous secondary outcome measures:
1. Tissue B and T cell subsets measured using flow cytometry at baseline and at week 12
2. Blood B and T cell subsets measured using flow cytometry at baseline and at weeks 12, 26, 39, 52, 65 and 78
3. B cell reconstitution in the blood measured by flow cytometry at weeks 12, 26, 39, 52, 65 and

78 in all patients
4. PR3 ANCA titres measured using enzyme-linked immunosorbent assays (ELISA) at baseline and at weeks 12, 26, 39, 52, 65 and 78
5. Clinical efficacy measured during patient consultations using the Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) scoring at weeks 12, 26, 39, 52, 65 and 78 to assess the following disease activity outcomes:
5.1. Time to disease remission
5.2. Time to first relapse of disease (in those who attained remission)
5.3. Time to first major or second minor disease relapse
5.4. Cumulative total of daily doses of corticosteroid
6. Safety measured by Serious Adverse Event (SAE) reporting throughout the duration of the trial concluding the end of the trial (week 78)

Completion date
10/07/2026

Eligibility

Key inclusion criteria
1. Capable of giving signed informed consent
2. Participants must be aged 18 years old and over at the time of signing the informed consent form.
3. Have a diagnosis of AAV (granulomatosis with polyangiitis or microscopic polyangiitis), according to the definitions of the Chapel Hill Consensus Conference (35).
4. PR3 ANCA positivity by ELISA at screening.
5. Have active disease defined by one major or three minor disease activity items on the Birmingham Vasculitis Activity Score for Wegener’s (BVAS/WG).
6. Women of child-bearing potential (WOCBP) must agree to use effective contraception methods and agree to follow these methods for at least 18 months after the last dose of rituximab or obinutuzumab.
7. Has received at least two doses of any COVID-19 vaccination.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
99 Years

Sex
All

Total final enrolment
30

Key exclusion criteria
1. Women who are pregnant, plan to become pregnant or breast feed during the trial.
2. Current participation in any other interventional treatment trials.
3. Compliance: is unlikely to comply with trial visits based on investigator judgment.
4. MPO ANCA or anti–GBM antibody positivity by ELISA during screening.
5. Presence of pulmonary haemorrhage with hypoxia.
6. Estimated glomerular filtration rate (eGFR) <15 ml/min/1.73m2.
7. Symptomatic herpes zoster within 3 months of screening.
8. Evidence of active or latent tuberculosis (TB) determined by a positive (not indeterminate) QuantiFERON®-TB Gold test (or equivalent).
9. Known hypersensitivity or significant allergies to monoclonal antibodies.
10. Malignant neoplasm within 5 years (from screening) excluding basal cell or squamous cell carcinoma of the skin treated with local resection only or carcinoma in situ of the uterine cervix treated locally and without metastatic disease for 3 years.
11. A history of a primary immunodeficiency.
12. IgA deficiency (IgA < 10 mg/dL).
13. IgG deficiency (IgG < 400 mg/dL).
14. Neutrophils < 1.5 x 109 cells/L.
15. B cell lymphopenia at screening (total CD19+ count <0.1x109/L).
16. Alanine transferase (ALT) >2.5x upper limit of normal (ULN).
17. Active bleeding disorders, and/or inability to support interruption to anticoagulant or anti-platelet therapies for nasal biopsy.
18. Severe nasal deformity precluding endoscopic assessment/biopsy of postnasal space
19. Severe heart failure (New York Heart Association Class IV) or other severe, uncontrolled cardiac disease.
20. Have a history of a major organ transplant or hematopoietic stem cell/marrow transplant.
21. Have an acute or chronic infection requiring management as follows:
21.1. Currently on any treatment for a chronic infection such as pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster, or atypical mycobacteria
21.2. Hospitalisation solely for treatment of proven infection requiring parenteral (IV or IM) antibiotics (antibacterials, antivirals, antifungals, or anti-parasitic agents) within 60 days of Day 1. NB Hospitalisation for a participant with active vasculitis with co-existent infection requiring IV or IM antibiotics is permitted.
21.3. Proven severe infection requiring outpatient treatment with parenteral (IV or IM) antibiotics (antibacterials, antivirals, antifungals, or anti-parasitic agents) within 60 days of Day 1. Prophylactic anti-infective treatment is allowed. Precautionary PO/IV antibiotics in a participant with active vasculitis is permitted.
22. Positive human immunodeficiency virus (HIV) antibody test.
23. Positive serology for Hepatitis B (HB), defined as: (i) HB surface antigen positive (HBsAg+) OR (ii) HB core antibody positive (HBcAb+).
24. Positive Hepatitis C (HCV) antibody test.
25. Have clinical evidence of significant unstable or uncontrolled acute or chronic diseases not due to vasculitis which, in the opinion of the principal investigator, could confound the results of the trial or put the participant at undue risk.
26. Have a planned surgical procedure, laboratory abnormality, or condition that, in the opinion of the principal investigator, makes the participant unsuitable for the trial.

Prior/Concomitant Therapy:
27. Live vaccine(s) within 30 days prior to Day 1, or plans to receive live vaccines during the trial.
28. Have received any anti-CD20 (or any other B cell depleting therapies including alemtuzumab) within 12 months of Day 1.
29. Have received any of the following within 180 days of Day 1:
29.1. Cyclophosphamide
29.2. Belimumab
30. Have received any of the following within 90 days of Day 1:
30.1. Anti-TNF or anti-IL-6 therapy (e.g., adalimumab, etanercept, infliximab, tocilizumab),
30.2. Abatacept,
30.3. Interleukin-1 receptor antagonist (e.g., anakinra),
30.4. Intravenous immunoglobulin (IVIG),
30.5. Plasmapheresis, leukapheresis.
31. Have received any investigational agent (that is not approved for use in the UK) within 60 days of Day 1.
32. Have received emergency IV steroid >3g methylprednisolone between 30 days prior to Screening Visit and up to Day 1 (including Day 1).

Date of first enrolment
09/01/2023

Date of final enrolment
17/01/2025

Locations

Countries of recruitment
United Kingdom

Study participating centre
Addenbrookes Hospital
Hills Road
Cambridge
England
CB2 0QQ

Sponsor information

Organisation
Cambridge Clinical Trials Unit

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Rachel Jones; email: Rachel.jones154@nhs.net. Consent will be obtained from the participants via the study consent form, with participants asked for consent to the following statement: I understand that de-identified information collected about me may be used to support other research in the future, including research conducted by both commercial and non-commercial organisations in the UK and abroad.

IPD sharing plan summary
Available on request, Stored in non-publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		17/07/2024	19/07/2024	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	version 2.0	09/09/2022	21/10/2022	No	Yes