ISRCTN16128829 https://doi.org/10.1186/ISRCTN16128829

Understanding how treatments that reduce self-attacking immune proteins affect gene readouts in ANCA-associated vasculitis

Submission date
07/07/2023

Recruitment status
No longer recruiting

Registration date
17/07/2023

Overall study status
Completed

Last Edited
08/08/2023

Condition category
Circulatory System

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

Plain English summary of protocol

Background and study aims
ANCA-associated vasculitis is an autoimmune condition, characterised by inflammation of blood vessels, which can affect any organ in the body. It has been transformed from a largely fatal to a chronic relapsing condition following the introduction of immunosuppression, initially glucocorticoids and cyclophosphamide, and more recently, rituximab, a drug which targets a particular type of immune cells called B cells. B cells have many functions including making antibodies, one of which is ANCA. Rituximab is effective at inducing remission but must be given repeatedly to maintain remission and the effect is not sustained when treatment is discontinued in many patients. Unfortunately, repeated dosing of rituximab can be harmful by weakening the immune system, leading to an increased risk of infection and poorer vaccine responses. Vaccination is hugely topical at present in light of the COVID-19 pandemic, and many patients who have received courses of rituximab have mounted sub-optimal antibody responses and remain vulnerable to the infection.
It is not clear why some patients have long-lasting remissions and others relapse. The repopulation of B cells or rising levels of ANCA cannot accurately predict future disease course. This is likely due to the interactions of B cells with other cells in the immune system. Furthermore, it is unclear why some patients appear more sensitive to rituximab developing low immunoglobulin levels and recurrent infections. Using new technologies and sophisticated computer methods, it is now possible to characterise in great detail the different types of immune cells and thereby better understand the impact of rituximab on the immune system. As part of the RITAZAREM clinical trial, which compared repeated doses of rituximab to azathioprine as maintenance treatment in relapsing ANCA-associated vasculitis, blood samples were collected at multiple time points. The analysis of these samples will allow researchers to model changes over time of both proportions of cells and individual cell characteristics to better understand the way B cell depletion with rituximab impacts other immune cell populations. This information in conjunction with clinical data will allow the researchers to further understand the effect of rituximab on the immune system and potentially explain the varied long-term clinical outcomes. This knowledge may in future allow more personalised treatment approaches.

Who can participate?
Data and biological samples from the participants of the RITAZAREM trial

What does the study involve?
The study will analyze the gene readouts found in blood samples collected at multiple timepoints to understand and model the changes of different types of immune cells during and after treatments that lower the activity of the immune system and their association with clinical outcomes of interest (i.e., disease relapses).

What are the possible benefits and risks of participating?
This study does not place any additional burden on participants. The participants whose samples and data are being used are unlikely to benefit directly from the proposed research. However, since the majority of patients with AAV experience at least one disease relapse and will require further treatment, advances in disease understanding and therapeutic approaches may be of benefit in future.

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?
November 2022 to April 2023

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

Who is the main contact?
Prof. David R.W. Jayne, dj106@cam.ac.uk

Contact information

Type(s)
Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
2012-001102-14

Integrated Research Application System (IRAS)
317294

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
IRAS 317294, CPMS 55468

Study information

Scientific Title
Transcriptomic deconvolution to dissect the immunological mechanism of B cell depletion therapy in ANCA-associated vasculitis

Study objectives
A greater understanding of the mechanism of B cell depletion in ANCA-associated vasculitis (AAV) will give insight into the subsequent disease course and will enable the individualisation of therapeutic strategies.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 14/02/2023, HRA and Health and Care Research Wales (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8000; contact@hra.nhs.uk), ref: 23/PR/0136

Study design
Post-hoc analysis of randomized control trial data (RITAZAREM trial)

Primary study design
Observational

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Understanding of the mechanism of B cell depletion in ANCA-associated vasculitis

Interventions
A bulk RNA sequencing of peripheral blood samples taken longitudinally from patients recruited into the RITAZAREM trial will be undertaken. Initially, it is planned to process samples collected at baseline and month 4 (remission), month 20 (last rituximab dose in maintenance course) and month 30 (off immunosuppression). Then, a detailed deconvolution analysis and modelling of longitudinal trajectories of both deconvoluted cell proportions and cell-intrinsic transcriptomic signatures to better understand the mechanism of B cell depletion therapy on other leucocyte populations will be performed.

Intervention Type
Other

Primary outcome(s)
Transcriptomic analysis of peripheral blood samples using bulk RNA sequencing at baseline and months 4, month 24, and month 36

Key secondary outcome(s))
1. Immune cell proportions following B cell depletion therapy, identified using deconvolution analysis at baseline and months 4, month 24, and month 36
2. Cell-intrinsic immune cell transcriptomes following B cell depletion, identified using deconvolution analysis at baseline and months 4, month 24, and month 36
3. Immune cell proportions and transcriptomes in rituximab and azathioprine-treated individuals, identified using deconvolution analysis at baseline and months 4, month 24, and month 36
4. Previously identified T cell exhaustion signatures known to be associated with clinical outcomes in AAV, assessed using deconvolution analysis at baseline and months 4, month 24, and month 36
5. Cell proportions or cell-intrinsic transcriptomes after withdrawal of immunosuppression in those who relapse against those who do not, identified using deconvolution analysis at baseline and months 4, month 24, and month 36

Completion date
30/04/2023

Eligibility

Key inclusion criteria
Participants from the RITAZAREM clinical trial who have provided biological samples as part of the original study protocol

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
99 years

Sex
All

Key exclusion criteria
Patients who were not enrolled in the RITAZAREM clinical trial

Date of first enrolment
01/05/2023

Date of final enrolment
30/04/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Cambridge University Hospitals NHS Foundation Trust
Cambridge Biomedical Campus
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Sponsor information

Organisation
Cambridge University Hospitals NHS Foundation Trust

ROR
https://ror.org/04v54gj93

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care 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

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a non-publicly available repository. The data management plan comprises three interrelated systems hosted by the Cambridge Service for Data-Driven Discovery (CSD3). https://www.hpc.cam.ac.uk/high-performance-computing

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

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes