ISRCTN11442263 https://doi.org/10.1186/ISRCTN11442263

Vaccine Response On/off Methotrexate (VROOM): does temporarily suspending methotrexate treatment for two weeks enhance COVID-19 vaccine response?

Submission date
22/07/2021

Recruitment status
No longer recruiting

Registration date
23/08/2021

Overall study status
Completed

Last Edited
25/01/2024

Condition category
Musculoskeletal Diseases

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

Plain English summary of protocol

Background and study aims
The purpose of the VROOM study is to find out if an individual's response to a vaccine can be improved. Specifically the VROOM study will aim to recruit individuals who have inflammatory conditions such as rheumatoid arthritis and psoriasis and routinely take a drug called methotrexate. The individuals needed for the study are these individuals and specifically those who are invited to and accept an invitation to have a booster vaccination against COVID-19 from the NHS vaccination programme.

Doctors and scientists believe there is a small amount of evidence that if individuals temporarily stop taking their methotrexate for the two weeks around when they receive their COVID-19 booster- it may improve their body's (immune) response. The study will also help understand the way in which methotrexate dampens the immune response to vaccines.

Methotrexate is the first-line treatment for inflammatory conditions such as rheumatoid arthritis and psoriasis. It does a good job at controlling such diseases but it also reduces the body's ability to fight infections. People taking methotrexate also don't get great responses to vaccines such as those against the flu and pneumonia. Better immunity usually means a better chance of not getting infected and fighting the virus if infected. Because there is no clear evidence on whether to halt or continue methotrexate during COVID-19 vaccinations, specialists have given conflicting advice that has confused patients. There is an opportunity to answer this question during the booster vaccinations in winter 2021.

Who can participate?
We will invite 560 people with inflammatory conditions such as rheumatoid arthritis and psoriasis receiving methotrexate to take part in our study looking at vaccine response in those who continue to take their methotrexate as usual or who take a 2-week break from taking their methotrexate around their COVID-19 booster vaccination.

What does the study involve?
Participants will be invited to 3 hospital visits to give some data and a small blood sample at each visit.

What are the possible benefits and risks of participating?
We hope that the valuable information from this study will give the NHS and other countries a clear answer to the question of whether temporarily stopping methotrexate for 2 weeks around the time of COVID-19 booster vaccination improves the vaccine response. We cannot promise that the study will benefit those that participate directly, but the information generated has the potential to benefit all those with inflammatory conditions who continue to be vaccinated against COVID-19 in the future. Thus, the results of this study may benefit those that participate in the future.

There is a small risk of a flare in a participant's inflammatory condition on interrupting methotrexate treatment for two weeks. However, all participants can access treatment for any flare-ups as usual.

Where is the study run from?
The study is sponsored by the University of Nottingham (UK) and runs from the Oxford Clinical Trials Research Unit (OCTRU), a UKCRC-registered CTU.

When is the study starting and how long is it expected to run for?
From July 2021 to September 2022

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

Who is the main contact?
VROOM study team
vroom@ndorms.ox.ac.uk

Study website
http://www.vroom-study.co.uk

Contact information

Type(s)
Public

Contact name
Dr Jennifer Williams

Contact details
VROOM Trial Manager
OCTRU, Botnar Research Centre
NDORMS
University of Oxford
Old Road
Headington
United Kingdom

OX3 7LD
+44 (0)1865 612661
vroom@ndorms.ox.ac.uk

Type(s)
Scientific

Contact name
Prof Abhishek Abhishek

ORCID ID
http://orcid.org/0000-0003-0121-4919

Contact details
Room A21 Clinical Sciences Building
Nottingham City Hospital
Hucknall Road
Nottingham
United Kingdom
NG5 1PB
+44 (0)1158231392
abhishek.abhishek@nottingham.ac.uk

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 50297, v1.0

Study information

Scientific Title
A multi-centre randomised controlled trial examining the effects of temporarily suspending low-dose methotrexate treatment for two weeks after SARS-CoV-2 vaccine booster on vaccine response in immunosuppressed adults with inflammatory conditions, including a nested mechanistic sub-study

Acronym
VROOM

Study objectives
A two-week temporary suspension in weekly low-dose methotrexate treatment after SARS-CoV-2 vaccine boosters will improve the anti-spike-receptor binding domain (RBD) response.

Mechanistic sub-study (in a subset of 100 participants):
The neutralising antibody response will correlate with the anti-spike-RBD antibody in this immune-suppressed population as in other healthy populations.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 20/08/2021, Yorkshire & The Humber - Leeds West Research Ethics Committee (Meeting held by video-conference via Zoom; +44 (0)207 972 2504, +44 (0)207 104 8088; leedswest.rec@hra.nhs.uk), ref: 21/YH/0209

Study design
Multi-centre interventional randomized controlled trial

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 (vroom@ndorms.ox.ac.uk) to request a participant information sheet

Health condition(s) or problem(s) studied
Inflammatory polyarthropathies, rheumatoid arthritis, psoriasis, seronegative spondyloarthritis, reactive arthritis, atopic eczema, polymyalgia rheumatica, systemic lupus erythematosus

Interventions
Participants will be randomised into the two arms (experimental intervention or control intervention) in a 1:1 ratio using the minimisation factors:
1. Inflammatory condition type (inflammatory rheumatic disease (+/- skin disease), skin disease alone)
2. Age group (<40 years, 40-64 years, ≥65 years)
3. Previous vaccination platform received (mRNA, vector, combination)
Allocation will occur using a bespoke randomisation system developed and validated within the Oxford Clinical Trials Research Unit (OCTRU) at the University of Oxford. Participants will enter their age group, inflammatory condition grouping, and which 2 COVID vaccinations were received previously into the randomisation system.

Experimental intervention: To suspend methotrexate for two weeks immediately after receiving the SARS-CoV-2 booster vaccination.

Control intervention: To continue on the same dose of methotrexate as usual after SARS-CoV-2 booster vaccination.

Intervention Type
Drug

Phase
Phase III/IV

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

Primary outcome measure
Anti-spike receptor binding domain (RBD) antibody level measured from blood sample collected at 4 weeks post SARS-CoV-2 booster vaccination

Secondary outcome measures
1. Level of anti-spike RBD antibody measured from blood sample collected at 12 weeks post booster vaccination
2. Patient assessments of disease activity measured using:
2.1. Global assessment using a numeric rating scale with one-week recall at baseline, 2, 4, and 12 weeks post booster vaccination
2.2. Current disease activity level and change since booster, 4 and 12 weeks post booster vaccination
3. Disease flare-up and actions taken to deal with them measured using patient self-report at 4 and 12 weeks post booster vaccination
4. Effect on quality of life measured using the EQ-5D-5L questionnaire at 4 and 12 weeks post booster vaccination
5. Adherence with advice to interrupt or continue methotrexate measured using patient self-report at 2 and 4 weeks post booster vaccination

Mechanistic sub-study only:
1. COVID-19 neutralising titre measured from blood sample collected at 4 and 12 weeks post booster vaccination
2. Adherence to methotrexate allocation measured using patient self-report at 4 and 12 weeks post booster vaccination

Overall study start date
01/07/2021

Completion date
26/09/2022

Eligibility

Key inclusion criteria
1. Aged ≥18 years
2. Diagnosed with inflammatory conditions such as rheumatoid arthritis, psoriasis with or without arthritis, seronegative spondyloarthritis, reactive arthritis, atopic eczema, polymyalgia rheumatica, or systemic lupus erythematosus. This is not an exhaustive list and people with

other inflammatory conditions where treatment may be interrupted for two weeks without the risk of a substantial increase in disease activity, or organ or life-threatening flare up will also be eligible to participate in the study in order to increase the generalisability of the study.
3. Prescribed with oral or subcutaneous methotrexate (≤25 mg/week) +/- hydroxychloroquine weekly administered for at least the previous three months
4. Able to temporarily suspend methotrexate for two weeks in the opinion of patients' consultant without the risk of substantial increase in disease activity, or organ or life-threatening flare-up
5. Able to give informed consent;
6. Eligible for planned booster vaccination for COVID-19 (i.e. have received any 2 vaccinations from the original NHS COVID Vaccination Programme 2020/21)

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
560

Total final enrolment
383

Key exclusion criteria
Current participant exclusion criteria as of 08/03/2022:
1. Diagnosed with any of: ANCA associated vasculitis, large vessel vasculitis, myositis, giant cell arteritis, solid organ transplant or any another inflammatory condition for which treatment cannot be interrupted safely.
2. Treated with Rituximab drip in the last 18 months or planning to start it
3. Concurrent immune suppressive treatments in the last two months specifically leflunomide, ciclosporin, azathioprine or mercaptopurine, sulfasalazine or other 5-amino-salicylic acid drugs, mycophenolate, apremilast, or biologic agents
4. Radiotherapy or cancer chemotherapy in last six months
5. Prednisolone dose >7.5 mg/day within 30 days of randomisation
6. Active solid organ cancer (people with skin cancer or those cured of solid organ cancer are eligible)

Previous participant exclusion criteria:
1. Diagnosed with inflammatory conditions for which treatment cannot be interrupted safely such as ANCA associated vasculitis, large vessel vasculitis, myositis, giant cell arteritis, or solid organ transplant
2. Treated with Rituximab drip in the last 18 months or planning to start it
3. Concurrent immune suppressive treatments in the last two months specifically leflunomide, ciclosporin, azathioprine or mercaptopurine, sulfasalazine or other 5-amino-salicylic acid drugs,

mycophenolate, apremilast, or biologic agents
4. Radiotherapy or cancer chemotherapy in last six months
5. Prednisolone dose >7.5 mg/day within 30 days of randomisation
6. Active solid organ cancer (people with skin cancer or those cured of solid organ cancer are eligible)

Date of first enrolment
30/09/2021

Date of final enrolment
07/03/2022

Locations

Countries of recruitment
England

United Kingdom

Wales

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

Study participating centre
Sherwood Forest Hospitals NHS Foundation Trust
Kings Mill Hospital
Mansfield Road
Sutton-in-ashfield
United Kingdom
NG17 4JL

Study participating centre
Royal Wolverhampton NHS Trust
Clinical Trials Unit
Cannock Chase Hospital
Brunswick Road
Cannock
Staffordshire

United Kingdom
WS11 5XY

Study participating centre
Great Western Hospitals NHS Foundation Trust
Great Western Hospital
Marlborough Road
Swindon
United Kingdom
SN3 6BB

Study participating centre
Aneurin Bevan University Health Board
Royal Gwent Hospital
Cardiff Road
Newport
United Kingdom
NP20 2EF

Study participating centre
Chesterfield Royal Hospital NHS Foundation Trust
Chesterfield Road
Calow
Chesterfield
United Kingdom
S44 5BL

Study participating centre
Cwm Taf Morgannwg University Local Health Board
Royal Glamorgan Hospital
Ansari Court
United Kingdom
CF72 8TB

Study participating centre
Gateshead Health NHS Foundation Trust
Queen Elizabeth Hospital
Sheriff Hill
Gateshead
United Kingdom
NE9 6SX

Study participating centre
Harrogate and District NHS Foundation Trust
Harrogate District Hospital
Lancaster Park Road
Harrogate
United Kingdom
HG2 7SX

Study participating centre
Imperial College Healthcare NHS Trust
Hammersmith Hospital
Du Cane Road
London
United Kingdom
W12 0HS

Study participating centre
Lancashire & South Cumbria NHS Foundation Trust
Royal Preston Hospital
Vicarage Lane
Preston
United Kingdom
PR2 8DW

Study participating centre
Midlands Partnership NHS Foundation Trust
Haywood Hospital
High Lane
Stoke on Trent
United Kingdom
ST6 7AG

Study participating centre
Norfolk and Norwich University Hospitals NHS Foundation Trust
Colney Lane
Colney
Norwich
United Kingdom
NR4 7UY

Study participating centre
North Cumbria Integrated Care NHS Foundation Trust
Clinical Research Department
The Cumberland Infirmary
Port Road
Carlisle
United Kingdom
CA2 7AF

Study participating centre
North West Anglia NHS Foundation Trust
Peterborough City Hospital
Bretton Gate
Bretton
Peterborough
United Kingdom
PE3 9GZ

Study participating centre
Oxford University Hospitals NHS Foundation Trust
Nuffield Orthopaedic Centre
Windmill Road
Oxford
United Kingdom
OX3 7LD

Study participating centre
The Dudley Group NHS Foundation Trust
Russells Hall Hospital
Pensnett Road
Dudley
United Kingdom
DY1 2HQ

Study participating centre
The Newcastle upon Tyne Hospitals NHS Foundation Trust
Freeman Hospital
Freeman Road
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
The Queen Elizabeth Hospital
Gayton Road
King's Lynn
United Kingdom
PE30 4ET

Study participating centre
The Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Foundation Trust
Gobowen
Oswestry
United Kingdom
SY10 7AG

Study participating centre
Torbay and South Devon NHS Foundation Trust
Torbay Hospital
Newton Road
Torquay
United Kingdom
TQ2 7AA

Study participating centre
University Hospital Southampton NHS Foundation Trust
Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre
University Hospitals Coventry and Warwickshire NHS Trust
University Hospital of Coventry and Warwickshire
Clifford Bridge Road
Coventry
United Kingdom
CV2 2DX

Study participating centre
University Hospitals Sussex NHS Foundation Trust
Royal Sussex County Hospital
Abbey Road
Brigton
United Kingdom
BN2 1ES

Study participating centre
Wirral University Teaching Hospital NHS Foundation Trust
Arrowe Park Hospital
Arrowe Park Road
Upton
Wirral
United Kingdom
CH49 5PE

Study participating centre
York and Scarborough Teaching Hospitals NHS Foundation Trust
York Hospital
Wigginton Road
York
United Kingdom
YO31 8HE

Sponsor information

Organisation
CTU0373

Sponsor details
Research and Innovation, University of Nottingham
East Atrium, Jubilee Conference Centre
Triumph Road
Nottingham
England
United Kingdom
NG8 1DH
+44 (0)1158467906
sponsor@nottingham.ac.uk

Sponsor type
University/education

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

ROR
https://ror.org/01ee9ar58

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
The study will be publicised to research, clinical and patient communities and other important stakeholders, such as self-help groups. Once the study is completed, in addition to the final report for the NIHR EME Programme, we aim to publish the study results in peer-reviewed high impact journals such as the BMJ or the Lancet and present at national and international meetings to ensure maximum impact and rapid dissemination. Additionally, we will seek to disseminate findings through publication in other journals, such as Pulse, newsletters to British Society for Rheumatology, British Association of Dermatology, and Royal College of General Practitioners. We will engage with patients; primary care clinicians; Royal College of General Practitioners. We will ensure that the study results are disseminated to the guideline writing groups.

Intention to publish date
01/10/2023

Individual participant data (IPD) sharing plan

Participant level dataset and statistical code will be made available upon reasonable request to OCTRU and the CI, once the VROOM study findings have been published in full. Some specific data items may not be shared in order to maintain participant anonymity.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		03/05/2022	04/05/2022	Yes	No
Results article		27/06/2022	01/07/2022	Yes	No
HRA research summary			28/06/2023	No	No
Results article		12/12/2023	25/01/2024	Yes	No