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The impact of pausing BTKi therapy and responsiveness of vaccination in blood cancer patients: A randomised controlled study – the IMPROVE study

Submission date
03/09/2022

Recruitment status
No longer recruiting

Registration date
20/09/2022

Overall study status
Completed

Last Edited
03/04/2025

Condition category
Cancer

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

Plain English summary of protocol

Background and study aims
Chronic lymphocytic leukaemia (CLL) is a blood cancer that affects the white blood cells called lymphocytes. It is the commonest adult leukaemia, with 3,800 people diagnosed each year in the UK. It is more common in people aged over 60 years. Currently some 31,900 people have CLL in the UK.
CLL develops slowly and there is no cure. People with CLL have a weakened immune system and are susceptible to infections. These infections can be severe and life-threatening. New drugs called Bruton Tyrosine Kinase inhibitors (BTKi) have transformed the outlook for CLL patients, however they stop the immune response to vaccination. They need to be taken daily and continuously. They are sometimes paused if a patient needs an operation. In the UK, they are used at all stages of treatment. The IMPROVE study aims to find out:
Does pausing BTKi inhibitor drugs for a total of three weeks before and after having the COVID vaccine improve the antibody response and is this well tolerated?

Who can participate?
Adults with well-controlled CLL who have been taking a BTKi inhibitor for at least a year, and are due to have a COVID vaccine

What does the study involve?
The study aims to recruit 120 people at up to 10 NHS hospital sites. Half (60) will be asked to pause their treatment for three weeks: one week before their vaccine, and two weeks after. The other half (60) will continue their treatment as usual. Blood samples will be taken to check everyone’s vaccine response three weeks and 12 weeks after vaccination. The participant's CLL will also be monitored and participants will be asked to complete questionnaires about their quality of life.

What are the possible benefits and risks of participating?
In March 2020 everyone with CLL was advised to shield. To date, most people with CLL continue

to shield as best they can. Advice from haematologists is to be as careful as possible. This means they are largely trapped in their homes, feeling increasingly left behind as the rest of society moves on. It is now COVID-19 that is restricting life for people with CLL and their families, rather than their CLL. The problem is people with CLL have very poor responses to COVID-19 vaccines in comparison to the general population. For those on BTKi inhibitor drugs, it is a double whammy as the drugs make it even more unlikely that patient will respond to COVID-19 vaccination. As COVID-19 is here to stay, further vaccine doses are likely to be recommended for clinically vulnerable patients. The IMPROVE study aims to see if this 3 week's pausing of BTKi therapy would help protect people with CLL and allow them to resume a more normal life.

With regards to risks, to participate in the study, 3 blood samples need to be taken – so there are the risks that come with a blood sample being taken. The questions/questionnaires used in this study are not mandatory and do not ask questions that might embarrass a participant.

Improving vaccination responses has been a hot topic between clinicians and the CLL community for many years. COVID-19 has made this a priority. People with CLL co-designed the IMPROVE study and are partners in governing, managing and advising throughout the study.

Where is the study run from?
The study is overseen by the University of Birmingham, and the Chief Investigator, Dr Helen Parry is based there. Researchers and those experienced in running clinical studies are managing the study at the University of Oxford. The researchers in Oxford are specifically based in the Oxford Clinical Trials Research Unit (OCTRU). Participants are aimed to be recruited from NHS hospitals across the UK that have the permissions to approach participants to consider taking part in the IMPROVE study.

When is the study starting and how long is it expected to run for?
August 2022 to January 2024

Who is funding the study?
National Institute for Health and Social Care Research (NIHR), Efficacy and efficiency mechanism (EME) programme (UK)

Who is the main contact?
improve@ndorms.ox.ac.uk

Study website
https://www.ndorms.ox.ac.uk/octru/trials-portfolio/trials-in-set-up-2/trials-in-set-up-1

Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
319057

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
IRAS 319057, CPMS 53957

Study information

Scientific Title
A multi-centre randomised controlled trial examining the effects of temporarily pausing Bruton Tyrosine Kinase inhibitor therapy to coincide with SARS-CoV-2 vaccination and its impact on immune responses in patients with Chronic Lymphocytic Leukaemia

Acronym
IMPROVE

Study objectives
The aim of this study is to assess whether a temporary three-week pause of daily Bruton tyrosine kinase inhibitor (BTKi) treatment around SARS-CoV-2 vaccination improves the immune response in people with chronic lymphocytic leukaemia (CLL) whilst maintaining disease control.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 09/09/2022, Leeds East Research Ethics Committee (Yorkshire and the Humber – Leeds East, NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, UK; +44 (0)207 104 8105, +44 (0)2071048170; leedseast.rec@hra.nhs.uk), ref: 22YH0226

Study design
Multicentre parallel-group two-arm superiority open-label randomized controlled study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Other

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Chronic lymphocytic leukaemia

Interventions
The intervention is a 3-week temporary pause (suspension) of existing ongoing BTKi therapy. The 3-week temporary pause starts 1 week before vaccination 6 days of no BTKi administration, then on day 7 of no BTKi – COVID vaccination is received and then another 14 days of no BTKi administration – in total 21 days of tablets are omitted). The BTKi therapy being paused will either be Acalabrutinib or Ibrutinib at any dose, and those participating in the study will have been on a BTKi for at least 12 months prior to study enrolment. The control group will not have any pausing in the BTKi administration for the purpose of COVID vaccination.

All participants will have data collection at Baseline (pre-vaccination), 3 weeks post-COVID vaccination and 12 weeks post-COVID vaccination.
Blood sampling will occur at each of these timepoints. Participants will be invited into clinics for blood sampling, and data collection. Participants will also have the option to answer some of the questionnaires at 3 and 12 weeks electronically before attending the clinic visit.

Participants are randomised when they know they have a confirmed COVID vaccination date and are randomised using an online tool by researchers in IMPROVE. Randomisation allocations will be including stratification and participants will equally (1:1) to intervention and control arms based on the stratification factor of the BTKi therapy the participant is taking – their first line or subsequent therapy for CLL.

Intervention Type
Other

Primary outcome measure
Anti-SARS-CoV-2 spike (S) protein receptor binding domain (RBD) antibody levels measured using Roche Elecsys® electrochemiluminescence assay (Roche S) at baseline and at 3 weeks post-SARS-CoV-2 vaccination

Secondary outcome measures
1. Anti-spike (IgG, IgA and IgM) RBD antibody levels measured using Roche Elecsys® electrochemiluminescence assay (Roche S) at baseline and at 12 weeks post-SARS-CoV-2

vaccination
2. Neutralising antibody titre levels at 50% and 90% against Wuhan D614G (B.1) and the current variant of concern (VOC)) will be assessed using validated laboratory methods at baseline, 3 and 12 weeks post SARS-CoV-2 vaccination
3. Antigen-specific T-cell response for ancestral Wuhan and 1 x VOC spike, and combined nucleocapsid and membrane response measured using the enzyme-linked immunosorbent spot (ELISpot) assay at baseline and 3 weeks post-SARS-CoV-2 vaccination
4. Antibody response to 4 strains of influenza present in the Autumn 22 vaccine (continuous OD 450nm read out) measured using ELISA [For those who receive flu vaccination only] at baseline and 3 weeks post SARS-CoV-2 vaccination
5. Disease activity questions (raised temperature, enlarged or new lymph nodes) measured using a non-validated questionnaire answered by participants electronically at baseline, 3 and 12 weeks post-SARS-CoV-2 vaccination or a participant attending their 3-week clinic visit – if the adherence questions have not been completed they will be asked to complete the questions at that visit
6. Full Blood Count (Haemoglobin, platelet levels and lymphocyte levels) measured using standard medical laboratory methods at baseline, 3 and 12 weeks post SARS-CoV-2 vaccination
7. Blood Film (presence of new prolymphocytes, smear cells or lymphocytosis) measured using standard medical laboratory methods at baseline, 3 and 12 weeks post SARS-CoV-2 vaccination
8. Lactate dehydrogenase levels measured using standard medical laboratory methods at baseline, 3 and 12 weeks post SARS-CoV-2 vaccination
9. Health-related quality of life (HRQoL) measured using the EORTC-QLQ-CLL17 scales (symptom burden, physical condition/fatigue, and worries/fears on health and functioning) at baseline, 3 and 12 weeks post-SARS-CoV-2 vaccination
10. Self-reported adherence measured using a non-validated questionnaire answered by participants electronically at 3 weeks post-SARS CoV-2 vaccination – or a participant attending their 3-week clinic visit – if the adherence questions have not been completed they will be asked to complete the questions at that visit

Overall study start date
01/08/2022

Completion date
31/01/2024

Eligibility

Key inclusion criteria
1. Aged 18 years and over
2. Confirmed diagnosis of chronic lymphocytic leukaemia
3. Taking oral NICE-approved BTKi therapy (Acalabrutinib or Ibrutinib) for at least 12 months since the date of initiation of therapy
4. Has achieved complete remission (CR; including CR with incomplete marrow recovery), partial remission (PR; including nodular PR or PR with lymphocytosis) or stable disease by the International Workshop on CLL (iwCLL) response criteria
5. Considered able to temporarily pause (suspend) BTKi therapy for three weeks without the risk of a substantial increase in disease activity
6. Anticipated to take BTKi over the next 4 months (i.e. not in the STATIC trial arm where therapy is stopped)

7. Willing to accept either study arm allocation
8. Able to give informed consent
9. Eligible for a planned vaccination for COVID-19

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
120

Total final enrolment
99

Key exclusion criteria
1. Insufficient time for applying the intervention prior to the planned COVID-19 vaccination.
2. Diagnosed with alternative conditions requiring treatment with BTKi
3. Treated with anti-CD20 antibody therapy in the last 18 months or planning to start it
4. Concurrent immune suppressive treatments in the last 3 months specifically: methotrexate, ciclosporin, BCL-2 inhibitors, azathioprine, mycophenolate, prednisolone, biologic agents
5. Any contraindication to COVID-19 vaccination
6. Richter's transformation requiring active therapy
7. Radiotherapy or cancer chemotherapy in the last 6 months
8. Active solid organ cancer (people with skin cancer or those cured of solid organ cancer are eligible)
9. Receiving or has received in the past 6 months immunoglobulin replacement therapy
10. Receiving or has received in the past 6 months monoclonal antibody against COVID-19 spike protein

Date of first enrolment
23/09/2022

Date of final enrolment
30/06/2023

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
University Hospitals Birmingham NHS Foundation Trust
Queen Elizabeth Hospital
Mindelsohn Way
Edgbaston
Birmingham
United Kingdom
B15 2GW

Study participating centre
Kings College Hospital Department of Haematology
Kings College Hospital
Denmark Hill
London
United Kingdom
SE5 9RS

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

Study participating centre
Nottingham University Hospitals NHS Trust - City Campus
Nottingham City Hospital
Hucknall Road
Nottingham
United Kingdom
NG5 1PB

Study participating centre
Oxford University Hospitals NHS Foundation Trust
Oxford Cancer and Haematology Centre
Oxford
United Kingdom
OX3 7LE

Study participating centre

Sandwell Healthcare NHS Trust
Sandwell District General Hospital
Lyndon
West Bromwich
United Kingdom
B71 4HJ

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

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

Study participating centre
Glan Clwd Hospital
Ysbyty Glan Clwydd
Bodelwyddan
Rhyl
United Kingdom
LL18 5UJ

Study participating centre
University Hospitals Plymouth NHS Trust
Derriford Hospital
Derriford Road
Crownhill
Plymouth
United Kingdom
PL6 8DH

Study participating centre

Aneurin Bevan University Local Health Board
St. Cadoc's Hospital
Lodge Road
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United Kingdom
NP18 3XQ

Sponsor information

Organisation
University of Birmingham

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researchgovernance@contacts.bham.ac.uk

Sponsor type
University/education

Website
https://www.birmingham.ac.uk/index.aspx

ROR
https://ror.org/03angcq70

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 sponsor will retain ownership of all data arising from the study.

Publication and dissemination of study results and associated study publications (e.g. the study protocol, statistical analysis plan (SAP) and secondary analyses) will be in accordance with the OCTRU Standard Operating Procedure and irrespective of study findings.

The study protocol will be published in an open-access peer-reviewed journal in accordance with the Standard Protocol Items: Recommendations for Interventional Trials statement (SPIRIT, www.spirit-statement.org/). The study results will be published in an open-access journal, in accordance with the NIHR's policy on open-access research. The study will be reported following the Consolidated Standards of Reporting Trials guideline (CONSORT) including any applicable extensions to this. The Template for Intervention Description and Replication (TIDieR) statement will be used for reporting the intervention.

Intention to publish date
31/03/2025

Individual participant data (IPD) sharing plan
The sponsor will retain ownership of all data arising from the study.

Participant level dataset and statistical code will be made available upon reasonable request to OCTRU and the CI, once the IMPROVE 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		28/09/2023	29/09/2023	Yes	No
Results article		01/04/2025	03/04/2025	Yes	No