ISRCTN42585840 https://doi.org/10.1186/ISRCTN42585840

Investigating the use of lenzilumab for acute graft versus host disease (when transplanted stem cells attack the body's cells)

Submission date
19/01/2022

Recruitment status
No longer recruiting

Registration date
08/02/2022

Overall study status
Ongoing

Last Edited
08/05/2024

Condition category
Injury, Occupational Diseases, Poisoning

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

Plain English summary of protocol

Background and study aims
Acute graft-versus-host disease (aGvHD) is a serious complication of stem cell transplantation where the donated stem cells view the recipient's body as foreign and attack the body. This is normally managed with steroids but some patients don't respond well to treatment. Identification of new safe and effective treatments for resistant aGVHD is very important. Patients with aGVHD respond differently to treatment. Evidence from research carried out in the US and Germany has shown that blood tests can identify patients with high-risk aGvHD who might respond less well to treatment.
GM-CSF (granulocyte monocyte-colony stimulating factor) is a protein that controls the growth of blood cells and has recently been shown to be important in the development of acute GvHD. Lenzilumab is an antibody that targets GM-CSF and blocks its activity. Lenzilumab has been used successfully for the treatment of other diseases but has not been tested previously for treating aGvHD.
The aim of this study is to find out how effective and safe lenzilumab is for treating patients with high-risk aGvHD. The researchers will be looking at whether the drug is safe, the effects lenzilumab has on aGVHD, and how long these effects last.

Who can participate?
Patients aged 16 years and over with acute GvHD following allogenic stem cell transplantation.

What does the study involve?
Eligible patients will have their blood assessed for its biomarker risk category. Patients who are high-risk may be eligible for an interventional group. In stage 1 20 patients will receive lenzilumab, and in stage 2 240 patients will be randomly allocated to receive lenzilumab or placebo (dummy drug). Patients who are low-risk may be eligible for stage 2 (observational) which does involve trial treatment. Participants receiving trial treatment will receive doses at weeks 0, 2, 5, 8, 11 and 14 for a total of 6 doses over 14 weeks. The visits may include a physical examination, vital signs, assessment of GvHD and disease, blood tests and a quality of life assessment.

What are the possible benefits and risks of participating?
There is no guaranteed benefit to taking part in this study. The main aim of the study is to see if lenzilumab is a safe and effective treatment for high-risk acute GvHD. The information collected during this study may help improve treatment for other people with acute GvHD in the future. Having blood taken may cause some discomfort, bleeding or bruising where the needle enters the body and, in rare cases, light-headedness and fainting. Participants may experience side effects but will be carefully checked by a doctor for any problems. There may be risks or side effects of the study drugs that are unknown at this time. Participants will be checked by a doctor throughout their time in the study and can withdraw at any time.

Where is the study run from?
University of Birmingham (UK)

When is the study starting and how long is it expected to run for?
November 2019 to January 2027

Who is funding the study?
1. Leukaemia UK
2. The IMPACT network (UK)
3. Humaingen, Inc. (USA)

Who is the main contact?
Rebecca Collings
RATinG@trials.bham.ac.uk

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-lenzilumab-for-acute-graft-versus-host-disease-rating

Contact information

Type(s)
Scientific

Contact name
Miss Rebecca Collings

Contact details
Centre for Clinical Haematology
Queen Elizabeth Hospital
Birmingham
United Kingdom
B15 2TH
+44 (0)121 371 7868
RATinG@trials.bham.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2021-001193-29

Integrated Research Application System (IRAS)
286785

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 51332, IRAS 286785

Study information

Scientific Title
RATinG (Risk Adapted Therapy in acute GvHD): investigating the use of lenzilumab for treating high-risk acute graft versus host disease following allogeneic stem cell transplantation

Acronym
RATinG

Study objectives
The aim of the study is to find out if there is a difference in the non-relapse mortality of patients with high-risk acute graft versus host disease (aGvHD) treated with lenzilumab versus placebo following allogenic stem cell transplantation.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 05/01/2022, East Midlands – Derby Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, UK; +44 (0)2071048211; derby.rec@hra.nhs.uk); REC ref: 21/EM/0280

Study design
Randomized; Both; Design type: Treatment, Drug, Validation of outcome measures

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Graft versus host disease following allogeneic stem cell transplantation

Interventions
RATinG is a multicentre trial in the UK in patients with acute Graft versus Host Disease (aGvHD) following allogeneic stem cell transplantation. It is a double-blind, randomised (1:1) controlled trial. The study comprises of two stages; Stage 1 of the study will recruit high-risk biomarker patients to a safety cohort treated with lenzilumab. In stage 2 of the study, patients with a high-risk biomarker category will be randomised to receive lenzilumab or placebo for 14 weeks or until GvHD progression, and low-risk patients will be recruited into an observational cohort. The

primary outcome of the study is to assess the safety of lenzilumab in the safety cohort and to evaluate non-relapse mortality, which is defined as the time to death without relapse or recurrence, in the treatment arms. The treatment arms will be compared in terms of toxicity (side effects), the rate of acute and chronic GvHD, overall survival, time to treatment failure, quality of life, steroid exposure, time to response or disease progression. Lenzilumab has been evaluated to date in studies of COVID19, asthma and rheumatoid arthritis. This will be the first study of lenzilumab in a haematological disease, but studies to date have shown that the drug is well tolerated. In stage 1 of the study, 20 patients will be recruited to a single-arm cohort treated with lenzilumab. Following this, in stage 2 of the study, a minimum of 220 patients with biomarker defined high-risk acute GvHD following allogeneic stem cell transplantation (SCT) will be randomised to receive treatment of either lenzilumab or placebo. Any patients who do not meet the criteria of being high risk will be recruited into an observational cohort of the study.

Interim Analysis
There are two interim analyses in this trial, one at the end of stage 1 of the trial and the other during stage 2 of the trial. The first interim analysis will be conducted once all 20 patients have been recruited to stage 1 of the trial and have completed 6 weeks of follow up after the completion of trial treatment. This interim analysis will be based upon assessments of safety, efficacy and feasibility and these will determine whether continuation onto the randomised element of the trial is justified. The following criteria have been defined for each of the components that will be considered at this timepoint:

Safety: Observation of cases of proven or probable invasive fungal infections (IFI) and/or observation of either mycobacterial infection (MBI) or pulmonary alveolar proteinosis (PAP)
Efficacy: Overall response rate of the patients at day 28 would be assessed
Futility: Assessment of the proportion of AA2/3 patients recruited to this cohort will be considered

The second interim analysis will be performed during the randomised stage of the trial following the recruitment and completion of 28-day follow up of 150 patients. This analysis will evaluate the day 28 response rate for these patients and will result either in early discontinuation of the trial due to insufficient evidence of improvement or continuation of the randomisation. The rates of adverse events (grade 3-4 and AEs of special interest) observed between the arms will be presented, however, there are no statistically defined criteria for stopping the trial due to safety at this timepoint.

Patients, Assessments and Treatment
Patients will be identified via inpatient wards or via multi-disciplinary teams if being referred from another hospital. Patients will be approached by their consultant and other, trained, members of the clinic team to introduce and discuss the trial. Patients will receive a patient information sheet and will be given at least 24 hours to review the information and ask any additional questions they may have.

Patients will attend the hospital for screening tests to determine if they are eligible for the trial. A blood sample will be sent to The Christie Pathology Partnership for biomarker testing to determine the patient's risk category (up to 60% of patients will be deemed high risk). Based on the risk category, a separate consent form and information sheet will be provided to patients. Patients will also have blood tests and a physical exam as part of screening, patients would receive these tests as part of standard care to ensure they are fit for therapy and confirm disease status. A quality of life questionnaire will also be given to the patients prior to the start of treatment.

20 high-risk patients will initially be recruited to receive single-arm treatment of lenzilumab. Once these patients have been recruited and completed 6 weeks of treatment, an analysis will take place before continuing recruitment to the randomised and observational components of the study.

Patients who are deemed as low risk by biomarker testing will be screened as per the protocol and will follow a simplified schedule of events with visits at day 28 for a biomarker assay, follow up at 6 months and annually until the end of the trial.

Patients deemed as high risk by biomarker testing will be treated with lenzilumab or placebo and will receive 6 doses of treatment; 1800 mg loading dose at week 0, followed by 5 doses of 600 mg at weeks 2, 5, 8, 11 and 14 delivered intravenously.

Patients in the treatment arms will attend the hospital for each dose of treatment and at day 28 for a repeat biomarker assay, they will also have pharmacokinetic (PK) samples taken at these visits. Following this, patients will be seen every 4 weeks during follow up until 26 weeks and will then be seen annually until the end of the trial. During treatment and follow up, patients will have blood tests and physical exams to monitor their disease, health and any side effects of treatment. Patients will not experience any additional visits or clinical tests compared to standard of care as a result of taking part in RATinG. Patients will be asked to complete a quality of life questionnaire pre-treatment and at weeks 14 and 26 after being entered into the trial. This is a short questionnaire that can be completed at clinic visits.

Intervention Type
Drug

Phase
Not Applicable

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

Primary outcome(s)
Stage 1: reported whilst on treatment and up to 6 months following completion/discontinuation:
1. The primary outcome measure of safety is defined to be the number of patients who experience one or more of the following events:
1.1. Invasive fungal infections (IFI): the threshold for continuation to the randomised stage of the trial is the observation of four cases of proven or probable IFI
1.2. Mycobacterial infection (MBI): the threshold for non-continuation to the randomised stage of the trial is the observation of a single case of MBI
1.3. Pulmonary alveolar proteinosis (PAP): the threshold for non-continuation to the randomised stage of the trial is the observation of a single case of PAP, confirmed by radiology and bronchoscopy
1.4. Other adverse events (AEs): no threshold for adverse events other than those defined above are proposed

Stage 2:
Time to non-relapse mortality (NRM), defined as the time from date of randomisation to date of death without relapse. Patients who relapse from their underlying disease will be considered a competing risk at their date of relapse. Patients who are alive and relapse-free at the end of the trial will be censored at their date last seen.

Key secondary outcome(s))

Stage 1:
1. Overall aGvHD response rate (complete and partial response) at day 28 from the start of trial treatment, response defined as per the REACH-2 trial as the proportion of patients with complete or partial response:
1.1. Complete response - score of 0 for aGvHD grading in all evaluable organs, indicating complete resolution of all signs and symptoms of aGvHD in all evaluable organs without administration of additional systemic therapies for any earlier progression, mixed response, or non-response of aGvHD
1.2. Partial response - improvement of 1 stage in one or more organs involved with aGvHD signs or symptoms without progression in other organs or sites without administration of additional systemic therapies for an earlier progression, mixed response, or non-response of aGvHD
2. Feasibility of recruitment to the randomised stage of the trial, defined as the proportion of patients screened that were high risk and length of recruitment. For the randomised element of the trial to be deemed feasible at least 40% of the patients screened for stage 1 will have to be categorised as high risk (AA2/3) GvHD patients and despite there being no defined threshold for either time to recruitment completion or laboratory turnaround time both will be reviewed as part of the feasibility assessment. Measured after completion of stage 1 recruitment (risk category assigned and the patient receives the first dose).

Stage 2:
1. Overall aGvHD response rate (complete and partial response) at day 28 from the start of trial treatment, response defined as per the REACH-2 trial as the proportion of patients with complete or partial response:
1.1. Complete response - score of 0 for aGvHD grading in all evaluable organs, indicating complete resolution of all signs and symptoms of aGvHD in all evaluable organs without administration of additional systemic therapies for any earlier progression, mixed response, or non-response of aGvHD
1.2. Partial response - improvement of 1 stage in one or more organs involved with aGvHD signs or symptoms without progression in other organs or sites without administration of additional systemic therapies for an earlier progression, mixed response, or non-response of aGvHD
2. Overall survival, defined to be time from date of randomisation/recruitment to date of death, from any cause. Patients alive at the end of the trial will be censored at their date last seen.
3. Time to relapse of underlying disease or death defined to be the time from the date of randomisation/recruitment to the date of the first event. For this outcome an event is defined to be relapse of underlying disease or death from any cause. Patients alive and relapse-free at the end of the trial will be censored at their date last seen.
4. Time to GvHD treatment failure, defined as the time from the start date of treatment to the date of the first event. An event here is defined to be any of the following; an increased dose of steroids for the purpose of GvHD treatment; starting of additional GvHD treatment; worsening of aGvHD; onset of chronic GvHD or death where the primary cause is given to be GvHD. Patients who discontinue treatment for reasons other than worsening of GvHD will be considered a competing risk at their date of discontinuation and patients who die for reasons other than GvHD will be considered a competing risk at their date of death. Patients alive and failure-free at the end of the trial will be censored at their date last seen.
5. Cumulative steroid exposure defined as the total mass of steroids given (in mg) for treatment of GvHD, measured from the start date of treatment to treatment completion/discontinuation or progression
6. Biomarker risk status as assessed by the MAGIC consortium at day 28 from the start of trial treatment
7. Incidence and severity of chronic GvHD measured at weeks 0, 2, 4, 5, 8, 11, 14, 18, 22, 26,

progression/end of treatment and then annually
8. Safety will be collected in accordance with CTCAE criteria version 5.0 and is defined to be the number of patients who experience one or more grade 3 or higher adverse event or serious adverse event of any grade, reported whilst on treatment, at Day 1 of treatment, and up to 28 days after patients complete/discontinue, and serious adverse events the same but up to 6 months following completion/discontinuation.
9. Quality of life, measured using FACT-BMT, assessed at weeks 0, 14 and 26 post-treatment and additionally at treatment discontinuation or GvHD progression

Completion date
01/01/2027

Eligibility

Key inclusion criteria
Stage 1 and Stage 2 - Randomised Cohort:
1. Aged ≥16 years
2. Recipient of allogeneic stem cell transplant
3. Acute graft versus host disease (aGvHD) (grade I-IV) requiring treatment with systemic steroids (PO prednisolone or IV methylprednisolone equivalent to prednisolone dose of ≥1 mg /kg)
4. Eastern Cooperative Oncology Group (ECOG) performance status 0-3 (see Appendix 2)
5. High-risk patients with an Ann Arbor high or intermediate risk score (Appendix 3)

Stage 2 - Observational Cohort:
1. Aged ≥16 years
2. Recipient of allogeneic stem cell transplant
3. aGvHD (grade I-IV) requiring treatment with systemic steroids (PO prednisolone or IV methylprednisolone equivalent to prednisolone dose of ≥1 mg/kg)
4. Eastern Cooperative Oncology Group (ECOG) performance status 0-3 (see Appendix 2)
5. Low risk patients with Ann Arbor low risk score (Appendix 3)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
16 years

Sex
All

Key exclusion criteria
All Cohorts:
1. Any additional treatment for GvHD excluding continuance of current prophylaxis or re-

institution of drugs previously used for prophylaxis
2. Patients requiring treatment with topical steroids only
3. Known HIV or active hepatitis B/C (currently receiving treatment)
4. Patients treated with >4 days of steroids for aGvHD (maximum of 20 mg for other indications)
5. Female patients who are pregnant or breastfeeding. All women of childbearing potential must have a negative pregnancy test before registration/randomisation

Stage 1 and Stage 2 - Randomised Cohort:
1. Adults of reproductive potential not willing to use appropriate, highly effective, contraception during the specified period

Date of first enrolment
01/01/2022

Date of final enrolment
01/01/2025

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
Gartnavel Royal Hospital
1055 Great Western Road
Glasgow
United Kingdom
G12 0XH

Study participating centre
King's College Hospital
Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
St James's University Hospital
Beckett Street

Leeds
United Kingdom
LS9 7TF

Study participating centre
St Mary's Hospital
Oxford Road
Manchester
United Kingdom
M13 9WL

Study participating centre
Freeman Hospital
Freeman Road
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
John Radcliffe Hospital
Headley Way
Headington
Oxford
United Kingdom
OX3 9DU

Study participating centre
Queen Elizabeth Hospital
Mindelsohn Way
Edgbaston
Birmingham
United Kingdom
B15 2GW

Study participating centre
The Royal London Hospital
80 Newark Street
London
United Kingdom
E1 2ES

Study participating centre
Bristol Royal Infirmary
Marlborough Street
Bristol
United Kingdom
BS2 8HW

Study participating centre
University College London Hospital
250 Euston Road
London
United Kingdom
NW1 2PG

Study participating centre
Addenbrookes Hospital
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
University Hospital of Wales
Heath Park
Cardiff
United Kingdom
CF14 4XW

Study participating centre
The Christie
550 Wilmslow Road
Withington
Manchester
United Kingdom
M20 4BX

Study participating centre

Leicester Royal Infirmary
Infirmary Square
Leicester
United Kingdom
LE1 5WW

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

Study participating centre
Queens Medical Centre
Nottingham University Hospital
Derby Road
Nottingham
United Kingdom
NG7 2UH

Study participating centre
Derriford Hospital
Derriford Road
Crownhill
Plymouth
United Kingdom
PL6 8DH

Sponsor information

Organisation
University of Birmingham

ROR
https://ror.org/03angcq70

Funder(s)

Funder type

Charity

Funder Name
Leukaemia UK

Alternative Name(s)
LUK

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Funder Name
The IMPACT network (UK)

Funder Name
Humaingen, Inc.

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No