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Cell therapy for acute liver injury trial

Submission date
20/12/2022

Recruitment status
Recruiting

Registration date
25/04/2023

Overall study status
Ongoing

Last Edited
18/12/2025

Condition category
Injury, Occupational Diseases, Poisoning

[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
The aim of this clinical trial is to test the safety of a cell therapy for liver injury. Healthy people with no liver disease can develop sudden acute liver injury (ALI) which, in severe cases, can lead to a syndrome called acute liver failure (ALF). ALF is characterised by bleeding because the liver cannot make enough clotting factors, excessive pressure in the brain, kidney failure, and infection. ALF has no effective treatment other than liver transplantation, which has only limited use because of its associated complications, the expense to the health provider and the scarcity of donor's livers. Medicines are the most common cause of ALF in the Western world, especially paracetamol when taken in overdose. The only treatment for paracetamol overdose is called acetylcysteine, which is optimally effective only if treatment is started within around 8 hours of taking the tablets. For other causes of ALF, there are currently no specific treatments. Our new treatment is an infusion of cells called macrophages, which are large white blood cells that clear away damaged liver cells, and reduce inflammation, and, in mice with ALF have been shown to promote the regeneration of healthy liver tissue.

Who can participate?
Adults (16 years old and over) with ALI due to paracetamol overdose

What does the study involve?
All participants will receive a single infusion of macrophage blood cells. Patients will be included in cohorts with increasing doses. A group of independent experts will review the safety of each dose and decide whether or not the study can continue to the next higher dose. The researchers will carry out different tests before, during (Day 0) and after the infusion (on Days 1, 2, 7 and 30). These include routine checks of patients' general well-being (temperature, blood pressure, breathing and pulse rate, blood oxygen levels), a tracing of the heart called an electrocardiogram (ECG), a physical exam and blood taking. We will also ask patients questions about their medical history, any other medications they take and any side effects they are experiencing.

What are the possible benefits and risks of participating?
The researchers do not know if patients will directly benefit from taking part in this trial. However, the information obtained from this study will help improve the treatment of people who require treatment in the future. This is a new treatment and the researchers do not yet know for certain what adverse effects, if any, it may have. However, different types of

macrophages have been given to humans with other conditions in studies before. These studies did not show any severe adverse effects from the macrophage treatment. Patients will be monitored closely during treatment and will be given appropriate medication to treat any side effects that might occur. Rare, known side effects of cell therapies include the following symptoms:
1. Nausea, vomiting, chest tightness, skin flushes and a rise in blood pressure and/or temperature.
2. Very rarely may cause a drop in blood pressure, a change in heart rate, difficulty in breathing or an acute allergic reaction.
These side effects last only a short time and can be treated.

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

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

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

Who is the main contact?
MAIL.Trial@ed.ac.uk (MAIL Trial Management Team, Edinburgh Clinical Trials Unit) (UK)

Contact information

Type(s)
Principal investigator

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Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2022-002584-29

Integrated Research Application System (IRAS)
1005258

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
AC22087, IRAS 1005258

Study information

Scientific Title
Macrophage Therapy For Acute Liver Injury (MAIL) trial: a phase I randomised, open-label, dose-escalation study to evaluate safety, tolerability, and activity of allogeneic alternatively activated macrophages (AAM) in patients with paracetamol-induced acute liver injury.

Acronym
MAIL

Study objectives
There is currently no effective treatment for Acute Liver Failure (ALF) other than liver transplantation, which has limited use because of its associated complications, expense to the health provider and the scarcity of donor livers. Medicines are the most common cause of ALF in the Western world, especially paracetamol when taken in overdose. The only treatment for paracetamol overdose is called acetylcysteine, which prevents ALF only if treatment is started

within around 8 hours of taking the tablets. For other causes of ALF there are currently no specific treatments. Previous research has shown that macrophages (large white blood cells which have the ability to “eat” dead cells) can help to reduce the damage and support regeneration of the liver. This study will test whether a new treatment for acute liver injury using macrophages is safe.

The secondary objective of the trial is to determine whether there is any evidence that treatment with macrophages may improve the health of the injured liver.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 08/03/2023, North East – York Research Ethics Committee (NHSBT Newcastle Blood Doner Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, UK; +44 (0)207 104 8079; york.rec@hra.nhs.uk) ref: 23/NE/0019

Study design
Interventional randomized single-arm dose-escalation study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Acute liver injury (paracetamol-induced)

Interventions
Participants will receive a single infusion of allogeneic alternatively activated macrophages (AAM). The first patient will be dosed with 10e6 macrophages; if there are no safety concerns, the highest dose in this trial will be up to 10e9 cells. Patients will be dosed in 5 cohorts with dose escalation decisions being guided by an independent Data Monitoring Committee. In dose cohorts 3-5, the dose of AAM will be randomised using a centralised online randomisation system. Participants will be followed-up for 30 days following the infusion.

Intervention Type
Biological/Vaccine

Phase
Phase I

Drug/device/biological/vaccine name(s)
Allogeneic alternatively-activated macrophages (AAM)

Primary outcome(s)
Dose-limiting toxicity occurring within 30 days of infusion. DLT is defined as a clinically significant adverse event or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications and either meeting the NCI common terminology criteria that are CTCAE Grade 3 or 4 OR deemed by the independent Data

Monitoring Committee (DMC) to be serious enough to prevent an increase in dose of treatment. All adverse events occurring in this study will be assessed against these criteria by an investigator and reviewed by the DMC within 30 days of dosing, assessed on days 1, 2, 3, 7 and 30.

Key secondary outcome(s))
Assessed on days 1, 2, 3, 7 and 30:
1. Safety: Adverse events of special interest (defined as: serious adverse events of transfusion reaction; macrophage activation syndrome; acute respiratory compromise) and all serious adverse events occuring within 30 days of infusion, clinical observations, clinical examination, electrocardiogram (ECG) and safety blood tests.
2. Activity measured by blood tests:
2.1. Pro-inflammatory – IL-6, TNF-alpha, IL-12, IL-8 (pg/mL). Anti-inflammatory - IL-10 (pg/mL). Assessed as change from baseline.
2.2. Liver injury – conventional markers of paracetamol-induced liver injury:ALT (U/L), INR, Lactate (mmol/L), Creatinine (µmol/L). Novel marker of paracetamol-induced liver injury: HMGB1 (ng/mL), GLDH (U/L), cytokeratin-18 (U/L) and miR-122 (copies/mL). Assessed as change from baseline.
3. Immunogenicity: Development of anti-HLA antibodies measured by blood test

Completion date
30/11/2026

Eligibility

Key inclusion criteria
1. Serum ALT activity > 1000U/L at screening.
2. History of paracetamol overdose within 5 days of ALT>1000. Overdoses of paracetamol alone and mixed overdoses are eligible.
3. Other causes of ALT increase excluded based on previous investigations and trial screening. This will be documented in the patient's medical notes.
4. Provision of written informed consent.
5. Adult male or female (16 yrs old or above).
6. Deemed safe for hospital discharge from a mental health perspective after full mental health assessment by a mental health professional. This will be documented in the patient's medical notes.
7. Patients with child bearing potential must have a negative urine or serum pregnancy test at screening. If the patient is of child bearing potential, or is a male with a female partner with child bearing potential, the patient, and their partner(s), must agree to use a highly effective method of contraception throughout the trial period and for 90 days post study completion.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit

16 years

Upper age limit
100 years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Patients who do not have the capacity to consent.
2. Any situation that in the Investigator's opinion may interfere with optimal study participation such as alcohol or drug abuse, potential non-compliance or inability to co-operate.
3. Patients with known viral hepatitis infection or known COVID-19 infection.
4. Patients who are pregnant, or are planning on becoming pregnant during the study, or are breastfeeding and wish to continue breastfeeding. Patients of childbearing potential, or male patients with a female partner of childbearing potential, must agree to use a highly effective method of contraception as detailed above.
5. Patients who have previously participated in this study or another ATMP.
6. Potentially life-threatening liver injury with an immediate need for transplantation as documented in the patient's medical notes.
7. Patients listed for any organ transplant.
8. Patients with stage 4 or 5 chronic kidney disease.
9. Any history of or suspected hypersensitivity to the cell product, excipients, or possible residual components used in manufacture.
10. Patients who are currently enrolled in another ATMP or Clinical Trial of an Investigational Medicinal Product (CTIMP).

Date of first enrolment
01/09/2023

Date of final enrolment
31/05/2026

Locations

Countries of recruitment
United Kingdom

Scotland

Study participating centre
Royal Infirmary of Edinburgh
51 Little France Crescent
Old Dalkeith Road
Edinburgh
Lothian

Scotland
EH16 4SA

Study participating centre
Royal Victoria Infirmary
Queen Victoria Road
Newcastle upon Tyne
England
NE1 4LP

Sponsor information

Organisation
NHS Lothian

ROR
https://ror.org/03q82t418

Organisation
Accord (United Kingdom)

ROR
https://ror.org/01x6s1m65

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
Consent will be sought from participants to permit sharing of anonymised data with funders and collaborators or published on publicly available resources as appropriate. Following publication of the primary MAIL Trial results, a de-identified individual participant data set will be prepared for sharing purposes. Access to de-identified data may be granted to other researchers upon reasonable request in line with ECTU policies at that time.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		04/11/2024	11/03/2025	Yes	No
HRA research summary			26/07/2023	No	No
Participant information sheet	version 6.0	29/07/2025	18/12/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes