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Effect of memory T cells after mismatched donor transplant in children with immunodeficiency

Submission date
26/05/2023

Recruitment status
Recruiting

Registration date
25/10/2023

Overall study status
Ongoing

Last Edited
11/03/2025

Condition category
Haematological Disorders

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

Plain English summary of protocol

Background and study aims
The study team plan to research the benefit of a cellular therapy called CD45RO+ memory T cell addback after stem cell transplantation from a mismatched donor in children with inborn errors of immunity (IEI). IEIs are associated with reduced quality of life and risk of death in early childhood in severe cases. Stem cell transplantation is an established curative therapy for affected patients, but about 25-60% of those eligible lack a suitable tissue-type-matched donor. An alternative is to use a mismatched family or unrelated donor, such as a parent, but there is a catch. Stem cell harvests include not only the stem cells that will go on to repopulate the patient's bone marrow, but also a mixture of mature immune cells that are armed and potentially dangerous. These cells include a group of white blood cells (good T cells) which are very useful for fighting infections. However, after a transplant, bad T cells from the donor can attack normal cells in the patients and cause a condition called "graft-versus-host disease" (GvHD). T cells are very sensitive to tissue type differences, so GvHD is a big risk in mismatched transplants. For this reason, it is standard practice to remove most T cells from the graft, but it takes a long time for the immune system to recover after this type of transplant. This leads to a high risk of serious infections and even death during the transplant period, until the immune system recovers. The new cellular therapy in this study is a way of giving back the good T cells (memory T cells, CD45RO+) from a portion of the donor graft as an "addback" (or boost) after T cell-depleted mismatched transplant.

Who can participate?
Children aged from 1 month to 18 years old deemed clinically eligible for allogeneic HSCT for non-SCID IEI at either the Great North Children’s Hospital (GNCH) or Great Ormond Street Hospital (GOSH).

What does the study involve?
Patients at GOSH will only be eligible to take part if they are receiving a T-cell depleted haploidentical donor transplant. 10 patients will be recruited and participants will receive the usual treatment for a T-cell depleted stem cell transplant and will not receive any addback. Two different groups of patients at GNCH will be eligible to take part;

1. 40 patients at GNCH who are receiving a stem cell transplant from a matched unrelated donor (MUD) will be recruited, they will receive the usual treatment for a MUD stem cell transplant and will not receive any addback.
2. 40 patients at GNCH who are receiving a T-cell depleted haploidentical donor transplant will be recruited, they receive the usual treatment for a T-cell depleted stem cell transplant plus a single dose of memory T-cell addback 7 days after their transplant.
All groups will be followed up closely to allow the team to collect information on how the participants recover following the transplant. Most of this information will come from routine tests and assessments that will be collected from the medical notes. Some additional blood samples will be taken and the legal representative/parent/child will be asked to complete a questionnaire (where possible) about their quality of life. Where possible all assessments will take place as an inpatient or at routine follow-up appointments.

What are the possible benefits and risks of participating?
There may be an increased risk of developing graft-versus-host disease (GvHD) for patients who receive the addback compared to standard care treatment of haploidentical donor transplant without addback. This will be closely monitored by trained and experienced clinicians throughout the course of the study.

Where is the study run from?
Newcastle University (UK)

When is the study starting and how long is it expected to run for?
May 2023 to September 2028

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

Who is the main contact?
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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1007527

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
10116, CPMS 59155

Study information

Scientific Title
Memory T cells to improve immunity after TCRαβ/CD19 depleted haploidentical donor stem cell transplantation for inborn errors of immunity

Acronym
HAPLO+4Kids

Study objectives
I. To determine the optimum dose of CD45RO+ memory T-cell addback in children with non-SCID IEI after TCRαβ/CD19 depleted haploidentical donor transplant (TCRαβ-HaploSCT).
The optimum dose will be that associated with the shortest time to T-cell immune reconstitution (defined as CD3+ T-cells ≥200 cells/μL), without causing significant GvHD during the first 3 months (91 days) following TCRαβ-HaploSCT (addback administered 7 days following TCR αβ-HaploSCT).

II. To determine whether the optimal dose of CD45RO+ memory T-cell addback can hasten T-lymphocyte immune reconstitution (defined as CD3+ T-cells ≥200 cells/μL), up to 6 months following TCRαβ-HaploSCT compared to the two prospective control groups (TCRαβ-HaploSCT without addback and matched unrelated donor (MUD) haematopoietic stem cell transplantation (HSCT)) and one historical cohort (TCRαβ-HaploSCT without addbacK).

To evaluate how the three different transplant strategies; TCR αβ-HaploSCT plus CD45RO+ memory T cell addback, TCR αβ-HaploSCT without addback (standard of care (SOC) when no MUD available) and MUD HSCT (SOC), affect the following post-transplant outcomes up to 6 months after transplant.

Ethics approval required

Ethics approval required

Ethics approval(s)
Approved 19/10/2023, London – Hampstead Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8345; hampstead.rec@hra.nhs.uk), ref: 23/LO/0514

Study design
Prospective 3-arm randomized open-label adaptive seamless two-stage multicentre study

Primary study design
Interventional

Secondary study design
Non-randomized, parallel assignment

Study setting(s)
Hospital

Study type(s)
Safety, Efficacy

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

Health condition(s) or problem(s) studied
Non-severe combined immunodeficiency inborn errors of immunity

Interventions
There are three arms across two sites with this trial; the intervention arm, control group 1 and control group 2.

The interventional cohort (n=40) will include only children who are receiving a TCRαβ-HaploSCT (because of the lack of a suitable fully matched donor, either related or unrelated). They will be recruited in two stages;
• Stage 1 will determine the optimum safe and effective dose of CD45RO+ memory T-cell addback.
• Stage 2 will determine whether CD45RO+ memory T-cell addback can accelerate immune reconstitution and reduce the incidence, duration and severity of viral infection after TCRαβ-HaploSCT.

Twelve participants at a single site (NUTH) will be randomised using Sealed Envelope and receive one of three different doses of CD45RO+ memory T-cell addback; 0.3 x 10^6/kg, 0.6 x 10^6/kg and 1.0 x 10^6/kg. Where a participant has been randomised but does not go on to receive the addback, for any reason, they will be withdrawn and an additional patient will be recruited. The next participant to reach the point of randomisation will automatically be allocated the same dose as the replaced participant and will effectively replace the participant who did not receive the addback. Randomisation should take place on Day -7 after baseline data collection is

completed and when the conditioning regimen is commenced, however, if for any reason this is not possible then randomisation should occur as soon as possible and no later than the day of SCT (day 0).

The addback will, in general, be administered on day 7 after TCRαβ-HaploSCT (day 0), but exceptionally its administration might be delayed by up to 2 days. If a participant does not receive addback within this window of 7 to 9 days post-transplant, an additional participant will be recruited to ensure data is available for twelve participants. An interim analysis will be performed after the first 12 participants complete three months' follow-up to determine the optimum dose of CD45RO+ memory T-cell addback to be used in stage 2. The optimum dose will be that which most rapidly achieves CD3+ T-cells ≥ 200 cells/μL, without causing significant GvHD.

Following the interim analysis, all participants recruited to the interventional cohort will receive the optimum dose (from stage 1) of CD45RO+ memory T-cell addback on day +7 after TCRαβ-HaploSCT. Recruitment will stop when a total of 40 eligible participants in stages 1 and 2 have been recruited and received CD45RO+ memory T-cell addback.

All participants in stages 1 and 2 of the intervention group and both prospective control groups will be followed up until six months after the index transplant.

Control 1 (n=10) and control 2 (n=40) will be recruited continuously from GOSH and GNCH, respectively.

Intervention Type
Other

Primary outcome measure
The following primary outcome measures are assessed 3 months post-SCT:
1. Time to T-cell immune reconstitution defined as CD3+ T-lymphocytes ≥ 200 cells/μL measured using flow cytometry
2. Incidence and severity of acute (Gluckberg criteria) and chronic GvHD (National Institutes of Health (NIH) consensus criteria) measured using clinical assessment
3. Time to T-cell immune reconstitution defined as CD3+ T-cells ≥ 200 cells/μL measured using flow cytometry

Secondary outcome measures
1. Lymphocyte/monocyte/T-cell (total, CD4+, CD8+, naive)/NK cell/B cell count measured using flow cytometry at 1, 2, 3, 4 and 5 months post-SCT
2. CMV, adenovirus, EBV and HHV6 measured in whole blood using viral polymerase chain reaction (PCR) and clinical assessment weekly during the first 90 days, at day +105, day +120 and day +180
3. Grade III-IV acute GvHD and extensive chronic GvHD according to Glucksberg criteria and NIH consensus criteria respectively measured using clinical assessment at days + 28, +56, +91, +105, +120, +180
4. Transplant-related mortality: defined as death between the day of transplantation (day 0) and the day of the event, not due to disease recurrence and considered related to transplant by the investigator measured using clinical data with death reported as an SAE
5. Overall survival: defined as survival from day 0 after HSCT to last follow-up or death; event-free survival: defined as survival without events (death, graft failure or second procedures); GvHD-free, event-free survival: defined as survival without events, Grade III-IV aGvHD or

extensive chronic GvHD: all measured using clinical data with events and time of onset on death, graft failure, second procedures, acute and chronic graft-versus-host disease being recorded
6. Cumulative incidence of graft failure after HSCT measured using clinical data and Graft failure and time of onset will be recorded
7. Time to neutrophil engraftment: defined as the first of 3 consecutive days with ANC ≥ 0.5 x 10e9/L after the first post-transplant conditioning regimen induced nadir measured using laboratory parameters from routine full blood counts at the time to first of 3 consecutive days with ANC ≥ 0.5 x 10e9/L post-SCT
8. Time to platelet engraftment: defined as the first 3 consecutive days with platelet ≥ 20 x 10e9 /L with no platelet transfusion in at least 7 preceding days measured using laboratory parameters from routine full blood counts
9. Chimerism analysis of peripheral blood mononuclear cells within the first 180 days (expressed as % donor) measured using the monitoring of short tandem repeat markers monthly from Day +28 to +180
10. Total days of inpatient stay from transplant, readmissions, parenteral nutrition and number of red blood cell and platelet transfusions from day 0 to day +180 measured using clinical data
11. Health-related quality of life measured using the Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales and PedsQL Stem Cell Transplant Module standard version, at baseline and 6 months
12. Quality of T-cell immune reconstitution after memory T-cell addback including T-cell abundance and phenotype, ex vivo anti-viral responses and TCR repertoire diversity measured using flow cytometry ± single cell transcriptomics measured using at Days +28, +91 and Day +180 (additional timepoints if viral reactivation occurs)
13. Serum concentrations of ATG (Grafalon) and alemtuzumab will be measured at different timepoints for pharmacokinetic (PK) analysis, to estimate the time at which circulating serotherapy falls to the sub-lympholytic level, alemtuzumab will be measured on day -8, -6, -4, 0, +1, +7, +14, +21 and +28 post-SCT and at ATG level on day -2, 0, +1, +2, +7, +14, +21, +28 post SCT using validated enzyme-linked immunosorbent assay (ELISA)
14. Pharmacokinetics (PK) of each conditioning chemotherapy agent (thiotepa, treosulfan, fludarabine). The plasma concentration of Fludarabine, Treosulfan and Thiotepa will be measured using high-performance liquid chromatography (HPLC) methods at specific time points after each chemotherapy infusion. Toxicity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Criteria up to 1-month post-SCT.

Overall study start date
24/05/2023

Completion date
01/09/2028

Eligibility

Key inclusion criteria
1. Age at least 1 month and up to 18 years at the time of scheduled transplant
2. Patients deemed clinically eligible for allogeneic HSCT for non-SCID IEI
3. No suitable conventional matched family donor#.
4. Patient has an eligible donor identified by the clinical transplant team:
4.1. Planned mismatched family or mismatched unrelated donor for TCRαβ-HaploSCT (Intervention and control group 1)*
OR

4.2. 10/10 HLA-matched unrelated donor for MUD HSCT (control group 2)
5. Capacity for patient or the patient’s parent or guardian to provide written informed consent

1. # Donor choice is independent of this study and will be decided by the clinical team according to best clinical practice. Generally the hierarchy of preferred donor is 10/10 matched family donor > 10/10 matched unrelated donor > mismatched family donor > mismatched unrelated donor. However, depending on the specific disorder, a family member might not be a suitable donor if they are a carrier of the genetic disease, or the underlying molecular defect is unknown.

Participant type(s)
Patient

Age group
Child

Lower age limit
1 Months

Upper age limit
18 Years

Sex
Both

Target number of participants
90

Key exclusion criteria
1. Lansky/Karnofsky performance score <30%
2. Ongoing active acute GvHD or chronic extensive GvHD due to previous allograft at the time of screening
3. Patient receiving an immunosuppressive treatment for GvHD due to previous allograft at time of screening
4. Presence of a medical condition indicating that survival will be dismal such as the requirement for a high setting of mechanical ventilation and severe failure of a major organ system
5. Pregnancy or breastfeeding in female patients

Additional exclusion criteria for intervention group and control group 1 only (TCRαβ-HaploSCT)
1. Patients with donor-specific antibodies (DSA) against the potential stem cell donor using the standard test according to the institutional guideline

Date of first enrolment
01/03/2024

Date of final enrolment
31/10/2028

Locations

Countries of recruitment

United Kingdom

Study participating centre
-
United Kingdom
-

Sponsor information

Organisation
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Sponsor type
University/education

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

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)

Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Peer reviewed scientific journals
2. Conference presentation
3. Publication on the website
4. Submission to regulatory authorities

Intention to publish date
01/09/2028

Individual participant data (IPD) sharing plan
Until the publication of the trial results, access to the full dataset will be limited to the Trial Management Group and to the authors of the publication. At the end of the trial, the de-identified dataset will be prepared and stored by Newcastle University. Requests for data sharing with bona fide study teams out with Newcastle University or NuTH will be considered by a Data Access Committee, with representation from the Sponsor and CI, and will be subject to the presentation of a clear plan of what the data will be used for, how the data will be analysed, how the results will be disseminated, and who the authors will be.
Data transfer will be subject to the completion of a Data Sharing Agreement between Newcastle University and the end users. Data will not be withheld from bona fide researchers requesting access unless the above criteria for sharing are not met.

IPD sharing plan summary
Available on request