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A randomised controlled trial to assess the safety and effectiveness of stem cell transplantation using a reduced intensity regimen in patients with treatment resistant Crohn's disease

Submission date 23/10/2017	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 31/10/2017	**Overall study status** Completed	
Last Edited 12/02/2024	**Condition category** Digestive System	

Plain English summary of protocol

Background and study aims
Crohn's disease is a long term condition that causes inflammation of the lining of the digestive system. There is no cure for Crohn's disease and current treatments only reduce symptoms and often carry complicated side effects. In addition, some patients fail to respond to these treatments or experience only temporary benefit. In the absence of an effective alternative, patients are likely to be exposed to a sequence of expensive therapies with diminishing potential for benefit and increasing risk of harm. An alternative therapy is haematopoietic stem cell transplantation (HSCT). The aim of this study is to evaluate whether HSCT with a low intensity treatment regime, can reduce the symptoms and activity of Crohn's disease and enhance quality of life.

Who can participate?
Patients aged 18-60 who have a Crohn's disease.

What does the study involve?
Participants are randomly allocated to one of two groups. Those in the first group receive HSCT therapy, some stem cells are removed (harvested) from the patient and stored for later use. The patient will then undergo a process to eliminate their immune cells. Then the stem cells that were harvested earlier are transplanted (re-infused) back into the patient's blood. The re-infused stem cells give rise to a new generation of immune cells, replacing cells of the original 'sick' immune system. Those in the second group receive the usual care offered by their local NHS organization. Participants are followed up to assess the progress of participants who undergo stem cell transplantation with those who receive the usual care. Imaging techniques and patient reported symptom measures will be used to measure symptom progression. The study will also explore the mechanisms involved in rebuilding the immune system and reactivity to biologic therapies after HSCT by comparing tissue samples collected over course of the trial.

What are the possible benefits and risks of participating?
It is not known whether the HSCT intervention will offer long-term benefits from Crohn's disease and this is the reason for carrying out this research. If the treatment is found to be more effective than the usual care patients receive, this will inform the treatment of future patients with Crohn's disease. By taking part in this study participants will be directly helping us to do this, as well as having the opportunity to access a treatment that is not usually available through usual care, particularly if their Crohn's disease has not responded to previous treatments. In addition, participants are contacted regularly by the study nurse and are likely to receive more frequent follow-up appointments than in normal clinical care, which they may find reassuring. It may be possible for patients allocated to receive HSCT, to speak to other patients who have undergone the procedure, but this will depend on differences between practices in the participating centres. Taking part in this study may mean additional burden of appointments at the recruiting NHS Trust. Although this means extra travel, participants will be reimbursed for their travel costs in attending these hospital appointments if required. Participation in the trial may affect medical insurance. Participants will be advised on the participant information sheet to contact any private medical insurance companies prior to joining the trial. Although autologous HSCT has been used to treat other conditions successfully, there are a number of possible side effects and complications that can occur. The treating physicians will do their utmost to prevent these from occurring and treat them as best as they can when serious complications do occur. Any adverse event requiring hospitalisation will be recorded as serious and reported accordingly. It is possible that HSCT may cause irreversible infertility. Participants will have the chance to discuss whether they wish to undergo sperm/egg cryo-preservation prior to commencing the trial. It is possible that if the treatment is given to a pregnant woman it will harm the unborn child. Pregnant women or women who plan to become pregnant during the study will not be allowed to take part and where appropriate a pregnancy test will be carried out to confirm eligibility for the trial. Women who could become pregnant, and male participants whose female partners could become pregnant, will be asked to use effective contraceptive during the course of this study. Any woman who finds that she has become pregnant while taking part in the study will be asked to immediately tell her research doctor.

Where is the study run from?
This study is being run by the Barts Health NHS Trust and takes place in hospitals in the UK.

When is the study starting and how long is it expected to run for?
August 2017 to November 2021

Who is funding the study?
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC) (UK)

Who is the main contact?
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Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2017-002545-30

Protocol serial number
35769

Study information

Scientific Title
Autologous Stem cell Transplantation In refractory Crohn's disease - Low Intensity Therapy Evaluation

Acronym
ASTIClite

Study objectives

The main aim of this study is to assess whether stem cell mobilisation with low dose cyclophosphamide 1g/m2 and G-CSF followed by autologous transplantation with a reduced intensity ('HSCTlite') conditioning regimen (fludarabine 125mg/m2, cyclophosphamide 120mg /kg and rabbit-ATG 7.5mg/kg) is safe and effective in inducing regression of ileo-colonic ulceration in patients with refractory CD when compared with standard care.

Ethics approval required
Old ethics approval format

Ethics approval(s)
London - Chelsea Research Ethics Committee, 06/11/2017, 17/LO/1690

Study design
Randomized; Interventional; Design type: Treatment, Drug, Cellular

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Refractory Crohn's disease

Interventions
Following consent, and confirmation of eligibility, participants are randomised, using a web-based system to receive either the HSCTlite intervention, or standard care, in the ratio 2:1.

HSCTlite Intervention:
Participants receive HSCT therapy, some stem cells are removed (harvested) from the patient and stored for later use. The patient will then undergo a process to eliminate their immune cells. Then the stem cells that were harvested earlier are transplanted (re-infused) back into the patient's blood. The re-infused stem cells give rise to a new generation of immune cells, replacing cells of the original 'sick' immune system. The following are the steps:
Mobilisation: Autologous stem cells are mobilised with cyclophosphamide 1g/m2 and G-CSF 5mcg/kg starting 5 days after the infusion of cyclophosphamide. Daily CD34+ counts commence on day 8 following cyclophoshamide. Existing treatment other than corticosteroids (eg prednisolone) are stopped prior to HSCT as specified in the protocol. Mesna is given in line with local practice to prevent haemorrhagic cystitis.
Leukapheresis: Once there are sufficient stem cells in the bloodstream (10x106/L), they are harvested via leukapheresis (minimum harvest is 2x106 CD34+ve cells). The collected cells are cryopreserved until later use at transplantation.
Immunoablation: The conditioning regimen comprises cyclophosphamide (60mg/kg/day) given on each of 2 days, with Fludarabine, 3 days prior to this at 25mg/m2/day for 5 days. Antithymocyte globulin ('ATG') is also given for 3 days starting the same day as cyclophosphamide at 2.5mg/kg/day. Methylprednisolone (1mg/kg/day) are used to reduce side effects. Mesna and all supportive care are given in line with local practice
Stem cell transplant (day 0): Stem cells are reinfused into the patient on trial day 0. G-CSF (5mcg /kg/day) starts after 5 days. Follow up tests and visits that are routine following HSCT are carried out according to local policies, and may be in addition to defined study visits.

Standard care group:
Participants randomised to standard care continue current gold standard medical care until the primary endpoint at 48 weeks plus 49 days. Day 0 is calculated as 49 days post randomisation for the usual care group, with the aim of mirroring the timeframe for HSCT. Usual care can include steroid therapy, immunomodulators, any licensed/approved biologic therapy and enteral or intravenous nutrition.

Participants are followed up at the following weeks:
Week 4: Participants who have undergone HSCTlite have an intestinal MRI to determine the early impact on mucosal disease (mechanistic substudy objective).
Week 8: All participants (HSCTlite and standard care) complete the HBI, CDAI, IBDQ, IBD Control, PRO2, EQ-5D-5L, WPAI and healthcare resource use questionnaires and have a general physical examination and blood and stool samples taken.
Week 14: All participants (HSCTlite and standard care) complete the HBI, CDAI, IBDQ, IBD Control, PRO2, EQ-5D-5L, WPAI and healthcare resource use questionnaires and have a general physical examination and blood and stool samples taken. At this point, any adverse event information will inform the 100 day safety for transplant endpoint.
Week 24: All participants (HSCT lite and standard care) will complete HBI, CDAI, IBDQ, IBD Control, PRO2, EQ-5D-5L, WPAI and healthcare resource use questionnaires. Blood and stool samples will be collected and a general examination performed. An MRI scan of their small bowel and colonoscopy with biopsies will be performed. 'HSCT lite' participants will commence a programme of revaccination. Anti-TNF therapy may be re-started in HSCTlite participants if there is evidence of disease activity as defined in the protocol.
Week 32: All participants (HSCTlite and standard care) complete the HBI, CDAI, IBDQ, IBD Control, PRO2, EQ-5D-5L, WPAI and healthcare resource use questionnaires and have blood and stool samples taken, as well as a general physical examination.
Week 40: All participants (HSCTlite and standard care) complete the HBI, CDAI, IBDQ, IBD Control, PRO2, EQ-5D-5L, WPAI and healthcare resource use questionnaires, and have routine clinical care blood samples taken, as well as a general physical examination.
Week 48 (primary endpoint): All participants (HSCTlite and standard care) complete HBI, CDAI, IBDQ, IBD Control, PRO2, EQ-5D-5L, WPAI and healthcare resource use questionnaires. Blood and stool samples are collected and a general examination performed. An MRI scan of their small bowel and colonoscopy with biopsies will be performed.

Intervention Type
Other

Phase
Phase III

Primary outcome(s)
Regression of mucosal ulceration is assessed using the SES-CD ulcer sub score on colonoscopy at week 48.

Key secondary outcome(s))
Current secondary outcome measures as of 15/03/2018:
Clinical secondary outcome measures:
1. Clinical remission is measured using the Crohn's Disease Activity Index (CDAI) at baseline, week 8, week 14, week 24, week 32, week 40 and week 48
2. Steroid free clinical remission is measured using the CDAI at baseline, week 8, week 14, week 24, week 32, week 40 and week 48

3. Clinical remission is measured using the Harvey Bradshaw Index (HBI) at baseline, week 8, week 14, week 24, week 32, week 40 and week 48
4. Clinical remission is measured using the PRO2 at baseline, week 8, week 14, week 24, week 32, week 40 and week 48
5. Absolute Crohn's Disease activity is measured using the CDAI at baseline and week 48
6. Endoscopic ulceration is measured using the SES-CD at baseline and week 48
7. Change in CDAI score is measured between baseline and week 48
8. Change in SES-CD score is measured between baseline and week 48
9. Complete endoscopic remission is measured using the SES-CD at baseline and week 48

Safety secondary outcome measures:
1. Toxicity of chemotherapy is measured using NCI CTCAE grading of adverse events at week 4, week 8, week 14, week 24, week 32, week 40 and week 48
2. Adverse events are measured through documentation of adverse events at week 4, week 8, week 14, week 24, week 32, week 40 and week 48

Patient-reported secondary outcome measures:
1. Crohn's disease specific quality of life is measured using the IBDQ at baseline, week 8, week 14, week 24, week 32, week 40 and week 48
2. Crohn's disease specific quality of life is measured using the IBD Control questionnaire at baseline, week 8, week 14, week 24, week 32, week 40 and week 48
3. Quality of life is measured using the EQ-5D-5L at baseline, week 8, week 14, week 24, week 32, week 40 and week 48
4. Healthcare resource use is measured using the healthcare resource utilisation questionnaire at baseline, week 8, week 14, week 24, week 32, week 40 and week 48

Exploratory secondary outcome measures:
1. Efficacy of re-introduction of anti-TNF therapy in patients with disease recurrence post-HSCT is measured using the change in CDAI between baseline and 6 weeks after initiation of anti-TNF therapy
2. Efficacy of re-introduction of anti-TNF therapy in patients with disease recurrence post-HSCT is measured using the change in SES-CD between 0 and 22 weeks after initiation of anti-TNF therapy
3. Safety of re-introduction of anti-TNF therapy in patients with disease recurrence post-HSCT is measured through documentation of adverse events at week 32, week 40 and week 48

Mechanistic secondary outcome measures:
1. Timeline of response to HSCTlite is measured through MRI at week 4 and week 48
2. Nature of immune re-constitution after HSCT is measured through blood sample analysis at week 8, week 14, week 24, week 32 and week 48
3. Immunological events that precede the onset of disease recurrence post HSCT is measured through blood sample analysis at week 8, week 14, week 24, week 32 and week 48
4. Mechanism of restoration of responsiveness to anti-TNF therapies if appropriate is measured through blood sample analysis at week 8, week 14, week 24, week 32 and week 48

Previous version:
Clinical secondary outcome measures:
1. Clinical remission is measured using the Crohn's Disease Activity Index (CDAI) at baseline, week 8, week 14, week 24, week 32, week 40 and week 48
2. Steroid free clinical remission is measured using the CDAI at baseline, week 8, week 14, week 24, week 32, week 40 and week 48
3. Clinical remission is measured using the Harvey Bradshaw Index (HBI) at baseline, week 8,

week 14, week 24, week 32, week 40 and week 48
4. Clinical remission is measured using the PRO2 at baseline, week 8, week 14, week 24, week 32, week 40 and week 48
5. Absolute Crohn's Disease activity is measured using the CDAI at baseline and week 48
6. Endoscopic ulceration is measured using the SES-CD at baseline and week 48
7. Change in CDAI score is measured between baseline and week 48
8. Change in SES-CD score is measured between baseline and week 48
9. Complete endoscopic remission is measured using the SES-CD at baseline and week 48

Safety secondary outcome measures:
1. Toxicity of chemotherapy is measured using NCI CTCAE grading of adverse events at week 4, week 8, week 14, week 24, week 32, week 40 and week 48
2. Adverse events are measured through documentation of adverse events at week 4, week 8, week 14, week 24, week 32, week 40 and week 48

Patient-reported secondary outcome measures:
1. Crohn's disease specific quality of life is measured using the IBDQ at baseline, week 8, week 14, week 24, week 32, week 40 and week 48
2. Crohn's disease specific quality of life is measured using the IBD Control questionnaire at baseline, week 8, week 14, week 24, week 32, week 40 and week 48
3. Quality of life is measured using the EQ-5D-5L at baseline, week 8, week 14, week 24, week 32, week 40 and week 48
4. Healthcare resource use is measured using the healthcare resource utilisation questionnaire at baseline, week 8, week 14, week 24, week 32, week 40 and week 48

Exploratory secondary outcome measures:
1. Efficacy of re-introduction of anti-TNF therapy in patients with disease recurrence post-HSCT is measured using the change in CDAI between baseline and 6 weeks after initiation of anti-TNF therapy
2. Efficacy of re-introduction of anti-TNF therapy in patients with disease recurrence post-HSCT is measured using the change in SES-CD between 0 and 22 weeks after initiation of anti-TNF therapy
3. Safety of re-introduction of anti-TNF therapy in patients with disease recurrence post-HSCT is measured through documentation of adverse events at week 32, week 40 and week 48

Mechanistic secondary outcome measures:
1. Timeline of response to HSCTlite is measured through MRI at week 4 and week 48
2. Nature of immune re-constitution after HSCT is measured through blood sample analysis at week 8, week 14, week 24, week 32 and week 48
3. Immunological events that precede the onset of disease recurrence post HSCT is measured through blood sample analysis at week 8, week 14, week 24, week 32 and week 48
4. Mechanism of restoration of responsiveness to anti-TNF therapies if appropriate is measured through blood sample analysis at week 8, week 14, week 24, week 32 and week 48
5. Responses to vaccination post HSCT is measured through blood sample analysis at week 8, week 14, week 24, week 32 and week 48

Completion date
30/11/2021

Eligibility

Key inclusion criteria
1. Participant of any gender, aged between 18 – 60
2. Participants must be willing and able to provide full informed consent
3. Participants should be well nourished and of healthy weight in the opinion of the PI (typically BMI >18.5)
4. Diagnosis of CD using colonoscopy, histology and/or radiology
5. Disease duration of at least six months
6. Disease distribution accessible to endoscopic assessment (ileal, ileo-caecal, or colonic)
7. Active clinical CD activity with impaired quality of life at any time within 3 months prior to randomisation into the trial, as assessed by a gastroenterology clinician
8. Participants will be refractory or intolerant to azathioprine, mercaptopurine or methotrexate
9. Participants will be refractory or intolerant to at least two classes of biologic therapy (currently anti-TNF therapy, Vedolizumab or Ustekinumab) despite dose optimisation
10. Participants where surgery is considered not appropriate or has been declined
11. Endoscopic evidence of active disease in screening (SES CD ulceration sub-score of 2 or more in at least one segment)
12. Satisfactory EBMT Autoimmune Disease Working Party (ADWP) recommended screening assessment prior to HSCT
13. Willingness to discontinue all immunosuppressant medication after randomisation if allocated to HSCT arm
14. Participants, who, in the opinion of the TMG, are fit enough to undergo treatment

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
45

Key exclusion criteria
1. Diagnosis of ulcerative colitis or indeterminate colitis.
2. No evidence of active CD on screening ileocolonoscopy.
3. Inability to assess for active disease at ileocolonoscopy due to strictures.
4. Undrained perianal fistulae (patients with previous perianal disease or perianal disease adequately drained with a seton in situ are eligible)
5. Presence of undrained perianal sepsis on screening pelvic MRI.
6. Evidence of intra-abdominal sepsis on abdominal MRI.
7. Active or latent mycobacterial infection.
8. Prior exposure to Hepatitis B, Hepatitis C or HIV.
9. Evidence of an enteric or systemic infection.

10. Participant is currently pregnant or breastfeeding, or planning pregnancy within the study duration. Current pregnancy will be confirmed with a pregnancy test at screening assessment.
11. Unwilling to use adequate contraception (if appropriate) until at least 12 months after the last dose of study drug.
12. Contraindication to the use of cyclophosphamide, fludarabine, filgrastim or rabbit ATG.
13. Participants with significant medical co-morbidity that precludes HSCT adjudicated by the TMG.
14. Participants with significant psychiatric co-morbidity.
15. Significant language barriers, which are likely to affect the participant's understanding of the study, or ability to complete outcome questionnaires.
16. Concurrent participation in another interventional clinical trial.
17. Participants who are not considered medically fit for HSCT defined by any of the following:
17.1. Renal: creatinine clearance <40 ml/min (measured or estimated)
17.2. Cardiac: clinical evidence of refractory congestive heart failure, left ventricular ejection fraction <45% by multigated radionuclide angiography (MUGA) or cardiac echo; uncontrolled ventricular arrhythmia; pericardial effusion with haemodynamic consequences as evaluated by an experienced echo cardiographer
17.3. Hepatic: AST > two times the upper limit of normal
17.4. Concurrent neoplasms or myelodysplasia
17.5. Bone marrow insufficiency defined as neutropenia with an absolute neutrophil count <1x10 (9)/l, or thrombocytopenia with a platelet count <50x10(9)/l, or anaemia with a haemoglobin <80 g/l
17.6. Uncontrolled hypertension, defined as resting systolic blood pressure >= 140 and/or resting diastolic pressure >= 90 mmHg despite at least 2 anti-hypertensive agents (subject to discussion at TMG).
17.7. Uncontrolled acute or chronic infection with HIV, HTLV – 1 or 2, hepatitis viruses or any other infection the investigator or TMG consider a contraindication to participation.
17.8. Other chronic disease causing significant organ failure, including established cirrhosis with evidence of impaired synthetic function on biochemical testing and known respiratory disease causing resting arterial oxygen tension <8 kPa or carbon dioxide tension >6.7 kPa. FEV1/FVC <50%. Patients not known to have respiratory disease need not have blood gas measurements.

Date of first enrolment
01/04/2018

Date of final enrolment
21/06/2020

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre

Barts Health NHS Trust (Sponsor Site)
The Royal London Hospital
Whitechapel
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Study participating centre
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Sponsor information

Organisation
Barts Health NHS Trust

ROR
https://ror.org/00b31g692

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC)

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?
Results article		07/02/2024	12/02/2024	Yes	No
Protocol article		31/05/2019	11/08/2022	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes