Autologous stem cell transplantation with low-dose cyclophosphamide to improve mucosal healing in adults with refractory Crohn's disease: the ASTIClite RCT

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Scientific summary

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Scientific summary

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Background

Crohn's disease (CD) is characterised by chronic inflammation of the gastrointestinal tract due to inappropriate effector lymphocyte reactivity to luminal dietary and microbial antigens. Despite recent developments in highly targeted biological therapies, not all patients enter sustained disease remission with currently available conventional and biologic treatments. Ongoing mucosal inflammation drives disease progression to stricturing and penetrating phenotypes that often mandate surgery to resect the involved intestinal segment. Furthermore, disease recurrence after surgery is frequent, such that some patients require multiple bowel resections that may result in the requirement for a stoma or intravenous nutrition. In addition, patients with treatment-refractory CD experience debilitating physical symptoms, poor quality of life and reduced productivity.

Previous, non-randomised, studies suggest that haematopoietic stem cell transplant (HSCT), which seeks to relieve symptoms by resetting the autoreactive immune system, may be an effective alternative treatment for patients with refractory CD. The randomised controlled autologous stem cell transplantation for Crohn's disease (ASTIC) study was designed to assess whether or not HSCT resulted in sustained disease regression and whether any observed benefits resulted from the cyclophosphamide used in the mobilisation and conditioning regimen or from the transplant itself.

Patients underwent high-dose cyclophosphamide (4 g/m^2) and granulocyte-colony stimulating factor (G-CSF) mobilisation before being randomised to receive immediate HSCT or standard care for 1 year. No benefit of HSCT compared with standard care was found using the ambitious primary end point of medication-free clinical remission for 3 months, with no imaging or endoscopic evidence of disease activity. Furthermore, HSCT was associated with a high burden of adverse (AEs) and serious adverse events (SAEs), including one patient death. These were felt likely to result from the high doses of cyclophosphamide used. Despite this, HSCT in the ASTIC trial was associated with a meaningful improvement in endoscopic inflammation in some patients.

In addition, a single centre cohort study of patients undergoing HSCT reported that, although treatment-free remission declined over time, 80% of patients responded to drugs to which they were previously

refractory, such that, when assessing remission rates on therapy, the marked reduction in drug-free remission reported over the study's 5-year period was reversed.

Objectives

The ASTIClite trial sought to assess the effectiveness, safety and long-term impact of low-dose cyclophosphamide/G-CSF mobilisation with reduced-intensity conditioning (HSCTlite) compared with standard care in inducing regression of intestinal ulceration in refractory CD patients at 1 year. Embedded mechanistic substudies sought to investigate the mechanisms by which HSCTlite improves CD, and the aetiology of relapse, should it occur.

Design and setting

The ASTIClite trial was a parallel-group, RCT that took place across nine hospital sites in the UK [one site (King's College Hospital, London, UK) did not recruit patients but was a treatment-only site].

Participants and study criteria

Participants with refractory CD were required to meet all of the following conditions to be eligible:

- Be of any gender and aged between 18 and 60 years.
- Be willing and able to provide full informed consent.
- Be well nourished and of healthy body weight in the opinion of the principal investigator (typically with a body mass index of > 18.5 kg/m^2).
- Have received a diagnosis of CD using colonoscopy, histology and/or radiology.
- Have had a disease duration of at least 6 months.
- Have a disease distribution accessible to endoscopic assessment (jejuno-ileal, ileo-caecal or colonic).
- Have had 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.
- Be refractory or intolerant to azathioprine, mercaptopurine or methotrexate.
- Be refractory or intolerant to at least two classes of biologic therapy [currently anti-tumour necrosis factor (TNF) therapy, vedolizumab (Entyvio, Takeda UK Limited, London, UK) or ustekinumab (Stelara, Janssen Pharmaceuticals, New Brunswick, NJ, USA)] despite dose optimisation.
- Be considered unsuitable for surgery or have had surgery declined.
- Have endoscopic evidence of active disease in screening [Simple Endoscopic Score for Crohn's Disease (SES-CD) ulcer size subscore of ≥ 2 in at least one segment]. SES-CD will be used as standard for patients with disease in the ileum and/or colon. Should the disease be only proximal to the ileum, the SES-CD would still be used to score the relevant bowel segment.
- Have undergone a satisfactory European Society for Blood and Marrow Transplantation. Autoimmune Disease Working Party-recommended screening assessment prior to HSCT.
- Be willing to discontinue all immunosuppressant medication after randomisation if allocated to the HSCT arm.
- Be, in the opinion of the Trial Management Group (TMG), fit enough to undergo treatment.

Participants were ineligible if any of the following conditions were met:

- Have received a diagnosis of ulcerative colitis or indeterminate colitis.
- Have no evidence of active CD on screening endoscopic assessment.
- Have strictures that prevent assessment for endoscopic active disease.
- Have undrained perianal fistulae (patients with previous perianal disease or perianal disease adequately drained with a seton in situ were eligible).

- Presence of undrained perianal sepsis on screening pelvic [magnetic resonance imaging (MRI) scan, or computerised tomography (CT) scan if MRI was contraindicated].
- Have evidence of intra-abdominal sepsis on abdominal MRI (or CT scan if MRI scan was contraindicated).
- Have an active or latent mycobacterial infection.
- Have had prior exposure to hepatitis B virus, hepatitis C virus or human immunodeficiency virus (HIV).
- Have evidence of an enteric or systemic infection.
- Be pregnant or breastfeeding, or planning pregnancy within the study duration. The possibility of current pregnancy was to be ruled out with a pregnancy test at the screening assessment.
- Be unwilling to use adequate contraception (if appropriate) until at least 12 months after the last dose of study drug.
- Have a contraindication to the use of cyclophosphamide, fludarabine, filgrastim or rabbit anti-thymocyte globulin (Thymoglobulin, Sanofi UK, Reading, UK).
- Have a significant medical comorbidity that precludes HSCT, as adjudicated by the TMG.
- Have significant psychiatric comorbidity.
- Have significant language barriers likely to affect their understanding of the study or their ability to complete outcome questionnaires.
- Be participating in another interventional clinical trial.

    - Be considered medically unfit for HSCT as defined by any of the following criteria –
    - Renal: creatinine clearance of < 40 ml/min (measured or estimated).
    - Cardiac: clinical evidence of refractory congestive heart failure, left ventricular ejection fraction < 45% as determined by multigated radionuclide angiography or echocardiography, uncontrolled ventricular arrhythmia or pericardial effusion with haemodynamic consequences as evaluated by an experienced echocardiographer.
    - Hepatic: aspartate transaminase levels more than two times the upper limit of normal.
    - Concurrent neoplasms or myelodysplasia.
    - Bone marrow insufficiency defined as neutropenia with an absolute neutrophil count of $< 1 \times 10^9$/l, or thrombocytopenia with a platelet count of $< 50 \times 10^9$/l, or anaemia with a haemoglobin level of < 80 g/l.
    - Uncontrolled hypertension, defined as resting systolic blood pressure of ≥ 140 mmHg and/or resting diastolic pressure of ≥ 90 mmHg despite at least two antihypertensive agents (patients with elevated blood pressure not on medication can be included subject to discussion at by the TMG).
    - Uncontrolled acute or chronic infection with HIV, human T-lymphotropic virus type 1 or 2, hepatitis viruses or any other infection the investigator or TMG considered a contraindication to participation.
    - 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 of < 8k Pa or carbon dioxide tension of > 6.7 kPa. Forced expiratory volume or forced vital capacity of < 50%. Patients not known to have respiratory disease need not have blood gas measurements.

Intervention

All potential patients were discussed in a multidisciplinary team meeting to ensure that they were appropriate for trial consideration. Patients were then consented and underwent screening investigations. Eligible participants were randomised in a 2 : 1 ratio to receive either HSCTlite or usual care. Participants in the intervention arm stopped immune-suppressing medication and underwent stem cell mobilisation with cyclophosphamide 1 g/m^2 and G-CSF 5 µg/kg. Stem cells were harvested once CD34$^+$ cell levels exceeded 10×10^6/l. A minimum of 2.0×10^6/kg CD34$^+$ cells were collected and cryopreserved, having allowed for 10% wastage. The earliest time point at which conditioning could begin was 3 weeks after the administration of cyclophosphamide during mobilisation; although, in most cases the interval was 6 weeks. The regimen comprised fludarabine 25 mg/m^2 (with reduced doses

permitted in the presence of impaired renal function) on days −6, −5, −4, −3 and −2, cyclophosphamide 60 mg/kg/day on days −3 and −2 and rabbit anti-thymocyte globulin 2.5 mg/kg/day on days −3, −2 and −1. Stem cells were reinfused at day 0. Administration of G-CSF 5 µg/kg/day (to the nearest vial) began on day +5 and continued until absolute neutrophil counts reached > 1.0×10^9/l for two consecutive days. Participants randomised to the usual-care arm continued with conventional, biologic or nutritional therapy for the management of CD, until the primary end point was assessed.

Follow-up

Participants were followed up at 8, 14, 24, 32, 40 and 48 weeks. Day 0 of the follow up was the date of stem cell reinfusion for HSCT arm participants and day 49, post randomisation, for usual-care arm participants to align the timelines in both groups.

Main outcome measures

The primary outcome was treatment success at week 48, defined as mucosal healing [no endoscopic ulceration (SES-CD ulcer subscore of zero, assessed by central readers blind to allocation and time of assessment)] without surgery or death. Key secondary outcomes included clinical remission using the Crohn's Disease Activity Index (CDAI), the Harvey–Bradshaw Index and patient-reported outcomes; SES-CD at week 48; change in CDAI SES-CD between baseline and week 48; assessment of safety through reports of AEs and SAEs; patient-reported quality of life; and healthcare resource use. Mechanistic outcomes included analysis of re-engraftment.

Results

The trial was halted because of unexpected SAEs after 23 patients (HSCT arm, $n = 13$; usual-care arm, $n = 10$) had been randomised. Patients had advanced disease [mean (standard deviation) CD duration 13.8 (7) years, mean CDAI at baseline 337.5 (182.4)], with 20 (91%) having undergone at least one resection and nine (41%) having a stoma (these figures are calculated based on the 22 participants in the intention-to-treat population, as opposed to the 23 participants randomised). Of the 13 participants randomised to receive HSCTlite, three withdrew before transplantation, 12 reached mobilisation, and 10 went on to receive stem cell reinfusion. Of the 10 usual-care arm participants, eight received medications specifically to treat CD (including biologic therapies and corticosteroids), one underwent surgery for CD (small bowel resection) and one withdrew.

All patients contributed to the safety analysis, and 10 patients who completed HSCT and nine patients receiving usual care contributed to the efficacy analyses. The primary outcome using central reading was available for 7 out of 10 HSCT and six out of nine usual-care patients at week 48. Absence of endoscopic ulceration without surgery or death (at 48 weeks) was reported in three out of seven (43%) HSCT patients, compared with zero out of six (0%) usual-care patients. Centrally read SES-CD scores [mean (SD)] were 10.8 (6.3) and 10.0 (6.1) at baseline, compared with 2.8 (2.9) and 18.7 (9.1) at week 48, in the HSCT and usual-care arms, respectively. Centrally read change in SES-CD fell by 6.4 (4.3) in HSCT patients, whereas it increased by 7.5 (3.5) in usual-care patients. Clinical remission (CDAI < 150) occurred in 57% and 17% of patients in the HSCT and usual-care arms, respectively, at week 48.

Serious adverse events were more frequent in patients undergoing HSCT [38 in 13 (100%) patients] than in those who received usual care [16 in 4 (40%) patients]. Importantly, nine suspected unexpected serious adverse reactions (SUSARs) were reported in six HSCT patients, including three cases of delayed renal failure due to proven thrombotic microangiopathy (TMA). Two patients in the HSCT arm died (one

from pulmonary venous occlusive disease at week 24 and one from infection and renal failure (not proven to be TMA) at week 60 after trial completion.

There was a marked difference in the profile of all the immune cell subsets studied between the HSCTlite and usual-care arms after HSCT. Of all the subsets studied, only the numbers of $CD3^+CD8^+CD31^+$ recent thymic emigrant cytotoxic T helper cells, $CD3^+CD8^+CD49d^+\alpha4integrin^+CCR9^+$ gut-homing cytotoxic T cells, $CD3^+CD4^+CD45RA^-CCR7-$effector memory T helper cells and $CD8^+$ cytotoxic T cells had returned to equivalence with the usual-care arm at week 48, with levels of $CD3^+$, $CD4^+$, $CD4^+$ recent thymic emigrants, $CD3^+CD4^+CD45RA-CCR7^+$ central memory T helper cells, $CD4^+$ effector T helper cells and $CD3^+CD4^+CD45RA^+CCR7^+$ naive T helper cells remained lower in the HSCTlite arm than in the usual-care arm. After in vitro stimulation, $CD4^+$ and $CD8^+$ lymphocytes from HSCT patients expressed higher levels of Th1 and Th17 cytokines [i.e. IFN gamma, TNF, interleukin (IL) 17] as well as Th2 cytokines (i.e. IL-4) than did lymphocytes from usual-care participants at most time points.

Conclusion

The ASTIClite trial was designed to assess the efficacy and safety of autologous stem cell transplantation in patients with treatment-refractory CD using a mobilisation and conditioning regimen with lower doses of cyclophosphamide than previously assessed.[17] Central reading of the endoscopic primary end point was used, as it was not possible to blind patients or investigators to treatment allocation. The trial was halted early because of several SUSARs and one patient death. Several patients undergoing HSCT experienced marked improvement in endoscopic disease activity with associated improvement in general and disease-specific quality of life. However, the large number of adverse events, including three cases of biopsy-proven TMA and one case of pulmonary venous occlusive disease, preclude the use of this regimen in future clinical practice. Further research is required to identify the optimal treatment for this population with refractory CD, which is associated with poor quality of life and significant morbidity.

Trial registration

This trial is registered as Current Controlled Trials ISRCTN17160440 and EudraCT 2017-002545-30.

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