HSCT for Crohn’s Disease: *is it ready for prime time?*

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Barts and The London School of Medicine  
Queen Mary University of London  
Consultant Gastroenterologist, Barts Health NHS Trust
CONFLICT OF INTEREST DISCLOSURES

None relevant to this presentation

Served as consultant and an advisory board participant:

AbbVie, Alergan (Warner Chilcott), Atlantic Healthcare, Celgene, Celtrion, Ferring, GSK, Janssen, MSD, Napp, Pfizer, Shire, Takeda and Vifor Pharma

Received speaker fees and sponsorship for academic meetings:

from AbbVie, Alergan (Warner Chilcott), Ferring, Janssen, MSD, Napp, Pfizer Shire, Tillott’s, Takeda

Received investigator led research grants

from Pfizer, Shire and Takeda
HSCT for Crohn’s Disease: is it ready for prime time?

What I hope to cover

• Introduction to Crohn’s disease

• Clinical outcomes of HSCT for Crohn’s disease
  – Controlled trial
  – Experience from case series / registries

• Predicting outcome from HSCT in Crohn’s disease

• What does the future hold?
An introduction to Crohn’s disease

Aetiology

- Peak onset in young adults
- Increasing incidence in the developing countries
- Rare mendelian genetic aetiology – Very Early Onset CD
  - XIAP, X linked CGD, IL-10 receptor deficiency
  - 1-3% of patients with refractory Crohn’s disease

Transmural inflammation from mouth to anus:
Diarrhoea, abdominal pain, fatigue, weight loss, fistula, abscess
An introduction to Crohn’s disease

Understanding the immune pathogenesis of IBD

Targeting distinct mechanisms that drive inflammation may provide long-term control and preserve intestinal function in IBD¹,²

How do we treat Crohn’s disease
The choice of drugs has increased...

Steroids, Azathioprine methotrexate

Tumour necrosis factor antagonists (anti-TNFs) D
Initial report in CD

Anti-TNFs for UC

Surgery

Vedolizumab Biosimilars
Ustekinumab S1p agonists
JAK antagonists Anti p19 antibodies

But has this choice increased long term remission and improved outcome?

No biologic / small molecule delivers mucosal healing in >50%
Best biologic is the first biologic
All biologics induce antidrug antibodies
Small molecules offer efficacy but also side effects
We are unable to predict which patient will response to each line of therapy

A proportion of patients remain with active disease refractory to therapy - poor QoL
Changing the natural history of autoimmune disease

**Autologous Haematopoietic Stem Cell Transplantation (HSCT)**

Stem cell mobilisation with cyclophosphamide and colony stimulating factors

Conditioning with cyclophosphamide and anti thymocyte globulin followed by stem cell rescue

Case reports suggested exceptional benefit, concern about safety
Autologous Haematopoietic Stem Cell Transplantation

Evidence from other autoimmune disease

Multiple Sclerosis – clear evidence of benefit of Stem cell transplantation

The MIST Trial

110 patients with relapsing MS
1 relapse with HSCT compared to 36 on DMARD
At 3 years treatment failure in 6% HSCT vs 60% control
No mortality, no grade IV non haematological CTC toxicity

Maria Pia Sormani, Multiple Sclerosis Journal, 2016.
Autologous stem cell transplantation in refractory CD

The ASTIC trial

ASTIC trial designed to answer

1. Does HSCT ‘cure’ Crohn’s disease?
2. Does any reported benefit arise from cyclophosphamide or the transplant itself?

Inclusion criteria

- Active CD with impaired QOL
- Endoscopic / radiological evidence of disease (Pts with stoma were eligible)
- Failed at least 3 immunomodulators / biologics
- Surgery inappropriate

Ambitious Primary Endpoint: Disease Regression

- Clinical symptomatic remission (CDAI<150) for at least 3 months
- Off all CD medication
- No evidence of active disease on OGD / colonoscopy / small bowel imaging

Hawkey et al. JAMA 2015;314(23):2524-2534
Autologous stem cell transplantation in refractory CD

The ASTIC trial design

Primary Endpoint
CDAI<150
Off IM for > 3/12
No evidence of active disease

TSC review

Baseline Assessment

Mobilisation

Cyclo 50mg/kg x 4
ATG 2.5 mg/kg x 3
Unselected graft
3.8-27 x 10^6
CD+ /kg

MePred and antibiotic cover

Control

0 1 2
Year

Hawkey et al. JAMA 2015;314(23):2524-2534
Autologous stem cell transplantation in refractory CD

The ASTIC trial results

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>HSCT (n=23)</th>
<th>Control (n=22)</th>
<th>Difference Median (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained disease remission</td>
<td>2 (8.7%)</td>
<td>1 (4.5%)</td>
<td>4.2% (-14.2% to 22.6%)</td>
<td>0.600</td>
</tr>
</tbody>
</table>

Components

<table>
<thead>
<tr>
<th>Component</th>
<th>HSCT (%)</th>
<th>Control (%)</th>
<th>Difference Median (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment last 3 months</td>
<td>14 (60.9%)</td>
<td>5 (22.7%)</td>
<td>38.1% (9.3% to 59.3%)</td>
<td>0.012</td>
</tr>
<tr>
<td>CDAI &lt; 150 last 3 months</td>
<td>8 (34.8%)</td>
<td>2 (9.1%)</td>
<td>25.7% (1.08% to 47.1%)</td>
<td>0.052</td>
</tr>
<tr>
<td>No active disease on imaging</td>
<td>8 (34.8%)</td>
<td>2 (9.1%)</td>
<td>25.7% (1.08% to 47.1%)</td>
<td>0.054</td>
</tr>
</tbody>
</table>

Secondary outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Median (IQR)</th>
<th>Median (IQR)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDAI change from baseline</td>
<td>-150.7 (-62.0 to -196.3)</td>
<td>-63.0 (+34.0 to -120.8)</td>
<td>-87.7 (-13.5 to -155.0)</td>
</tr>
<tr>
<td>SES-CD change from baseline</td>
<td>-7 (-4 to -13) n=21</td>
<td>0 (+5 to -8.5) n=19</td>
<td>-7 (-13 to -1)</td>
</tr>
</tbody>
</table>

76 serious adverse events in 19 patients undergoing HSCT

1 patient undergoing HSCT died

38 serious adverse events in 15 control patients: median difference in number SAE 0

(95%CI -1 to 4; p=0.7)

Hawkey et al. JAMA 2015;314(23):2524-2534
Autologous stem cell transplantation in refractory CD

The ASTIC trial combined results

AIM (1) Assess outcome at one year for all patients undergoing HSCT (A+B)

AIM (2) Identify baseline factors that predict relevant endpoints
Analysis of all patients undergoing HSCT in ASTIC trial

Baseline data for subjects included in this analysis

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>N=40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline, years (IQR)</td>
<td>33.7 (26.4-40.3)</td>
</tr>
<tr>
<td>Female N (%)</td>
<td>23 (57.5%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>8 (20%)</td>
</tr>
<tr>
<td>Number of previous operations for CD (IQR)</td>
<td>2 (0.75-3.25)</td>
</tr>
<tr>
<td>Ileostomy</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Age at diagnosis, years (IQR)</td>
<td>19.6 (12.9-25.5)</td>
</tr>
<tr>
<td>Disease duration, years (IQR)</td>
<td>15.0 (9.2-16.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior Drugs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine / Mercaptopurine</td>
<td>39 (97.5%)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>33 (82.5%)</td>
</tr>
<tr>
<td>Anti-TNF agents</td>
<td>40 (100%)</td>
</tr>
<tr>
<td>Number (IQR)</td>
<td>5 (4.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease activity (IQR)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CDAI</td>
<td>323.6 (250.0-410.6)</td>
</tr>
<tr>
<td>PRO2</td>
<td>21.7 (16.3-30.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory results (IQR)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin g/dL</td>
<td>12.3 (11.6-13.6)</td>
</tr>
<tr>
<td>Platelets x 10^12/L</td>
<td>293.5 (230.0-390.3)</td>
</tr>
<tr>
<td>Albumin g/dL</td>
<td>36.5 (32.3-41.0)</td>
</tr>
<tr>
<td>CRP mg/L</td>
<td>15.0 (4.5-32.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality of Life and functional status (IQR)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>IBDQ (37 – 224)</td>
<td>121 (102-140)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ileocolonoscopic evaluation (IQR)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SES-CD score</td>
<td>11.5 (7-20)</td>
</tr>
</tbody>
</table>
Analysis of all patients undergoing HSCT in ASTIC trial

RESULTS – Crohn’s disease activity index (CDAI)

Reduction in mean (SE) CDAI from baseline to one year: 336.7 (18.5) to 196 (21.9); p<10^{-4}
Benefit evident from first visit at week 6 (CDAI 212) with 38% clinical remission (CDAI<150)
At one year 43 % were in clinical remission
Analysis of all patients undergoing HSCT in ASTIC trial

**RESULTS – other indices of disease activity**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Baseline</th>
<th>One year</th>
<th>p value (paired)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDAI</td>
<td>37</td>
<td>336.73 (18.46)</td>
<td>195.95 (21.91)</td>
<td>&lt;10-4</td>
</tr>
<tr>
<td>PRO2</td>
<td>37</td>
<td>24.03 (1.74)</td>
<td>12.45 (1.61)</td>
<td>&lt;10-4</td>
</tr>
<tr>
<td>IBDQ</td>
<td>30</td>
<td>119.57 (6.12)</td>
<td>152.23 (8.24)</td>
<td>&lt;10-4</td>
</tr>
<tr>
<td>SESCD</td>
<td>36</td>
<td>14.11 (1.5)</td>
<td>5.44 (1.1)</td>
<td>&lt;10-4</td>
</tr>
</tbody>
</table>

**Perianal disease:** no benefit

**Re-treatment:** Anti TNF therapy was required in 7 (18%) patients after 18 (14-39) wk CDAI fell from 319 (55) to 174 (39); p=0.016 71.4% patients experienced a clinical response (CDAI fall > 70 points)
Analysis of all patients undergoing HSCT in ASTIC trial

RESULTS – clinically relevant endpoints

Steroid free remission for > 3 months in 38.2%

Mucosal healing in 50%
Analysis of all patients undergoing HSCT in ASTIC trial

**RESULTS – Serious adverse events**

<table>
<thead>
<tr>
<th>Duration (range), days</th>
<th>Conditioning</th>
<th>Follow up</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SAE</td>
<td>Patients</td>
<td>SAE</td>
</tr>
<tr>
<td><strong>Total SAEs</strong></td>
<td>44</td>
<td>18</td>
<td>32</td>
</tr>
<tr>
<td><strong>Infectious SAEs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral</td>
<td>8</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Sepsis</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Localised</td>
<td>2</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>GI SAEs</td>
<td>6</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Disease flare</td>
<td>1</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Non-flare Symptoms</td>
<td>5</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Hematologic SAEs</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Anaemia</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Fever SAEs</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Renal SAEs</td>
<td>5</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory SAEs</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>
Analysis of all patients undergoing HSCT in ASTIC trial

What is the immunological impact of HSCT

Insight into Crohn’s disease aetiology
Restoring diversity to T cell receptor repertoire and mucosal healing

<table>
<thead>
<tr>
<th>SES-CD</th>
<th>I</th>
<th>RC</th>
<th>TC</th>
<th>LC</th>
<th>R</th>
<th>SES-CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>906</td>
<td></td>
<td>6</td>
<td>9</td>
<td>9</td>
<td>24</td>
</tr>
<tr>
<td>One year</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

Le Bourhis L, et al. ECCO 2017; OP4
Single centre series of HSCT in Crohn’s disease

Clinical outcome of 29 patients from Barcelona (13 ASTIC)

**Mobilisation:** 4g/m2 cyclophosphahide

**Conditioning:** 200 mg/kg cyclophosphamide, rATG 7.5 mg/kg

**Drug free clinical & endoscopic remission:**
61% at 1 year, 52% at 2 years, 47% at 3 years, 39% at 4 years, and 15% at 5 years

High burden of adverse events (neutropenic sepsis)

6/29 [21%] required surgery

One patient died (systemic cytomegalovirus infection 2 months after transplant).

Single centre series of HSCT in Crohn’s disease

Clinical outcome of 29 patients from Barcelona (13 ASTIC)

Inclusion criteria:

- Patients aged $\geq 18$ undergoing HSCT primarily for CD 1997-2015
- Not included in the ASTIC study
- 99 patients in 27 centres identified in registry
- Data obtained for 82 patients transplanted in 19 centres in 8 countries from 1996 to 2015
- Median age 30 (20-65); 63% female, follow up duration 42 (6-174) months

### European review of HSCT outcome in Crohn’s disease

*Retrospective EBMT registry based review*

<table>
<thead>
<tr>
<th>Mobilisation regimen</th>
<th>72 (91%)</th>
<th>73% resumed medical therapy after 10 (range 1-79) months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide/G-CSF</td>
<td>72 (91%)</td>
<td></td>
</tr>
<tr>
<td>G-CSF alone</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td>Transplant regimen</td>
<td></td>
<td>37% (30/82) required surgery post-AHSCT,</td>
</tr>
<tr>
<td>Cyclophosphamide/ATG</td>
<td>69 (86%)</td>
<td>At last follow-up, 42/78 (54%) were on treatment.</td>
</tr>
<tr>
<td>Cyclophosphamide/CD34 selection</td>
<td>9 (11%)</td>
<td></td>
</tr>
<tr>
<td>Median dose CD34+ (x 10^6/kg)</td>
<td>5.4 (2.4-40.6)</td>
<td></td>
</tr>
<tr>
<td>Median time to neutrophil engraftment / days</td>
<td>+10 (6-22)</td>
<td></td>
</tr>
<tr>
<td>Median time to platelet engraftment / days</td>
<td>+10 (1-44)</td>
<td></td>
</tr>
<tr>
<td>Engraftment</td>
<td>82 (100%)</td>
<td></td>
</tr>
</tbody>
</table>
European review of HSCT outcome in Crohn’s disease

Retrospective EBMT registry based review

<table>
<thead>
<tr>
<th>Percentage %</th>
<th>100 days</th>
<th>1 year</th>
<th>Last follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsening</td>
<td>4</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Stable/ no change</td>
<td>5</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Improvement</td>
<td>28</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>Remission</td>
<td>64</td>
<td>43</td>
<td>44</td>
</tr>
</tbody>
</table>

European review of HSCT outcome in Crohn’s disease
Retrospective EBMT registry based review

- 22/82 (27%) developed an infection requiring treatment
  - 9/82 (11%) bacterial,
  - 11/82 (12%) viral

- 9/82 (11%) reported secondary autoimmune disease, mostly thyroid

- 5/82 developed new cancer
  - 3 skin, 1 testicular, 1 prostate

- One patient died at 56 days post-AHSCT due to CMV infection & sepsis
  - Transplant-related mortality 1.2%
  - One patient died at 8 years post-AHSCT of sepsis & multi-organ failure

HSCT for Crohn’s Disease: is it ready for prime time?

What I hope to cover

• Introduction to Crohn’s disease

• Clinical outcomes of HSCT for Crohn’s disease
  – Controlled trial
  – Experience from case series / registries

• Predicting outcome from HSCT in Crohn’s disease
Predicting outcome of HSCT

Data from the ASTIC trial

Factors predicting clinical benefit: multivariate analysis
Time from diagnosis to HSCT OR = 0.64 (0.41-0.997) p=0.048
Baseline CDAI OR =0.98 (0.97-0.998) p=0.031
Baseline SES CD OR =1.18 (1.0-1.41) p=0.053

Factors predicting serious adverse event: multivariate analysis (Poisson regression)
Smoking OR = 3.07 (1.75-5.38) p=0.0001
Perianal disease OR = 3.97 (2.17-7.25) p=0.00001
Analysis of all patients undergoing HSCT in ASTIC trial

Predicting outcome of HSCT

Extracted RNA & performed a miRNA array (>2100 miRNAs)
Data were processed & principal component analysis (PCA) performed
Responders and non-responders were defined as:

i. CDAI<150
ii. CDAI<150 + endoscopic healing (SES CD score =0)
Baseline mucosal miRNA profiles differ between responders and non-responders

**Analysis 1: CDAI<150:** Responders n=8; Non-responders n=6

Analysis of all patients undergoing HSCT in ASTIC trial

*Predicting outcome of HSCT*
Baseline mucosal miRNA profiles differ between responders and non-responders

Analysis 2: CDAI<150 + Endoscopic Remission: Responders (n=5); Non-responders (n=9)

- Increase stringency of response definition
- Fewer responders & more non-responders
- Greater separation of the two groups
- No overlap
### Analysis of all patients undergoing HSCT in ASTIC trial

**Predicting outcome of HSCT**

Differentially expressed mucosal miRNAs: responders Vs. non-responders

#### Fold change (Log2) in responders

<table>
<thead>
<tr>
<th>miRNA ID</th>
<th>Lower</th>
<th>miRNA ID</th>
<th>Higher</th>
</tr>
</thead>
<tbody>
<tr>
<td>miR-155-5p</td>
<td>-1.32</td>
<td>mir-4800-3p</td>
<td>1.98</td>
</tr>
<tr>
<td>miR-891a-5p</td>
<td>-1.04</td>
<td>mir-4467</td>
<td>1.95</td>
</tr>
<tr>
<td>miR-3646</td>
<td>-1.01</td>
<td>mir-4708-3p</td>
<td>1.86</td>
</tr>
<tr>
<td>miR-320a</td>
<td>-0.95</td>
<td>mir-371b-5p</td>
<td>1.80</td>
</tr>
<tr>
<td>miR-3149</td>
<td>-0.89</td>
<td>mir-4443</td>
<td>1.73</td>
</tr>
<tr>
<td>miR-320b</td>
<td>-0.87</td>
<td>mir-3960</td>
<td>1.63</td>
</tr>
<tr>
<td>miR-196a-3p</td>
<td>-0.86</td>
<td>mir-943</td>
<td>1.60</td>
</tr>
<tr>
<td>miR-3685</td>
<td>-0.85</td>
<td>mir-3124-3p</td>
<td>1.47</td>
</tr>
<tr>
<td>miR-1299</td>
<td>-0.82</td>
<td>mir-1273g-3p</td>
<td>1.02</td>
</tr>
<tr>
<td>miR-3924</td>
<td>-0.76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>miR-5681b</td>
<td>-0.69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>miR-3591-5p</td>
<td>-0.69</td>
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<td></td>
</tr>
<tr>
<td>miR-378a-3p</td>
<td>-0.67</td>
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</tr>
<tr>
<td>miR-422a</td>
<td>-0.63</td>
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<tr>
<td>miR-584-5p</td>
<td>-0.59</td>
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<td></td>
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<tr>
<td>miR-1270</td>
<td>-0.56</td>
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<td></td>
</tr>
<tr>
<td>miR-4436b-5p</td>
<td>-0.47</td>
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<tr>
<td>miR-4429</td>
<td>-0.40</td>
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</tr>
</tbody>
</table>

**miRNAs panel fully differentiates responders**

[Tree diagram showing differentiation between responders and non-responders]
Mucosal miR-155-5p levels predict response to HSCT

Analysis of all patients undergoing HSCT in ASTIC trial

Predicting outcome of HSCT

HSCT for Crohn’s Disease: is it ready for prime time?

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• Clinical outcomes of HSCT for Crohn’s disease
  – Controlled trial
  – Experience from case series / registries

• Predicting outcome from HSCT in Crohn’s disease

• What does the future hold?
**HSCT in refractory Crohn’s disease**

*Where next?*

**ASTIClite**

**Autologous** Stem cell **Transplantation** In refractory Crohn’s disease **low Intensity Therapy Evaluation**

NIHR EME funded project commenced August 2017
First site opened June 2018

**Objectives of trial**

1) Assess efficacy of low intensity HSCT regimen compared to standard care using an endoscopic endpoint at 48 weeks

2) Assess safety of low intensity regimen compared to standard of care

3) Clinical and patient reported secondary outcomes

4) Assess safety and efficacy of re-introduction of anti TNF therapy in patients with recurrent disease on colonoscopy / MRI at week 24

5) Long term efficacy and safety over further 4 years via EBMT registry

6) **Mechanistic sub studies**
HSCT in refractory Crohn’s disease

**ASTIClite trial timeline**

- **Identification**
- **MDT discussion**
- **Consent & Screening**
- **Colonoscopy / MRI Mechanistic bloods**
- **Randomisation**
  - HSCTlite
    - Week 4
    - Week 8 / 14
    - Week 24
    - Week 32 / 40
    - Week 48 endpoint
  - Anti TNF if active disease

- **Standard care**
  - Week 8 / 14
  - Week 24
  - Week 32 / 40
  - Week 48 endpoint

Any licensed therapy

Ongoing clinical care; Long term follow up via EBMT
**HSCT in refractory Crohn’s disease**  
*ASTIClite trial mobilisation regimen*

- Can be inpatient or outpatient
- One hour infusion of cyclophosphamide $1\text{g/m}^2$
- Mesna to prevent haemorrhagic cystitis (dose as per local practice)
- G-CSF $5\mu\text{g/kg}$ subcutaneously starting 5 days after Cyclophosphamide until stem cell harvest
- Full blood count and CD34+ monitoring from day 8 until CD34+ levels exceed $10\times 10^6/\text{L}$
- Stem cell harvest (min. target $2\times 10^6/\text{kg}$)

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<thead>
<tr>
<th>Day</th>
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<tbody>
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<td>Cyclophosphamide ($1\text{g/m}^2$)</td>
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<tr>
<td>G-CSF (filgrastim) ($5\mu\text{g/kg}$)</td>
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<tr>
<td>Mesna (dose as per local practice)</td>
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<td>Peripheral blood CD34+ count</td>
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<tr>
<td>Stem cell harvest (*approx. day will depend on adequate CD34+ counts)</td>
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*HSCT in refractory Crohn’s disease: ASTIClite trial mobilisation regimen.*
# HSCT in refractory Crohn’s disease

**ASTIClite trial conditioning regimen**

- Fludarabine 25mg/m² IV (reduced for impaired renal function)
- Cyclophosphamide 60mg/kg/day in 500ml of normal saline, IV over 1 hour with Mesna
- Rabbit ATG (Genzyme) 2.5mg/kg IV
- Methylprednisolone 1mg/kg IV to cover febrile reactions due to ATG
- Stem cell reinfusion

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<td>Mesna (dose as per local practice)</td>
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<td>Rabbit ATG (2.5mg/kg/day)</td>
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<td>Methylprednisolone (1mg/kg/day)</td>
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<td>Stem cell reinfusion</td>
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<tr>
<td>G-CSF (filgrastim) (5μg/kg/day) (*cont. until absolute neutrophils &gt;1.0x10⁹/L for 2 days)</td>
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</table>
PBMCs
- Gene expression profiling
- Digital IHC

Mucosal biopsy
- Digital replica of the immune topography
- Lamina propria immune infiltrate

Gene expression profiling (NanoString)
- TCR repertoire analysis
- Mucosal microbiota analysis

Protein analysis
- Intra-cellular cytokine production
- TCR excision DNA circle (TREC) analysis
- TCR repertoire analysis

Multi-colour flow cytometry
- Predictive, mechanistic and prognostic immune gene signatures

Serum
- Anti TNF levels / ADA
- Response to vaccines
- Proteomics

Stool
- Faecal microbiota: structure and function

Metagenomics
- Gene expression profiling
- TCR repertoire analysis
- Mucosal microbiota analysis

Mucosal biopsy
- Digital replica of the immune topography

Immune monitoring
- Immune reconstitution
- HSCT in refractory Crohn’s disease

ASTICLite: mechanistic sub-studies
HSCT in refractory Crohn’s disease
ASTIClite trial progress to date

<table>
<thead>
<tr>
<th>Site</th>
<th>Principal Investigator (Gastroenterology)</th>
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</thead>
<tbody>
<tr>
<td>Barts Health NHS Trust</td>
<td>Prof. James Lindsay</td>
</tr>
<tr>
<td>Sheffield NHS Foundation Trust</td>
<td>Prof. Alan Lobo</td>
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<tr>
<td>Nottingham University Hospitals NHS Trust</td>
<td>Prof. Chris Hawkey</td>
</tr>
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<td>Cambridge University Hospitals NHS Trust</td>
<td>Dr Miles Parkes</td>
</tr>
<tr>
<td>Oxford University Hospitals NHS Trust</td>
<td>Prof Simon Travis</td>
</tr>
<tr>
<td>NHS Lothian Edinburgh</td>
<td>Dr Shahida Din</td>
</tr>
<tr>
<td>Royal Liverpool Hospitals NHS Trust</td>
<td>Dr Sree Subramanian</td>
</tr>
<tr>
<td>Guy’s &amp; St Thomas’ NHS Foundation Trust</td>
<td>Dr Peter Irving</td>
</tr>
</tbody>
</table>

44 patients have been referred for discussion with Trial MDT

20 have been consented:
  3 has been randomised
  17 are undergoing screening
HSCT in refractory Crohn’s disease – ready for prime time?

Summary of talk

• Significant advances in targeted biologic and small molecule therapies for Crohn’s disease
  – A proportion of patients remain refractory to all therapies
  – Surgery may leave them with a permanent stoma or TPN dependent

• Interest in AHSCT driven by case series and experience in other autoimmune diseases
  – The ASTIC trial did not achieve its stringent primary endpoint
    • Significant benefits seen in many patients, balanced against burden of serious infections and 1 death
    • Possibility to predict response using miRNA
  – Further case series confirm benefit, but significant number relapse

• ASTIClite is a UK NIHR funded trial to assess benefit and risk of reduce intensity HSCT
  – Currently recruiting across 8 sites in the UK