The Lebanese Society of Gastroenterology:
2nd Inflammatory Bowel Disease Congress

Autologous Bone Marrow Transplantation for Refractory CD:
When All Else Fails

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Queen Mary University of London
Consultant Gastroenterologist, Barts Health NHS Trust
HSCT in refractory Crohn’s disease – when all else fails

Disclosures and conflicts of interest

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: when all else fails

What I hope to cover

• Introduction to HSCT

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

• What does the future hold?
How do we treat Crohn’s disease in 2019

The choice of drugs has increased...

- Steroids, Azathioprine, Methotrexate
- Anti-TNFs for UC
- Tumour necrosis factor antagonists (anti-TNFs) D
- Initial report in CD

- Surgery

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)

1. Stem cell mobilisation with cyclophosphamide and colony stimulating factors
2. Conditioning with cyclophosphamide and anti thymocyte globulin
3. 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
Autologous stem cell transplantation in refractory CD

The ASTIC trial design

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

<table>
<thead>
<tr>
<th>Component</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><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
<tr>
<td><strong>Components</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
<td>0.038</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>
<td>0.033</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)
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>
<tr>
<td><strong>Prior Drugs</strong></td>
<td></td>
</tr>
<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>
<tr>
<td><strong>Disease activity (IQR)</strong></td>
<td></td>
</tr>
<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>
<tr>
<td><strong>Laboratory results (IQR)</strong></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin g/dL</td>
<td>12.3 (11.6-13.6)</td>
</tr>
<tr>
<td>Platelets x 10^9/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>
<tr>
<td><strong>Quality of Life and functional status (IQR)</strong></td>
<td></td>
</tr>
<tr>
<td>IBDQ (32 – 224)</td>
<td>121 (102-140)</td>
</tr>
<tr>
<td><strong>Ileocolonoscopic evaluation (IQR)</strong></td>
<td></td>
</tr>
<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 – 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>

**Mucosal healing:** SES CD ulcer subscore 50%

**Disease Regression:** No evidence of disease on endoscopy (SESCD=0) and radiology in 26.8%

**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 – 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>14</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Break down for infectious SAEs</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><strong>GI SAEs</strong></td>
<td>6</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Break down for GI SAEs</td>
<td></td>
<td></td>
<td></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><strong>Hematologic SAEs</strong></td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Break down for hematologic SAEs</td>
<td></td>
<td></td>
<td></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><strong>Fever SAEs</strong></td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Renal SAEs</strong></td>
<td>5</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>Respiratory SAEs</strong></td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>10</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

**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

*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></td>
<td>6</td>
<td>9</td>
<td>9</td>
<td>24</td>
<td></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>

**Rectum**

Baseline

![Baseline T cell receptor repertoire](chart1)

Year 1

![Year 1 T cell receptor repertoire](chart2)

Le Bourhis L, et al. ECCO 2017; OP4
Analysis of all patients undergoing HSCT in ASTIC trial

Predicting outcome of HSCT using mucosal miRNA profiles

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 using mucosal miRNA profiles

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 using mucosal miRNA profiles**

Mucosal miR-155-5p levels predict response to HSCT

- Promotes inflammation in CD
- Regulates immune cell function
- Linked to response to HSCT in Multiple Sclerosis

ROC analysis (deep Remission)

AUC= 0.91 ± 0.096

<table>
<thead>
<tr>
<th>CDAI&lt;150</th>
<th>Endo remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Single centre series of HSCT in Crohn’s disease

Clinical outcome of 29 patients from Barcelona (13 ASTIC)

Mobilisation:
4g/m² cyclophosphamide

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

Drug free clinical & endoscopic remission:
61% at 1 yr, 47% at 3 yrs, and 15% at 5 yrs

High burden of adverse events (neutropenic sepsis); one death (systemic CMV)

6/29 [21%] required surgery

Inclusion criteria:

- Patients aged >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></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>

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INFECTIONS
- No post ASCT infection
- Bacterial
- EBV
- CMV
- Other viral

CANCER
- No 2º malignancy
- 2º malignancy: skin (n=3), testis (n=1)

AUTO-IMMUNITY
- None
- Thyroid disease
- Joint disease
- Other
HSCT in refractory Crohn’s disease

Where next?

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

**ASTIClire: mechanistic sub-studies**

**Immune monitoring**

- **PBMCs**
  - Multi-colour flow cytometry
  - Gene expression profiling
  - Immune reconstitution
  - Intra-cellular cytokine production
  - TCR excision DNA circle (TREC) analysis
  - TCR repertoire analysis

- **Serum**
  - Protein analysis
  - Predictive, mechanistic and prognostic immune gene signatures
  - Anti TNF levels / ADA
  - Response to vaccines
  - Proteomics

- **Stool**
  - Metagenomics
  - Faecal microbiota: structure and function

- **Mucosal biopsy**
  - RNA / DNA profiling
  - TCR repertoire analysis
  - Mucosal microbiota analysis
  - Gene expression profiling (NanoString)
  - Digital IHC
  - Digital replica of the immune topography
  - Lamina propria immune infiltrate
HSCT in refractory Crohn’s disease

ASTIClite trial progress to date

44 patients have been referred for discussion with Trial MDT
25 have been consented:
   8 has been randomised
   17 are undergoing screening

<table>
<thead>
<tr>
<th>Site</th>
<th>Principal Investigator (Gastroenterology)</th>
</tr>
</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>
</tr>
<tr>
<td>Nottingham University Hospitals NHS Trust</td>
<td>Prof. Chris Hawkey</td>
</tr>
<tr>
<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>
HSCT in refractory Crohn’s disease – when all else fails

Summary of talk

• **Significant advances in 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 HSCT driven by case series and results from other diseases**
  – The ASTIC trial did not achieve its stringent primary endpoint
    • Significant benefits seen in many patients, balanced against serious infections and 1 death
    • Possibility to predict response using miRNA
  – Further case series confirm benefit, but a significant number relapse

• **ASTIClite is a UK trial to assess benefit and risk of reduce intensity HSCT**
  – Currently recruiting across 8 sites
HSCT in refractory Crohn’s disease – when all else fails

Research required all members of the MDT

The Barts Health Inflammatory Bowel Disease MDT