Haematopoietic stem cells/mesenchymal stromal cells for autoimmune diseases

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Disclosure

Nothing to disclose
In SSc, like in SLE, different organs, may require different treatment

Treatment strategies target:

- scleroderma renal crisis
- PAH
- fibrotic processes (skin, lung)
- vascular pathologies (RF, SRC)
- GI tract involvement
Haematopoietic stem cells

- Bone marrow cells which are self-renewing and capable of giving rise to all haematopoietic mature cell types and possibly to some non-haematopoietic cell types
- They are characterized by a lack of cell-surface lineage markers and the expression of CD34 in humans
### Outcome of patients undergoing first autologous HSCT

<table>
<thead>
<tr>
<th></th>
<th>MS</th>
<th>SSc</th>
<th>Crohn</th>
<th>SLE</th>
<th>RA</th>
<th>JIA</th>
<th>Vasculitis</th>
<th>Cytopenia</th>
<th>IDDM</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>827</td>
<td>379</td>
<td>115</td>
<td>107</td>
<td>75</td>
<td>75</td>
<td>39</td>
<td>42</td>
<td>20</td>
<td>160</td>
</tr>
<tr>
<td>100 days NRM %</td>
<td>1.1</td>
<td>5</td>
<td>0.9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3 years NRM %</td>
<td>1.5</td>
<td>7.2</td>
<td>0.9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RI %</td>
<td>34.4</td>
<td>31.1</td>
<td>60.4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PFS %</td>
<td>64</td>
<td>61.8</td>
<td>38.7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>OS</td>
<td>95.5</td>
<td>80.3</td>
<td>96.7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

IDDM, insulin dependent diabetes mellitus; JIA, juvenile idiopathic arthritis; MS, multiple sclerosis; NRM, non relapse mortality; OS, overall survival (time from transplant to death independent of cause); PFS, progression or relapse-free survival; RA, rheumatoid arthritis; RI, relapse or progression incidence; SSc, systemic sclerosis; SLE, systemic lupus erythematosus.

Adapted with permission [21].
Transplants by year and disease subgroup.

CD, Crohn's disease; MS, multiple sclerosis; SSc, systemic sclerosis.
Autologous HCT as a therapy for autoimmune disease.
Mechanisms by which HCT might ameliorate autoimmune diseases

Immunosuppressive conditioning

- ATG
- TBI
- CY
- Other
- Anti CD22
- Anti CD52
- Fludarabine

Regulatory T cells

- CD4+CD25+
- TGFβ?
- IL-10?
- CD4+CD25+
- CD4+CD25+
Systemic sclerosis

**Vasculopathy**
- Raynaud’s phenomenon
- Renal crisis
- PAH

**Fibrosis**
- Skin
- Lung
- Bowell
- Heart

**Autoimmunity**
- Antinuclear Abs

Gabrielli et al. NEJM 2006 and 2009
**B lymphocyte abnormalities in SSc**

Breg (in SSc; < B10)

- IL-6
- TGF-β

Bcell

- CD19
- anti CD22

- Inhibition of inhibitory CD22

pDC

- Th2-cells

- IL-13 & IL-4

- TGFβ

↑ ECM

Autoantibodies, fibrosis and vasoconstriction

Pooled standardized mortality ratio (SMR) of the Australian, Canadian, and Spanish inception and prevalent cohorts.

Forest plot of SMR of inception cohorts

<table>
<thead>
<tr>
<th>Country</th>
<th>SMR (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>3.40 (2.30, 4.50)</td>
<td>35.50</td>
</tr>
<tr>
<td>Canada</td>
<td>5.10 (4.00, 6.20)</td>
<td>44.59</td>
</tr>
<tr>
<td>Spain</td>
<td>3.20 (2.30, 4.20)</td>
<td>19.42</td>
</tr>
<tr>
<td>Overall (I-squared = 78.4%, p = 0.014)</td>
<td>4.06 (3.35, 4.85)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Forest plot of SMR of prevalent cohorts

<table>
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<tr>
<th>Country</th>
<th>SMR (95% CI)</th>
<th>% Weight</th>
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</thead>
<tbody>
<tr>
<td>Australia</td>
<td>2.80 (2.40, 3.30)</td>
<td>42.89</td>
</tr>
<tr>
<td>Canada</td>
<td>3.80 (3.30, 4.20)</td>
<td>45.39</td>
</tr>
<tr>
<td>Spain</td>
<td>4.20 (3.30, 5.00)</td>
<td>11.72</td>
</tr>
<tr>
<td>Overall (I-squared = 84.9%, p = 0.001)</td>
<td>3.39 (3.06, 3.71)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Hao et al 2017
## Randomized controlled HSCT trials in systemic sclerosis

<table>
<thead>
<tr>
<th>References</th>
<th>Study/phase (HSCT/control)</th>
<th>Patients</th>
<th>Control regimen</th>
<th>Graft manipulation</th>
<th>Transplantation</th>
<th>Duration (month)</th>
<th>End point (primary and secondary)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burt et al (2011)</td>
<td>ASSIST/I 10/9</td>
<td>Monthly IV CYC1 g/m² 26 doses</td>
<td>None</td>
<td>Autologous HSCT</td>
<td>48</td>
<td>Improvement mRSS and FVC/ disease progression</td>
<td>improved</td>
<td></td>
</tr>
</tbody>
</table>

HSCT, haematopoietic stem cells transplantation; IV CYC, intravenous cyclophosphamide; PFS, progression-free survival; TRM, transplant-related mortality; mRSS, modified Rodnan Skin Score FVS, forced vital capacity. GRCS= Global rank composite score

## Randomized controlled HSCT trials in systemic sclerosis

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<th>Duration (month)</th>
<th>End point (primary and secondary)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Laar et al.</td>
<td>ASTIS/II</td>
<td>79/77</td>
<td>Monthly IV CYC</td>
<td>CD34 selection</td>
<td>Autologous HSCT</td>
<td>48</td>
<td>Event-free survival/PFS,TRM</td>
<td>Improved</td>
</tr>
<tr>
<td>(2014)</td>
<td></td>
<td></td>
<td>750 mg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12 doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sullivan et al.</td>
<td>SCOT/II-III</td>
<td>36/39</td>
<td>Monthly IV CYC</td>
<td>CD34 selection</td>
<td>Autologous HSCT</td>
<td>54</td>
<td>Event-free survival (GRCS)</td>
<td>improved</td>
</tr>
<tr>
<td>(2018)</td>
<td></td>
<td></td>
<td>500 mg/m² and 750 mg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>11 doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HSCT, haematopoietic stem cells transplantation; IV CYC, intravenous cyclophosphamide; PFS, progression-free survival; TRM, transplant-related mortality; mRSS, modified Rodnan Skin Score FVS, forced vital capacity. GRCS= Global rank composite score
Death/organ failure
FVC
Events (1st year)
Long term mortality (after 4 yrs)
Relapses

<table>
<thead>
<tr>
<th></th>
<th>HSCT</th>
<th>CYC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death/organ failure</td>
<td>19/3</td>
<td>23/8</td>
</tr>
<tr>
<td>FVC</td>
<td>+ 6.3%</td>
<td>- 2.8%</td>
</tr>
<tr>
<td>Events (1st year)</td>
<td>16.5%</td>
<td>8.0%</td>
</tr>
<tr>
<td>Relapses</td>
<td>16.5%</td>
<td>26%</td>
</tr>
</tbody>
</table>

van Laar et al 2014

van Laar et al 2014
Autologous HSCT in SSc: primary and key secondary outcomes (SCOT-Trial)

Improved:
- GRCS: 67% vs 33%
- EFS*: 79% vs 50%

HQoL

* At 54 months

EFS = event free survival; GRCS = global rank composite score

Sullivan et al 2018
Mesenchymal stem/stromal cells (MSC)

- Reside within connective tissue of multiple organs (bone marrow, skeletal muscle, adipose tissue, umbilical cord, synosium lung circulatoty system, fetal bòlood, amniotic fluid)

- Multipotent cells (limited differentiation potential, at least osteogenic, chondrogenic, adipogenic)

- Lack lack self-renew potential

- Functionally heterogeneous

- Express markers including CD29, CD44, CD51, CD73, CD105, CD106, CD166, Stro1, CD49 a-f

- Lack haematopoietic markers

Phinney et al 2007
Interaction of MSCs and immune cells demonstrated in vitro

Tyndall A 2014
Summary of some of the anti-inflammatory effects of MSCs.
Publications in which MSCs were administered to animal models for the diseases indicated

- Cancers: 6,286
- Heart disease: 1,509
- Cirrhosis: 1,055
- Skin Diseases: 998
- Eye diseases: 389
- Orthopedics: 519
- Renal diseases: 607
- Arthritis: 696
- Lung Diseases: 714
Bleomycin e.t.

hUC-MSC i.v. (2.5 × 10^5 cells)

Mice sampling

Days

0 1 7 8 14 21
hUC-MSC down-regulate bleomycin-induced lung inflammation

Moroncini et al PLoS one 2018
hUC-MSC down-regulate bleomycin-induced lung fibrosis.
Time course of cytokines and matrix components in lung tissue assessed by quantitative real-time PCR.
Decrease of galectin-3 positive cells in bleomycin-injured lung tissue upon administration of hUC-MSC.
Decrease of arginase-I positive cells in bleomycin-injured lung tissue upon administration of hUC-MSC.
Detection of hUC-MSC by quantitative real-time PCR assay for human GAPDH.
Detection of hUC-MSC in lung tissue by vimentin IHC.
Detection of hUC-MSC in lung tissue by HLA-I and CD105 IHC
Two independent populations of MRTMs exist across most tissues in steady state with conserved specific subtissular niche-dependent phenotype.

Chakarov et al 2019
Concluding remarks

- Systemic autoimmune diseases lack disease modifying therapeutic modalities

MSC may be a promising therapy for autoimmune diseases characterized by fibrosis and/or lung involvement