Extracorporeal Photopheresis: From Graft vs Host disease to Scleroderma

Peter Taylor
Consultant Haematologist,
Honorary Senior Lecturer, University of Sheffield
Director of Photopheresis, Rotherham ECP Unit

Chair, UK Photopheresis Society
Objectives

• Review clinical features and pathogenesis of GvHD

• Mechanistic similarities between GvHD and Scleroderma

• The role and action of photopheresis

• Biomarker developments
Chronic GvHD – Heterogeneous Disease

Variable clinical presentation involving:
• Skin, mouth, eyes, liver, gut, respiratory tract, oesophagus, genitalia and fascia

Variable pathology:
• SKIN: Inflammatory infiltrate leading dermal/epidermal junction destruction and then fibrosis and sclerosis
• GLANDS: Tuboalveolar gland destruction
Chronic GvHD - Aetiology?

- Defective, negative selection of T cells – thymic damage
- Fibrosis and aberrant production of TGFβ
- B cell homeostasis altered
- T regulatory cells downregulated?
Role of B cells - Evidence

- Presence of autoantibodies
- Clinical presentation of cGvHD with autoimmune manifestations
- Improvement in cGvHD induced by anti-CD20 therapy
- Enhanced CD 86 expression after stimulation of B cells
- Raised BAFF levels
- High BAFF levels at 6 months in asymptomatic patients predicts onset of cGvHD
- Antibodies to mHA encoded on the Y chromosome in male recipients receiving female transplants have increased cGvHD incidence
B regulatory cells

- CD 19 deficiency on donor B cells led to expansion of IL-6 producing macrophages, cCD8 T cells, Th1 cells, TGFβ producing macrophages and T cells
- Donor derived B-regs suppress murine sclerodermatous cGvHD
- Le Huu et al. Blood 2013 121(3)3274
Immune tolerance and T regs - Evidence

• Acute GvHD impairs the negative selection of T cells and results in reduced T reg numbers
  Morohashi Immunobiology 2000 202, 268

• Conflicting data - T reg numbers in cGvHD
  Reiger Blood 2006 107, 1717 vs Clark Blood 2004 103,2410

• T reg suppression of cGvHD is mediated via cytokines TGFβ, IL-10, or by contact with DC’s (via Indoleamine 2,3 dioxygenase)
  J Clin Invest 2007 117, 2570

• Absence of T reg control of Th1 and Th17 cells is responsible for the autoimmune mediated pathology in cGvHD
  Chen Blood 2007 110,3804

The Rotherham NHS Foundation Trust
T Regs in GvHD !!

- Acute

- Chronic
Skin Assessments

NIH Assessment uses Rule of 9s
8 body areas

Vienna Skin Score
10 body areas
Biomarkers Scleroderma

• Not available for
  – Early diagnosis / Assessment of disease activity / predicting prognostic value
• Autoantibodies
• Endothelial cell function (vWF, adhesion molecules)
• Pulmonary fibrosis markers
• Cellular immunity / cytokines (IL2, CXCL2, CXCL 10 etc)
• Fibrosis – TGFβ
• Gene expression profiling – DNA microarrays
• Proteomics – study of the proteome

Biomarkers cGvHD

• Acute GvHD
  – Proteomics
    • Reg 3a - Gut GvHD (prognostic)
    • Elafin – Skin GvHD (diagnostic and prognostic)

• Chronic GvHD
  – BAFF (prognostic)
  – TNF receptor 1 (predictive)
  – Panels now being used to drive pre-emptive therapy

Levine et al Biol Blood Marrow transplant 2012 S116-24
doi: 10.1016/j.bbmt2011.10.019
Sclerotic cGvHD

- Review of 977 HCT patients between May 2000 – Dec 2009
- 7% presented with sclerosis
- 20% sclerotic at 3 yrs
- Multivariate analysis
  - Increase risk
    - Mobilised blood stem cells
    - TBI conditioning
  - Decreased risk
    - HLA mismatch
    - ABO mismatched donor
- No overall impact on mortality, but increased morbidity

Inamoto et al Blood 2012 doi 10.1182/Blood-2012-10-464198
**Sclerodermatous GvHD - Aetiology**

*TBI is associated with increased risk of development of ScGVHD.* The association between TBI and ScGVHD was demonstrated most strongly among patients treated with reduced-intensity conditioning (RIC). Of 15 patients who received TBI as part of a RIC conditioning regimen, 14 demonstrated ScGVHD ($P = .0114$).

Martires et al  Blood 2011, 118  4250
Severity of ScGvHD and survival

**Percent BSA and survival.** Survival among patients with ScGVHD with percent BSA involvement above and below the median (37.4%) for the entire ScGVHD group. Log-rank ($P = .015$). In multivariable analysis, after adjusting for NIH lung score, Karnofsky score, and lymphocyte count (factors associated with survival in this cohort on previous analyses), percent-BSA ScGVHD was no longer associated with survival.

Martires et al  Blood 2011, 118  4250
Impact of cGvHD on Health outcomes

- Prevalence of HCT survivors with adverse health outcomes by cGVHD status
Case report

Successful treatment of chronic graft-versus-host disease with extracorporeal photopheresis

M. Owsianowski¹, H. Gollnick¹, W. Siegert², R. Schwerdtfeger² & C.E. Orfanos¹

¹Department of Dermatology, University Medical Center Benjamin Franklin and ²Department of Hematology and Oncology, University Medical Center Rudolf Virchow, The Free University of Berlin, Berlin, Germany

- Owsianowski BMT 1994, 14: 845-848
- Allo sib BMT 1986 for CML
- 2 yrs progressive cGvHD despite steroids / cyclosporin / PUVA
- Paired treatments 4 weekly
- Healing of ulcers by 24 weeks
U.K. consensus statement on the use of extracorporeal photopheresis for treatment of cutaneous T-cell lymphoma and chronic graft-versus-host disease


Consensus Conference on Clinical Practice in Chronic GVHD: Second-Line Treatment of Chronic Graft-versus-Host Disease

Daniel Wolff,¹ Michael Schleuning,² Stephanie von Harsdorf,³ Ulrike Bacher,⁴ Armin Gerbitz,⁵ Michael Stadler,⁶ Francis Ayuk,⁴ Alexander Kiani,⁷ Rainer Schwerdtfeger,² Georgia B. Vogelsang,⁸ Guido Kobbe,⁹ Martin Gramatzki,¹⁰ Anita Lawitschka,¹¹ Mohamad Mohty,¹² Steven Z. Pavletic,¹³ Hildegarde Greinix,¹⁴ Ernst Holler¹

Wolff et al Biology of Blood and Marrow Transplantation 17(1) 1-17

BCSH Guideline: Diagnosis and Management of Chronic Graft-versus-Host Disease

Fiona L.Dignan¹,², Persis Amrolia³, Andrew Clark⁴, Jacqueline Cornish OBE⁵, Graham Jackson⁶, Prem Mahendra⁷, Julia J.Scarisbrick⁸, Peter C. Taylor⁹, Bronwen E. Shaw ¹,¹⁰, Michael N. Potter¹ on behalf of the Haemato-oncology Task Force of the British Committee for Standards in Haematology and the British Society for Blood and Marrow

Dignan et al BJ Haem March 2012
ECP Eligibility – UK Perspective

- Cutaneous, mucosal, hepatic cGvHD
- Steroid refractory/resistant/intolerant cGvHD
- Extensive cGvHD - Seattle
- Biopsy – compatible with GVHD

- * Respiratory, gastro-intestinal, ophthalmmic
Extracorporeal Photopheresis

The photoactivated white blood cells are returned to the patient.

Photoactivation with UVA light

Methoxsalen

White blood cells are treated with methoxsalen and exposed to UVA light.

Blood is separated by centrifugation and red blood cells are returned.

The UVAR XTS Instrument draws blood from the patient.
## ECP – cGvHD Organ response rates

<table>
<thead>
<tr>
<th>Organs</th>
<th>Pre ECP N=178</th>
<th>Response at 14 wks %</th>
<th>Response at 28 wks %</th>
<th>Response at 56 wks %</th>
<th>Response at 112 wks %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>134</td>
<td>68</td>
<td>64</td>
<td>79</td>
<td>69</td>
</tr>
<tr>
<td>Eyes</td>
<td>63</td>
<td>39</td>
<td>36</td>
<td>49</td>
<td>46</td>
</tr>
<tr>
<td>Oral</td>
<td>63</td>
<td>67</td>
<td>65</td>
<td>63</td>
<td>78</td>
</tr>
<tr>
<td>Lung</td>
<td>86</td>
<td>7</td>
<td>12</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Liver</td>
<td>51</td>
<td>53</td>
<td>41</td>
<td>78</td>
<td>75</td>
</tr>
<tr>
<td>Gut</td>
<td>40</td>
<td>53</td>
<td>55</td>
<td>70</td>
<td>56</td>
</tr>
</tbody>
</table>
ECP cGvHD Steroid response (withdrawal)

<table>
<thead>
<tr>
<th>Time point</th>
<th>No of Patients</th>
<th>&gt;50% reduction</th>
<th>Steroids stopped</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 weeks</td>
<td>150</td>
<td>53</td>
<td>8</td>
</tr>
<tr>
<td>28 weeks</td>
<td>132</td>
<td>69</td>
<td>20</td>
</tr>
<tr>
<td>56 weeks</td>
<td>105</td>
<td>76</td>
<td>37</td>
</tr>
<tr>
<td>112 weeks</td>
<td>77</td>
<td>84</td>
<td>52</td>
</tr>
</tbody>
</table>
Response and Survival in the ECP treated cohort  n=219

Three months response

Six months response

Garg, Taylor et al  EBMT  2013
Clinical response....
# ECP and Systemic Sclerosis

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>No.</th>
<th>Treatment Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rook AH</td>
<td>Arch Derm</td>
<td>1992</td>
<td>79</td>
<td>D-pen vs ECP&lt;br&gt;ECP – response in skin score, %skin, oral aperture&lt;br&gt;D-Pen – no response</td>
</tr>
<tr>
<td>Schwartz</td>
<td>Int J Derm</td>
<td>1997</td>
<td>5</td>
<td>Partial response</td>
</tr>
<tr>
<td>Krasagakis</td>
<td>Derm</td>
<td>1998</td>
<td>14</td>
<td>PR 6, Stable 5, progressive 5</td>
</tr>
<tr>
<td>Enomoto</td>
<td>J AM Acad Derm</td>
<td>1999</td>
<td>19</td>
<td>ECP vs no treatment&lt;br&gt;No difference</td>
</tr>
<tr>
<td>Knobler</td>
<td>J AM Acad Derm</td>
<td>2006</td>
<td>64</td>
<td>ECP vs Sham ECP&lt;br&gt;ECP arm significant improvement in skin scores</td>
</tr>
</tbody>
</table>
1 ‘Vaccination against autoimmunity’

Transferable anti-clonotypic response generated by infusion of pathogenic T cells

Edelson  Scientific American August 1988 referencing work of Cohen
Mechanism of Action of ECP

1. Leukocytes
2. Methoxalen and UV radiation
3. Apoptosis
4. Tolerogenic DC/APC
5. Treg

- Anti-inflammatory cytokines (e.g., IL-10, TGF-β)
- Proinflammatory cytokines (e.g., IL-12, IFNγ)
- Stimulation of T effector cells
- Reduction in BAFF

Receptor-mediated signaling
B cell Homeostasis

• Dysregulation of the B cell compartment is a hallmark of cGvHD
  Socie Blood 2011 117, 2086

• Clinical features of autoimmune disease

• B cell Activating Factor (BAFF) is elevated in GvHD and is related to the development of autoimmunity
  Sarantopoulos Clin Cancer Res 2007 13,6107
B cell populations in cGvHD

- Immature CD21⁺ immature transitional B cells and deficiency of CD 27⁺ memory cells is associated with cGvHD
  Greinix Biol Blood Marrow Transplant 2008 14, 208

- Reduced CD21⁺ cells are a marker of response to GvHD
  Kuzmina Blood 2009 114, 744
B cell Activating factor and cGvHD

- Persisting levels of BAFF at 4 weeks is predictive of response of cGvHD to ECP, independent of reduction in immunosuppression
  Whittle, 2011 Blood 118, 6446

- Persisting high BAFF levels are associated with an increased risk of GvHD failure or of need to re-escalate steroids
  Whittle, 2012 Bone Marrow Transplantation, 47
FIGURE 1 | Overview of chemokine and chemokine receptor expression in the major organs targeted by GVHD. Shown are the major target organs that are affected by GVHD, the intestine, liver, lung, and skin, and the major chemokines and chemokine receptors that are expressed during the course of the disease.
Passive adsorption of capture antibodies onto assay ‘spots’

1. Electro-chemiluminescence technology – Meso Scale Discovery™

2. Detection ab labelled with SULFO-TAG™

3. Chemiluminescence reaction

4. Signal intensity interpreted
Do chemokine levels predict response to treatment? – 12 month response

CXCL10 in cutaneous cGVHD response to ECP therapy

Skin response groups at 12 months ECP

Inactive disease; Skin score <10 at 12m, n=15, Median total skin score =1

Full resolved 11/15

Active disease; Skin score > 20, n=8, Median score =77

CXCL10 pg/ml

Skin score <10 at 12m

Skin score >20 at 12m

6m for score<10 at 12m

6m for score >10 at 12m

P=0.02

P=<0.01

Do chemokine levels predict response to treatment? – 12 month response
Changes in CCL17 and CCL22 in cutaneous cGVHD response to ECP therapy

**Skin response at 6m; CCL17 modulation**

<table>
<thead>
<tr>
<th></th>
<th>Pre-ECP</th>
<th>1M</th>
<th>3M</th>
<th>6M</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCL17 TARC pg/ml</td>
<td>3000</td>
<td>4500</td>
<td>6000</td>
<td>0</td>
</tr>
</tbody>
</table>

Complete or partial skin resolution 6m, n=15

**Skin response at 6m; CCL22 modulation**

<table>
<thead>
<tr>
<th></th>
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<th>1M</th>
<th>3M</th>
<th>6M</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCL22 (MDC) pg/ml</td>
<td>5000</td>
<td>7500</td>
<td>10000</td>
<td>0</td>
</tr>
</tbody>
</table>

Complete or partial skin resolution 6m, n=15
Conclusions

• Systemic sclerosis and Sclerotic cGvHD are clinically similar
• The search for biomarkers has proved challenging in both
• There are emerging biomarker pathways in cGvHD, which shortly will start to be incorporated in treatment algorithms
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Data management
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J Ball

www.photopheresis.co.uk  www.ukps.org