Extracorporeal Photopheresis and Crohn’s Disease

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Outline

1. Crohn’s Disease (CD)
2. Extracorporeal Photopheresis (ECP)
3. Pilot studies of ECP and CD
4. Future trials?
Crohn’s Disease Overview

- Chronic inflammatory bowel disease
- All areas of gut can be affected
- Characterized by skip lesions
• Incidence in USA is ~7 cases per 100,000 persons
• Female predominance
• Typical presentation before age 30
• 4x more common in Caucasians vs. African or Asian
• Smoking is major risk factor
Clinical Features

- Intermittent diarrhea, abdominal pain, weight loss, fatigue and fever
- Extraintestinal manifestations common
Macroscopic Features
Radiographic Features

Cobblestone pattern

String Sign
Microscopic Features
Treatment

- Corticosteroids
- 5-Aminosalicylates
- Azathioprine
- 6-mercaptopurine
- Methotrexate
- Cyclosporine

- Anti-TNF-α

Very effective
~50% will have side effects

Up to 65% effective
~25% will have side effects

40-60% remission...
Loss of response in 70%
Etiology

• Unknown

• **Theory:** Dysregulated immune response to intestinal microbes

• **Implicated players:** Dendritic cells, T-cell populations
Extracorporeal Photopheresis
• **Thousands of years ago**
  • Egyptians treated vitiligo with *Ammi majus* and sunlight exposure

• **1900’s**
  • Niels Finsen earned Nobel Prize in Medicine (1903) for “light treatment of lupus vulgaris”

• **1948 -1953**
  • Active ingredient of *Ammi majus*: 8-methoxypsoralen (8-MOP) a photoactive compound
• **1974-1979**

  • Oral 8-MOP and UVA (PUVA) used to treat psoriasis [Parrish] and Cutaneous T Cell Lymphoma (CTCL) [Gilchrest]

  • **ECP combines PUVA and leukapheresis cytoreduction for leukemic CTCL**
Extracorporeal Photopheresis

• Immunomodulatory therapy
  • Leukopheresis
  • Ex-vivo irradiation of lymphocytes in the presence of 8-methoxypsoralen (8-MOP)
  • Re-infusion into the patient
ECP Steps

Red Cells and Plasma

White cells and Plasma

Treated WBC undergoing apoptosis

8-MOP
Inert until photoactivated
Covalently binds DNA bases, surface and cytosolic proteins

UVA
Treated WBC
• Graft rejection after transplantation is characterized by a clonal expansion of activated T cells...

*CTCL is also characterized by a clonal population of T cells*
Table 1
Implementation of extracorporeal photopheresis (ECP) in solid organ transplantations for the treatment of acute rejection episodes.

<table>
<thead>
<tr>
<th>Type of solid organ allotransplant</th>
<th>Year of introduction (and reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>1987 [88]</td>
</tr>
<tr>
<td>Heart</td>
<td>1992 [12]</td>
</tr>
<tr>
<td>Lung</td>
<td>1995 [99]</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1995 [90]&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Liver</td>
<td>2000 [103]</td>
</tr>
<tr>
<td>Composite tissue allotransplant (partial face transplantation)</td>
<td>2006 [2]</td>
</tr>
<tr>
<td>Small bowel</td>
<td>–</td>
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</tbody>
</table>

<sup>a</sup> The third patient presented among the case reports had received a combined kidney and pancreas transplantation and is cited as the first implementation of ECP for pancreas transplantation, even if the function of the pancreas is not described after the ECP therapy.

2010 ASFA Categories for ECP

- **CTCL**
  - Erythrodermic: Category I – Grade 1B
  - Non-erythrodermic: Category III – Grade 2C

- **Cardiac Transplant**
  - Prophylaxis: Category I – Grade 1A
  - Treatment of Cellular Rejection: Category II – Grade 1B

- **Lung Transplant**
  - Rejection: Category II – Grade 1C

- **Graft vs Host Disease**
  - Skin: Category II – Grade IB (Chronic) – Grade 2C (Acute)
  - Non-Skin (Acute/Chronic): Category III – Grade 2C

Proposed Mechanisms

- Enhanced maturation of dendritic cells
- Production of immune effector cells
- Uptake of apoptotic cells by APC
- Generation of tolerogenic dendritic cells
- Vaccine Effect: Eradication of clonal T cells, CTCL, Transplant
- Soluble Factors: Cytokine products skew towards anti-inflammation
- Tolerance: Production of T-reg
Key Players in Tolerance

Apoptotic Cell
Billions die each day as part of normal physiology

Dendritic Cell
Immature DC efficiently engulf apoptotic cells

T-reg Cells
Central role in maintaining immune homeostasis

http://joelotron.wordpress.com/2010/02/28/dendritic-cell/

T cell: Lawrence Berkeley Lab
Immunogenicity vs Tolerance

ECP and Tolerance

• Apoptotic cells promote an anti-inflammatory environment conducive for tolerance
  • Decrease expression of pro-inflammatory cytokines and vital co-stimulatory proteins on APC
  • Increase expression of anti-inflammatory cytokines and preventing maturation of immature DC

Promotion of tolerogenic phenotype
ECP promotes transplant tolerance, but what about restoring lost tolerance in autoimmune conditions?
• Pemphigus vulgaris  
  Category III – Grade 2C

• Scleroderma  
  Category IV – Grade 1A

Inflammatory bowel disease  
Adsorptive cytapheresis  
Category II – Grade 2B

Pilot studies of ECP and CD
• Pathogenic/resident bacteria stimulate CD4+T-cells leading to chronic inflammation
• No curative treatment
• Therapy wrought with side-effects
• ECP a possible safe alternative?
• Phase I – 24 patients
  • Standardized steroid taper, maintenance dose ≥ 10 mg/day
• Phase II – 10 patients
  • Continued steroid-withdrawal with ECP
• Phase III – 9 patients
  • Duration of remission/response
Remission – 3 of 4 maintained through Phase III
Responder/Non-Responder – Modest decrease in dose
Homing of cells staining with anti-8-MOP to colonic mucosa

Pre-ECP

Post-ECP

Anti-8-MOP adduct
Summary

• 4 of 10 patients discontinued steroids, 4 of 10 cut their dose in half

• ECP is a promising, safe, steroid-sparing adjunctive for patients with refractory Crohn’s disease
• Prospective, uncontrolled pilot study
• 28 patients with moderate-severe active CD
• Refractory to immunosuppressive, anti-TNF
• Steroids permitted if ≤ 25 mg/day
• 12 weeks ECP, if response, 12 additional weeks ECP
Crohn’s Disease Activity Index

<table>
<thead>
<tr>
<th>Clinical or laboratory variable</th>
<th>Weighting factor</th>
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<tbody>
<tr>
<td>Number of liquid or soft stools each day for seven days</td>
<td>x 2</td>
</tr>
<tr>
<td>Abdominal pain (graded from 0-3 on severity) each day for seven days</td>
<td>x 5</td>
</tr>
<tr>
<td>General well being, subjectively assessed from 0 (well) to 4 (terrible) each day for seven days</td>
<td>x 7</td>
</tr>
<tr>
<td>Presence of complications</td>
<td>x 20</td>
</tr>
<tr>
<td>Taking Lomtit or opiates for diarrhea</td>
<td>x 30</td>
</tr>
<tr>
<td>Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite)</td>
<td>x 10</td>
</tr>
<tr>
<td>Hematocrit of &lt;0.47 in men and &lt;0.42 in women</td>
<td>x 6</td>
</tr>
<tr>
<td>Percentage deviation from standard weight</td>
<td>x 1</td>
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Additional Point: arthritis, uveitis, fistulas, fever in the previous week
Response to ECP

Improvement of >70 points = Partial Response
Improvement of >100 points = Clinical Response
CDAI <150 = Remission
The majority of patients with clinical response had evidence of improvement by 6 weeks.

Clinical response maintained at week 24 in 75% of patients who had response at week 12.

Rates of response, remission, steroid d/c, and fistula closure encouraging.

Additional trials needed.
Prospective, uncontrolled study
31 patients with steroid dependent remission
24 week ECP and steroid taper
Patients completing steroid taper could receive additional 24 week ECP
Subjects Enrolled (ITT Population)
N = 31

- Investigator Decision
  N = 10 (47.6%)
- Adverse Events
  N = 7 (33.3%)
- Protocol Noncompliance
  N = 2 (9.5%)
- Consent Withdrawn
  N = 2 (9.5%)
- Administrative Factors
  N = 1 (4.7%)

Early Termination
N = 21 (67.7%)

Subjects Who Did Not Complete
N = 21 (67.7%)

Subjects Who Completed the Study
N = 10 (32.2%)

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32 subjects were enrolled. However, one subject never received any VPA treatment.

FIGURE 2. Disposition of the enrolled patients.
• 7 of 31 patients achieved remission and discontinued steroids after 24 weeks of ECP
• After 48 weeks ECP only 3 steroid free remission
  • 7 in remission at significantly reduced dose of steroids
Future trials?
IOIBD and ECCO recommendations for CD trials

• Trials for 1\textsuperscript{st} line therapy should be compared against placebo
• Trials for 2\textsuperscript{nd} line therapy test agent or placebo added to treatment patient already using
• Objective evidence of inflammation
• Maintenance trials should last 6-24 months and incorporate steroid withdrawal
• Consider high placebo effect
• Controlled randomized prospective trials
• Recruitment based on symptom-based criteria that correlates poorly with inflammatory activity
  • Need objective measures – biomarkers? Endoscopy? Radiology?
Gut Facts:

- In adults the gut surface area is roughly the size of a tennis court.
- The intestinal lumen contains $\sim 10^{14}$ bacteria...this is 10 times more then the number of cells in our body!
- Largest immune organ in body.