ECP for Autoimmune Diseases

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ECP-Procedure

1. Collection of MNCs
2. Processing
3. Reinfusion

ECP Systems:
- UVAR®
- XTS™
- Cellex™ Therakos

irradiated nucleated cells & plasma

red cells & plasma

whole blood

nucleated cells & plasma

GvHD

UVA light + 8-MOP
Applications of ECP

Autoimmune Disease

CTCL

Skin Disease

Viral

Allograft Rejection

ATOPIC DERMATITIS LICHEN PLANUS PEMPHIGUS-VULGARIS SYSTEMIC-SCLEROSIS BULLOUS

SLE
RA
CROHN’S MULTIPLE-SCLEROSIS DM1 NEPHROGENIC-SYSTEMIC FIBROSIS

GVHD HEART, LUNG(BOS) LIVER, KIDNEY, PANCREAS ANGIOPLASTY FACE

HEPATITIS C HIV
Mechanism of Action

- Induction T cell anergy and apoptosis (24-72h)
- Modulation of dendritic cells
- Alter production of inflammatory cytokines

Anti-inflammatory cytokines (IL-10, TGF-β, IL-1Ra, HGF)

Pro-inflammatory cytokines (IL-1a,b, IL-6, IL-12, IFNγ, TNF a), BAFF

- Induction of CD4^+CD25^+Foxp3^+GITR^+CD62L^+ T-regulatory cells
Lymphocytes

- CD8 lymphocytes
- Th17 IFNγ-secreting Th1 cells
- sIL-2 receptor α and sTNFα R1

- IL-4, IL-5 and IL-10-secreting Th2 cells

- Th1/Th2 balance restoration toward Th2
- Normalization of CD4/CD8 ratio
- Induction of Tregs synthesizing IL-10
- Apoptosis
Monocytes

- CD36+ Monocytes
- TNFα, IL-1, IL-6, IL-10 production

- Delayed apoptosis
- Differentiation into immature CD83+ DCs which actively phagocytose apoptotic cells
Generation of Tolerogenic Dendritic cells

- Plasmocytoid DC2 (CD83+ CD86+)
- Upregulation of anti-inflammatory cytokines
  - DC1/DC2 balance restoration in favor of DC2 population
  - Activation of PS receptor, B2 integrins
  - Low surface HLA class II
  - Low costimulatory molecules
  - High inhibitory molecules

- Monocytoid DC1 (CD80+ CD123+)
- Down regulation of costimulatory molecules
NK cells

Autoimmunity:
SLE, MS, RA,
DM1, Sjögren’s,
psoriasis

ECP
B cells/BAFF

Proportions of CD19⁺CD21⁻ B lymphocytes predict response to ECP
Significant difference in CD19⁺CD21⁻ B Cells in ECP-responders (CR+PR) versus nonresponders 6 Months after start of ECP

BAFF level (less 4 ng/mL) at 1 month of ECP predicted 3- and 6-month skin disease response associated with significant skin improvement and complete resolution

Kuzmina, Z. Blood, 2009

Wittle R. Blood, 2011
CD4+CD25+Foxp3 Tregs

- Decreased Tregs population in autoimmunity:
  - Type 1 diabetes *Sgouroudis 2009*
  - SLE *Kuhn 2009*
  - Rheumatoid arthritis, asthma *Akbari 2002*
  - Inflammatory bowel disease/autoimmune gastritis *Kamikozuru 2009*
  - Primary biliary cirrhosis *Rong 2009*

Responders to ECP Show Significantly Lower Th17 and Higher T-regs

Biaso I, Biagi E, Transplantation 2009
Apoptosis induced by ECP

60% of CD3+ and CD14+ monocytes underwent apoptosis after 48 hours

DC phagocytose PBMC

Lamioni A, Carsetti R, Transplantation 2009
Applications of ECP

Autoimmune Disease
- SLE
- RA
- CROHN’S
- RRR-MULTIPLE-SCLEROSIS
- DM1
- NEPHROGENIC-SYSTEMIC FIBROSIS

Skin Disease
- ATOPIC DERMATITIS
- LICHEN PLANUS
- PEMPHIGUS-VULGARIS
- SYSTEMIC-SCLEROSIS
- BULLOUS

Allograft Rejection
- GVHD
  - HEART, LUNG(BOS)
  - LIVER, KIDNEY
  - PANCREAS
  - ANGIOPLASTY
  - FACE

Viral
- HEPATITIS C
- HIV
### Chronic GVHD

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- **23 studies – 633 patients**
- **Response:** 64% (31-100)
  - Skin: OR 64% - CR 35%
  - Liver: OR 56% - CR 27%
  - Oral mucosa: OR 47%
  - GI: OR 57%
  - Sicca: OR 50%
  - Lungs: OR 66%
- Steroid taper in 38% - 257 patients
- Steroid discontinuation at 1 year 22%
- No increase in infection
- Overall survival 88%
Summary

• Mostly retrospective
• Devices and methods
• Treatment schedule, duration
• Patient selection criteria
• Response evaluation
• Biomarker validation
Advantages and Limitations of ECP

**Advantages**
- Not immunosuppressive, antigen-specificity
- Taper of IS, steroids
- No increased incidence of infection or NRM
- No organ damage
- Safe, few side-effects (no long term)
- Tolerable
- Improve quality of life and survival
- No negative effect on GVL

**Disadvantages**
- Time-consuming (4 hours)
- Duration (6 months)
- I.V. Access
- Inpatient, ECP center
- Experienced staff necessary
- Limited access
- Costs
- Unvalidated procedure
- Few randomized trials
- “Methoxalen is carcinogenic”
Contraindications

- Allergy to 8-MOP
- Light-sensitive disease
- Aphakia
- Pregnancy
- Plt > 20 000, HCT > 33%
Patient

- Patient population (adults, children)
- Patient location, mobility (in the hospital/outpatient, mobile patients, equipment)
- Available/required vascular access, (peripheral/central lines, single/dual needle procedures)
- “Ideal” inclusion criteria
  - which patient has a high probability of response
  - when should we treat a patient with ECP (first line/salvage/therapy-refractory/prophylaxis)
  - eligibility (high infection, relapse risk)

Operator

- Who will perform the procedures (nurses, technologists, physicians)
- Who will provide the training
- Criteria of efficacy, response definition (CR, PR, stable, progression..)
- Evaluation tools for severity
- Average response time evaluation (4-6 months)

Procedure

- How many procedures are expected (daily, weekly, monthly and annually)
- How many and what types of instruments are needed
- What is the desired level of operator control
- “Optimal” rhythm of administration-dose-effect (2ECP/week) and duration
- “Optimal” combinations with immunosuppression
- Drug interactions (pharmacokinetics and pharmacodynamics)