Extracorporeal Photopheresis (ECP)

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Review

Extra corporeal photochemotherapy in steroid refractory graft versus host disease: A review of guidelines and recommendations

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What is ECP

- Cell therapy
- Consists on 3 steps :
  - MNC collection
  - Transformation
    - Addition of 8-MOP
    - UVA irradiation
  - Re injection

1st step : MNC collection

- As a Stem cell collection
- 1-3 Hours
- The Patient looks at a film on laptop or listen the music
- Full automatic procedure
  - Optia (Terumo)
  - Comtec (Fresenius)
  - Amicus (Fresenius)

Blood

2nd Step : Exposure of MNC to UVA/8-MOP (transformation) - 1

15 to 30 minutes

- Transfer of MNC to special bag
- Addition of 8-MOP
- Irradiation by the UVA light

Technical Aspects

After Apheresis:

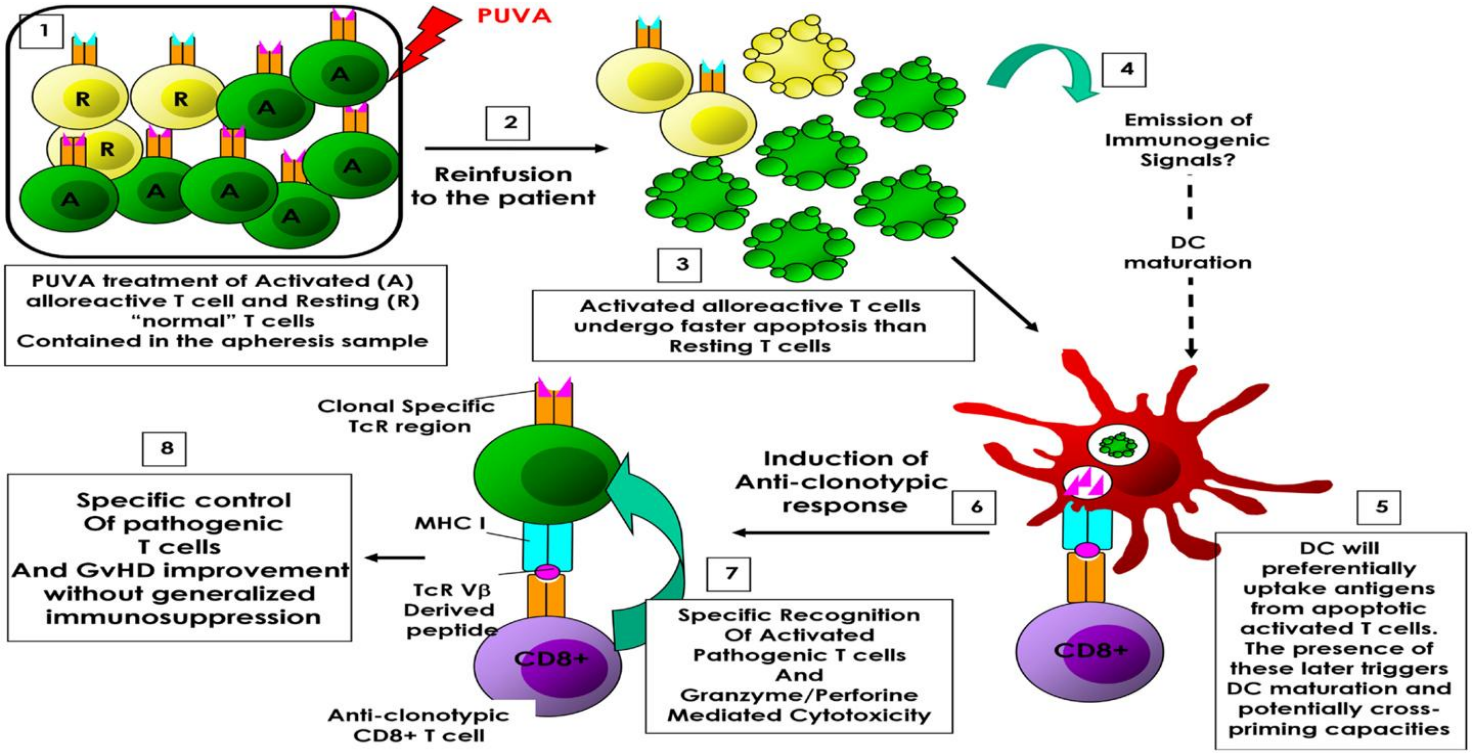
- Approximately **2TPBV**
- The product should be treated with 8-MOP diluted to a final concentration :

Pediatric :

- In-line technologies **34 mg/100 mL**
- Off-line technologies **20 mg/100 mL**

3rd Step : Reinjection

- As an autotransfusion
- 15 to 30 minutes



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Extracorporeal photopheresis-induced immune tolerance: a focus on modulation of antigen-presenting cells and induction of regulatory T cells by apoptotic cells

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ECP in cGVHD

Graft-Versus-Leukemia effect seems not to be impaired by ECP

Inclusion criteria

- ECP was strongly recommended as **second-line therapy**(grade 1b) for :
  - Skin
  - Oral
  - liver

- As a **third-line treatment**(grade 2C**) :**
  - Other organs involving

- The median (range) interval between HSCT and ECP **start was 193 days.**

Extracorporeal Photopheresis (ECP) for Adults and Pediatric cGVHD

***Complete response (CR) :** Resolution of active GVHD manifestations without systemic immunosuppression

*** Partial response (PR) :** 50% improvement of organ involvement scores (skin, liver or oral mucosa) from baseline investigation or > 50% reduction in immunosuppression. (Tapering of therapy to one cycle every 4 weeks).

Minimal response: 50% improvement of organ involvement scores from baseline investigation /or 25–50% reduction in immunosuppression.

Chronic GVHD

Treatment initiation

One cycle of treatment (i.e. ECP on two consecutive days) every 2 weeks, during the second and third months .

Monitoring Protocol

Evaluation of treatment response at 3 months (after Six- eight cycles) and at 3-monthly intervals.

After 6 month

1- ***CR:** Taper /stop ECP.
2- ***PR:** Continue one cycle per month until maximal response or stopped corticosteroid, then taper and stop.
3- **If > 50% reduction of corticosteroid dose but less than Partial Response:** Consider reduction to one cycle per month and reduce immunosuppressant as tolerated.
4- **If no further response from 3 months or progressive disease**: Taper and stop ECP.

After 3 month

1- ***CR or PR** :
Reduce to one cycle every 4 weeks.
2- **Minimal change or no change despite reduction of corticosteroid by 50%:**
Continue one cycle every 2 weeks.
3- **If neither of above:**
Stop therapy

Baseline assessment

Medical historyand clinical examination to assess cGVHD symptoms /signs.
Drug history:corticosteroid dose and other cGVHD treatment.
Skin assessment: skin score, pruritus score if indicated (0–10 visual analogue scale score), +/- clinical photography.
Mouth scoresif oral disease.
Joint assessment: Karnovsky's scale (0–100), +/- physiotherapy assessment if indicated.
Eye assessment: Schirmer's test if eye involvement, +/-ophthalmology assessment.
Respiratory assessment: pulmonary function tests if lung disease (FEV1 and DLCO), +/-respiratory assessment.
Liver assessment: bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase.
Gastrointestinal assessment: frequency of stools per day, weight, gastrointestinal endoscopy if indicated.
Hematology assessment: hemoglobin, white cell count, eosinophil count, platelets
Quality of life assessment: Skindex-29 if skin involvement, EORTC 30, FACT-BMT At each visit for extracorporeal photopheresis treatment.
Biochemistry: urea and electrolytes, liver function tests.
Hematology: full blood count

- Should be measured in **skin, oral mucosa and liver** where these organs are affected with cGVHD.

- The overall response should reflect the **most severely affected organ** but poor responses on other organs may also be considered.

Before

After

ECP in aGVHD

- Second-line therapy should be considered :
  - **Progressive aGVHD :** after 3 days
  - **Un-improving grade III/IV aGVHD**: after 1 week of persistent
  - **Persistent un-improving grade II aGVHD** : after 2 weeks

- British Society of Blood and Marrow Transplantation:
  - **After 5 days** of first-line therapy
  - **After 3 days** in those with progressive disease.

Extracorporeal Photopheresis (ECP) for Adults and Pediatric aGVHD

Acute GVHD

After 1 month

Complete clinical response:

1- Steroid dose of <20 mg/day methylprednisolone or 25 mg prednisolone.

2- May be able to stop ECP treatment after 8 weeks of therapy.

3- There is no need to taper the frequency of ECP before discontinuation of therapy.

Partial clinical response at 8 weeks:

Requiring steroid doses of >20 mg / day methylprednisolone or 25 mg / day prednisolone to continue with weekly cycles of ECP with weekly assessments and stop as soon as no further response.

Patients receiving therapy for lower GI aGVHD :

1- Often take longer to respond.

2- For those who show a response to ECP, a tapering schedule is advised, dropping to 2-weekly cycles after 8 weeks and then to monthly cycles according to response.

→ **Patients without at least a PR after 8 weeks:**

Should be considered for alternative therapy such as mesenchymal stromal cells.

Monitoring protocol

Initial response:

First two to three cycles of weekly Treatments :

- ✓ ASFA: after 2-3 week or 2-3 times of ECP.
- ✓ European Dermatology : after 2-3 week or 4-6 times of ECP .
- ✓ UK consensus statement : after 2-3 week or 2-3 times of ECP

Maximal responses:

- ✓ Often occurring after six to eight Cycles or after 6-8 week.
- ✓ If early improvements are not observed, then ECP therapy is unlikely to be successful.

Treatment Schedule

ASFA recommended:

- ✓ One cycle per week until diseas response.
- ✓ Then tapered to alternate weeks before discontinuation.

European Dermatology guidelines:

- ✓ 2–3 times per week with rapid taper of Corticosteroids
- ✓ ECP may be discontinued at CR.

UK consensus statement :

- ✓ One cycle of treatment (ECP on two consecutive days) per week
- ✓ Minimum of eight cycles

Before ECP

After ECP

Fig. 1. Differences between skin manifestations of aGVHD before and after ECP.

Product	Identifier	Cell therapy	n
MSC	NCT02359929	Autologous BM-derived MSC for the treatment of acute and chronic GVHD	24
	NCT02032446	Umbilical cord derived MSC in combination with pentostatin for steroid-refractory acute GVHD	47
	NCT03847844	Umbilical cord derived MSC for steroid-refractory acute GVHD	40
Treg	NCT02423915	Fucosylated Treg at day −1 pre-HCT to prevent GVHD	47
	NCT01795573	Donor Treg cells at day −2 pre-HCT to prevent GVHD	48
	NCT02749084	Donor Treg to treat refractory chronic GVHD	20
	NCT02385019	Donor Treg to treat refractory chronic GVHD	22
	NCT03683498	Donor Treg to treat ruxolitinib-refractory chronic GVHD	16
	NCT01903473	Donor Treg in combination with rapamycin to treat ruxolitinib-refractory chronic GVHD	35

Search terms: "graft versus host disease" and "MSC," "Treg," "ILC," "dendritic cells," "iNKT cells," MDSC," "CAR T cells," and "CHAR T cells." The latter 6 search terms did not yield any active studies.

BM, bone marrow; n, expected number of patients to be included in the trial.