Extracorporeal photopheresis: Review of technical aspects
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Abstract:
Extracorporeal photochemotherapy (ECP) is considered as an immune modulating therapy primarily targeting the T cells of the immune system. ECP induces an anti-inflammatory condition with tolerogenic responses without inducing a global immunosuppression state which is a typical feature of other therapeutic options such as steroids. Clinical indication of ECP has grown over time since its initial applications. Our review discusses the technical aspects of the concept of photopheresis with the available methods for its clinical applications.

Keywords:
Extracorporeal photopheresis, graft-versus-host disease, leukapheresis, T cells

Introduction
Extracorporeal photopheresis (ECP) is considered as an immune modulating therapy primarily targeting the T cells of the immune system. Edelson et al.[1] was one of the first scientists to develop ECP as a treatment for patients with cutaneous T-cell lymphoma (CTCL). In 1988, the US Food and Drug Administration approved the use of ECP as standard therapy for the treatment of patients with advanced refractory CTCL.[2] Afterward, ECP has been applied as a treatment modality for several autoimmune T-cell-mediated diseases such as pemphigus vulgaris,[3,4] systemic sclerosis,[5,6] rheumatoid arthritis,[7,8] Crohn’s disease,[9,10] and multiple sclerosis.[11] ECP is also recommended for managing solid organ allograft rejections,[12-14] acute and chronic graft-versus-host disease (cGVHD) postallogenic hematopoietic stem cell transplantation not responding to the conventional steroids and immunosuppressive therapy.[17-23]

The historical origin of ECP dates back to ancient Egypt where people with vitiligo ingested a plant (Ammi majus) found on the banks of the Nile river, bathed in the sun, and noticed recovery in melanin production.[24] Psoralen (8-methoxypsoralen [8-MOP]) is a photoreactive substance isolated from these plants. 8-MOP is an inert, naturally occurring compound and is activated by exposure to ultraviolet-A (UVA) irradiation.[25] Recent ECP treatment is derived from “oral Psoralen and UVA rays” (PUVA) applied in dermatology. ECP was originally meant “extracorporeal photochemotherapy,” the similar to “cutaneous photochemotherapy,” which was the name for PUVA treatment. Later, the term “extracorporeal photochemotherapy” was changed to “extracorporeal photopheresis,” without changing the abbreviation ECP.[25]

ECP is defined as a technique of manipulating white blood cell (lymphocytes) external to the body in a way that, when they are re-infused to the patient, causes downregulation of lymphocytes (majorly T-lymphocyte activity) in patients.[24] Since the psoralen is now administered only to the collected white cells (by leukapheresis) instead to the whole body, hence, the total dose needed is typically dropped down to 0.25% of the oral form.

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Technical Aspects

There are two methods to perform ECP procedure [Figure 1]. Both the methods differ in the devices used for the collection of lymphocytes as well as for UVA irradiation. They can be classified into “on-line” and “off-line” methods based on the type of devices used to perform ECP [Table 1].

The “on-line” method can be performed on either the Therakos UVAR XTS or the Therakos CELLEX Photoapheresis System (Therakos, Raritan, NJ, USA). In this method, all the phases (leukapheresis, photoactivation, reinfusion) are achieved sequentially in extracorporeal circulation using a single instrument.[19] The instrument separates and collects the lymphomonocyte fraction (buffy coat) through centrifugal force while the other components (red cells and plasma) are returned back to the patient. The buffy coat fraction remains in the system where it is treated with 8-MOP and is subsequently then exposed to the UVA. The time of photoactivation is automatically calculated by the instrument based on the volume, on the hematocrit of lymphomonocytic fraction, and on the residual power of the UVA lamps.[26,27] Finally, treated lymphocytes are reinfused back to the patients.

The “off-line” method was developed in 1994, when Andreu et al.[28] proposed to modify the ECP procedure where all the phases of ECP occur in a sequential manner using separate equipment [Figure 1]. The leukapheresis is performed using continuous flow cell separator using a sterile disposable kit. Under sterile conditions (laminar flow cabinet), the collected cells have to be transferred to an appropriate special bag in which the 8-MOP is added and after irradiation, cells are reinfused into the patient, using a standard transfusion filter.[28] At present, various devices (CE marked) are used for irradiation in an “off-line” method such as theraflex-ECP (MacoPharma, Mouvaux, France) and photo immune therapy system (Med Tech Solutions, Modena, Italy). This method was found to be safe, reproducible, and effective and is becoming more common in Europe than in USA where only “in-line” method is available.

“Off-line” method may offer some advantages on the “in-line” method such as applicability to pediatric patients as equipment for “in-line” method have a higher extracorporeal volume hence limiting its applications. In “off-line” methods, new apheresis devices used offer higher collection efficiency of lymphocytes resulting in greater cellular harvest which can be extracted in less time and with low concentration of anticoagulant exposure. Although greater number of cells processed and irradiated in ECP, they have yet not shown proportionate increase in the therapeutic response.

Mechanism of Action

Mechanism resulting in the therapeutic activity of ECP is still under investigation, but there are numerous theories which are proposed to support the effect on the collected lymphocytes. ECP is postulated to affect primarily the T-cell component of the immunological activity which may result in upregulation of the immune system in cases of CTCL[13] and can also cause downregulation in cases of graft-versus-host disease (GVHD) posttransplant and in cases of solid organ allograft rejection.[14] The effect of ECP is due to (a) multiple changes induced in the mononuclear cells by the environmental changes of harvested cells, (b) cellular changes due to treatment of cells by psoralen and exposure to UVA rays and finally, and (c) changes in cytokine environment in the recipient following the reinfusion of the treated cells [Figure 2].

Extracorporeal surface exposes the cells to the plastic material inducing activation (rolling mechanism) and differentiation of mononuclear cells into dendritic cells (DCs).[29] Other environmental changes inducing cellular changes and activation are decrease of temperature in the circuit, centrifugation in the cell separator resulting in modification of cellular structure as well as pH modifications due to anticoagulation.[25,30,31] Furthermore, UVA irradiation of mononuclear cells in the presence of 8-MOP induces antigenic modifications and cell membrane damage. The photoactivated 8-MOP binds to pyrimidine bases of DNA resulting in cross-linking of the two DNA strands and further induces the treated cells to apoptosis along with activating antigen presenting cells (APCs).[14,29] Up to 5%–15% of treated mononuclear cells undergo apoptosis on reinfusion and mainly localize in spleen or liver where they are phagocytized by APCs.

Lamioni et al.[32] studied the effect of ECP in cGVHD patients where on analyzing viability of leukocytes
showed 60% of both T-lymphocytes (CD3+) and monocytes (CD14+) underwent apoptosis after 48 h on leukocyte culture. Similarly, many authors showed the induction of apoptosis in T cells and monocytes following the infusion of treated cells as well as functional modifications with phenotypic alterations. In vitro analysis also showed that ECP-induced differentiation of monocytes to DCs can not only be achieved UVA irradiation and plastic surface but presence of cytokines is also essential.

On reinfusion of irradiated cells, the cytokine network shifts with increase in inhibitory cytokines (interleukin [IL]-10, IL-4, transforming growth factor beta [TGF-β]) and decrease in inflammatory cytokines (IL-12, interferon-α, tumor necrosis factor-α, IL-1) resulting in shift from Th1 to Th2 response. Therefore, ECP reduces cell-mediated immune activity by inducing apoptosis of mononuclear cells (lymphocytes) after treating with photoactivated psoralen, phagocytosis of these apoptotic lymphocytes by APCs, switch of APC activity in favor of anti-inflammatory cytokines and production of antigen-specific T-regulatory cells.

**Scope in India and Its Application**

Allogenic bone marrow transplants (BMTs) are increasingly offered by tertiary care centers across India. Now with the availability of indigenous unrelated donor marrow registries and hematologists exploring the option of haploidentical transplants, the field of clinical hematology is growing with each passing year. As we grow, our centers will have to offer treatment options for post-BMT complications such as GVHD as well. ECP is a novel treatment option for patients with GVHD and our center is one of the first centers to install “off-line” ECP setups in India. At present, steroids are the only treatment option available to treat these complications, ECP is considered more efficacious than steroids as it offers reduction in alloreactivity without global immunosuppression in both acute as well as cGVHD. At present, there are various protocols for initiating ECP treatments, but none of them have been standardized.

Clinical indication of ECP has grown over time since its initial applications. Table 2 discusses the current indications as per the American Society of Apheresis guideline 2016. ECP induces an anti-inflammatory condition with tolerogenic responses without inducing a global immunosuppression state which is a typical feature of other therapeutic options such as steroids. Patients undergoing this therapy respond normally to vaccination and illness. As well as there is no evidence that patient on such therapy is at an increased risk of infections or malignancy.

**Regimens of ECP**

There are numerous published protocols for photopheresis sessions, mostly biweekly/weekly cycles are considered. These cycles are gradually tapered and tailored as per indication, institution, and clinical response. Each cycle of ECP consists of two sessions of ECP on consecutive days, with clinical assessment for the response every week in acute GVHD (aGVHD) and every 8–12 weeks in cGVHD. ECP has also shown benefits in prophylactic use for patients undergoing cardiac transplants as well as BMT with similar regimens.

Number of lymphomononuclear cells treated with each ECP cycle is one of the major challenges in standardization of this treatment modality. At least 1 × 10^9/L cells in the peripheral blood are required before initiating the ECP therapy. There is still no recommendation of minimum number of cells to be processed per ECP session or amount of blood volume to be processed for collection of cells. They have been reported from as low as 3.3 × 10^9 (mini ECP) up to 2.8 × 10^10 with adequate clinical response. Mini ECP is another form of “off-line” method of ECP where whole blood is collected from the patients (majorly children) and buffy coat is prepared from that, which is further treated with 8-MOP before irradiating and reinfusing it back.

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**Table 1: Comparison between “In-Line” and “Off-Line” Method of ECP**

| Parameters                  | UVAR-XTS                  | “In-Line” Method                        | “Off-Line” Method                  |
|-----------------------------|---------------------------|----------------------------------------|------------------------------------|
| Main Principle              | Integrated system on single instrument | Integrated system on single instrument | Separate Instrument for each step  |
| UV-A Dose                   | 1.2 J/cm²                 | 1.2 J/cm²                              | 2 J/cm²                            |
| Apheresis Technique         | Discontinuous             | Discontinuous or Continuous             | Continuous                          |
| Venous Access               | Single                    | Single or Double                       | Double                             |
| Anticoagulant               | Heparin                   | Heparin                                | ACD                                |
| QC of cells                 | No                        | No                                     | Yes                                |
| Duration                    | 1.5-2 hours               | 1.5-2 hours                            | 3-4 hours                          |
| Pediatric Use               | No                        | Yes;                                   | Weight >40 Kg                       |

ACD = Acid Citrate Dextrose, QC = Quality control
Table 2: Indications for extracorporeal photopheresis as per the American Society of Apheresis guidelines 2016[37]

| Category | Indications |
|----------|-------------|
| Category I (disorders where apheresis [photopheresis] is accepted first line of therapy) | CTCL; mycosis fungoides; Sezary syndrome (erythrodermic) |
| Category II (disorders where apheresis [photopheresis] is accepted second line of therapy) | Cardiac transplant (cellular or recurrent rejection and rejection prophylaxis); Chronic GVHD (skin and nonskin); Acute GVHD (skin and nonskin); Lung allograft rejection (bronchiolitis obliterans syndrome); Cardiac transplant (rejection prophylaxis); Pemphigus vulgaris (severe) |
| Category III (disorders where optimal role of apheresis [photopheresis] therapy not established) | Psoriasis; Atopic (neuro-) dermatitis; Scleroderma (systemic sclerosis); Crohn’s disease; CTCL (nonerythrodermic); Nephrogenic systemic fibrosis |
| Category IV (disorders where photopheresis to be ineffective) | Dermatomyositis/polymyositis |

CTCL = Cutaneous T-cell lymphoma, GVHD = Graft versus host disease

Validation

Validation of 8-MOP and irradiation should ideally be done using functional tests. These tests should be done with the first two sessions of ECP in the first cycle (as further from next cycle, it will be difficult to prove any difference), change of UVA illuminator, or cell separator (especially in the cases of off-line ECP). Validation of irradiation could be assessed by evaluating the change in the number of 7-aminoactinomycin D (7-AAD)+ cells within 72–96 h post-ECP.[23]

Patient Preparation for ECP and Follow-Ups

Each session of ECP is an invasive procedure (depending on the type of method used). Patient variables to be assessed for the initiation of therapy apart from indications include hemoglobin level (>10 g/dl), platelets count (>20 × 10^9/L), weight (>20 kg; specifically for “In-Line” method). Posteach session, the patient should be prescribed high SPF sun cream (15 or above) and UVA sunglasses (for 48 h post each session), to avoid the adverse effect of 8-MOP used. Patients with known sensitivity to psoralen compounds are contraindicated for such therapies as well as patients having aphakia (risk of retinal damage), pregnancy, and uncontrolled infection.

There are very few adverse reactions reported with each ECP sessions. They can be related to either leukapheresis such as reactions to volume shift in the extracorporeal circuit, citrate toxicity due to anticoagulant used, or bleeding from the cannula sites. Reaction related to exposure to psoralan can include increased urinary output, metallic taste, and sparkly bits in the eyes. On re-infusion of the ECP products, some patients complain of mild fever, tiredness, and hematuria (due to reinfusion of red blood cell postexposure to 8-MOP).

Need of ECP

With the growth of allogenic transplants, there is a corresponding increase in the incidence of aGVHD, reported up to 10%–80% depending upon the type of donor and degree of human leukocyte antigen matching. Steroids have been the mainstay of treatment and prophylaxis of aGVHD. Use of immunosuppressive drugs, monoclonal antibodies (directed against T cells and their receptors), mesenchymal stromal cells, and ECP are considered in cases of failure or resistance to steroids in cases of aGVHD.[41] Although none of these measures have been found to be superior to another in controlled trials, ECP offers advantages with induction of tolerance in the immune system without suppressing it.

Steroids are also the mainstay for managing cGVHD, it is often combined with calcineurin inhibitors. For steroid resistant cGVHD, there is still no consensus between mycophenolate mofetil, pentostatin, and tyrosine kinase inhibitors.[42] ECP is considered as an efficient mode of therapy shown by few controlled trials.[43,44]

Conclusion

Extracorporeal photopheresis (ECP) is an immune modulating therapy leading to reduction in alloreactivity and promotion of immune tolerance to self. ECP is able to maintain the integrity of both naive and memory response of the patients.[23] It leads to improvement in quality of life in patients who respond to the therapy whereas prediction of nonresponders is difficult; hence, it is important; the future researches should focus on standardization of the ECP protocols, prognostic markers to better selection of patients, and optimization of the therapy. This therapy offers great hope to patients who do not respond to the standard of care and thus has become an essential part of any tertiary care center.

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Conflicts of interest
There are no conflicts of interest.

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