Extracorporeal Photopheresis: How, When, and Why

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Extracorporeal photopheresis (ECP) is a well-tolerated procedure that suppresses T-lymphocyte activity in a clonally-specific way. It is an effective therapy that has established indications in the management of cutaneous T-cell lymphoma, graft-versus-host disease and some scenarios of solid-organ transplant rejection. It is being used increasingly around the world. Its applications are evolving, including exploration of its potential for treating autoimmune diseases where cytotoxic T-cell-mediated mechanisms appear to be involved, such as Crohn’s disease. This article reviews scientific insights into its mechanism of action on the immune system, details of the clinical procedure, its clinical applications in various diseases, and the current evidence for its efficacy and place in medical therapeutics. J. Clin. Apheresis 26:276–285, 2011.

INTRODUCTION

Extracorporeal photopheresis (ECP) is a method of manipulating white blood cells (WBCs) external to the body in a way that, when they are reinfused to the patient, causes down-regulation of T-lymphocyte activity. ECP was first developed for the treatment of cutaneous T-cell lymphoma (CTCL) by Edelson et al. [1], who established its importance in the treatment of that disease. Thereafter ECP began to be applied to diseases in which tissue injury is mediated by cytotoxic T-cells. This type of immune injury is seen in the cellular rejection of solid-organ transplants, in graft-versus-host disease (GVHD) following blood marrow transplantation, and in a few autoimmune diseases where cell-mediated mechanisms predominate. In contrast, it is a different mechanism, antibody-mediated injury, which accounts for the “humoral” form of transplant rejection and the majority of autoimmune diseases. Both antibody-mediated and cell-mediated damage can be treated with corticosteroid and immunosuppressive drugs. However, only the antibody-mediated mechanism responds to plasmapheresis therapy, as has been confirmed by extensive clinical experience over several decades [2,3]. Photopheresis (ECP), on the other hand, since it targets the cell-mediated mechanism, is gaining recognition as an important treatment for several complications of transplantation, and is being tried also for some diseases in which cell-mediated autoimmunity is implicated, for instance Crohn’s disease.

DEVELOPMENT OF ECP

ECP utilizes psoralens, which are plant compounds that are activated by sunlight and have been used topically in the treatment of skin diseases since ancient Egyptian times. In the modern era, systemic administration of psoralens was first utilized for PUVA, a treatment named for psoralen plus ultraviolet “A” (UVA) light. It is used for psoriasis and some other skin diseases. In PUVA, the patient takes 8-methoxy-psoralen (8-MOP) orally and then stands in a light box while affected skin is dosed with UVA light.

ECP treatment was derived from PUVA. ECP originally meant “extracorporeal photochemotherapy,” the same noun as in “cutaneous photochemotherapy,” which is the other name for PUVA treatment. Later the term “extracorporeal photochemotherapy” was replaced by the term “extracorporeal photopheresis,” without changing the abbreviation ECP. In the original form of ECP, the patient took 8-MOP orally and then underwent white cell apheresis; the collected white cells were treated with UVA light and subsequently returned to the patient. Modern ECP is different only in that 8-methoxy-psoralen can now be given by injection, so it is added to the collected white cells before UVA exposure. Since the psoralen is now administered just to the collected white cells instead of to the whole body, the total dose needed is typically only 0.25% of that used in oral form.

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Received 6 June 2011; Accepted 5 July 2011
Published online 5 September 2011 in Wiley Online Library (wileyonlinelibrary.com).
DOI: 10.1002/jca.20300

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This greatly reduces the posttreatment risk from photo-sensitization, although the patient must still take precautions. The mechanism of action of ECP is described in detail later. In brief, photoactivated psoralens cause cross-linking of DNA in cell nuclei. This damage induces lymphocytes to undergo programmed cell death (apoptosis). When these lymphocytes are returned to the patient, both their clonal identity and the apoptotic cell-surface markers are recognized by the immune system, which through a series of signals results in the down-regulation of active T-cell clones.

**PERFORMANCE OF ECP**

ECP is usually performed on machines designed specifically for photopheresis procedures, although in some parts of the world other centrifugal apheresis systems have been coupled to UVA irradiation devices for the same purpose. In the USA, there are two systems approved by the FDA (Federal Drug Administration), both made by the same manufacturer. The Therakos® UVAR™ XTS™ machine has been the predominant instrument for many years. This incorporates a discontinuous centrifugation system (Latham bowl) for white cell separation, and uses single-needle venous access. In 2009, the Therakos® CellEX™ was introduced, which employs an advanced continuous-flow centrifuge and allows either single- or double-needle access. All modern systems employ a disposable, presterilized plastic blood circuit that integrates the centrifuge insert and photoactivation chamber with all other components of the blood flow path.

The ECP process commences with centrifugal separation of the incoming blood, collecting the WBCs and returning the red cells (RBCs) and plasma to the patient. Adequate WBC collection usually requires 3–6 cycles on the discontinuous centrifugal system, and the last cycle is usually an elutriation centrifugation to further purify the WBC product. A low hematocrit in the WBC product is important because RBC contamination interferes with UVA light access to the WBCs. The photoactivation stage occurs after the injection of psoralen into the WBC product. Usually this is 8-MOP, which has the generic drug name methoxsalen, in a 20 mcg/mL solution at a dose of 0.017 mL per mL of WBC product. After mixing, the WBC product circulates through the irradiation chamber between two banks of UVA light bulbs, which produce UVA light of 352 nm wavelength. The duration of photoactivation is determined automatically in modern systems, and depends on the luminosity of the bulbs (which declines with usage) and the optical density of each WBC preparation. Typical exposure times are from 25 to 45 min. On completion of the photoactivation process, the WBC product is infused back to the patient, and the procedure is terminated.

Access to the blood stream for ECP is often via a needle placed in an antecubital vein. The Therakos UVAR XTS™ system works satisfactorily using a single needle at a blood flow rate of only 25–30 mL/min, which does not require a particularly large arm vein. In patients whose arm veins are insufficient, jugular catheters can be used, although there has been success in avoiding catheters by instead using subcutaneous ports such as the AngioDynamics® Vortex®. However, while lower flow access sites have some advantages, a higher blood flow allows the procedure to be run more quickly. The Therakos CellEX™ machine achieves treatment completion times of the order of 1.5 h, compared to twice that with older systems.

Most treatment regimens are based on the use of two ECP procedures on successive days, repeated every 2 weeks, although the frequency may be more or less depending on the desired intensity of treatment. The pairing of treatments on adjacent days is a relic of the historical use of high-dose oral psoralen, since much of the ingested dose would remain from one day to the next. This pairing is no longer needed with low-dose psoralen injection, but the efficacy of treatment has been established in this tradition, which therefore continues in most instances. The optimal timing and pattern of treatment is not really known, since comparative clinical studies are lacking.

**MECHANISM OF ACTION OF ECP THERAPY**

An understanding of the mechanism of action of ECP has been pieced together from multiple lines of evidence obtained by laboratory research. Key aspects of this evidence are reviewed below. The story that has evolved can be appreciated in outline by comparing the cellular events during a new T-cell immune response to those that occur when ECP-treated white cells are reinfused and taken up by the immune system (Fig. 1). Central to both is the role of antigen presenting cells (APCs). These are pivotal in determining whether the cellular immune system will be tipped toward an active immune response or toward unresponsiveness (“tolerance”). It turns out that apoptotic T-cells, which are generated by ECP treatment, move the balance toward unresponsiveness, shutting down previously active cellular immune responses. This suppressor effect of T-cell apoptosis may be a normal component of immune system signaling, one of several that move the balance of immune responsiveness toward tolerance. ECP simply exploits and amplifies this signal by introducing excess apoptotic cells.

During ECP, photoactivated 8-MOP causes cross-linking of DNA within the nuclei of lymphocytes, leading to apoptosis of these cells. When the treated WBC product is reinfused, APCs recognize the cell-surface markers of apoptosis, which modify the response of the APCs. APCs that have picked up apoptotic T-cells interact in the spleen with cells of the same antigen-specific lineage. The suppressive effect on cellular immunity is executed by the production of regulatory
T-cells (T-regs). These T-regs are also antigen-specific, meaning they correspond to the same clones of cytotoxic T-cells that were present in the apoptotic cell product of ECP. This makes ECP suppressive only for cellular immune responses that are active at the time that ECP is performed, since most of the T-cells collected in the WBC product for ECP are from the expanded clones that predominate in the bloodstream during an active immune response.

The science that underlies this account of events is drawn from many sources. Evidence that apoptotic cells inhibit the production of pro-inflammatory cytokines by APCs includes the work of Morelli et al. [4]. They demonstrated reduced levels of IL-1α, IL-1β, and IL-6, and reduction in mRNA for IL-12 and TNFα, when dendritic cells (APCs) were incubated with apoptotic cells. Finiania et al. proposed a mechanism of action of ECP in GVHD which included the uptake of apoptotic lymphocytes by APCs, and also reviewed the role for ECP in promoting differentiation of dendritic cells into mature APCs [5]. Lamioni et al. analyzed mononuclear cells in the blood of children receiving ECP for chronic heart and lung transplant rejection [6]. By comparing samples collected before and after treatment, they showed that ECP is associated with a change in dendritic cell phenotype, and with the appearance of increased numbers of T-regs. Maeda et al., using a hypersensitivity model in mice, showed that apoptotic cells produced by ECP induce antigen-specific T-regs, and that these T-regs, when subsequently transferred to other syngeneic mice, create the same antigen-specific immune suppression in the recipient [7]. This same group went on to demonstrate that ECP also generates the inhibitory cytokine IL-10, another piece of the switch of immune system balance from active immunity toward nonreactivity [8].

The key steps, therefore, by which ECP reduces cell-mediated immune activity, are apoptosis of mononuclear WBCs (mainly lymphocytes) after treatment with photoactivated psoralen, phagocytosis of these apoptotic lymphocytes by APCs, a switch in APC activity in favor of antiinflammatory cytokines and away from pro-inflammatory cytokines, and production of antigen-specific T-regulatory cells.

The importance of T-regs in this effect has been further demonstrated in animal models of disease. George et al. showed that ECP extends solid organ graft survival, even in fully histo-incompatible strain combinations.

Fig. 1. Possible mechanisms by which photopheresis (ECP) down-regulates T-cell activity. On the left side above are depicted the events that lead to an active cellular immune response. Uptake of a foreign antigen by APCs is followed by antigen presentation to T-cell clones that have antigen-binding sites that are specific for that antigen. Pro-inflammatory cytokines are secreted which stimulate clonal expansion of specific cytotoxic T-cells (CTLs). These then go on to mount a cellular immune attack on the foreign antigen. In the right panel are shown the effects of ECP (photopheresis). Active cytotoxic T-cells are rendered apoptotic by ECP, which when reinfused are taken up by APCs. The APCs have receptors that recognize apoptosis-specific proteins on the T-cell. This signal causes the APCs to produce antiinflammatory cytokines and to promote the development of regulatory T-cells (T-regs), which suppress the active cellular immune response. The effect is clonally specific. Abbreviations: ECP = extracorporeal photopheresis; APC = antigen-presenting cell; Ag = antigen; CTL = cytotoxic T-lymphocyte; “A” = apoptotic cell (T-lymphocyte); T-reg = regulatory T-lymphocyte. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
with no immunosuppression. The effect can be transferred to untreated recipients using minimal numbers of CD4(+)CD25(+) T-cells, indicating that T-regs play a key role [9]. Gatza et al. were able to reverse established GVHD by transferring T-regs from ECP-treated donors [10].

ADVANTAGES AND LIMITATIONS OF ECP THERAPY

The antigen-specificity of the immune down-regulation achieved by ECP confers advantages as compared to other therapies for allo- and auto-immune diseases. Immunosuppressive drugs and corticosteroids globally reduce cellular immune function and are notoriously permissive of opportunistic infections, as well as having other chemical side effects. Because ECP appears to inhibit only clones that have already been activated, it may not impair responses to subsequent antigenic challenges. Thus, for instance, active transplant rejection may be targeted without significantly increasing the risk of future infectious complications. Nevertheless, if an infectious organism is already present, such as a fungus residing in a transplanted lung, ECP theoretically may reduce immune control over the fungus at the same time as reducing the immune attack on the transplanted organ.

There are few contraindications to ECP therapy. Allergy to methoxsalen (8-methoxy-psoralen) is one. Another is pregnancy, because methoxsalen may cause fetal harm. Psoralsen may also cause a temporary reduction in female fertility [11]. Thus women of child-bearing potential should be counseled before embarking on a course of ECP. Methoxsalen administered orally for PUVA therapy is carcinogenic, but because the dose of methoxsalen in modern ECP therapy is approximately 200 times less and the skin is not exposed to high dose UVA light, the risk of developing skin cancer is thought to be much lower with ECP. Nevertheless, the presence or history of basal cell carcinoma is a specific caution, and requires close observation and treatment. A history of a light-sensitive disease is regarded as a contraindication to methoxsalen use, as is aphakia (absence of the lens of the eye) because of the significantly increased risk of retinal damage from ambient light [12]. Since platelet losses can occur in the machine, a starting platelet count of at least 20,000 is required.

All patients must take precautions while undergoing ECP treatment. The WBC product that returns to the patient at the end of treatment contains psoralen, which causes photosensitization. Wrap-around sunglasses for 24 h after each treatment are obligatory whenever in direct or indirect sunlight, whether outdoors or exposed through a window. The patient must also stay indoors as much as possible for 24 h, and be fully covered when outdoors. Dietary discretion before ECP is advised because a high fat meal that renders the plasma opalescent may confuse optical sensing of the interface between plasma and cells, thus disrupting automated WBC collection. It may also interfere with penetration of the WBC product by UVA light during photoactivation.

As with all extracorporeal blood treatments, the patient’s ability to withstand volume depletion has to be assessed. The Therakos UVAR XTSTM system employs a Latham bowl centrifuge, which continues to fill with blood while plasma and white cells are collected, and does not stop drawing blood from the patient until the bowl is filled with packed red cells. Thus to achieve the same packed-cell volume in the centrifuge, an anemic patient has to put out more whole blood into the machine than a nonanemic patient. Thus a hematocrit <33% is a contraindication, use of the larger (225 mL) Latham bowl is not advised with a hematocrit <36%, and a body weight <45 kg usually makes the use of this machine inadvisable. The newer Therakos CellEXSTM machine does not have these limitations.

Overall, ECP is regarded as a safe and well-tolerated treatment. The most common complication is transient hypotension due to volume shifts. Transient fevers of 37.7–38.9°C have been reported 6–8 h after treatment. In patients who need an indwelling vascular catheter, the risk from ECP itself is dwarfed by the potential for catheter-related infections and thrombosis.

CLINICAL APPLICATIONS OF ECP THERAPY

In the USA, photopheresis (ECP) therapy is approved by the FDA only for the treatment of CTCL. Thus all other uses are “off-label” applications. However, this constraint has only modestly inhibited the successful expansion of ECP to treating an increasing range of serious illnesses. The United States Medicare system now recognizes and pays for ECP not only for CTCL, but also for GVHD and heart transplant rejection. The American Society for Apheresis (ASFA) has published detailed practice guidelines for all types of apheresis, including most of the indications for which ECP is now being used [2] (see Table I). These indications are discussed in the following sections.

ECP FOR CTCL (CUTANEOUS T-CELL LYMPHOMA)

CTCLs are a group of malignant T-cell neoplasms that infiltrate the skin. Mycosides fungoides is the most common form, usually indolent, and often treated with PUVA therapy. More aggressive are Sezary syndrome and CD30-negative forms. Sezary syndrome has a 3-year median survival rate from diagnosis, although diagnosis is often delayed. ECP has been repeatedly shown to be of benefit in CTCL. Edelson et al.’s first series reported response in 27 of 37 patients, with the reduction in cutaneous involvement averaging 60% [1].
Several studies showed doubling of the survival time in erythrodermic CTCL when treated with ECP. A review and meta-analysis in 2003, combining 19 series of cases, revealed an overall 55% response rate to ECP, with a complete response (CR) in approximately 15% of patients [13]. In the same year, management guidelines were published in Britain recommending ECP as first-line treatment at Stage III of CTCL, defined as T4 N0/1 (erythroderma, with no palpable nodes or nodes with negative histology) [14]. Approaches combining ECP with other available therapies have been reviewed recently [15]. Although ECP is an undisputed part of the routine treatment of CTCL, many United States photopheresis providers report that only approximately 5–10% of their ECP usage is for this indication (personal communications). A typical treatment regimen consists of two ECP procedures on successive days repeated at 2-week intervals for at least 6 months.

### ECP FOR GVHD

After allogeneic hematopoietic stem cell transplantation (formerly bone marrow transplantation), acute GVHD occurs in 20–50% of patients, and chronic GVHD occurs in 30–50% of engrafted survivors. The etiology includes alloreactivity of the donor marrow to host antigens. GVHD is usually treated with steroids and immunosuppressive drugs, but ECP has also proven highly effective and has become a frequent part of the treatment program for selected patients in most centers. A meta-analysis in 2002 reviewed 31 studies using ECP, amassed 76 patients with acute GVHD and 204 patients with chronic GVHD [16]. The acute GVHD patients received ECP for 1–24 months. Skin manifestations regressed in 83% (CR in 67%). Complete regression of liver disease was reported in 38%, and of gastrointestinal disease in 54% of the patients. In patients with chronic GVHD in this meta-analysis, ECP treatment times ranged from 3 to 40 months, and response rates were: cutaneous 75–76% (35–38% CR), lung 48%, liver/cholestasis 39%, and oral lesions 63%. There was a tendency to better results with earlier treatment. The overall 1-year patient survival was 79% (vs. 56–71% with conventional treatment).

A subsequent prospective study of acute GVHD in steroid-refractory and steroid-dependent patients confirmed the excellent results of ECP therapy in this form of disease [17]. In 59 patients, ECP was performed on two successive days every 1–2 weeks initially, and every 2–4 weeks after some improvement occurred. Complete resolution of acute GVHD was seen in 82% of patients with cutaneous disease, in 61% with liver disease, and in 61% with gut disease. These remissions were rapid, within a median of four cycles (eight treatments). Remissions were durable, and the overall survival was improved. Similar results were observed by Messina et al. in 33 children with acute GVHD [18].

The effects of ECP have been positive also in further studies of chronic GVHD, even though many cases have long-standing, entrenched pathology. Steroid-resistant or steroid-dependent cutaneous disease showed some improvement with ECP in 80% of 25 cases reported by Foss et al. [19], and in 56% of 32 cases reported by Apsarvanthanarax et al. [20]. Most patients in these series needed to continue long-term therapy, although both studies noted that a majority of patients were able to achieve a meaningful reduction in their steroid dose. The pediatric series of Messina et al. included 44 children with chronic GVHD, in whom ECP was followed by complete remissions in 15 (44%) and partial remission in 10 (29%) [18]. A prospective study of 95 adults with chronic cutaneous GVHD compared conventional therapy to conventional therapy plus ECP (in an aggressive regimen: three treatments in the first week, then two per week for 12 weeks, then two every other week for another 12 weeks) [21]. Complete remissions occurred in 40% of ECP treated patients versus 10% with conventional therapy alone (P = 0.0024). Response rates in other manifestations of chronic GVHD are not so well documented, although a retrospective study of ECP treatment in 71 patients showed that the best response rates were seen with cutaneous, hepatic, oral, and eye disease [22]. It is of note also that the devastating complication of lung involvement (bronchiolitis obliterans) in chronic GVHD also responds to ECP [22,23]. The response rate to ECP is similar to that of bronchiolitis obliterans in the setting of lung transplant rejection.

### ECP FOR HEART TRANSPLANT REJECTION

Early case reports and series suggested that ECP could reverse heart transplant rejection and reduce the...
rate of rejection episodes among patients at high-risk, and might allow reduction in standard immunosuppressive doses, thus minimizing associated morbidity and mortality [24–28]. In 1998, Barr et al. reported a prospective randomized study in which 27 patients received standard therapy and 33 received standard therapy plus ECP on two successive days every 2 weeks for 6 months [29]. This showed fewer rejection episodes in the ECP group (mean 0.91 vs. 1.44), and fewer patients with recurrent episodes (six patients in the ECP group experienced two or more rejections vs. 13 in the standard therapy group). A multicenter trial in 23 patients was unable to show a difference in acute rejection episodes; however, despite the small number of subjects, the ECP group demonstrated significantly less intimal thickening of the coronary arteries at 1 year (0.23 vs. 0.49 mm) and at 2 years (0.28 vs. 0.46 mm) [30]. A retrospective analysis at the University of Alabama of 343 consecutive heart transplants (excluding lymphoid irradiation cases) showed that ECP added to conventional therapy for 36 patients at high-risk of rejection resulted in a reduced rate of hemodynamic compromise, and fewer-than-expected deaths from rejection [31]. The standard protocol for ECP in heart transplant recipients at the University of Alabama is initially more intense, comprising pairs of treatments weekly for the first month before reducing to every 2 weeks, then later reducing to monthly pairs of procedures. ECP is now used in many heart transplant centers for the treatment and prevention of cellular rejection episodes.

A further therapeutic possibility arises from recent work in Beijing which found, after heart transplantation in humans, that ECP can produce not only apoptotic lymphocytes of recipient origin, but also apoptotic lymphocytes of donor origin, and that these also can induce antigen-specific T-regs in the recipient [32]. This opens the door to the possible use of ECP-treated donor lymphocytes to induce tolerance.

**ECP FOR LUNG TRANSPLANT REJECTION**

Lung transplant rejection in its acute form can be recurrent, and in its chronic form creates the pathological process known as bronchiolitis obliterans, which is a progressive disease with a bad prognosis. Early case series documented improvement or stabilization in several patients with ECP therapy [33–37]. Two large single-center studies have now been reported describing the effect of ECP treatment on recurrent acute rejection and progressive bronchiolitis obliterans syndrome after lung transplantation [38,39]. In both studies the rate of decline of lung function over time was expressed as the rate of change of the FEV1 (forced expiratory volume in 1 s) in milliliter per month. In the Zurich series, 24 patient received ECP treatments in pairs on successive days every 4–6 weeks, and pretreatment function was compared with function after 12 pairs of treatment were completed [38]. In the St. Louis series, 60 patients received ECP on successive days in five pairs in the first month (10 treatments), in pairs every 2 weeks for the next 2 months (8 treatments), and in pairs every month for the next 3 months (6 treatments) [39]. Results were analyzed before and after this 6 months of ECP treatment. In both series, patients with bronchiolitis obliterans showed a marked slowing in the mean rate of decline of lung function, from 112 mL/month to 12 mL/month in the Zurich series ($P = 0.011$), and from 116 mL/month to 29 mL/month in the St. Louis series ($P = 0.0001$). In the St. Louis series, 25% of patients actually improved in the 6 months of treatment, with a mean increase in their FEV1 of 20 mL/month. Several patients were observed out to 12 months of therapy. ECP treatment was well tolerated, and the only significant complications were related to indwelling venous access catheters (eight episodes of bacteremia and one thrombotic complication).

Both studies, thus, show worthwhile benefit from ECP, with a significant reduction in the rate of decline in lung function associated with lung transplant rejection. Like chronic GVHD, bronchiolitis obliterans is a chronic problem, and patients who respond to ECP may benefit from therapy over prolonged periods. Many lung transplant programs make routine use of ECP for patients who have biopsy-proven rejection or bronchiolitis obliterans.

**ECP FOR LIVER TRANSPLANT REJECTION**

Early reports of ECP in liver transplant recipients describe reversal of biopsy-proven rejection in all cases, and subsequent successful reduction of immunosuppressive medications in half the cases [40,41]. A special need exists in hepatitis-C liver transplant recipients, because minimization of the doses of corticosteroids and immunosuppressive drugs helps avoid progression of viral infection posttransplant, which is a significant cause of mortality. ECP, which is selective and does not reduce antibody-mediated defenses, is particularly attractive for treatment in this situation. Urbani et al. have reported results in 302 hepatitis-C liver transplant recipients, studied in three successive periods [42]. In the first period, 133 patients were transplanted, and none received ECP therapy. During the second period, 91 patients were transplanted, and ECP was used only as 3rd-line rescue therapy for biopsy-proven rejection. In the third period, all 78 patients had antivirals and ECP added to their maintenance drug regimen, with intensification of the ECP regimen if rejection occurred. It was found that immunosuppressive drug dosages could be successfully reduced with this protocol, and that the 18-month mor-
tality in this group was only 10%, significantly better than the prior two groups, whose 18-month mortality rates were 22% and 28%, respectively. No randomized prospective study of this use of ECP has yet been performed, but the approach appears promising. A further use of ECP prophylaxis was in 11 cases of ABO-incompatible liver transplantation in the same center, none of whom developed cellular rejection [43]. ECP is not yet in widespread use in liver transplant management, and further studies are needed.

**ECP FOR KIDNEY TRANSPLANT REJECTION**

There are only sporadic reports of ECP in the treatment of kidney transplant patients, despite the fact that the kidney is by far the most frequently transplanted organ. Early reports describe success in treating recurrent rejection with ECP [44–46]. ECP was also associated with significant improvement in renal function in renal transplant patients with acute rejection unresponsive to conventional antirejection therapy [47,48]. One study of prophylactic ECP in renal transplant patients showed induction of regulatory T cells in treated patients, and suggested that prophylactic ECP might reduce chronic kidney transplant rejection [49]. In a series of 10 patients, ECP was used together with methylnitrosolone and antilymphocyte globulin for problematic rejection; all 10 patients had durable resolution of the rejection episode, although three later died (two malignancies and one sepsis), and one graft loss was from recurrent disease [50]. Few if any clinical programs currently use ECP in their routine management of kidney transplant rejection.

**ECP FOR SCLERODERMA (PROGRESSIVE SYSTEMIC SCLEROSIS)**

Progressive systemic sclerosis (PSS) involves the skin (scleroderma) and internal organs. Initial reports suggested that skin involvement might be benefited by ECP treatment, but without evidence of improvement in internal organ involvement [51–54]. However, this was challenged by studies of long-term treatment (5 years or more of monthly pairs of ECP treatment) which reported improvement not only of skin thickening, but also in joint mobility, overall functional status, and even lung function status [55,56]. An early prospective trial, published in 1992, compared ECP and D-penicillamine treatment in patients with recent onset disease [57]. The assessing rheumatologist was blinded with regard to which treatment was being given. An improvement in skin severity score after 6 months of ECP was seen in 68% of patients receiving ECP, compared to 32% on D-penicillamine. A second prospective trial, of cross-over design, compared ECP to no treatment in 19 patients; the improvement in skin scores with ECP was insufficient to reach statistical significance [58].

The most recent prospective study sought to resolve this question in a randomized, double-blind, placebo-controlled design [59]. Sixty-four patients with recent-onset PSS were randomized to receive sham ECP versus real ECP. Although statistical significance was not achieved when comparing the outcomes in the two treatment groups with each other, serial measurements within each group showed skin scores had improved significantly after 6 months and 12 months of real ECP, but not significantly with sham ECP. Thus, while the two more recent trials showed only a trend, the first prospective study showed evidence of benefit from ECP. Informed opinion in this disease continues to diverge: some conclude that patients with cutaneous disease who start ECP early and maintain treatment for years are likely to benefit [15]. On the other hand, the ASFA clinical guidelines assign category IV, indicating that the evidence is sufficient to make the judgment that ECP is ineffective. However, the discussion on that point is brief [2].

**ECP FOR CROHN’S DISEASE**

Crohn’s disease is a T-cell mediated inflammatory disease of the intestine. Two small pilot studies suggested some benefit from ECP [60,61]. A recent multicenter prospective study evaluated ECP in 28 patients who had moderate to severely active Crohn’s disease and were refractory to or intolerant of immunosuppressive medications and/or anti-TNF therapies [62]. ECP was performed twice weekly for 4 weeks, then twice every other week for a total of 12 weeks (16 treatments total). The Crohn’s Disease Activity Index (CDAI) was used to assess clinical response. At 12 weeks, 50% of patients had responded, as defined by a reduction in CDAI score of at least 100 points, and all but one of these had attained the response within the first 6 weeks. Seven patients (25%) achieved remission at 12 weeks, as defined by a CDAI score below 150, and of 5 patients with open fistulae, 3 had fistula closure. Patients who responded were offered a further 12 weeks of ECP treatment twice every other week, and the 12 who entered this extension study maintained their response throughout this period. ECP treatment was well tolerated. A larger randomized prospective trial has now been initiated to determine the efficacy of ECP in severe Crohn’s disease.

**OTHER INDICATIONS FOR ECP THERAPY**

Nephrogenic systemic fibrosis (NSF), otherwise known as nephrogenic fibrosing dermopathy, occurs in patients with renal insufficiency who have received gadolinium, the contrast agent used in magnetic resonance imaging.
Before this etiology was recognized, the resemblance to scleroderma and eosinophilic fascitis prompted speculation of a cellular immune pathogenesis. ECP was tried, and case reports suggested possible benefit [62]. Steroid and immunosuppressive therapies have also been tried, but all have failed to produce convincing evidence of efficacy.

Anecdotal success has been reported with ECP in other skin diseases including atopic dermatitis and lichen planus [15]. Pemphigus vulgaris is an autoantibody disease amenable to treatment with steroids, immunosuppression, and plasmapheresis [3]; a rationale for the use of ECP is difficult to construct, although ECP has been used with apparent success [63].

The use of ECP in solid-organ transplantation has been extended into the realm of composite tissue allograft transplantation, specifically face transplantation. Two patients with second rejection episodes responded well to ECP, with remission from rejection [64].

**CONCLUSION**

In summary, ECP is a safe and well-tolerated therapy which works on the cellular immune system to reduce T-cell activity. It has a secure place as an effective treatment in CTCL, GVHD, and heart and lung transplantation. It has promise for other applications, including liver transplant rejection and Crohn’s disease.

**ACKNOWLEDGMENTS**

The contents of this review were presented at the September 2010 Therapeutic Apheresis Academy, University of Virginia, Charlottesville, VA.

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*Journal of Clinical Apheresis* DOI 10.1002/jca

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