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Minireview

The use of extracorporeal photopheresis in solid organ transplantation—current status and future directions

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ABSTRACT

Prevention and management of allograft rejection urgently require more effective therapeutic solutions. Current immunosuppressive therapies used in solid organ transplantation, while effective in reducing the risk of acute rejection, are associated with substantial adverse effects. There is, therefore, a need for agents that can provide immunomodulation, supporting graft tolerance, while minimizing the need for immunosuppression. Extracorporeal photopheresis (ECP) is an immunomodulatory therapy currently recommended in international guidelines as an adjunctive treatment for the prevention and management of organ rejection in heart and lung transplantations. This article reviews clinical experience and ongoing research with ECP for organ rejection in heart and lung transplantations, as well as emerging findings in kidney and liver transplantation. ECP, due to its immunomodulatory and immunosuppressive-sparing effects, offers a potential therapeutic option in these settings, particularly in high-risk patients with comorbidities, infectious complications, or malignancies.

Abbreviations: ABMR, antibody-mediated rejection; ACR, acute cellular rejection; APC, antigen-presenting cell; BKV, BK virus; BOS, bronchiolitis obliterans syndrome; cABMR, chronic antibody-mediated rejection; caABMR, chronic-active antibody-mediated rejection; caTCMR, chronic-active T cell-mediated rejection; CAV, cardiac allograft vasculopathy; CLAD, chronic lung allograft dysfunction; CMV, cytomegalovirus; CNI, calcineurin inhibitor; DNA, deoxyribonucleic acid; dnDSA, de novo donor-specific antibodies; DSA, donor-specific antibodies; ECP, extracorporeal photopheresis; eGFR, estimated glomerular filtration rate; FEV_1, forced expiratory volume in 1 second; HC, hemodynamic compromise; HLA, human leukocyte antigen; HTx, heart transplantation; IL, interleukin; irAE, immune-related adverse event; IS, immunosuppression; ISHLT, International Society for Heart and Lung Transplantation; iT35, induced regulatory T cell; KTx, kidney transplantation; LTx, lung transplantation; MDSC, myeloid-derived suppressor cell; MMF, mycophenolate mofetil; NK, natural killer; NKreg cell, natural killer regulatory cell; PTLD, posttransplant lymphoproliferative disorder; RAS, restrictive allograft syndrome; SOT, solid organ transplantation; SoC, standard of care; Teff, effector T cell; TGF-β, transforming growth factor beta; Th, helper T cell; Treg, regulatory T cell; TNF, tumor necrosis factor; Tx, transplant.

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1. Introduction

In solid organ transplantation (SOT), there are still major obstacles to overcome, including acute or chronic allograft rejection or serious complications of lifelong immunosuppression, to ensure the long-term graft function and survival of transplant recipients with an appropriate quality of life. Alternative therapies are therefore needed that provide immunomodulation rather than blanket immunosuppression so that the effector cells that cause graft damage are targeted while healthy immune cells that protect from infections remain unaffected. This article reviews clinical experience with extracorporeal photopheresis (ECP), an established leukapheresis-based immunomodulatory therapy,[1] in the settings of heart transplantation (HTx), lung transplantation (LTx), kidney transplantation (KTx), and liver transplantation (LiTx).

2. Unmet medical needs in SOT

The challenges to successful SOT are multifactorial, but the key unmet medical needs awaiting effective therapeutic solutions are described below.

2.1. Acute rejection

The incidence of acute rejection (occurring in the 12 months after transplantation) varies according to the type of SOT and across studies, but is reported to be 12% to 25% in HTx,[2] around 27% in LTx,[3] 3% to12% in KTx,[4] and 15% to 25% in LiTx.[5] Acute cellular rejection (ACR) often responds well to increased immunosuppressive therapy; however, a minority of patients can be refractory to standard therapies, warranting consideration of alternative approaches. Antibody-mediated rejection (ABMR) can also be resistant to treatment due to its more complex biology.[6] For some types of SOT, patients who have preformed donor-specific antibodies (DSA) to human leukocyte antigen (HLA) at the point of transplantation or who develop de novo DSA following transplantation are at higher risk of developing acute ABMR, progressing to chronic rejection, and allograft loss.[6]

2.2. Chronic rejection and graft fibrosis

Chronic rejection, which occurs months or years after transplantation, is a leading cause of graft loss characterized by progressive vasculopathy and tissue fibrosis.

Cardiac allograft vasculopathy (CAV) is a manifestation of chronic rejection in HTx recipients and is characterized by a chronic inflammatory reaction in blood vessel walls resulting in intimal smooth muscle cell proliferation and vessel occlusion.[2] CAV is a significant contributor to graft failure and mortality in HTx recipients who survive the first year, with a reported prevalence of 8%, 29%, and 47% at 1-, 5-, and 10 years postHTx, respectively.[3]

In LTx, chronic lung allograft dysfunction (CLAD), comprising restrictive allograft syndrome (RAS; immune-mediated alveolar damage) and bronchiolitis obliterans syndrome (BOS; immune-mediated airway damage), is a major cause of mortality and retransplantation in LTx. CLAD affects around 10% of recipients each year and 50% within 5 years, resulting in a gradual loss of lung function, respiratory failure, and eventually death.[7]

Chronic KTx rejection is characterized by a progressive decline in renal graft function, usually accompanied by hypertension and proteinuria.[8] Its incidence ranges from 4.6% to 20.2% over 1 to 10 years.[4] Histology of chronic ABMR is characterized by transplant glomerulopathy (glomerular basement membrane double contours) and arterial intimal fibrosis of new onset, and histology of chronic T cell-mediated rejection by tubular atrophy, interstitial fibrosis, inflammation within sclerotic areas, and arterial intimal fibrosis with mononuclear cell inflammation in fibrosis and formation of neointima.[8]

Chronic LiTx rejection is characterized by damage to intrahepatic vessels and bile ducts that can result in graft failure but is relatively uncommon with improved immunosuppressive regimens.[9] The incidence of chronic cell-mediated rejection is around 2% to 5% after a median of 5 years in adults, while figures for chronic ABMR are debated.[9]

2.3. Limitations and complications of immunosuppressive therapies

A variety of immunosuppressive regimens are employed in SOT recipients over their lifetime, either as induction therapy, maintenance treatment, or for management of active rejection. However, the benefits of these agents in preventing organ rejection must be balanced against the increased risk of developing opportunistic bacterial, viral (including cytomegalovirus [CMV] and BK virus [BKV]), and fungal infections, as well as other short-, medium-, and long-term complications and toxicities, and an increased risk of certain cancers.[10]

3. Current understanding of the mechanism of action of ECP and its role in SOT

ECP is described as an immunomodulatory therapy that does not cause generalized immunosuppression, and, therefore, it is not associated with an increased incidence of infections.[11] The International Society of Heart and Lung Transplantation and other scientific societies recommend ECP as an adjunctive therapy for rejection prophylaxis, the treatment of recurrent or resistant ACR and refractory ABMR in HTx, or the treatment of CLAD post LTx.[12,13] There is currently no established guideline recommendation for ECP use in KTx or LiTx rejection. However, the immunologic mechanisms underlying the effects of ECP have not yet been fully defined (Fig.).[14]

The technique of ECP treatment consists of collecting leukocytes by apheresis from venous whole blood. The collected cells are mixed with the photosensitizing drug methoxsalen and exposed to ultraviolet-A light to initiate an apoptotic cascade before being returned to the patient. It is generally acknowledged that the mechanism of action of ECP is due to the modulation of the immune system by the resulting apoptotic leukocytes.[13] Apoptotic cells interact with certain subsets of dendritic cells (DCs) in the lymphoid tissue, leading to (1) stimulation of subtypes of regulatory T cells (Tregs) with different immune

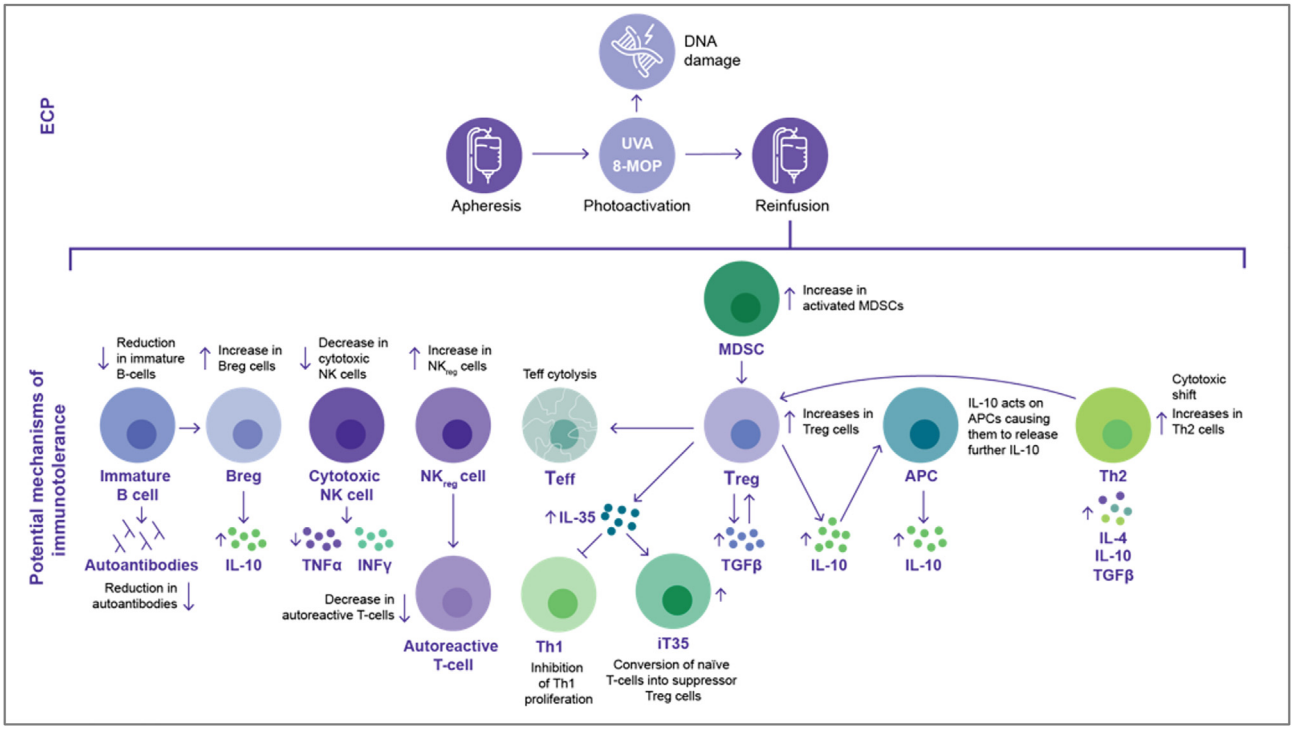

Figure. The proposed mechanism of action of extracorporeal photopheresis (ECP). [14] Ultraviolet radiation A (UVA) activation of 8-methoxypsoralen (8-MOP), a photosensitizing agent, results in DNA cross-linking, which triggers cell death, most likely apoptosis, which is considered to be the direct effect of ECP. When the buffy coat, comprising leukocytes and platelets, is reinfused into the patient, it contains living, dead, and dying cells, as well as subcellular fragments and soluble factors. The UVA-treated leucocytes are engulfed by phagocytic cells, leading to a range of indirect, downstream immunomodulatory effects. These effects may differ depending on the baseline immune condition of the patient. In patients with graft-versus-host disease, it has been shown that it leads to a shift toward a tolerogenic immune profile.
Image provided courtesy of Mallinckrodt Pharmaceuticals.
APC, antigen-presenting cell; DNA, deoxyribonucleic acid; IL, interleukin; irAE, immune-related adverse event; iT35, induced regulatory T cell; MDSC, myeloid-derived suppressor cell; NK, natural killer; NKreg cell, natural killer regulatory cell; Teff, effector T cell; TGF-β, transforming growth factor beta; Th, helper T cell; Treg, regulatory T cell; TNF, tumor necrosis factor.

functions, (2) alterations of cytokine expression from a proinflammatory to an anti-inflammatory profile, and (3) suppression of alloantigen-responding T cells after DC cross-presentation of antigens from apoptotic T cells.[15] Such T cell-dependent ECP effects seem to be responsible for the beneficial clinical ECP effects regarding the prevention and treatment of SOT rejection. More recently, however, a T cell-independent effect of ECP has also been postulated.[16] In an experimental model of BOS, ECP treatment led to a downregulation of transforming growth factor-β-dependent fibrogenesis. Such an antifibrotic effect may be responsible for earlier clinical observations regarding the prevention or stabilization of graft fibrosis in the heart or lung.[17,18] Nevertheless, clinical experience is needed to confirm these observations and determine whether it is possible to incorporate ECP as a valuable weapon in the fight against chronic graft fibrosis in SOT.

ECP has an established safety profile and is known to be well tolerated both in its approved indications and from reports of its use in other immune-mediated disorders.[13] Blood collection during the ECP procedure is undertaken using either a single or double-needle system, with peripheral, rather than central, intravenous access generally preferred. Although there is a potential for the development of infections, from the launch of the Therakos ECP system up to 31 March 2023, around 1.5 million treatments have been administered worldwide, corresponding to an estimated 100 000 patient exposures to the ECP procedure (Data on file. Mallinckrodt Pharmaceuticals). Therakos postmarket surveillance data since January 2015 has identified a 0.017% reportable serious adverse event rate, which equates to 1.7 serious adverse events per 10 000 kits (1 kit equates to 1 treatment).

3.1. ECP for prevention of allograft rejection

Studies from the past 10 years reporting the use of ECP for the prevention of allograft rejection in HTx are summarized in Table 1 (for earlier studies, see Supplementary Material 1). No published studies have been identified in the last decade evaluating the use of ECP prophylaxis in LTx, KTx and LiTx, however, results for earlier studies are described in Supplementary Material 1.

3.2. Heart transplantation

In adult HTx, ECP appears to be a well-tolerated addition to traditional immunosuppression post-transplant for acute rejection prevention and does not increase the risk of infections.[20] ECP is

Table 1
Studies published since 2015 on the prophylactic use of extracorporeal photopheresis (ECP) for the prevention of allograft rejection in heart transplantation (HTx). No published studies have been identified in this period on the use of ECP prophylaxis in lung, kidney, or liver transplantation.

Publication and study type	Study population and treatment regimen	Results
HEART		
Barten et al[11] (2023) Multicenter retrospective study	A total of 105 HTx recipients were treated with ECP at 7 Tx centers in 5 European countries (Austria, Germany, France, Hungary, and Italy). Prevention of rejection was a reason to start ECP in 34 (32.4%) patients. Patients followed for an average of 2 y after the initiation of ECP. Mean time from ECP treatment initiation to last visit: 22.5 mo.	In the prevention of rejection group, 88% remained free from any rejection despite a reduction in IS, in particular CNIs. Overall survival (all patients) was 95%, and no deaths were related to ECP.
Gökler et al[19] (2022) Prospective study	A total of 28 HTx recipients are at high risk for either early postoperative infection or cancer recurrence treated with 6 mo of ECP in conjunction with a reduced IS regimen (no induction therapy and CNI delay of at least 3 d). ECP schedule: d 1+ 2, 5 + 6, 10 + 11, 17 + 18, and 27 + 28, followed by 2 consecutive d every other wk (in mo 2 and 3) and 2 consecutive d once a mo (in mo 4-6) for a total of 24 treatments.	Low rate of ACR (14.3%) in the first y (all occurred within the first mo); no rebound of ACR was observed after the end of ECP therapy. Incidence of severe infections: 17.9%, despite 66.7% of patients being considered at elevated risk due to infection and/or ECMO support preTx. No postTx recurrence in all patients within ≥5 y after cancer detection.

ACR, acute cellular rejection; CNI, calcineurin inhibitor; ECMO, extracorporeal membrane oxygenation; IS, immunosuppression; Tx, transplant.

reported to significantly reduce ACR episodes compared with standard immunosuppression alone. Due to its favorable safety profile, ECP has been evaluated in HTx recipients in combination with reduced-intensity immunosuppression incorporating calcineurin inhibitors (CNIs) and steroid delay.[19] ECP was effective in preventing allograft rejection, with ABMR observed in 1 (3.6%) patient and ACR in 4 (14.3%) patients within the first year posttransplant, and was accompanied by a low overall rate of severe infections (5 [17.9%] patients).

A large European retrospective chart review study has recently been undertaken at 7 transplant centers across 5 European countries to assess the effectiveness and safety of ECP for both the prevention and management of rejection in 105 HTx recipients.[11] The study included 34 patients who received ECP prophylactically. Of these, 88% remained free from any rejection despite a reduction in CNI.

In terms of immunologic mechanisms, studies by Dieterlen and colleagues suggest that an individualized immunologic profile, which consists of immune cells and functions, (eg, subsets of both T regulatory and dendritic cells, as well as pro- and anti-inflammatory cytokines), may help to define the optimal ECP schedule to treat acute and chronic rejection.[15]

3.3. Lung transplantation

The prophylactic use of ECP as a form of induction treatment in combination with standard immunosuppressive therapy has been investigated in a randomized controlled trial of LTx recipients and the publication of the full results is expected soon (NCT05721079). Endpoints include the incidence of acute and chronic rejection episodes, as well as the onset of CMV infections, in the first 2 years posttransplant. The study also aims to get better insight into the mechanisms of ECP in the context of T cell responses.

3.4. Kidney transplantation

Studies of ECP prophylaxis in KTx are limited and none have been published in the last 10 years. However, a single-center, randomized, controlled, open-label study is now underway to assess the impact of ECP in combination with standard immunosuppression (anti-thymocyte globulin, prednisone, tacrolimus, and everolimus or mycophenolate) versus standard immunosuppression alone for the prevention of acute rejection in highly-sensitized de novo KTx recipients (calculated panel reactive antibodies ≥ 90%) in the first year posttransplant (NCT04414735).

4. ECP in the treatment of allograft rejection

Studies from the past 10 years reporting the use of ECP plus immunosuppressive therapy for the treatment of acute and chronic rejection in LTx, HTx, and KTx are summarized in Table 2 (for earlier studies, Supplementary Material 2). No published studies have been identified in the last decade evaluating the use

Table 2
Studies published since 2015 on extracorporeal photopheresis (ECP) for the treatment of allograft rejection in heart, lung, and kidney transplantation. No published studies have been identified in this period on the use of ECP prophylaxis in liver transplantation.

Publication and study type	Study population and treatment regimen	Study outcomes
HEART		
Teszak et al[21] (2023) Single-center retrospective study	A total of 22 patients with moderate-to-severe or persistent ACR or mixed rejection were treated with standard IS (tacrolimus, MMF, and methylprednisolone) plus ECP. ECP schedule: 2 consecutive treatments, initially weekly and biweekly, then tapered to monthly depending on allograft function and grade of rejection; median of 11 cycles of ECP (22 treatments).	No episode of ISHLT grade 3R ACR over the study period. 2R ACR episodes were reversed; decreased rates of subsequential rejection episodes, and normalized allograft function were observed in patients completing the ECP course.
Barten et al[11] (2023) Multicenter retrospective study	A total of 105 HTx recipients were treated with ECP at 7 Tx centers in Europe for ACR (37; 35.2%), ABMR (15; 14.3%), or mixed rejection (19; 18.1%). Patients followed for an average of 2 y after ECP initiation. Mean time from ECP initiation to last visit: 22.5 mo.	ACR and mixed rejection groups: 10 and 11 patients, respectively, had biopsy data showing an ACR grading of 2R and 1R at the start of ECP treatment, which improved to 1R (4 patients) or 0R (17 patients), respectively. ABMR and mixed rejection group: histologic grading reduced from pAMR2 or 1 (n = 6 and 4) to pAMR 1 or 0 (n = 3 and 7).
Savignano et al[22] (2017) Retrospective case series	A total of 8 HTx recipients were treated with ECP for recurrent rejection (n = 6), persistent rejection (n = 1), or mixed rejection with HC (n = 1). ECP schedule (offline system): 2 consecutive treatments/2 wk for mo 1 and 2, then monthly for mo 3-12.	Response rate (37.5%): 3 patients had negative biopsies with no rejection at the end of treatment; 4 patients showed no response to ECP; 1 could not be evaluated.
LUNG		
Benazzo et al[33] (2023) Multicenter retrospective study	A total of 631 LTx (87% BOS, 13% RAS) recipients were from 3 European centers. ECP schedule: initially a 2-d treatment cycle was performed every second wk for the first 2-6 mo, according to institutional preferences. Then, a 2-d treatment cycle was performed once a mo.	Long-term stabilization of lung function was achieved in 42% of patients, improvement in 9%, and no response in 26%. Both lung function stabilization ($P = .013$) and response to ECP ($P < .001$) were associated with survival.
Greer et al[24] (2023) Retrospective study	A total of 373 LTx recipients were with CLAD. ECP was initiated following a $\geq$ 10% decline in FEV_1 from baseline, despite azithromycin treatment. ECP schedule: patients must have completed at least 3 mo of ECP treatment (schedule not specified).	Statistical modeling revealed 5 different temporal CLAD phenotypes based on the FEV1 course: fulminant (7% of patients), mild (9% of patients), moderate (26% of patients), advanced progressive (42% of patients), and advanced chronic (16% of patients). Early initiation of ECP

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Table 2 (*continued*)

Publication and study type	Study population and treatment regimen	Study outcomes
		treatment may optimize clinical outcomes, in particular survival.
Leroux et al[25] (2022) Retrospective study	A total of 12 LTx recipients were with BOS: 4 stage 1, 3 stage 2, and 5 stage 3. ECP schedule: 2 consecutive d every 2 wk × 6 mo, then extended to every 4, 6, and 8 wk, depending on response and tolerance.	ECP stabilized lung function during the subsequent 6-24 mo ($P = .002$). ECP rapidly stabilized the FEV_1 decline in refractory BOS patients compared with nontreated decliners.
Vazirani et al[26] (2021) Retrospective study	A total of 12 LTx recipients were with CLAD: 2 stage 2, 10 stage 3. ECP schedule: 3/wk for 1 wk, then 2/wk for 7 wk, then tapered based on response.	In total, 67% of patients responded to ECP. The mean rate of FEV_1 decline slowed from 9 mL/d per ECP to 1.4 mL/d ($P = .01$) with ECP treatment.
Hage et al[27] (2021) Prospective, multicenter study	A total of 30 LTx recipients were receiving BOS refractory to standard IS therapy: 12 stage 1, 8 stage 2, 8 stage 3. ECP schedule: 24 ECP treatments over 6 mo with 2 procedures on successive d. Patients received ECP on d 1 and 2, 5 and 6, 10 and 11, 17 and 18, and 27 and 28 during mo 1 (10 treatments), biweekly for the next 2 mo (8 treatments), then monthly for 3 mo (6 treatments).	In total, 19 evaluable subjects demonstrated a significant 93% decrease in the mean rate of FEV_1 decline after 6 mo of ECP treatment ($P = .0002$). A total of 95% (18/19) of patients responded to ECP with ≥ 50% decrease in the rate of decline in FEV_1.
Benazzo et al[28] (2020) Retrospective study	A total of 16 LTx recipients had acute ABMR. ECP schedule: ECP started within 1 wk after first-line treatment. Initially, a 2-d treatment cycle/wk for the first 3 mo, then a 2-d treatment cycle/mo for ≥6 mo (median 14 treatments).	A total of 94% (15/16) of patients developed dnDSA: 63% (10) against HLA class I and 88% (14) against HLA class II. Adjunctive ECP treatment was associated with a reduction in dnDSA. Circulating DSA was cleared in 88% of patients, and lung function was restored in 38%.
Karnes et al[29] (2019) Retrospective study	A total of 60 LTx recipients were with BOS: 5 stage 1, 20 stage 2, and 35 stage 3. ECP schedule: 24 ECP treatments over 6 mo with 2 procedures on successive d. Patients received ECP on d 1 and 2, 5 and 6, 10 and 11, 17 and 18, and 27 and 28 during the first mo (10 treatments), biweekly for the next 2 mo (8 treatments), and then monthly for 3 mo (6 treatments).	BOS patients with baseline FEV_1 rates of decline ≥ 40 mL/mo were 12 times more likely to respond to ECP ($P < .0001$). FEV_1 prior to ECP ≤ 1.5 L was 87% sensitive and 60% specific as a predictor of mortality at 16 mo.
Moniodis et al[30] (2018) Retrospective study	A total of 17 LTx recipients were with BOS (n = 13) or RAS (n = 4), 15 stage 1, and 2 stage 2. ECP schedule: 2 treatments/wk for 4 wk, 2	Lung function decline was significantly stabilized within 6 mo after commencing ECP treatment.

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Table 2 (*continued*)

Publication and study type	Study population and treatment regimen	Study outcomes
	treatments/fortnight for 1 mo, 2 treatments/mo for 4 mo.	
Robinson et al[21] (2017) Retrospective study	A total of 12 LTx recipients were with BOS (3 stage 2; 7 stage 3) or RAS (n = 2). ECP schedule: median of 44 ECP cycles (2 treatments on consecutive d).	A total of 11 (33%) patients had stabilization of kidney function at 12 mon postECP with a graft survival rate of 61%.
Pecoraro et al[31] (2017) Retrospective study	A total of 15 LTx recipients were with BOS: 1 stage 1, 4 stage 2, and 10 stage 3. ECP schedule: 2 treatments/wk for 4 wk, 2 treatments biweekly for 3 rounds, then 2 treatments/mo for 6 mo.	Lung function stabilization was achieved in 80% of patients. Significantly better survival was observed in ECP-treated patients versus controls (155.6 mo vs 113.8 mo) from the diagnosis of BOS.
Del Fante et al[32] (2015) Retrospective study	A total of 48 LTx recipients: 14 with RAS; 34 with BOS (28 stage 1, 10 stage 2, 10 stage 3); and 58 control patients who received SoC. ECP schedule (offline system): 2 treatments/wk for 3 wk, biweekly for the next 1-2 mo, monthly thereafter.	Stabilization of lung function declined in the ECP group ($P < .001$) over a median of 51 mo but not in the SoC group; the mortality rate was significantly higher in the SoC group. RAS was associated with poorer survival.
KIDNEY		
Xipell et al[35] (2022) Retrospective case series	A total of 4 KTx recipients: cABMR (n = 1), caABMR (n = 1), caTCMR (n = 1), history of ABMR with BK nephropathy requiring decreased IS (n = 1). Two patients had concomitant viral infections (cytomegalovirus and BK virus, respectively). ECP schedule (offline system): 2 treatments/wk (48 h apart) for 2 wk, then 1/wk for 2 wk, then 1 treatment/2 wk, totaling 16 treatments.	Stabilization of renal function occurred in 3 of 4 patients during ECP treatment, with 2 of 4 patients remaining stable after ECP completion. There was no improvement in 1 patient despite ECP, with progression to kidney graft failure. In the 2 patients with active viral infection, the infection was successfully controlled during ECP treatment.
Augusto et al[36] (2021) Case series	A total of 3 KTx recipients with PTLD who developed mixed ACR following IS minimization were treated with ECP, methylprednisolone, and IV immunoglobulin. ECP schedule: patient 1: 16 sessions; patient 2: 20 sessions; patient 3: number of sessions not stated.	Graft function improved in all patients and stabilized on long-term follow-up (24-33 mo). DSA decreased in 2 patients after the initiation of ECP, suggesting ECP may influence antibody-producing B cells.
Gregorini et al[37] (2021) Prospective observational study	A total of 14 KTx recipients had cABMR and grade 2-3 chronic renal failure. ECP schedule (offline system): 1 cycle (2 procedures)/wk for 3 wk, then 1 cycle/2 wk 2-3 times, then 1 cycle/mo; maintenance frequency: 1 cycle every 2 mo.	In total, 8 of 11 (72.7%) patients responded to ECP (3 patients dropped out). In total, 63.6% experienced an increase in eGFR. Persisting eGFR stabilization occurred in ECP responders with continued treatment for up to 3 y. There was a significant reduction in DSA levels

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Table 2 (*continued*)

Publication and study type	Study population and treatment regimen	Study outcomes
		after ECP treatment; anti-HLA antibody levels were reduced or completely cleared in 6 of 8 (75%) ECP responders.
Fernandez Granados et al[38] (2020) Retrospective descriptive study	A total of 8 KTx recipients with ACR or ABMR were treated with ECP due to contraindication to conventional therapy (n = 4), mainly concomitant infection (50%), or being refractory (n = 4) to the treatment prescribed. ECP schedule: 2 consecutive sessions/wk for 5 wk, with additional sessions depending on progress.	Improvement in graft function in terms of creatinine reduction at the end of ECP treatment in patients with early ACR (n = 4), which was sustained 3 mo after cessation of treatment. No grafts with an ABMR component to the rejection showed improvement in renal function with ECP treatment.
Tamain et al[39] (2019) Retrospective study	A total of 33 KTx recipients: ACR (n = 8), ABMR (n = 23) and cABMR (n = 2). ECP schedule (offline and online systems): 1-2 sessions/wk in mo 1, then 1 session weekly, then 1 session/2 wk, then 1 session/mo.	Stabilization of kidney function 12 mo postECP in 111 (33%) patients with a graft survival rate of 61%.

ACR, acute cellular rejection; ABMR, antibody-mediated rejection; cABMR, chronic antibody-mediated rejection; caABMR, chronic-active antibody-mediated rejection; caTCMR, chronic-active T cell-mediated rejection; CLAD, chronic lung allograft dysfunction; DSA, donor-specific antibodies; dnDSA, de novo DSA; ECP; eGFR, estimated glomerular filtration rate; HC, hemodynamic compromise; HLA, human leukocyte antigen; HTx, heart transplantation; IS, immunosuppression; ISHLT, International Society for Heart and Lung Transplantation; KTx, kidney transplantation; LTx lung transplantation; LiTx, liver transplantation; MMF, mycophenolate mofetil; PTLD, posttransplant lymphoproliferative disorder; RAS, restrictive allograft syndrome; SoC, standard of care; Tx, transplant.

of ECP for the treatment of rejection in LiTx, however, results for earlier studies are described in Supplementary Material 2.

4.1. Heart transplantation

A range of single-center case series and several randomized trials in HTx recipients have shown clinical benefits of ECP alongside good tolerability for the treatment of organ rejection due to both ACR and ABMR.[20] However, many of these investigations were not sufficiently powered, or not specifically designed, to confirm a difference between treatment groups. Table 2 describes the results of the 3 retrospective studies of ECP in HTx published in the last decade.[11,21-23] The successful reversal of rejection with ECP has been reported in the recent pan-European retrospective study of 105 HTx recipients, which included 37 patients who received ECP treatment for ACR, ABMR, or mixed rejection (ACR plus ABMR).[11] Both ACR and ABMR gradings were found to have improved with ECP treatment.

Although ECP is commonly used as an adjunctive treatment option for ABMR in HTx recipients, the clinical evidence in this setting has been based on a small cohort of studies and 1 large multicenter trial, so further studies are needed to confirm these data. However, the good tolerability profile of ECP makes it a valuable option as a long-term treatment for patients with asymptomatic ABMR to prevent further escalation.

4.2. Lung transplantation

The role of ECP as an adjunct therapy for allograft rejection in SOT has been best studied in LTx recipients. ECP has shown promising results for the management of CLAD following LTx, in particular for BOS (Table 2).[24-33] Evidence has primarily been derived from small, single-center retrospective studies, but these have shown that ECP treatment is associated with improvement or stabilization of lung function, a significant and sustained decrease in the rate of decline in lung function, and is also well tolerated.[34]

A single-center retrospective study found that titers of de novo DSA against HLA classes I and II were significantly reduced or completely cleared with ECP treatment in LTx patients who had developed ABMR.[28]

A large multicenter retrospective study evaluated ECP treatment in 631 patients (87% with BOS and 13% with RAS) from 1989 to 2021 at 3 European centers in Austria, Germany, and Italy.[33] Two-thirds of the cohort had a sustained response to ECP treatment along with good long-term results. Long-term lung stabilization was achieved in 42% of patients, with improvement in 9%. Survival 5 years after the initiation of ECP was 70% in responders. A separate analysis of data from the Austrian cohort of 373 LTx patients with CLAD suggested that early initiation of ECP treatment could optimize clinical outcomes, particularly survival benefits and that it may be possible to predict ECP

outcomes for different phenotype groups using data obtained prior to ECP initiation.[24]

To provide prospective, randomized, and controlled evidence for ECP treatment of chronic rejection in LTx recipients, a study is now underway E-CLAD UK (ISRCTN 10615985), funded by the UK's National Institute for Health and Care Research (NIHR130612)—to compare the efficacy of ECP plus standard care versus standard care alone in the treatment of CLAD.

4.2. Kidney transplantation

Data on the use of ECP for the treatment of rejection in KTx are limited, and studies often include only small numbers of patients (Table 2). They comprise mostly retrospective studies, with 1 prospective study, but all report beneficial effects of ECP treatment in terms of stabilization or improvement of kidney function, including in patients with persistent or resistant acute and chronic rejection.[35-39]

Recently, the largest of these, a multicenter, retrospective study, evaluated ECP treatment in 33 KTx recipients with ACR, acute ABMR, or chronic ABMR who were resistant to standard therapies or where these therapies were contraindicated due to concomitant infections or cancers.[39] At 12 months postECP, 11 (33%) patients had stabilization of kidney function, and the graft survival rate was 61%.

The effectiveness of ECP in KTx recipients with biopsy-proven chronic ABMR and stage 2 to 3 chronic renal failure has been investigated in a small single-center study of 11 subjects.[37] Anti-HLA antibody titers were reduced (or cleared in 6 of the 11 patients identified as "responders" to ECP). Renal failure progression was halted in 8 of 11 ECP responders, and in 7 responders, renal function was improved.

These data suggest that ECP may have an adjunctive role in acute rejection following KTx, particularly in patients who have clinical conditions that preclude the use of high-dose immunosuppressive drugs (e.g., cancer and infections) or those with infectious complications where there is a need to minimize immunosuppression.

5. ECP and immunosuppression sparing, infections, and malignancies

Several studies in HTx and KTx have shown that ECP has a potential role as an immunosuppression-sparing agent in SOT recipients, in particular those at high risk of (or who have pre-existing) infections or malignancy.[19,39]

In the multicenter European study of ECP treatment of rejection in HTx recipients, of those who remained on steroid therapy, 41% (14/34) of patients were able to reduce the dose by a mean of 63%.[11] In the subgroup of patients who received ECP prophylaxis, 84.2% (16/19) patients were also receiving tacrolimus at the start of ECP treatment. By the end of the study, of the 11 patients who had data available for trough tacrolimus levels, 63% (7) patients had a mean decrease of 34%, thereby reducing the potential for CNI renal toxicity.[11] ECP prophylaxis administered for 6 months postHTx has also been found to allow treatment with a low-dose immunosuppressive regimen (low-dose tacrolimus with delayed start, mycophenolate mofetil, and low-maintenance steroid with delayed start) in patients with a high risk of infection or malignancy, and this combination was effective in minimizing allograft rejection.[19]

ECP has also been associated with a reduced incidence of CMV infections in both HTx and LTx recipients. In the original study of ECP prophylaxis in HTx, a significant reduction was observed in CMV DNA levels in ECP-treated patients versus those who received standard immunosuppressive therapy.[40] Similarly, in a study of LTx recipients who developed BOS, those given adjunctive ECP treatment developed fewer CMV infections than those who received standard therapy alone.[18]

BKV-related nephropathy is a significant contributor to allograft loss in KTx recipients.[35] Reduction of immunosuppression is the primary treatment strategy, and the use of ECP might allow immunosuppression sparing and maintain allograft tolerance. A single-center case series demonstrated the impact of concomitant ECP treatment in KTx recipients with opportunistic infections. Two patients had active viral infections (1 CMV and 1 BKV), which were successfully controlled with ECP treatment.[35] This strategy has also been evaluated in a case series of KTx recipients that developed posttransplant lymphoproliferative disorder, a condition where the Epstein-Barr virus plays a central role.[36]

6. Summary and conclusions—the future for ECP in SOT management

Studies to date suggest that ECP may have a role in addressing some of the unmet needs in the management of SOT. ECP has an immunomodulatory rather than immunosuppressive effect. As such, it is not associated with an increased risk of infection and allows CNI and steroid-sparing without negatively impacting graft survival.

This effect may favor ECP as a long-term treatment of chronic rejection rather than other therapies, including biological agents or total lymphoid radiation, which could cause an increase in severe side effects (infections, bone marrow depression, organ dysfunction, or malignancies) with time on treatment.

Studies are now ongoing to generate both randomized, controlled trials and real-world evidence of the efficacy and tolerability of ECP in SOT that can support the existing evidence base and help guide treatment decisions in these challenging cases.

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Declaration of competing interest

The authors of this manuscript have conflicts of interest to disclose, as described by the *American Journal of Transplantation*. M.J. Barten reported receiving honoraria for lectures, presentations, and speaker bureaus. A. Fisher reported serving as Chief Investigator of the E-CLAD UK trial, currently recruiting

and receiving honoraria from Mallinckrodt for lectures, presentations, and speaker bureau. A. Hertig reported receiving honoraria from Mallinckrodt for the speaker bureau.

Data availability

The data that support the findings of this study are available on request from the corresponding author.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajt.2024.03.012.

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