OPEN

Exploring the Role of Extracorporeal Photopheresis in Kidney Transplant Management

Michael Nicoli, MSc,[1,2] Jordi Rovira, PhD,[1] and Fritz Diekmann, MD, PhD[1,3]

Abstract. Extracorporeal photopheresis (ECP) is emerging as an apoptotic cell-based therapy that suppresses alloimmunity, promotes donor-specific regulation, and reduces the need for conventional maintenance immunosuppression. ECP therapy is associated with regulatory T-cell proliferation, anti-inflammatory effects, and reduction of anti-HLA antibodies, making ECP a possible alternative or adjunct treatment for preventing and treating transplant rejection. Presently, we have a limited understanding of the mechanisms of ECP action, and clinical evidence for efficacy in kidney transplantation is sparse. Promising results in acute cellular or antibody-mediated rejection were reported, but beneficial effects in chronic settings are less evident. The absence of reliable markers for patient stratification and therapeutic monitoring further complicates its application. Working with the European Union–funded exTra network, our group is studying the therapeutic action of ECP in kidney transplantation with the ultimate goal of conducting a large multicenter study to standardize and harmonize treatment indications and approaches.

(*Transplantation Direct* 2025;11: e1809; doi: 10.1097/TXD.0000000000001809.)

EXTRACORPOREAL PHOTOPHERESIS AND TRANSPLANTATION

Extracorporeal photopheresis (ECP) is an immunomodulatory therapy based on the infusion of autologous cellular products, obtained through leukapheresis and exposure to UVA light in the presence of a photosensitizer, 8-methoxypsoralene. ECP was initially developed as T-cell depletion therapy for patients with cutaneous T-cell lymphoma, given that this procedure induces apoptosis of the treated leukocytes.[1,2] Preclinical studies demonstrated its potential in modulating immune responses, paving the way for its introduction in graft-versus-host disease and solid organ transplantation (SOT).[3] The exact mechanism of action is unclear, but it seems likely that the immunomodulation occurs through activation of monocytes, which differentiate into tolerogenic dendritic cells (DCs)[4,5] and phagocytize apoptotic cells, presenting antigens to induce specific tolerance. During the procedure, soluble factors are released.[6] After engraftment, tolerogenic DCs drive regulatory T cell (Treg) responses and expression of anti-inflammatory mediators, reducing proinflammatory cytokine production.[7,8] ECP can be performed in an off-line mode, where blood is extracted, the buffy coat is isolated, the drug is added, and the mixture is exposed to UVA light in a separate machine before reinfusion. Alternatively, it can be performed in an in-line mode, using a single machine that executes the entire procedure semi-automatically (Figure 1).

In SOT, ECP is currently used as an adjunct therapy for the treatment and prophylaxis of acute T cell–mediated rejection (TCMR) and acute antibody-mediated rejection (AMR) after heart transplantation (HTx), as well as for the treatment of chronic lung allograft dysfunction (CLAD) in lung transplant recipients.[9] Both prophylactic use and treatment for rejection on HTx have shown promising results,[10,11] including a reduction in the panel-reactive antibodies.[12] Similar results have been obtained in CLAD, with a reduction in de novo donor-specific antibody (DSA) formation. However, ECP was only an add-on therapy in addition to immunoadsorption and

Received 20 November 2024. Revision received 3 April 2025.

Accepted 5 April 2025.

[1] Laboratori Experimental de Nefrologia i Trasplantament (LENIT), Fundació de Recerca Clinic Barcelona-Institut d'Investigacions Biomèdiques August Pi i Sunyer (FRCB-IDIBAPS), Barcelona, Spain.

[2] Faculty of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain.

[3] Department of Nephrology and Kidney Transplantation, Institut Clínic de Nefrologia i Urologia (ICNU), Hospital Clínic Barcelona, Barcelona, Spain.

This work was funded by the European Union through the exTra doctoral network (https://extra-horizon.eu/; grant 101119855) and Innovative Applications of ExtraCorporeal Photopheresis in Solid Organ Transplantation.

The authors declare no conflicts of interest.

M.N., J.R., and F.D. participated in writing the article.

J.R. and F.D. participated equally in the writing and revising of the work.

Correspondence: Michael Nicoli, MSc, Laboratori Experimental de Nefrologia i Trasplantament (LENIT), Fundació de Recerca Clinic Barcelona-Institut d'Investigacions Biomèdiques August Pi i Sunyer, C/ del Rosselló, 149, Barcelona 08036, Spain. (nicoli@recerca.clinic.cat).

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001809

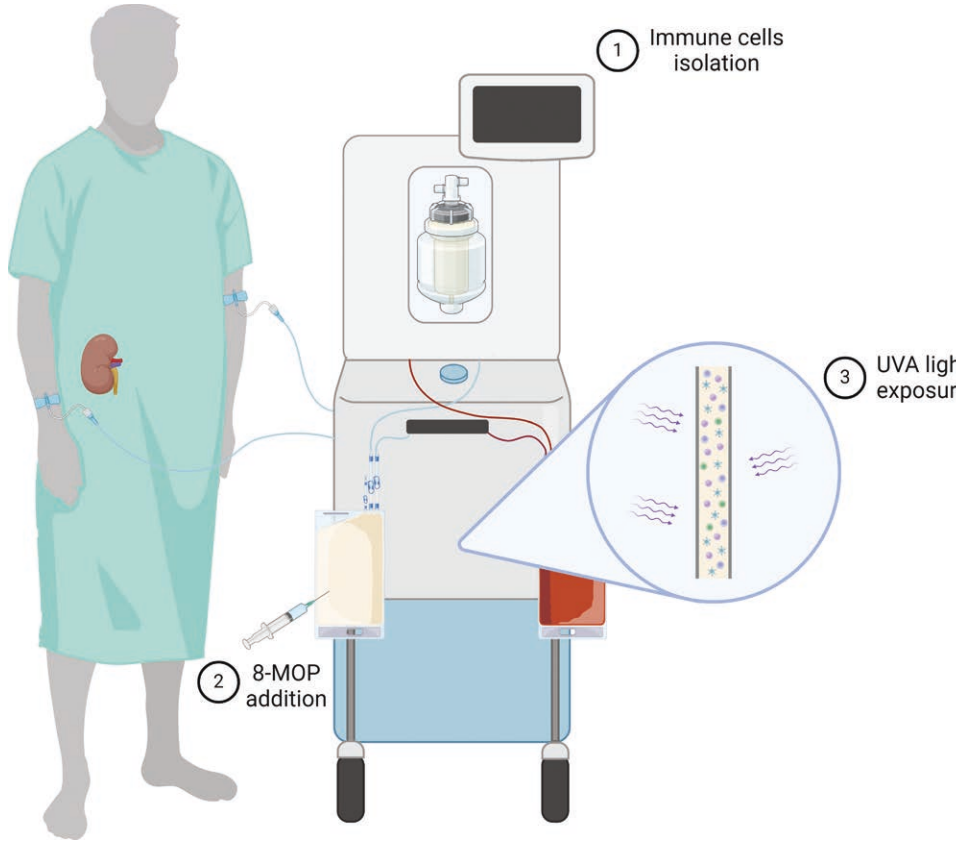

FIGURE 1. In-line procedure of extracorporeal photopheresis: 1, immune cells isolation using centrifugation; 2, adding of 8-MOP to the buffy coat; and 3, UVA light exposure of the buffy coat and reinfusion. Created with Biorender. 8-MOP, 8-methoxypsoralen.

IVIG.[13,14] ECP is generally well tolerated with almost no significant side effects.

ECP AS A THERAPEUTIC APPROACH FOR RENAL TRANSPLANTATION

In kidney transplantation, effective management of rejection and transplant-associated complications, such as infections, is crucial for patient and graft survival. Currently, plasma exchange (PLEX) combined with IVIG is the standard of care in cases of AMR.[15] Rituximab in chronic active AMR has proven ineffective and is associated with a significant increase in infectious complications.[16]

AMR, in both its acute and chronic forms, remains the main obstacle to improving long-term transplant outcomes.[17] Beyond the acute or chronic worsening of allograft function, this condition is characterized by the presence of DSAs, complement activation, and microvascular damage. The molecular mechanisms underlying AMR are complex and multifaceted. The inflammatory environment surrounding the graft activates both the innate and adaptive immune systems. This process involves antigen presentation to T cells and activation of B cells, which differentiate into antibody-secreting plasma cells. The antibodies produced bind to graft-expressed antigens, activating the complement system and recruiting innate immune cells (natural killer cells, macrophages, and neutrophils) that exert cytotoxic activity.

In this context, ECP could provide significant benefits through its immunomodulatory mechanisms. ECP-induced increases in regulatory Treg that could suppress the antigen-presenting capacity of antigen-presenting cells and their costimulation of effector T cells.[18,19] Furthermore, the release of interleukin (IL)-10 and transforming growth factor (TGF)-β reduces inflammation, inhibits antigen-presenting cells, and promotes the expression of FoxP3, a key transcription factor for Treg.[20,21] These cells, by expressing high levels of CD25, sequester IL-2 from their environment.[22] Additionally, through the expression of CD39 and CD73, they convert free ATP into adenosine, a molecule with anti-inflammatory properties.[23,24]

Treg ($CD4^+$ $CD25^+$) also exert a direct inhibitory action on the B-cell compartment, particularly on antigen-presenting B cells.[25] In contrast, ECP seems to enhance the regulatory B-cell compartment,[26,27] which produce cytokines, such as IL-10, TGF-β, IL-35, and granzyme B. These molecules contribute to reducing inflammation and promoting immunomodulation.[28]

The existing literature on the use of ECP to prevent or treat rejection in renal transplantation is scarce. Our group demonstrated, in a fully mismatched rat kidney transplant model characterized by the early development of AMR, that the photopheresis added to a very short course of tacrolimus could prolong allograft survival compared with control animals given only tacrolimus monotherapy. Additionally, a reduction in DSAs was reported in rats treated with ECP at 23 d posttransplant, compared with day 9 in the tacrolimus-only group.[29] It is important to highlight that a high dose of ECP was crucial to achieve these effects.

The clinical trials and cases that have been conducted to date in renal transplantation are listed and summarized in Table 1. It should be noted that a significant proportion of these studies were underpowered and varied in terms of

TABLE 1.

Summary of clinical studies on the use of ECP in kidney transplantation

Reference	Patient condition	Treatment	Outcomes
[30]a	6 pediatric kidney transplant recipients: 4 control vs 2 ECP	SI vs SI + 3 ECP cycles (2 sessions/cycle) for the first 2 wk after transplantation	No signs of acute rejection during the first 12 mo after the transplant in both groups. A 6-mo biopsy showed a normal renal histology
[31]a	20 consecutive kidney allograft recipients received kidneys from 10 deceased donors (10 pairs). ECP vs control	Si vs SI + 1 cycle (2 sessions/cycle) per week for the first month after Tx then 1 cycle every 2 wk with a maximum of 8 cycles	Increase of eGFR 3 mo after transplantation and no rejection detected (53 ± 11 vs 47.1 ± 9)
[32]b	33 KT recipients with allograft rejection (24 aAMRs, 2 cAMRs, 7 ACRs). No CTRL group	ECP in concomitance with immunosuppression was performed 18 mo after transplantation and 3 mo after the diagnosis of rejection. 27 patients received 1 cycle and 6 patients 1 session in the first week, then all, 1 session weekly, 1 every 2 wk and once per month	20 patients reported functional grafts 12 mo after ECP (15 ECP sessions). 12 patients received only 10 ECP sessions, and only 1 reported a functional kidney 12 mo after ECP
[33]b	14 patients with cAMR and an average allograft age of 9.25 y before their first ECP. No CTRL group	SI + ECP 1 cycle per week for 3 wk, 1 cycle every 2 wk and 1 cycle per month. Then 1 cycle every 2 mo	12 mo after ECP start: 8 patients show stable eGFR 7 show an increase in eGFR 3 show a reduction in eGFR 6 patients had a complete clearance of HLAab
[34]b	4 patients with ACR 2 patients with ACR and CAHR 1 patient with ACR and AHR 1 patient with borderline rejection No CTRL group	1 cycle for 5 wk (2 ECP sessions per cycle in 2 consecutive days)	4 patients with early ACR report improvement in the graft function. No improvement for AMR
[35]b	3 patients with acute AMR. No CRTL group	PT, IVIg, and ECP 1 cycle in the first 2 wk then 3 times at 15 d intervals and 3 times every month	2 patients did not experience new episodes of rejection, at the time of the last follow-up showed a functional graft (25 and 21 mo). The last patient interrupted the treatment
[36]b	3 patients with PTLD and acute rejection. No CTRL group	ECP sessions not specified + methylprednisolone + IVIG	Long-term follow-up with renal function stabilization and not PTLD recurrence
[37]b	4 patients with at least 3 acute rejection episodes. 3 of these with grade 3/2 acute rejection. No CTRL group	1 cycle per week in the first month, 1 cycle every 2 wk during the second and third months, then monthly for the other 3 mo	3 patients show stabilization in the renal function 1 y after ECP withdrawal. In the 3 patients, acute rejection has been resolved after 3 mo since ECP started. 1 patient shows persistent proteinuria and a progressive deterioration of renal function
[38]b	8 patients with biopsy-proven cAMR. No CTRL group	1 cycle for 6 wk then 1 session weekly for 6 wk and maintenance with 1 cycle monthly until biopsy	Stable renal function for 3 patients, decreased for 1 and increased for 4 patients. Microvascular inflammation reduction in 5, stabilization in 1 and worsening in 2 patients
[39]b	4 high immunological risk recipients. No CTRL group	1 cycle for 2 wk, 1 session weekly for 2 wk + 1 session every 2 wk after the first month	Stable renal function for 3 patients, 2 of whom remained stable after finishing the therapy, the third one left the study with worsened function. One had no improvement with kidney failure
[40]b	7 patients with biopsy-proven acute refractory rejections, no CTRL group	Triple immunosuppression + 2–3 treatments per week for 6–26 sessions	All patients show a functioning graft at the last follow-up (9–43 mo). 5 patients show improvement in renal function
[41]b	10 patients with recurrent cellular and/or vascular rejection. No CTRL group	Tacrolimus + mycophenolate + 1 cycle per week for the first 2 wk + 1 treatment at 15 d interval up to 12 sessions	Resistant rejection resolved in all patients with stabilization or improvement of serum creatinine (median 132.5 µmol/L (98–192) at the end of the therapy)

[a]Prophylactic use.
[b]Treatment.
ACR, acute cellular rejection; AMR, antibody-mediated rejection; aAMR, acute AMR; cAHR, chronich active humoral rejection; cAMR, chronic AMR; CTRL, control; ECP, extracorporeal photopheresis; eGFR, estimated glomerular filtration rate; HLAab, HLA antibody; KT, kidney transplant; PT, plasma treatment; PTLD, posttransplant lymphoproliferative disorder; SI, standard immunosuppression; TCMR, T cell–mediated rejection; Tx, transplant.

treatment frequency and duration. In addition, the studies could be categorized according to their primary objective as either prophylactic or therapeutic.

ECP PROPHYLACTIC TREATMENT IN KIDNEY TRANSPLANTATION

Two small studies have been conducted on the first renal transplant recipients from deceased donors. One study, which involved pediatric patients, reported the absence of rejection signs at 12 mo posttransplant after 6 ECP cycles and an increase in regulatory T cells with an initial reduction of tumor necrosis factor-α.[30] In the second study, 20 adult kidney allograft recipients who received kidneys from deceased donors were randomized and assigned to the ECP-treated (n = 10) or the control (n = 10) group. Both groups received mycophenolate mofetil or sodium plus calcineurin inhibitor and prednisone. None of the ECP-treated patients showed

signs of acute rejection, whereas 1 patient from the control group experienced acute, biopsy-proven rejection. In the ECP-treated group, all patients registered an increase in circulating Treg after 3 mo, along with an improvement in estimated glomerular filtration rate (eGFR) and a higher percentage of immature myeloid DCs at 6 mo.[31] By contrast, no change in DC counts was recorded.

Given the increased risk of acute rejection episodes in highly sensitized patients and the lack of standardized treatments, we propose that ECP might be valuable in preventing acute rejection in this cohort. To this end, we designed and initiated a single-center, randomized, controlled, open-label clinical trial to evaluate the impact of ECP in combination with standard immunosuppression versus standard immunosuppression alone for the prevention of acute rejection in participants with calculated panel-reactive antibody >90% in the first year after transplantation (NCT04414735). We designed the protocol based on prophylactic ECP in HTx trials.[10,42] Additionally, evidence indicates that early use of ECP is linked to improved patient outcomes.[32] Our animal model further highlights that an aggressive ECP therapy strategy is essential for stabilizing renal function.[29] The trial protocol involves 13 cycles of ECP (26 sessions), beginning with 5 cycles in 4 wk. At week 4, the frequency is reduced to 1 cycle every 2 wk until week 12. Afterward, the frequency is reduced to 1 cycle per month until month 6.

ECP FOR REJECTION TREATMENT AFTER KIDNEY TRANSPLANTATION

As seen in other contexts, ECP in kidney transplantation is associated with an increase in Treg and a decrease or no change in Th17 cells after therapy.[32,33] One study reported that responding patients also exhibited decreased IL-6 levels compared with nonresponders 1 y posttreatment.[33]

In cases involving a humoral rejection component, a substantial group of patients (6/8 responders; 75%) had a decrease, up to complete clearance, of anti-HLA antibodies. In nonresponders, anti-HLA levels did not change post-ECP and even increased upon therapyinterruption.[33] Interestingly, when ECP was used as a single therapy (3 participants with acute AMR and other comorbidities), there was a >25% reduction in DSA and graft survival in all patients at 24 mo after the end of the treatment.[32,43] Despite this, a direct effect of ECP on DSA production cannot be confirmed, as it may instead result from indirect effects related to other factors.

The largest retrospective study conducted included 33 cases with different rejection types and protocols, reporting a graft survival rate of 61% at 12 mo post-ECP. However, none of the patients who started ECP while dialysis-dependent regained renal function. Among the 13 participants who lost their grafts at 12 mo, 6 were dialysis-dependent within 1 mo since initiation of ECP and received <10 sessions during 3.5 mo, and 4 were dialysis-dependent 1 mo after ECP completion. ECP was consistently ineffective in patients with poor renal function at the start of treatment and appeared less effective in those with a long delay between rejection and therapy initiation.[32]

Another study reported similar results for the treatment of either acute TCMR or mixed TCMR and humoral rejection. Among the 2 patients with a component of chronic active antibody-mediated rejection, 1 patient had to stop treatment and experienced a deterioration in kidney function, whereas the other patient lost the graft during the observation period. In the 3 cases where treatment completion was not possible (<10 sessions), 2 patients did not experience any reduction in creatinine levels. However, participants with early TCMR responded to the therapy, showing a decrease in creatinine levels by the end of treatment.[34]

The combined use of ECP with PLEX to target both cellular and humoral components has been tested. Among the 3 observed patients, 2 achieved positive outcomes with stable grafts at the last follow-up, whereas 1 patient lost the graft in the context of voluntary withdrawal of therapy.[35] The combination of ECP and IVIG for posttransplant lymphoproliferative disorder shows acute glomerular lesion regression and DSA reduction in all cases without chronic AMR-related lesions.[36]

At the allograft level, a significant reduction (>86%) in infiltrating lymphocytes and monocytes with a decrease in HLA-DR and intercellular adhesion molecule 1, vascular cell adhesion molecule 1 in tubular cells was also described.[37]

In chronic AMR, gene expression analysis of biopsies post-ECP revealed a potential antifibrotic effect. Notably, there was an upregulation of caveolin-1, a molecule known to modulate TGF-β signaling and potentially counteract fibrotic lesions, alongside a downregulation of CD19, IL-21, PAX5, and the profibrotic surfactant protein A2.[38,44]

To date, clinical studies on ECP have predominantly involved patients with contraindications or those refractory to other therapies. These individuals often present with severely compromised organ function at the start of treatment, which may introduce biases into the results. As reported, in cases of severe organ damage or delayed initiation of therapy, ECP is ineffective in improving outcomes, often leading to graft loss and a return to dialysis.[32,34]

To address the lack of effective methods for stratifying patients, a specific renal function threshold has been proposed to identify those who are most likely to benefit from the procedure. Serum creatinine levels of >276 μmol/L were associated with a higher probability of graft loss at 1 y, with an estimated sensitivity of 80% and specificity of 75%. Levels >412 μmol/L had a sensitivity of 50% and a specificity of 100%.[32] However, the lack of robust and consistent tools to evaluate and monitor treatment response remains a significant challenge, underscoring the need for more reliable biomarkers and monitoring systems.[45]

In consideration of the use of ECP as an add-on therapy (PLEX+IVIG) for the management of acute antibody-mediated rejection, we propose a treatment regimen inspired by the approach used for CLAD after lung transplantation.[13] Specifically, we suggest an initial regimen of 2 cycles per week for the first 2 wk, followed by 1 cycle per week until week 8, with a maximum of 10 cycles (20 sessions), should be used. If eGFR does not demonstrate recovery, treatment should continue with 1 cycle every 2 wk until week 12.

ECP IN THE MANAGEMENT OF RECIPIENTS OF KIDNEY TRANSPLANTS WITH CONCOMITANT VIRAL INFECTION

One of the advantages of ECP is the potential to reduce immunosuppression without inducing transplant rejection, which is particularly beneficial in the presence of

comorbidities such as infections and cancer. In previous HTx studies, plasma levels of cytomegalovirus (CMV) DNA were significantly reduced in ECP-treated patients.[10] A small case report shows a reduction of 90% after 14 d up to 99.9% at 6 mo for BK virus in 1 patient treated with ECP plus everolimus, but after completing ECP there was a rebound. Another patient with CMV had a decrease of 99% of CMV viral load after 3 wk of ECP with valganciclovir and rapamycin, up to negativization at 3 mo.[39]

CONCLUSIONS

Evidence suggests that ECP has the potential to function as an immunomodulatory therapy for kidney transplantation, exhibiting minimal side effects. However, its practical application is restricted by the current body of research. The paucity of research participants and the heterogeneity of research methodologies have resulted in difficulties in interpreting results and developing universally. The results observed in kidney transplant recipients are comparable with those in other SOT, suggesting that ECP may offer benefits. The immunomodulation induced by the procedure allows for the suppression of T-cell activity by inhibiting antigen presentation through the action of Treg, thus potentially decreasing the DSA. Additionally, ECP exerts its effects directly at the transplant site by reducing local inflammation and injury associated with rejection. However, it is important to note that these beneficial effects are not observed when the organ already has significant dysfunction, suggesting that ECP may be more effective when used preventively or during early rejection episodes, rather than for refractory rejection.

Many issues remain unresolved, including the lack of guidelines for using ECP in kidney transplantation and an effective patient stratification strategy. We must develop reliable biomarkers to monitor treatment efficacy and conduct controlled, randomized clinical trials to gain widespread acceptance of ECP in clinical practice. To address these challenges and enhance our understanding of ECP in SOT, the exTra consortium has been established. Its ultimate goal is to conduct a multicenter clinical study on various patient cohorts, aiming to standardize, harmonize, and homogenize the procedure.

REFERENCES

1. Edelson R, Berger C, Gasparro F, et al. Treatment of cutaneous T-cell lymphoma by extracorporeal photochemotherapy. Preliminary results. *N Engl J Med*. 1987;316:297–303.
2. Stępień J, Eggenhofe E. ECP induced apoptosis: how noninflammatory cell death counterbalances ischemia-reperfusion injury. *Transplant Direct*. 2025;11:e1816.
3. Morgando I, Vinnakota J, Zeiser R. Extracorporeal photopheresis: from animal models to clinical practice. *Transplant Direct*. 2025;11:e1824.
4. Girardi M, Berger CL, Wilson LD, et al. Transimmunization for cutaneous T cell lymphoma: a phase I study. *Leuk Lymphoma*. 2006;47:1495–1503.
5. Legitimo A, Consolini R, Failli A, et al. *In vitro* treatment of monocytes with 8-methoxypsolaren and ultraviolet A light induces dendritic cells with a tolerogenic phenotype. *Clin Exp Immunol*. 2007;148:564–572.
6. Garcia-Almeida J, Heger L, Hackstein H. Extracorporeal photopheresis: soluble factors that promote immunomodulation. *Transplant Direct*. 2025;11:e1840.
7. Gatza E, Rogers CE, Clouthier SG, et al. Extracorporeal photopheresis reverses experimental graft-versus-host disease through regulatory T cells. *Blood*. 2008;112:1515–1521.
8. George JF, Gooden CW, Guo WH, et al. Role for CD4+CD25+ T cells in inhibition of graft rejection by extracorporeal photopheresis. *J Heart Lung Transplant*. 2008;27:616–622.
9. Benazzo A, Bagnera C, Ius F, et al. A European multi-center analysis of extracorporeal photopheresis as therapy for chronic lung allograft dysfunction. *Transpl Int*. 2024;36:11551.
10. Barr ML, Meiser BM, Eisen HJ, et al. Photopheresis for the prevention of rejection in cardiac transplantation. *N Engl J Med*. 1998;339:1744–1751.
11. Kobashigawa J, Watanabe J, Shafi H, et al. Clinical and mechanistic outcomes of photopheresis after heart transplantation. *Am J Transplant*. 2013;13(suppl 5). Available at https://atcmeetingabstracts.com/abstract/clinical-and-mechanistic-outcomes-of-photopheresis-after-heart-transplantation/. Accessed May 23, 2025.
12. Rose EA, Barr ML, Xu H, et al. Photochemotherapy in human heart transplant recipients at high risk for fatal rejection. *J Heart Lung Transplant*. 1992;11(4 Pt 1):746–750.
13. Benazzo A, Worel N, Schwarz S, et al. Outcome of extracorporeal photopheresis as an add-on therapy for antibody-mediated rejection in lung transplant recipients. *Transfus Med Hemother*. 2020;47:205–213.
14. Alemanno S, Jaksch P, Benazzo A. Extracorporeal photopheresis in lung transplantation: present applications and emerging research. *Transplant Direct*. 2025;11:e1831.
15. Montgomery RA, Loupy A, Segev DL. Antibody-mediated rejection: new approaches in prevention and management. *Am J Transplant*. 2018;18:3–17.
16. Piñeiro GJ, De Sousa-Amorim E, Solé M, et al. Rituximab, plasma exchange and immunoglobulins: an ineffective treatment for chronic active antibody-mediated rejection. *BMC Nephrol*. 2018;19:261.
17. Nankivell BJ, Borrows RJ, Fung CL-S, et al. The natural history of chronic allograft nephropathy. *N Engl J Med*. 2003;349:2326–2333.
18. Akkaya B, Oya Y, Akkaya M, et al. Regulatory T cells mediate specific suppression by depleting peptide—MHC class II from dendritic cells. *Nat Immunol*. 2019;20:218–231.
19. Ono M, ed. *Regulatory T-Cells: Methods and Protocols*. Vol 2559. Springer US; 2023. doi:10.1007/978-1-0716-2647-4
20. Marie JC, Letterio JJ, Gavin M, et al. TGF-β1 maintains suppressor function and Foxp3 expression in CD4+CD25+ regulatory T cells. *J Exp Med*. 2005;201:1061–1067.
21. Rubtsov YP, Rasmussen JP, Chi EY, et al. Regulatory T cell-derived interleukin-10 limits inflammation at environmental interfaces. *Immunity*. 2008;28:546–558.
22. Chinen T, Kannan AK, Levine AG, et al. An essential role for the IL-2 receptor in Treg cell function. *Nat Immunol*. 2016;17:1322–1333.
23. Perrot I, Michaud HA, Giraudon-Paoli M, et al. Blocking antibodies targeting the CD39/CD73 immunosuppressive pathway unleash immune responses in combination cancer therapies. *Cell Rep*. 2019;27:2411–2425.e9.
24. Wardell CM, Boardman DA, Levings MK. Harnessing the biology of regulatory T cells to treat disease. *Nat Rev Drug Discov*. 2024;24:93–111.
25. Zhao DM, Thornton AM, DiPaolo RJ, et al. Activated CD4+CD25+ T cells selectively kill B lymphocytes. *Blood*. 2006;107:3925–3932.
26. Wei YX, Sun B, Xiao L, et al. Infusion of lymphocytes treated with 8-methoxypsoralen and ultraviolet a light induces CD19+IL-10+ regulatory B cells and promotes skin allograft survival. *Transplant Proc*. 2018;50:3906–3910.
27. Wang L, Ni M, Hückelhoven-Krauss A, et al. Modulation of B cells and homing marker on NK cells through extracorporeal photopheresis in patients with steroid-refractory/resistant graft-vs.-host disease without hampering anti-viral/anti-leukemic effects. *Front Immunol*. 2018;9:2207.
28. Catalán D, Mansilla MA, Ferrier A, et al. Immunosuppressive mechanisms of regulatory B cells. *Front Immunol*. 2021;12:611795.
29. Piñeiro GJ, Lazo-Rodriguez M, Ventura-Aguiar P, et al. Extracorporeal photopheresis improves graft survival in a full-mismatch rat model of kidney transplantation. *Transpl Int*. 2023;36:10840.
30. Lamioni A, Carsetti R, Legato A, et al. Induction of regulatory T cells after prophylactic treatment with photopheresis in renal transplant recipients. *Transplantation*. 2007;83:1393–1396.
31. Kusztal M, Kościelska-Kasprzak K, Gdowska W, et al. Extracorporeal photopheresis as an antirejection prophylaxis in kidney transplant recipients: preliminary results. *Transplant Proc*. 2011;43:2938–2940.
32. Tamain M, Sayegh J, Lionet A, et al. Extracorporeal photopheresis for the treatment of graft rejection in 33 adult kidney transplant recipients. *Transfus Apher Sci*. 2019;58:515–524.

33. Gregorini M, Del Fante C, Pattonieri EF, et al. Photopheresis abates the anti-HLA antibody titer and renal failure progression in chronic antibody-mediated rejection. *Biology*. 2021;10:547.
34. Granados SF, Tagarro EF, Puga AR, et al. Extracorporeal photopheresis and renal transplantation. *Nefrol Engl Ed*. 2020;40:687–689.
35. Lai Q, Pretagostini R, Gozzer M, et al. Multimodal therapy with combined plasmapheresis, photoapheresis, and intravenous immunoglobulin for acute antibody-mediated renal transplant rejection: a 2-year follow-up. *Transplant Proc*. 2011;43:1039–1041.
36. Augusto J, Gatault P, Sayegh J, et al. Successful treatment of acute kidney allograft rejection using extracorporeal photopheresis in the context of post-transplant lymphoproliferative diseases: three successive cases. *Transpl Int*. 2021;34:2415–2417.
37. Dall'Amico R, Murer L, Montini G, et al. Successful treatment of recurrent rejection in renal transplant patients with photopheresis. *J Am Soc Nephrol*. 1998;9:121–127.
38. Lionet A, Van Triempon M, Figeac M, et al. Extracorporeal photopheresis reduces fibrotic and inflammatory transcriptomic biological marker of chronic antibody-mediated kidney rejection. *Transplant Direct*. 2024;10:e1587.
39. Xipell M, Molina-Andújar A, Cid J, et al. Immunogenic and immunotolerogenic effects of extracorporeal photopheresis in high immunological risk kidney recipients. A single center case series. *J Clin Apheresis*. 2022;37:197–205.
40. Kumlien G, Genberg H, Shanwell A, et al. Photopheresis for the treatment of refractory renal graft rejection. *Transplantation*. 2005;79:123–125.
41. Jardine MJ, Bhandari S, Wyburn KR, et al. Photopheresis therapy for problematic renal allograft rejection. *J Clin Apheresis*. 2009;24:161–169.
42. Gökler J, Aliabadi-Zuckermann A, Zuckermann A, et al. Extracorporeal photopheresis with low-dose immunosuppression in high-risk heart transplant patients—a pilot study. *Transpl Int*. 2022;35:10320.
43. Nogueira F, van Ham S, ten Brinke A. Extracorporeal photopheresis in solid organ transplantation: modulating B cell responses to improve graft survival. *Transplant Direct*. 2025;11:e1833.
44. Arella F, Riquelme P. The potential use of ECP to promote tissue reparative macrophages. *Transplant Direct*. 2025;11:e1812.
45. Veltman H, Iglesias-Escudero M, Martinez-Caceres E. Measuring the immunomodulatory effects of extracorporeal photopheresis in solid organ transplantation. *Transplant Direct*. 2025;11:e1817.