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Extracorporeal Photopheresis for Bronchiolitis Obliterans Syndrome After Lung Transplantation

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Background. Lung transplantation is a therapeutic option for select patients with end-stage lung disease. However, successful lung transplantation is hampered by chronic lung allograft dysfunction, in particular bronchiolitis obliterans syndrome (BOS). Although there is no approved or standard treatment for BOS, which may have several distinct phenotypes, extracorporeal photopheresis (ECP) has shown promising results in patients who develop BOS refractory to azithromycin treatment. **Methods.** We reviewed all relevant clinical data indexed on PubMed from 1987 to 2017 to evaluate the role of ECP in patients with BOS. **Results.** Seven small studies investigated the immunomodulatory effects of ECP in patients after solid organ transplant, and 12 studies reported clinical data specific to ECP therapy for BOS. Studies indicate that ECP triggers an apoptotic cellular cascade that exerts various immunomodulatory effects mediated via increases in anti-inflammatory cytokines, a decrease in proinflammatory cytokines, and an increase in tolerogenic regulatory T cells. Clinical evidence derived from relatively small single-center studies suggests that ECP therapy is associated with improvement or stabilization in lung function and sustainable, statistically significant, decreases in the rate of lung function decline in patients with BOS. Additionally, when adverse event data were reported, ECP was generally well tolerated. None of the comparative studies were randomized. **Conclusions.** Immunomodulation mediated via ECP is a rational therapeutic option that may improve clinical outcomes in patients with BOS, particularly in the context of in-depth patient phenotyping as part of a stratified approach to treatment; good quality randomized controlled trials are needed to confirm observational findings.

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OVERVIEW OF CHRONIC REJECTION AFTER LUNG TRANSPLANTATION

Lung transplantation is a therapeutic option for select patients with end-stage lung disease.^{1,2} However, according to the International Society for Heart and Lung Transplantation

(ISHLT) Registry, the median survival of patients transplanted between January 1990 and June 2014 is only 5.8 years.²

Poor outcomes are often associated with chronic lung allograft dysfunction (CLAD) comprising multiple distinct phenotypes,³ for which an appropriate nomenclature is currently being developed to allow uniformity of description and grading of severity.^{1–3} Bronchiolitis obliterans syndrome (BOS) is the most common form of CLAD (Figure 1), affecting 50% of patients within 5 years and 76% of patients within 10 years, and remains the most common cause of death beyond the first year after lung transplantation.^{2–4} Bronchiolitis obliterans, a histologic diagnosis, is characterized by abnormal remodeling of the membranous and respiratory bronchioles, resulting in an obstructive pulmonary function defect (BOS, defined by forced expiratory volume in 1 second [FEV₁] ≤80% of baseline), with high-resolution computed tomography imaging revealing air trapping, and no or minimal airway inflammation.^{3,4} The mechanisms of bronchiolitis obliterans involve both alloimmune-mediated and alloimmune-independent pathways, which lead to fibroproliferative responses.^{3,4} Subsequently, the resulting fibroproliferative scarring in the bronchioles leads to narrowing and obstruction of the airway lumen, airflow limitation, and breathlessness. Staging for BOS is accomplished according to spirometry-measured changes in FEV₁ that cannot be explained by other causes.^{3–5}

Observational studies suggest that BOS-related decline in FEV₁ is not continuous. In general, FEV₁ decline is steepest during the first 6 months and can stabilize thereafter.⁵ However,

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FIGURE 1. Classification of lung allograft dysfunction (flowchart). ARAD, azithromycin-responsive allograft dysfunction; BOS, bronchiolitis obliterans syndrome; CLAD, chronic lung allograft dysfunction; FVC, forced vital capacity; RAS, restrictive allograft syndrome. Reprinted from Verleden G, et al. *J Heart Lung Transplant* 2014;33:127-33.³

the natural history of BOS varies substantially between patients, with rapid onset of BOS, female sex, pretransplant diagnosis of idiopathic pulmonary fibrosis, and single-lung transplantation associated with worse pulmonary function after BOS onset,⁵ which may impact prognosis and therapeutic options.

Currently, there is no approved or standard treatment for BOS beyond azithromycin, and successful treatment is defined as stabilization or reduction in the rate of FEV₁ decline. An important focus of treatment of BOS patients is optimizing immunosuppression to prevent further lung allograft rejection. Augmentation of maintenance immunosuppression (typically a triple-drug regimen combining a calcineurin inhibitor, an antimetabolite, and a corticosteroid) through switching cyclosporine to tacrolimus is currently the most common initial treatment approach, although traditional immunosuppressive measures also include repeated high-dose methylprednisolone and augmentation of immunosuppressive therapy with antithymocyte globulin.^{6,7} Other treatment strategies include inhaled cyclosporine, cell-cycle inhibitors, mammalian target of rapamycin inhibitors, and total lymphoid irradiation.⁸⁻¹⁴ Although each of these regimens effectively suppresses the immune system, most patients do not have a durable response, and the clinical course is characterized by progressive decline in lung function while exposing patients to all of the side effects of augmented immunosuppression.

Azithromycin has been shown to improve lung function and overall survival in a subset of patients with BOS in observational and randomized trials.^{9,14} Initially, azithromycin responders were defined as having neutrophilic-reversible allograft dysfunction, because this subset is characterized by bronchoalveolar lavage neutrophilia. Notably, a phenotype of neutrophilia did not predict benefit in a randomized, controlled trial.¹⁴ Unless contraindicated, a 3-month trial of azithromycin has been recommended by the ISHLT/American Thoracic Society/European Respiratory Society clinical practice

guidelines in all lung transplant recipients who develop a decline in lung function consistent with BOS onset.¹⁵

The majority of reports of uncontrolled treatments for BOS have demonstrated a reduction in the rate of decline rather than improvements in lung function.^{6-8,10-13,16,17} Patients with BOS often experience a progressive deterioration in lung function and, ultimately, graft failure and death. Extracorporeal photopheresis (ECP), first approved by the United States Food and Drug Administration for the treatment of cutaneous T-cell lymphoma in 1988, has shown positive results in patients who develop CLAD and do not respond to azithromycin treatment.¹⁸ Here, we review the role of ECP in patients with BOS.¹⁸

ROLE OF ECP IN BOS

Extracorporeal photopheresis is a cell-based, immunomodulatory treatment that combines leukapheresis and photodynamic therapy. During ECP, blood is separated by centrifugation, and red blood cells and plasma are returned to the patient. White blood cells (leukocytes) are treated ex vivo with methoxsalen and exposed to long-wavelength ultraviolet A light (~1.5 J/cm²).^{7,19} The photoactivated white blood cells are then returned to the patient. The only approved integrated instruments designed to carry out ECP are the THERAKOS UVAR-XTS and CELLEX systems, which have the advantage of carrying out the procedure using a sterile, closed-loop system. In addition to being approved as palliative therapy for cutaneous T-cell lymphoma, ECP is being evaluated in graft-versus-host disease (acute and chronic), rejection after organ transplantation, and select autoimmune diseases (eg, systemic sclerosis).^{20,21} One treatment cycle consists of ECP administered on 2 consecutive days. Although there are variations in treatment regimens, a common treatment course consists of 1 cycle every 2 weeks

for the first 2 months, followed by once monthly cycles; the optimum treatment duration has not been established and long-term continuation has been reported to maintain clinical response.⁷

Immunomodulatory Effects

A number of studies have examined the immunomodulatory effects of ECP therapy in patients after solid organ transplantation (Table 1).²²⁻²⁸ Treatment with ECP triggers an apoptotic cellular cascade by inducing DNA cross-linking in leukocytes. After reinfusion, the apoptotic leukocytes are phagocytosed by immature dendritic cells that subsequently mature into antigen-presenting cells.^{22-24,29,30} This cascade exerts various immunomodulatory effects mediated via an increase in anti-inflammatory cytokines, a decrease in proinflammatory cytokines, a decrease in the cytotoxic capacity of natural killer cells, an increase in neutrophil granulocyte apoptosis, and an increase in tolerogenic regulatory T (T_{reg}) cells.³¹⁻³⁴ Additionally, ECP induces the differentiation of monocytes into immature dendritic cells that produce substantial amounts of the anti-inflammatory cytokine interleukin-10.³⁵ Most of the studies reviewed here have used a THERAKOS photopheresis system.^{22,23,25-27}

Several studies found that ECP therapy increased or stabilized T_{reg} cells in solid organ transplant recipients.²²⁻²⁷ These data are notable because T_{reg} cells are known to modulate immune responses of other cells and promote immune tolerance. For example, 4 of 10 children with chronic heart and lung transplant rejection (ie, BOS) received ECP in addition to traditional immunosuppressive treatment.²² Evaluation of blood samples before and after each cycle of ECP therapy demonstrated that T_{reg} cell levels were significantly increased in patients who received ECP compared with those who did

not.²² A similar increase in T_{reg} cell levels was observed in both adults ($n = 10$) and children ($n = 2$) with renal transplants who received prophylactic ECP treatment.^{23,25} Compared with controls, ECP increased the percentage of T_{reg} cells in both studies.^{23,25} Moreover, nearly 80% of heart transplant recipients who received ECP for prophylaxis or treatment of acute cellular rejection showed an increase in T_{reg} cells, compared with control heart transplant recipients who did not receive ECP therapy.²⁶

The effects of ECP on T_{reg} cells also have been demonstrated in adult lung transplant recipients after developing BOS. In 3 of 5 adult lung transplant recipients who developed BOS, ECP treatment led to slightly increased or stabilized T_{reg} cell levels and stabilization of lung function.^{24,27} Similar results were observed in a case study of an adult patient with BOS where the clinical response to ECP therapy paralleled an increase in T_{reg} cells.²⁷ These studies suggest that the percentage of T_{reg} cells increases with ECP therapy.

In addition to effects on T_{reg} cells, studies have shown a shift in cytokine secretion after ECP therapy in patients who underwent solid organ transplantation.^{23,26,28} For example, expression of the proinflammatory cytokine tumor necrosis factor alpha ($TNF\alpha$) decreased in 2 pediatric renal transplant recipients after prophylactic treatment with ECP, compared with transplant recipient controls.²³ Heart transplant recipients who received prophylactic ECP demonstrated a shift toward increased levels of T-helper cell type 2 cytokine, which has anti-inflammatory properties.²⁶ Finally, recent evidence suggests that immunomodulatory effects may contribute to the beneficial effect of ECP in reducing the decline in lung function.²⁸ Serum collected from lung transplant recipients with BOS before and after ECP therapy showed a reduction in the levels of circulating

TABLE 1.
Summary of clinical evidence of ECP-mediated immunomodulatory effects

	Immunomodulatory action	Clinical results
T_{reg} cells	<ul style="list-style-type: none"> Increased T_{reg} cells in 4 patients with chronic heart and lung transplant rejection treated with ECP²² Increased Foxp3⁺ T_{reg} cells in 2 renal transplant patients after ECP²³ Slight increase or stabilization in CD4⁺, CD25⁺ T_{reg} cells in 3 of 5 lung transplant recipients treated with ECP²⁴ Significant increase in T_{reg} cells after ECP treatment in kidney transplant patients ($N = 10$; $P = 0.025$)²⁵ Increased T_{reg} cells in heart transplant patients treated with ECP²⁶ Clinical response to ECP therapy was paralleled by an increase in T_{reg} cells and a decrease of natural killer cells in a patient with progressive BOS after double-lung transplantation²⁷ 	<ul style="list-style-type: none"> NR NR Clinical stabilization in 3 of 5 patients with BOS²⁴ Positive trend for increase in GFR in ECP-treated group²⁵ ~80% of patients responded to ECP therapy with an increase in T_{reg}²⁶ Clinical response to ECP therapy was paralleled by an increase in T_{reg} cells and a decrease of natural killer cells in a patient with progressive BOS after double-lung transplantation²⁷
Shift in cytokine secretion	<ul style="list-style-type: none"> Reduced expression of proinflammatory cytokine $TNF\alpha$ in 2 renal transplant patients after ECP²³ Shift toward anti-inflammatory Th2 cytokine profile in heart transplant patients treated with prophylactic ECP²⁶ ECP associated with a decline in donor-specific antibody levels, antibodies to lung-associated self-antigens, and circulating levels of proinflammatory cytokines, and increased levels of anti-inflammatory cytokines²⁸ 	<ul style="list-style-type: none"> NR 44% of patients responded to ECP therapy with an increase in Th2 cells²⁶ Immunologic changes associated with a 63% reduction in the rate of decline in FEV_1 over 1 y²⁸

GFR, glomerular filtration rate; NR, not reported; Th2, T-helper cell type 2; $TNF\alpha$, tumor necrosis factor alpha.

donor-specific HLA antibodies, antibodies to lung-associated self-antigens (K α 1T, collagen I, and collagen V), and several proinflammatory cytokines.²⁸

Together, these data indicate that ECP therapy has a marked immunomodulatory effect on patients after solid organ transplantation, including patients who develop BOS after lung transplantation. Furthermore, these data suggest the potential clinical benefit of using ECP to treat patients with BOS.

Efficacy and Safety

A number of studies have evaluated ECP therapy in patients with BOS,^{3,36-50} often using THERAKOS photopheresis systems.^{37,38,40-43} Table 2 summarizes the more recent evaluations, which include case studies, retrospective analyses, and 1 prospective trial.^{39-43,47-50} This level of evidence is similar

to that available to date for other therapies considered second/late line in CLAD-BOS.¹⁷ Overall, the case studies reported improvement or stabilization in FEV₁ with no serious side effects or toxicities.³⁶⁻³⁹ Data from the retrospective analyses and prospective clinical trial are similar to those reported in the case studies.^{40-43,47-49} Two single-center, retrospective analyses included comparisons of ECP with other treatments; a long-term retrospective cohort study comparing 48 patients with CLAD (including 34 patients with BOS) undergoing long-term ECP therapy (>10 years for some patients; 3 weeks: 1 cycle per week, 4-6 weeks: 1 cycle fortnightly, then 1 cycle per month if improved/stabilized, progressively lengthening the treatment intervals to 2 months maintenance regimen), with 58 control patients with CLAD (43 with BOS) receiving standard care demonstrated slowing decline or stabilization of lung function after treatment with

TABLE 2.

Summary Of recent case studies and clinical studies evaluating ECP treatment in BOS

Study (type)	Patients, n	BOS status	Efficacy/safety
Villanueva et al, 2000 ³⁹ (retrospective case studies)	14	BOS diagnosed by clinical staging (n = 3) and biopsy (n = 11)	<ul style="list-style-type: none"> Stabilized lung function of patients with BOS 0b or BOS 1, but not BOS 2 or BOS 3
Benden et al, 2008 ⁴⁰ (retrospective)	12	Not reported	<ul style="list-style-type: none"> No adverse reactions to ECP Rate of FEV₁ decline was significantly reduced after ECP ($P = 0.011$).
Morrell et al, 2010 ⁴¹ (retrospective)	60	BOS diagnosed per ISHLT 2002 criteria ⁴⁴	<ul style="list-style-type: none"> Median survival of study cohort: 7.0 y; 4.9 y post-ECP Significant difference in FEV₁ rate of decline before and after ECP treatment: 87.1 mL/mo ($P < 0.0001$) Improved lung absolute FEV₁ in 25% patients Median survival: 7.5 y after transplant, 4.7 y after BOS, 2.6 y after ECP
Jaksch et al, 2012 ⁴² (prospective)	51	BOS staging per ISHLT classification ⁴⁶	<ul style="list-style-type: none"> 61% of patients responded ($\pm 5\%$ change FEV₁ from baseline) to ECP. Responders had significantly longer survival compared to nonresponders ($P = 0.001$). ECP responders had significantly longer survival than patients with no ECP treatment ($P = 0.05$).
Greer et al, 2013 ⁴³ (retrospective)	65	RAS, neutrophilic CLAD, and rapid decliners (64 patients deteriorated on azithromycin; 1 had azithromycin contraindications)	<ul style="list-style-type: none"> 54% of patients progressing on azithromycin responded to ECP.
Del Fante et al, 2015 ⁴⁷ (retrospective)	48	BOS diagnosed per ISHLT 2002 criteria ⁴⁴	<ul style="list-style-type: none"> ECP treatment responders ($\pm 10\%$ change FEV₁ from baseline) had longer PFS compared with nonresponders (401 vs 133 days). Among ECP patients, the FEV₁ slope flattened out after initial decline ($P = 0.001$). No ECP side effects or complications
Pecoraro et al, 2017 ⁴⁸ (retrospective)	54	BOS diagnosed per ISHLT 2002 criteria ⁴⁴	<ul style="list-style-type: none"> Stabilization of lung function in 80% of ECP patients.
Moniodis et al, 2017 ⁴⁹ (retrospective)	17	CLAD diagnosed as per published criteria ³ and by analysis of lung biopsies	<ul style="list-style-type: none"> No increase in adverse events or incidence of infections. Significant change of FEV₁ rate of decline by 3 and 6 mo ($P = 0.0005$).
Robinson et al, 2017 ⁵⁰ (retrospective)	15	BOS diagnosed per ISHLT criteria ¹⁵	<ul style="list-style-type: none"> No significant difference between ECP and alemtuzumab for FVC rate, infection and survival Significant decline in lung function after ECP was stopped ($P = 0.003$). 58% of patients died within 12 mo after ECP was stopped.

ECP, without observing any side effects or complications.⁴⁷ Similarly, a retrospective comparison of patients with refractory BOS who received ECP ($n = 17$; 4 weeks: 1 cycle weekly, 1 month: 1 cycle fortnightly, then 1 cycle per month to 6 months) or alemtuzumab ($n = 14$) found a significant decrease in the rate of FEV₁ decline at 6 months after treatment initiation compared to baseline in both groups.⁴⁹ When the results were adjusted for potential confounders, no significant difference between the FEV₁ slope was detected; however, the study arms were small, and the study was underpowered to detect differences in treatment effectiveness.⁴⁹ The retrospective nature of these studies also limits treatment comparison, due to significant differences between treatment groups in terms of baseline demographics and disease characteristics.^{47,49}

One prospective study evaluated ECP therapy in patients with BOS. This single-center, open-label, nonrandomized trial enrolled patients who developed BOS after lung transplantation ($n = 194$).⁴² Patients in the control arm ($n = 143$) received triple-drug immunosuppression therapy (calcineurin inhibitor, mycophenolate mofetil, and prednisolone). Patients in the ECP arm ($n = 51$) received ECP therapy in addition to triple-drug immunosuppression; ECP therapy was administered every 2 weeks for 3 months and every 4 weeks thereafter for 6 or 12 months, depending on ECP response.⁴² Patients who developed BOS within the first 3 years after transplantation showed better response to ECP than patients who developed BOS later. Of the patients treated with ECP, 61% ($n = 31$) responded to therapy (30% with improved FEV₁ and 31% with stabilized FEV₁) and showed sustained stabilization of lung function over 6 months. Additionally, patients receiving ECP therapy had significantly longer survival than those not receiving ECP therapy ($P = 0.046$).⁴² Although these results suggest that certain subgroups of BOS patients might benefit from ECP, there were significant differences between the ECP and control group, particularly with regard to the BOS stage, due to the nonrandomized nature of the study.⁴²

To further understand patient phenotyping and allow prediction of treatment response and possibly prognosis, a retrospective, single-center analysis sought to identify predictors of response to ECP in patients with established CLAD ($n = 65$).⁴³ Patients received ECP therapy biweekly for 3 months, and thereafter, therapy was tapered based on response; ECP therapy was initiated only after a 10% or greater decline of FEV₁ from baseline despite azithromycin treatment. In this study, 54% of patients responded to ECP therapy with FEV₁ stabilization (median follow-up of 1.5 years).⁴³ Moreover, ECP responders (ie, nonprogressive) had longer progression-free survival (401 days) than ECP nonresponders (ie, progressive; 133 days).⁴³ Notably, patients who progressed early during azithromycin (<1 year) were more likely to stabilize with ECP therapy than those progressing later (25 vs 14 patients; $P = 0.03$); however, the study's limitations, such as being single-center, lacking a control group and treatment randomization need to be considered.⁴³ Additionally, analyzed data from patients who had stopped ECP treatment due to withdrawal of reimbursement by health insurance providers, found that lung function significantly declined ($P = 0.003$) within 6 months after treatment cessation.⁵⁰

Overall, data from these studies suggest that ECP therapy is associated with improvement or stabilization in lung function

and sustainable, statistically significant decreases in the rate of lung function decline in patients with BOS. Furthermore, 2 studies reported that 25% to 30% of patients with BOS have an improvement in lung function after treatment with ECP.^{41,42} Extracorporeal photopheresis was generally safe and well tolerated. When reported, ECP side effects include blood loss from the extracorporeal circuit, hypocalcemia due to anticoagulant, mild cytopenia, and catheter-associated bacteremia; however, unlike immunosuppressive therapies, ECP treatment is not associated with an increased risk of infections compared to standard therapy.^{7,51,52} It should also be noted that most of these early studies were not BOS-specific as defined by recent guidelines and may have included patients with various CLAD phenotypes. These data were used to support the inclusion of ECP for the treatment of BOS in clinical guidelines developed by the American Society for Apheresis and the European Dermatology Forum.⁷

CONCLUSIONS AND FUTURE DIRECTIONS

Clinical evidence from several small studies has shown that ECP has a beneficial effect on the rate of lung function decline. However, an ideal treatment would improve lung function rather than merely slow the rate of decline. Patient stratification based on in-depth phenotyping may be the key to improving clinical outcomes, supporting a stratified approach to therapy, inclusive of ECP. Data reviewed here provide the rationale for prospective, rigorously designed studies of ECP in patients who develop BOS after lung transplantation. Utility of ECP in clinical practice is also limited by the associated inconvenience to patients, requiring regular travel to treatment centers over several months or even years,⁵² and variable coverage by private and government based insurance providers.

Currently, there is an ongoing study on record with the United States National Institutes of Health clinical trials registry (<https://clinicaltrials.gov>) that is an observational cohort study examining ECP for the treatment of BOS in Medicare-eligible lung transplant recipients (NCT02181257).¹⁹ This is a registry study with a planned enrollment of 160 patients from multiple centers in the United States to confirm that ECP significantly reduces the rate of FEV₁ decline in patients with BOS that is refractory to standard immunosuppressive drug therapy, and to capture and assess specified patient demographic, treatment-related, diagnostic, functional, and comorbidity-related variables that may predict outcomes after ECP therapy.¹⁹ Notably, ECP treatment of BOS will be reimbursed by Medicare for Medicare beneficiaries when provided as part of any registered clinical research study. As of October 2017, a protocol amendment for this study has been approved which includes the addition of early detection, an randomized controlled trial cohort where ECP will be used as first-line therapy and compared with institutional standard of care, and a cohort of patients with refractory BOS or control randomized patients who become eligible for crossover ECP rescue therapy. The planned enrollment for the randomized controlled trial is 782 patients over 6 years across 20 centers in the United States.⁵³ No studies of ECP therapy for BOS are currently on record with the European Union clinical trials register (<https://www.clinicaltrialsregister.eu>).

Evidence from small studies indicates that immunomodulation mediated by ECP therapy is a rational therapeutic approach that may improve clinical outcomes in patients with BOS. Data from

planned trials are needed to further elucidate the role of ECP therapy in patients with BOS.

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