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**ADJUVANT TREATMENT OF REFRACTORY LUNG TRANSPLANT REJECTION WITH
EXTRACORPOREAL PHOTOPHERESIS**

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Background: Extracorporeal photopheresis is an immunomodulatory technique in which a patient's leukocytes are exposed to ultraviolet-A light after pretreatment with 8-methoxypsoralen (methoxsalen). There have been few reports describing the use of extracorporeal photopheresis in lung transplant recipients. **Methods:** We reviewed our experience using extracorporeal photopheresis in 8 lung transplant recipients since 1992. All 8 patients had progressively decreasing graft function and 7 were in bronchiolitis obliterans syndrome grade 3 before the initiation of photopheresis. One patient had undergone a second transplant operation for obliterative bronchiolitis. Two patients had a pretransplantation diagnosis of chronic obstructive pulmonary disease, 1 α_1 -antitrypsin deficiency, 1 cystic fibrosis, 1 bronchiectasis, 1 idiopathic pulmonary fibrosis, and 2 primary pulmonary hypertension. Before refractory rejection developed, all patients had been treated with 3-drug immunosuppression and anti-T-cell therapy. The median time from transplantation to the start of extracorporeal photopheresis was 16.5 months and the median number of treatments was 6. **Results:** The condition of 5 of 8 patients subjectively improved after extracorporeal photopheresis therapy. In these 5 patients photopheresis was associated with stabilization of the forced expiratory volume in 1 second. In 2 patients there was histologic reversal of rejection after photopheresis. With a

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median follow-up of 36 months, 7 patients are alive and well. Three patients required retransplantation at a median of 21 months after completion of the treatments. Four patients have remained in stable condition after photopheresis. There were no complications related to extracorporeal photopheresis. Conclusion: We believe that this treatment is a safe option for patients with refractory lung allograft rejection when increased immunosuppression is contraindicated or ineffective. (J Thorac Cardiovasc Surg 1999;117:1063-9)

Lung transplantation is recognized as definitive therapy for patients with end-stage pulmonary failure. However, long-term success with lung transplantation has been limited by chronic rejection. Data from 2 centers have demonstrated that chronic rejection refractory to medical therapy may develop in as many as 60% to 80% of lung transplant recipients.¹ Current immunosuppressive strategies commonly involve a triple-drug regimen for maintenance therapy and high-dose steroids and/or antilymphocyte antibodies for rejection episodes. Corticosteroid therapy is associated with significant adverse effects that are related to the duration of use and cumulative drug dose.² Antilymphocytic antibodies are limited by the production of anti-idiotypic antibodies and are associated with the development of viral infections and lymphoproliferative disease. Other treatments used for acute or refractory rejection, such as methotrexate, have been associated with an increased incidence of leukopenia and infectious complications.² The limitations of the currently available immunosuppressive drugs underscore the need for the development of other agents or techniques for the treatment of allograft rejection.

Extracorporeal photopheresis (ECP) is a therapy that produces a clone-specific antilymphocyte immune response. ECP is performed by treating lymphocytes obtained by leukapheresis, with 8-methoxypsoralen (methoxsalen) followed by ultraviolet-A light (UVA) exposure in an extracorporeal circuit. The treated leukocytes are then reinfused to the patient, with the apparent effect of down-regulating a specific immune response. This therapy has been used for the treatment of cutaneous T-cell lymphoma (CTCL), autoimmune diseases, and allograft rejection. There are reports detailing the efficacy of ECP for the treatment and prevention of acute allograft rejection.²⁻¹⁰ Taken together, these reports suggest that ECP is a safe, effective therapy with only minimal side effects.

The literature contains only sporadic reports detailing the use of ECP for the treatment of pulmonary allograft rejection.¹¹ At our institution ECP has been used as res-

cue therapy for patients with chronic rejection refractory to medical therapy. We performed this study to test the hypothesis that ECP may arrest the decline of pulmonary function and improve survival of lung transplant recipients in bronchiolitis obliterans syndrome (BOS) grade 3 with refractory rejection. Although all patients were in BOS grade 3 at the initiation of ECP, our review suggests that ECP may be associated with increased survival and a preservation of pulmonary function.

Patients and methods

Patients. Between 1992 and 1998, eight patients with chronic refractory pulmonary graft rejection were treated with ECP at the University of Minnesota (Table I). All patients were having a progressive loss in pulmonary function and 7 were in BOS grade 3 at the initiation of ECP. Patient 1 had undergone retransplantation for obliterative bronchiolitis with no subsequent improvement in pulmonary function. The median time from transplantation to the development of BOS grade 3 in the ECP group was 12.8 months (range 3-44 months). Seven patients underwent ECP as part of an open label trial that was approved by the University of Minnesota Human Subjects Committee. One patient was treated with ECP before the initiation of the open label trial, on a compassionate use basis with approval from University of Minnesota Human Subjects Committee. During the same time period, a concurrent, nonrandomized comparison group was chosen from transplant recipients with BOS grade 3 who were treated with medical therapy. The median time from transplantation to the development of BOS grade 3 in the comparison group was 27.2 months (range 6-68 months, log rank $\chi^2 = 1.86$, $P = .17$ compared with the ECP group).

Clinical characteristics. Of the 8 patients, 3 were female and 5 were male (Table I). Two patients had a pretransplantation diagnosis of chronic obstructive pulmonary disease (COPD), 1 α_1 -antitrypsin deficiency, 1 cystic fibrosis, 1 bronchiectasis, 1 idiopathic pulmonary fibrosis, and 2 primary pulmonary hypertension. The median age of the patients was 43 years with a range of 13 to 60 years. Four patients had undergone a single lung transplant and 4 had undergone bilateral single lung transplants. The comparison group had similar demographics. Seven of the 20 patients were male. Five patients had a pretransplantation diagnosis of COPD, 7 α_1 -

Table I. Clinical data

Patient (age, sex)	Primary illness	Type of transplant	Time to initiation of ECP (mo)	No. of ECP treatments	Clinical outcome
1 (13, F)	PPH	Bilateral SLT	7	12	Clinically stable, reversal of biopsy-proven rejection
2 (60, M)	COPD	Left SLT	17	3	Retransplant 15 mo after treatment
3 (45, M)	α_1	Right SLT	19	4	Retransplant 21 mo after treatment
4 (43, M)	Bronchiectasis	Bilateral SLT	12	6	Reversal of biopsy-proven rejection
5 (30, F)	PPH	Bilateral SLT	16	6	Clinically stable
6 (41, M)	Cystic fibrosis	Bilateral SLT	7	4	Died 18 mo after treatment
7 (57, F)	COPD	Right SLT	32	8	Retransplant 25 mo after treatment
8 (52, M)	PPH	Left SLT	42	13	Stable

ECP, extracorporeal photopheresis; PPH, primary pulmonary hypertension; COPD, chronic obstructive pulmonary disease; α_1 , α_1 -antitrypsin deficiency; SLT, single lung transplantation.

Table II. Rates of change in FEV₁ per month

Subject	Before ECP					After ECP				
	Rate of change	95% CI	t	P value	No. of data points	Rate of change	95% CI	t	P value	No. of data points
1	.008	-.005, .022	1.3	.22	17	.006	.000, .012	2.2	.04	21
2	-.090	-.107, -.072	-11.3	<.001	13	-.03	-.061, -.002	-2.5	.04	9
3	-.116	-.148, -.084	-7.8	<.001	15	-.007	-.016, .003	-1.8	.12	8
4	-.117	-.19, -.043	-3.6	.006	11	.044	-.007, .094	2.05	.08	9
5	-.090	-.139, -.041	-4.8	.005	7	-.005	-.119, .109	-.57	.67	4
6	-.366	-.562, -.170	-4.6	.004	8	.0005	-.003, .004	.42	.7	5
7	-.014	-.018, -.011	-8.1	<.001	25	-.01	-.019, -.007	-5.6	.001	8
8	-.024	-.030, -.017	-7.8	<.001	19	.006	-.039, .051	.59	.62	4

FEV₁, Forced expiratory volume in 1 second; ECP, extracorporeal photopheresis; CI, confidence interval.

antitrypsin deficiency, 1 Eisenmenger's syndrome, and 1 lymphangiomyomatosis. The median age at transplantation was 44 years with a range of 26 to 61 years. There were no significant demographic differences between the 2 groups.

Immunosuppression. After transplantation, all patients were maintained on a standard 3-drug immunosuppression protocol consisting of cyclosporine (INN: ciclosporin) or tacrolimus, azathioprine or mycophenolate mofetil, and prednisone. Acute rejection episodes were treated with a steroid bolus and taper. Rejection episodes refractory to glucocorticoid therapy were treated with anti-T-cell agents or methotrexate. All 8 patients had previously received at least one course of anti-T-cell therapy (antithymocyte globulin or OKT3). Two patients were treated with methotrexate as rescue therapy.

ECP. PATIENT 1. The COBE Spectra (Cobe Laboratories, Inc, Denver, Colo) primed with red blood cells and albumin was used for the collection of mononuclear cells. Approximately 2 blood volumes (3500-4000 mL) were processed with an average collection of 6.49×10^9 mononuclear cells. The patient was given oral 8-methoxypsoralen 1.5 hours before the procedure was begun. The mononuclear cells were exposed to UVA light for 1.5 hours using the Therakos UVAR

Photopheresis System (Therakos, Inc, Exton, Pa). After the UVA exposure the mononuclear cells were reinfused.

PATIENTS 2 to 8. ECP was performed with the Therakos UVAR Photopheresis System. During each photopheresis treatment, approximately 300 mL of plasma and 240 mL of buffy coat were separated and collected in 6 cycles of blood collection. Subsequently 200 μ g of liquid 8-methoxypsoralen, UVADEX (Therakos) was injected into the buffy coat. The photoactivation of leukocyte-rich mixture occurred during an exposure of 1.5 hours to UVA light. The mixture was reinfused immediately after the procedure.

Clinical follow-up. All 8 patients were followed up in the standard fashion for lung transplant recipients at the University of Minnesota. At scheduled intervals pulmonary function tests were performed. Bronchoscopic graft biopsy specimens were taken on a scheduled basis and as dictated by the clinical course. Medical records were reviewed as necessary to complete the data set.

Statistical methods. Rates of change in forced expiratory volume in 1 second (FEV₁) were determined for each individual subject for the period before ECP and the period after the initiation of ECP by regressing their months after transplantation on FEV₁. Rates of change before ECP were deter-

Fig 1. Rates of decline in FEV₁ before and after ECP. The middle dot along each curve indicates the initiation of ECP. Numbers at each line correspond to the subjects as listed in Table I.

mined from the date that the baseline FEV₁ was set for each subject according to the criteria established by the International Society for Heart and Lung Transplantation (ISHLT).¹ Rates of change after ECP were determined from the start date of ECP treatments. The assumption of linearity was assessed by plotting the FEV₁ against the months after transplantation for each subject individually. No evidence that associations were nonlinear was observed. The β -coefficients resulting from these regressions are the rate of change in FEV₁ per month, and the hypothesis that the β is zero was tested for each subject's rate of change at both time periods. Because of the non-normal distribution of the rates of change, a 1-sample Wilcoxon signed-rank test was performed to assess whether the rate of change in FEV₁ for pre-ECP and post-ECP periods was significantly different from zero. A Wilcoxon matched-pairs signed-rank test was used to determine whether there was a significant difference between rates of change before to after ECP.¹² To better illustrate the rate of change in FEV₁ across subjects before and after ECP, a presentation of each individual subject's regression coefficients (rate of change), 95% confidence intervals, *t* statistics, *P* values, and graphed regression lines are presented both before and after ECP. Survival from the diagnosis of BOS grade 3 (or for patient 1 the initiation of ECP) was determined by means of the Kaplan-Meier method, comparing the group that received ECP with the comparison group. Differences in the survival curves between groups were assessed by means of a log-rank χ^2 test. Statistical analysis was performed with the use of SPSS (SPSS, Inc, Chicago, Ill) and SAS (SAS Institute, Inc, Cary, NC) software.

Results

ECP treatments. The median time from transplantation to the initiation of ECP was 16.5 months (range 7-42 months). The median number of treatments was 6

Fig 2. Kaplan-Meier survival curves comparing patients who underwent ECP to a concurrent, nonrandomized comparison group. Graph includes patients alive at selected points and 95% confidence intervals. Log-rank $\chi^2 = 2.1$; degrees of freedom = 1; *P* = .095.

(range 3-13). There was no evidence of a decline in leukocyte, platelet, or red blood cell count in any patient after the initiation of ECP. No adverse effects were reported from the ECP treatment, and no evidence of an increase in opportunistic infections after ECP was detected.

Pulmonary function tests. We examined the effect of ECP on the rate of decline of FEV₁. Fig 1 depicts individual subject's rate of decline in FEV₁ before and after ECP. In the ECP group, 7 of 8 patients had statistically significant rates of decline in their FEV₁ before ECP. Five of these 7 patients had positive rates of change or rates of change not significantly different from zero after the initiation of ECP. Table I illustrates the individual rates of change before and after ECP. The median slope ($B = -.09$) in the pre-ECP period is statistically different from zero (*P* = .02), whereas the median slope ($B = -.002$) in the post-ECP period is not significantly different from zero (*P* = 1.0). The difference in the rate of decline of FEV₁ before and after ECP is significant with a *P* value of .025.

Clinical efficacy. As depicted in Fig 2, ECP appears to offer a trend toward improved survival when compared with standard therapy. With a median follow-up of 36.4 months (range 4-72), 7 of 8 patients (88%) in the ECP group and 11 of 20 patients (45%) in the comparison group are alive. Four patients are in clinically stable condition, and in 2 of these patients bronchoscopic pulmonary biopsy specimens have demonstrated histologic reversal of a concurrent acute rejection process associated with the onset of ECP. Three patients have required retransplantation for progressive pulmonary failure at 15, 21, and 25 months after ECP.

Fig 3. Pre-ECP transplant lung biopsy specimens from patient 4, demonstrating chronic lymphocytic bronchitis and acute grade 2 rejection.

Fig 4. Post-ECP biopsy specimens from patient 4, demonstrating improved chronic lymphocytic bronchitis and no evidence of rejection.

All 3 patients are in clinically stable condition. One patient died 18 months after ECP of progression of his primary illness. In the comparison group, 3 of 20 patients have undergone retransplantation, and 1 of these patients died in the early postoperative period.

Patients 1 and 4 had pulmonary biopsy specimens that demonstrated reversal of an acute rejection episode associated with ECP. Figs 3 and 4 are biopsy sections from patient 4. The pre-ECP biopsy specimen demonstrates chronic lymphocytic bronchitis and acute grade 2 rejection, and the post-ECP specimen demonstrates improvement in the chronic lymphocytic bronchitis and no evidence of acute rejection.

Discussion

ECP is an apheresis-based immunomodulatory therapy that was first used clinically to treat CTCL. CTCL is a lymphoid malignant disease characterized by the expansion of a single lymphoid clone. After the report by Edelson and associates¹³ that demonstrated ECP to

be highly efficacious for the treatment of CTCL, multiple groups have applied ECP to other diseases, which are characterized by the expansion of a single T-cell clone. ECP has been used successfully to treat pemphigus vulgaris, rheumatoid arthritis, and allograft rejection. In general, ECP is very well tolerated, with only sporadic reports of mild nausea, transient hypotension associated with the apheresis, and rare low-grade fevers after reinfusing the treated lymphocytes. Depletion of the formed blood elements has not been noted.

The dominant mechanism of action by which ECP modulates T cells remains to be identified. However, multiple reports suggest that ECP acts via a variety of mechanisms. First UVA light activates 8-methoxypsoralen (methoxsalen), leading to the cross-linking of DNA and resulting in the inhibition of cell proliferation and subsequent “photodestruction.”¹⁴ This represents only a minor mode of action of ECP since only 2% to 5% of the entire white blood cell pool is affected with each ECP treatment.¹⁴ Second, ECP has been shown to

induce a nonspecific release of inflammatory mediators (tumor necrosis factor- α , interleukin-1, and interleukin-6), affecting the entire immune cell population.¹⁵ Third, ECP induces apoptosis of peripheral blood T-cell populations, which may play an important immunomodulatory role.¹⁶ Last, most authors would suggest that the primary mechanism of action is due to the induction of a clone-specific suppressor T-cell response.¹⁴⁻¹⁷ When ECP results in sublethal cellular injury, a phenotypically altered cell is produced. The altered cell actively immunizes the patient after reinfusion of the treated cells.¹⁸

Multiple reports have been published demonstrating the efficacy of ECP for the treatment or prophylaxis of heart transplant rejection.^{2-10, 19-21} Rose and colleagues⁷ reported the successful use of ECP as adjuvant immunotherapy in 4 heart transplant recipients with elevated levels of panel-reactive antibodies. Meiser and associates⁶ demonstrated that ECP as adjuvant immunotherapy for heart transplant recipients significantly decreased the number of acute rejection episodes without increasing the number of infectious complications. Dall'Amico and colleagues⁴ used ECP in heart transplant recipients with recurrent rejection. In this study ECP reduced the number and severity of rejection episodes and allowed a 44% reduction in the daily immunosuppression therapy. Costanzo-Nordin and coworkers² reported a randomized study of 16 heart transplant recipients in whom ECP was compared with corticosteroid therapy. This study suggested that ECP was as effective as corticosteroid therapy for the treatment of heart transplant rejection and was associated with no significant toxicity. Barr and associates¹⁰ compared ECP with triple-drug immunosuppression to triple-drug therapy alone in 23 heart transplant recipients. They did not identify a difference in the incidence of acute rejection episodes or infections; however, the ECP group demonstrated a trend toward a decreased incidence of heart transplant atherosclerosis (20% vs 36%).

Far fewer reports have been published describing the use of ECP for acute or chronic rejection in lung transplant recipients. Andreau and coworkers¹¹ reported a case in which ECP was used to treat an acute episode of lung rejection in a patient who had a severe infection. This patient had clinical improvement and histologic reversal of the rejection episode. All other published reports detailing the use of ECP for the treatment of lung transplant rejection have been abstracts or letters. O'Hagan and colleagues²² reported the use of ECP in 4 lung transplant recipients with refractory obliterative bronchiolitis. In their series the decline in FEV₁

was stabilized in 3 of 4 patients. Achkar and associates²³ presented the use of ECP in 11 lung transplant recipients with severe BOS. They reported improvement or stabilization in 6 of 11 patients. Slovis, Loyd, and King²⁴ reported the use of ECP in 3 patients with biopsy-confirmed obliterative bronchiolitis. Similar to the other investigators, in their series 3 of 3 patients had stabilization or improvement in pulmonary function.

Our results are consistent with those previously reported. The condition of the majority of our patients improved after the initiation of ECP. As a group, there appeared to be enhanced survival, stabilization in the decline in FEV₁, and in 2 patients there was histologic reversal of a concurrent acute rejection process. Three patients were bridged to retransplantation, and in contrast to the comparison group all patients undergoing retransplantation are alive and well. It is important to note that in the present series ECP was used as rescue therapy and that there was no increase in the rate of infectious complications. Given the favorable results of this review, we have begun to initiate ECP before the development of BOS grade 3 and in any patient in whom additional immunosuppression is contraindicated.

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Discussion

Dr Larry R. Kaiser (*Philadelphia, Pa*). Please describe the characteristics of BOS grade 3. You showed what appeared to be acute rejection. You are seeing a decline in FEV₁. How much of this is an obliterative bronchiolitis picture, and how much is a Fick problem?

Dr Salerno. BOS grade 3 is a clinical diagnosis that suggests that the patients have lost 50% of their FEV₁ since the

time of transplantation. We do not have biopsy data on every patient before and after ECP to suggest that all of them have evidence of obliterative bronchiolitis. However, all these patients had had multiple episodes of acute rejection before the initiation of therapy and documented declines in their pulmonary function, in addition to their ability to do exercise and perform activities of daily living.

Dr David J. Sugarbaker (*Boston, Mass*). There really are not too many ways out of the box when you encounter this chronic, severe rejection. What are some of the contraindications to this therapy, which patients would you determine are not candidates, which ones would be treated by total body irradiation, and how do you select patients for this?

Dr Salerno. The one thing that should be stressed is that this therapy is essentially nontoxic. In most of the studies that have been published, especially in heart transplant recipients, there are no significant adverse effects from this treatment. The one group in whom it may not work is patients who do not have any evidence of a competent immune system, because a competent immune system is needed to react to the autovaccine. I think the only patient who could not undergo this therapy is one who could not undergo the withdrawal of 500 mL of blood—someone who is either volume limited for the machine or who is too hemodynamically unstable to have the procedure.

Dr Walter Klepetko (*Vienna, Austria*). Did the presence of clinical infectious episodes influence your choice of whether to offer the patient ECP?

Dr Salerno. No, it actually did not. Of interest, there was no increased evidence of infectious complications after the initiation of therapy, specifically cytomegalovirus. One of these patients has been treated for cytomegalovirus for a year and still has no increased evidence of infection.

Dr Klepetko. Did you also offer ECP to patients who had repeated episodes of chronic infection within the lung affected by obliterative bronchiolitis before the initiation of therapy?

Dr Salerno. Yes.

Mr Peter Goldstraw (*London, England*). If ECP is so good, why don't you use it earlier? Why don't you use it before transplantation?

Dr Salerno. My hunch is that if this therapy was used earlier, the decline of the pulmonary function would never have gotten as far as it has. One of the problems with this technology is that it is still not approved by the Food and Drug Administration for this application, so there are some issues with reimbursement and not many centers have the machine. I agree with you that it probably should be used earlier. There is some evidence in the heart transplant recipients that prophylactic therapy inhibits evidence of chronic rejection in those patients.