Evidence Table for the Refractory Acute Cardiac Allograft Rejection Indication

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<tr><th rowspan="2">Author/ Year</th><th rowspan="2">Study Design</th><th rowspan="2">Demographics</th><th rowspan="2">Outcome measures</th><th colspan="2">Results</th><th rowspan="2">Methodological Comments</th></tr>
<tr><th>Intervention group</th><th>Control group</th></tr>
<tr><td>Costanzo-Nordin MR, 1992</td><td>Prospective, uncontrolled clinical trial

Inclusion: histological evidence of moderate cardiac Tx rejection despite routine immunosuppressive regimen

Exclusions: leukopenia, hemodynamic compromise

UVAR system; Oral 8-MOP

Up to 2 rounds of photopheresis administered</td><td>N= 7

3 men; 4 women

Age range: 19-64 years</td><td>Change in EMB histology

Efficacy based on EMB results classified as:

Ongoing rejection
Resolving rejection
Absent rejection</td><td>Average 5 months of post-photopheresis follow-up

9 episodes of rejection—5 required 1 photopheresis procedure and 4 required 2 procedures

No adverse events occurred during photopheresis

8/9 rejection episodes successfully treated with photopheresis

Resolution of histological evidence of rejection seen average 33 days after photopheresis

No deaths and 2 infections occurred post-photopheresis (details not provided)</td><td>Not Applicable</td><td>Very small sample size and uncontrolled nature of trial severely limit the usefulness of the results.</td></tr>
<tr><td>Dall'Amico R, 1995</td><td>Prospective, uncontrolled clinical trial

Inclusion: multiple acute rejection episodes (details not provided)

UVAR system; 200 ug 8-MOP administered ex vivo

Photopheresis performed over 2 days interval every 4 weeks for 6 months

Routine immunosuppression regimen: ATG, cyclosporine, azathioprine

Rejection therapy: steroids; OKT3 or methotrexate as needed</td><td>N= 8

6 men; 2 women

Age range: 36-58 years</td><td>Change in EMB histology

Comparison of dose of each immunosuppressive drug before and after photopheresis</td><td>Fraction EMB negative for rejection increased from 13% to 41% after photopheresis

Dose reduction of:

- steroid: 44% (in 7 patients)
- cyclosporine: 21% (in 5 patients)
- azathioprine: 29% (in 3 patients)</td><td>Not Applicable</td><td>Very small sample size and uncontrolled nature of trial severely limit the usefulness of the results.</td></tr>
<tr><td>Dall'Amico R, 1997</td><td>Prospective, uncontrolled clinical trial

Inclusion: history of ≥2 acute rejection episodes during prior 3 months refractory to standard rejection therapy (steroids, OKT3, ATG, or methotrexate)

UVAR system; 100 ug 8-MOP administered ex vivo

2 photopheresis groups:

Group 1—photopheresis performed over 2 days interval every 4 weeks for 6 months
Group 2—photopheresis performed weekly x 1 month then every 2 weeks for 2 months, then monthly for 3 months</td><td>N= 22 (12 in Group 1; 10 in Group 2)

15 men; 7 women

Mean age: 49.8 years in Group 1 and 50.4 years in Group 2</td><td>Change in EMB histology

Grade 0 or 1A considered to represent complete resolution of rejection</td><td><table><tr><th></th><th>Group 1</th><th>Group 2</th></tr><tr><td># drop outs</td><td>1 (lack of vascular access)</td><td>1 (death due to Hep C infection)</td></tr><tr><td># with resolution of rejection (mean time to resolution)</td><td>9/11 (29.5 days)</td><td>9/9 (13.8 days)</td></tr><tr><td># photopheresis treatments/patient</td><td>12</td><td>22</td></tr><tr><td>Mean # rejection relapses per patient during 6 months of photopheresis</td><td>1.36</td><td>0.8</td></tr><tr><td># courses of steroid-based rejection therapy during 6 months of photopheresis</td><td>7</td><td>1</td></tr><tr><td># courses of methotrexate-based rejection therapy during 6 months of photopheresis</td><td>1</td><td>1</td></tr></table>1 patient in Group 1 had herpes zoster infection</td><td>Not Applicable</td><td>Small sample size.

Uncontrolled nature of trial severely limits the usefulness of the results.</td></tr>
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<tr><td></td><td></td><td></td><td></td><td>1 patient in Group 2 had interstitial pneumonia

1 patient in Group 2 had symptomatic hypotension during a photopheresis procedure (pre-existing anemia and low body weight)</td><td></td><td></td></tr>
<tr><td>Giunti G, 1999</td><td>Prospective, uncontrolled clinical trial

Inclusion: history of recurrent acute rejection despite daily triple immunosuppressive therapy

UVAR system; 200 ug 8-MOP administered ex vivo

Photopheresis performed over 2 consecutive days per week x 1 month, then weekly x 1 month, then biweekly x 2 months, then monthly x 2 months

All episodes of acute rejection treated with methylprednisolone and/or ALG</td><td>N= 6

All men

Age range: 50-66 years</td><td>Change in EMB histology</td><td>Moderate acute rejection episodes decreased from 0.4 to 0.07 rejections per month per patient (p<0.02)</td><td>Not Applicable</td><td>Very small sample size.

Uncontrolled

Limited reporting of results.</td></tr>
<tr><td>Dall'Amico R, 2000</td><td>Prospective, uncontrolled clinical trial

Inclusion: history of acute rejection (grade 3A-3B); ≥2 rejection episodes in 3 months prior to photopheresis despite standard immunosuppression therapy (oral methylprednisolone, cyclosporine, azathioprine)

UVAR system; 200 ug 8-MOP administered ex vivo

Photopheresis performed over 2 consecutive days per week x 1 month, then 2 treatments biweekly x 2 months, then monthly x 3 months

Acute rejection treated with hi dose methylprednisolone and/or OKT3</td><td>N= 11

5 men; 6 women

Age range: 35-65 years</td><td>Change in EMB histology

Grade 0 or 1A considered to represent complete resolution of rejection</td><td>2 drop-outs: 1 death due to hepatitis C infection; 1 patient had rejection relapse unresponsive to photopheresis and hi dose steroids

Results of EMB
<table><tr><th>Histological Grade</th><th>Pre-photopheresis (% of biopsies)</th><th>During Photopheresis (% of biopsies)</th></tr><tr><td>Negative (Grade 0)</td><td>25</td><td>27</td></tr><tr><td>1A</td><td>21</td><td>45</td></tr><tr><td>1B</td><td>6</td><td>2</td></tr><tr><td>2</td><td>6</td><td>8</td></tr><tr><td>3A</td><td>29</td><td>17</td></tr><tr><td>3B</td><td>13</td><td>1</td></tr></table>
6 rejections occurred during 60 month post-photopheresis follow-up:

4 reversed with photopheresis
1 reversed with hi dose steroids
1 reversed with methotrexate after failure of steroids and photopheresis

All rejections reversed after mean time of 14.2 days (range 7-32 days)

During photopheresis there was 1 case of interstitial pneumonia and 1 case of symptomatic hypotension in a patient with anemia and low body weight</td><td>Not Applicable</td><td>Small sample size.

Uncontrolled</td></tr>
<tr><td>Lehrer MS, 2001

(submitted by requestor)</td><td>Case study

Each patient had acute heart transplant rejection (Grade III or IV) refractory to standard immunosuppression therapy (cyclosporine, azathioprine, and prednisone) and anti-rejection therapy

3/4 patients began to experience rejection within weeks of transplantation

Details of photopheresis administration were not provided</td><td>N= 4

3 men; 1 woman

Age range: 20-54 years</td><td>Change in EMB histology</td><td>All patients tolerated the photopheresis well

Photopheresis resulted in a change of the rejection status to Grade 0 or I for all 4 patients

2/4 patients experienced a sustained response to photopheresis (4 months and 6 years after completion of photopheresis). The remaining 2 patients had rejection-related complications within 1 year of completing photopheresis that resulted in death</td><td>Not Applicable</td><td>Small sample size.

Not a true clinical trial.

Uncontrolled</td></tr>
</table>

Legend: Tx—transplantation EMB—endomyocardial biopsy 8-MOP—8-methoxypsoralen

Evidence Table for Refractory Chronic Graft versus Host Disease

Author/ Year	Study Design	Demographics	Outcome measures	Results		Methodological Comments
				Intervention group	Control group	
Foss, 2005	Prospective, uncontrolled, single center clinical trial Inclusion: steroid-resistant or refractory cGvHD while on a standard immunosuppressive regimen UVAR system; 8-MOP administered ex vivo 2 ECP groups: Group 1 (n= 16)—ECP performed over 2 day interval every 2 weeks Group 2 (n= 7)—ECP performed over 2 day interval weekly ECP performed til response plateau of ≥ 2 months or progression (details not provided) All episodes of acute rejection treated with methylprednisolone and/or ALG Response assessed monthly while ECP performed and defined as: Skin-- ≥50% improvement in rash; improvement in joint mobility or ability to pinch skin over involved areas Liver-- ≥50% decrease in serum bilirubin GI—decrease frequency of stools	N= 25 (23 adults) 16 men; 7 women Age range: 18 - 59 years	Overall response rate (response in ≥ 1 area of disease) overall survival correlation between clinical parameters and response to ECP was determined Change in dose of immunosuppression drugs	ECP performed for a median of 9 months (range 3-24 months) Overall response rate= 64% 20/ 25 patients: improvement of cutaneous manifestations of cGvHD 6/13 patients: healing of oral mucosal ulcerations 3/6 patients: increased flexibility of joints 1/25 patient: 50% improvement of DLCO 1/25 patient: resolution of diarrhea Median survival= 51 months (measured from day 0 of transplantation) Median survival for responders v. non-responders not significantly different 15 patients had serious adverse events (not ECP related) 1 patient discontinued ECP due to primary disease recurrence 10 deaths reported but details not provided Dose reduction/discontinuation of: - steroid: 11 patients - MMF: 12 patients - tacrolimus: 5 patients No significant correlation found between various clinical parameters and response	Not applicable	Small sample size Lack of control group No patients ≥65 years of age studied
Garban, 2005	Prospective, uncontrolled, single center clinical trial Inclusion: steroid-resistant acute or cGvHD Cobe system used to separate cells; 8-MOP added ex vivo 6 courses of ECP given during the first 3 weeks (induction regimen); if complete response or no response seen, no more courses given; if partial response, 1 course/week given til complete response seen (consolidation regimen) Complete response= total resolution of all	N= 15 chronic Age range: 14-62 years	Complete clinical response Partial clinical response Change in hemoglobin and platelet counts	12 patients with cutaneous involvement had complete response; most responses occurred in the first weeks of treatment Cutaneous and GI involvement resolved in parallel fashion; hepatic improvement was only transient; stabilization of bronchiolitis obliterans occurred without need for steroids 4 patients became totally free of immunosuppression for more than 1 year 6 patients died from relapse of malignant disease 4/15 patients developed thrombocytopenia; most patients did not receive RBC transfusions Duration of response (range): none to 72 months	Not applicable	Small sample size Lack of control group No patients ≥65 years of age studied Only general statements provided regarding the response to treatment; lacking detailed listing of data/results.

	manifestations of cGvHD and discontinuation of all immunosuppression drugs Partial response= ≥ 50% resolution of skin manifestations or 100% resolution but continuation of immunosuppression; ≥50% improvement in one involved organ (details not provided)					
Couriel, 2005	Retrospective chart review, single center Inclusion: all patients regardless of age with steroid-refractory cGvHD who were treated with ECP between 01/98 and 10/02 cGvHD diagnosis based on clinical manifestations, not the date of onset UVAR system; 8-MOP administered ex vivo ECP performed 2-4x/week til partial response observed, then # of treatments was decreased by 1/week; maintenance consisted of 2 treatments every 2 weeks; treatment discontinuation, amount of titration, and duration was determined by treating physician	N= 71 33 men; 38 women Age range: 5-70 years (median= 39 years)	Response to therapy (complete, partial, mixed or no response) Non-relapse mortality Overall survival Predictors of non-relapse mortality, and timing of the response were also analyzed	Overall response rate: 61% (n= 43; 14 complete response, 29 partial response) Median time from onset of ECP to complete response: 27 days (13-238) 30/43 patients maintained the initial response for a median duration of 18 months (0.4-65 months); the remaining 13 of 43 initial responders progressed after a median of 23 days (16-188) Overall survival at 5 years: 19% Cumulative incidence of non-relapse mortality: 46% Causes of death: GvHD plus infection- 67%, relapse- 29%, infection outside setting of GvHD or its treatment- 2%, hemorrhage- 2% 4 patients with mild, reversible toxicity that did not require discontinuing ECP- abdominal pain (n=1), hypertension (n=1), hypotension (n=1), fever (n=1) thrombocytopenia at onset of ECP was associated with a lower response response to ECP and platelet count at initiation of ECP were the strongest predictors of non-relapse mortality	Not applicable	Retrospective design lack of control group Unsure of number of pediatric patients and how pediatric results impacted the overall results Used the new definition of chronic GvHD to categorize patients
Rubegni, 2005	Prospective, uncontrolled, single center clinical trial Inclusion: patients with steroid-refractory cGvHD UVAR system; 8-MOP administered ex vivo Frequency of ECP was not stated	N= 32 20 men; 12 women Age range: 18-60 years	Response to therapy (per organ of involvement) Overall outcome calculated using the following categories: Determinant= complete response in all involved organs + ≥50% reduction in immunosuppression Good= status assigned if outcome is between determinant and ineffective Ineffective= disease progression in an organ, or need to increase immunosuppression, or complete response	Overall outcome: 78% responders (22% Determinant, 56% Good) ; 22% non-responders Minor side effects noted (slight hypotension, venipuncture site hematomas)	Not applicaable	Small sample size Lack of control group Lack of information regarding ECP regimen

			not seen in any organ + immunosuppression not reduced by ≥50% Score of Determinant or Good= responder; Ineffective= non-responder			
Ilhan, 2004	Case study, uncontrolled Inclusion: patients with steroid-refractory Cutaneous and/or visceral cGvHD UVAR system; 8-MOP administered ex vivo ECP performed over 2 consecutive days every 4 weeks til GvHD signs/symptoms resolved (8 months maximum)	N= 8 2 men; 6 women Age range: 17-45 years	Response to therapy (per organ of involvement) Change in dose of immunosuppression drugs	6/8 patients had a favorable response (e.g., improvement in respiratory function, complete resolution of cutaneous and oral mucosal lesions, regression of cholestatic parameters) 1 patient experienced Grade 4 thrombocytopenia	Not applicable	Observational study design Small sample size Lack of control group No patients ≥65 years of age studied Only general statements provided regarding the response to treatment; lacking detailed listing of data/results. For example, according to the authors there was a reduced need for hospitalization but no data were provided to support this statement.
Apisarnthanarax, 2003	Retrospective chart review, single center Inclusion: steroid-refractory or dependent cutaneous cGvHD who were treated with at least 4 weeks of ECP between 09/98 and 08/01 cGvHD diagnosis based on date of onset after transplantation (>100 days) UVAR or UVAR XTS system; 8-MOP administered ex vivo ECP performed using varying schedules and intensity depending on disease severity over the 36 month study period	N= 32 Men: women ratio= 1:1.3 Age range: 5-70 years (30 adults)	Response to therapy (complete, partial, steroid-sparing) Overall and cGvHD-related mortality	34% of patients had steroid-refractory disease 66% had steroid-dependent disease Median number of ECP sessions= 6/month Median number of total sessions= 34 ECP sessions discontinued due to: - lack of response or response plateau in 10 patients - resolution of disease in 5 patients - death due to visceral GvHD progression or infection in 5 patients - access difficulty in 1 patient - central line infection in 1 patient - fluid overload in 1 patient - deep vein thrombosis in 1 patient Overall response rate= 56% Complete response rate= 22% Responders received median of 6 sessions and nonresponders received a median of 7 sessions/month	Not applicable	Retrospective design lack of control group Used the old definition of chronic GvHD to categorize and select patients for inclusion High variability regarding ECP regimen used for each patient

				18/28 (64%) initially on steroids had a 50% reduction in dose (6/18 eventually discontinued all steroid use) 3 patients had complications related to the indwelling catheter Minor treatment-related side effects such as transient hypotension noted but not quantified		
Seaton, 2003	Prospective, uncontrolled, single center clinical trial Inclusion: patients with steroid-refractory cGvHD UVAR or UVAR XTS system; 8-MOP administered either IV or ex vivo ECP performed over 2 consecutive days every 2 weeks for 4 months then monthly; at 6 months a decision was made to halt or continue treatment depending on clinical response and patient preference	N= 28 20 men; 8 women Age range: 18-51 years	Response to therapy (per organ of involvement) Clinical response= >25% change in score + stable or reduced immunosuppression doses	Median duration of treatment: 6 months (range, 1-58) Cutaneous outcome: 8/21 responders at 3 months; 10/21 at 6 months; complete remission in 1/21 Hepatic outcome: 7/25 responders at 3 months Pulmonary outcome: median vital capacity in 8 patients reduced by 2% 5 patients had severe complications: 4 deaths due to advanced cGvHD, 1 case of ARDS that fully resolved Pre-treatment immunosuppression doses remained stable in 15/28, were reduced in 9/28, and were increased in 4/28	Not applicable	Small sample size Lack of control group No patients ≥65 years of age studied
French, 2002	Retrospective, uncontrolled, single center clinical study Inclusion: patients with cGvHD that developed >100 days after transplantation UVAR system; 8-MOP administered orally ECP performed over 2 consecutive days once a month (total duration of treatment not stated)	N= 12 7 men; 5 women Age range: 25-59 years	Response to therapy (per organ of involvement): complete response, partial response, no change	Response rate: Cutaneous- 8/12 (2 complete responses) Musculoskeletal- 5/6 (1 complete response) Oral/mucosal- 5/5 (0 complete response) Hepatic- 2/2 (1 complete response) 9/12 patients had a decrease in the dose of at least 1 immunosuppressive drug	Not applicable	Retrospective study design Small sample size Lack of control group No patients ≥65 years of age studied Used the old definition of chronic GvHD to categorize and select patients for inclusion Focus of study was on assessing the correlation of ECP response with degree of T cell clonality, and not on health outcomes. Safety/toxicity not addressed.
Child, 1999	Case study, uncontrolled Inclusion: refractory cGvHD UVAR system; 8-MOP administered ex vivo ECP performed 2x a month for 4 months, then 1x a month for 3 months	N= 11 9 men; 2 women Age range: 18-47 years	Response to therapy (per organ of involvement)	3 drop-outs: 1 death from cyclosporine-induced renal failure; 1 pneumonia that was successfully treated and patient restarted on ECP; 1 withdrawal after 4 months by patient request Overall improvement rate= 48% In majority of patients the improvement in skin disease was greater during the first 4 months of treatment than during the next 3 months	Not applicable	Observational study design Small sample size Lack of control group

				All patients able to reduce dose of immunosuppressive drugs Response rate: Cutaneous- 10/10 (0 complete response) Oral/mucosal- 2/4 (0 complete response) Hepatic- 1/6 (0 complete response) Pulmonary- 2/5 (0 complete response) No significant side effects		
Smith, 1998	Prospective, uncontrolled, single center, pilot clinical study Inclusion: refractory cGvHD UVAR system; 8-MOP administered orally—dose of 8-MOP adjusted based on serum levels ECP performed over 2 consecutive days every 3 weeks then 2-3x per week; frequency of treatment then modified on an individual basis	N= 18	Response to therapy (per organ of involvement) : complete response, partial response, no response	3 complete responses 3 partial responses 2 responses with progression of disease 10 no response 11/18 deaths related to GvHD progression, primary disease relapse, and/or infection Toxicities included: GI upset, catheter-related complications (n= 5) including sepsis (n= 4) , increased need for red blood cell and platelet transfusions (n= 1)	Not applicable	Small sample size Lack of control group Variable administration of ECP Used the old definition of chronic GvHD to categorize and select patients for inclusion
Greinix, 1998	Case study, uncontrolled Inclusion: all consecutive patients with refractory cGvHD that were treated with ECP since 1993 UVAR system; 8-MOP administered ex vivo ECP performed over 2 consecutive days every 2 weeks for 3 months and then every 4 weeks until resolution of sign/symptoms of cGvHD	N= 15	Response to therapy (per organ of involvement): complete response, partial response, no change, no response Survival	Response rate: Cutaneous- 15/15 (12 complete responses) Musculoskeletal- 4/4 (0 complete response) Oral/mucosal- 11/11 (11 complete response) Hepatic- 9/10 (7 complete response) Ocular- 5/6 (1 complete response) Thrombocytopenia- 2/3 (2 complete responses) Survival: 14/15 after median follow-up of 15 months; the 1 death was due to relapse of non-Hodgkin's lymphoma	Not applicable	Observational study design Small sample size Lack of control group
Besnier, 1997	Case study, uncontrolled Inclusion: steroid-refractory or intolerant cGvHD Cobe system used to separate cells; 8-MOP added ex vivo ECP performed over 3x per week for 3 weeks and then frequency tapered per sign/symptoms of cGvHD	N= 5 (only 3 were adults) Age range: 26-42 years	Response to therapy (per organ of involvement) Need for immunosuppression	42 year old patient had initial improvement without immunosuppressive drugs then relapse of cutaneous signs/symptoms 7 months after discontinuing cGvHD 39 year old patient had significant improvement of muscular cGvHD after 3 weeks of ECP along with decrease in immunosuppressive drug regimen; by 3 months patient had regained normal strength and all immunosuppression drugs stopped; clinically stable at 1 year 26 year old patient with severe bronchiolitis obliterans necessitating placement on wait list for lung had slight decrease in steroid dose after ECP treatments; clinically stable at 6 months but still awaiting transplantation	Not applicable	Observational study design Small sample size Lack of control group

Legend: cGvHD—chronic graft versus host disease; 8-MOP—8 methoxypsoralen

Evidence Table for the Pemphigus/Pemphigoid Indication

Author/ Year	Study Design	Demographics	Outcome measures	Results		Methodological Comments
				Intervention group	Control group	
Shih et al. 2005	Review: Treatment of PV : current and Emerging.	Re: ECP-N=13 patients in 6 studies (3 by Rook) – Age 31-78 yrs. Mean 46.5	Stop progression: All progressed.	NA. All 13 patients in 6 studies were treated with ECP	None	Underpowered, too small sample sizes
Wollina 1999	Retrospective cohort - Short-Time ECP in the treatment of drug-resistant autoimmune Bullous diseases	N=7 31-85 yrs	Complete remission	6 of 7 patients experienced complete remission on 8-methyoxy-psoralen with ECP	None	N=7 Some PV some PB
Liang 1992	Case Report: PV treated with photophoresis	N=1 31 yrs old	Near complete remission	Success	NA	N=1
Rook 1990	Case Reports	N=4	Near complete remission	Partial success for 4 patients	NA	N=4
Gollnick 1993	Case Report	N=1	Near complete remission	Partial success	NA	N=1