Utility and Potential of ECP Immunomodulation in Heart Transplant Patients

Therakos Industry Theatre Session at the International Society for Heart and Lung Transplant Annual Meeting 2018, Nice, France, 12th April 2018

Chairs: Andreas Zuckermann, MD, Medical University of Vienna, Austria and Markus J. Barten, MD PhD, University Heart Center, Hamburg, Germany

Disclosure: All speakers received honoraria from Therakos (Mallinckrodt Pharmaceuticals) to attend the meeting. Presentations included discussions of experimental therapies used off-label in clinical practice and clinical trial settings. The meeting purpose was educational; no promotional material was presented during the sessions.
The first reports for the use of extracorporeal photopheresis (ECP) after heart transplantation date back to the early 1990s. Since then, a limited number of single centre reports have been published, and there remains only one multicentre randomised controlled trial (RCT). In more recent years, an increasing number of centres in Europe and the United States of America have explored the use of ECP in heart transplant patients for the treatment of acute cellular rejection (ACR) and chronic humoral rejection. This report presents a summary of data and case studies presented during a symposium that highlighted the utility and potential application of ECP immunomodulation in heart transplant patients.

**Session 1: ECP Immunomodulation in Heart Transplant – Single Centre Data in Patients with Recurrent or Recalcitrant Rejection**

Jignesh K. Patel, MD PhD, Cedars-Sinai Heart Institute, Beverly Hills, CA, US

- ECP appears to be particularly useful in the management of select heart transplant recipients at high risk of rejection or with a history of recurrent rejection.
- In the long term, ECP may abrogate development of cardiac allograft vasculopathy (CAV).
- Larger studies that focus on clinical outcomes and cellular and immune mechanisms are needed.

ECP is a cell-based immune modulatory therapy (Figure 1). Although little is known about the exact molecular mechanisms involved, evidence suggests that ECP modulates the recipient’s antigen-specific immune responses and inflammation in transplantation by *in vivo* generation of apoptotic leukocytes. Phagocytosis of cells in early apoptosis is known to exert anti-inflammatory effects on antigen presenting cells (APCs) such as dendritic cells (DCs).

In solid organ transplant (SOT), DCs are involved in the induction of tolerance following transplantation and play a key role in regulating the T cell response. Plasmacytoid DCs (pDCs) acquire alloantigens in the allograft and then induce the generation of regulatory T (TREG) cells. Studies have suggested that both pDC and TREG levels increase following ECP treatment.

Although data are limited, ECP appears to be particularly useful in the management of select heart transplant recipients at risk of rejection, with recurrent rejection, or rejection associated with hemodynamic compromise. Table 1 provides a summary of clinical experience of ECP as an add-on therapy to standard triple immunosuppression in heart transplantation patients.

**Table 1. Summary of Clinical Experience of ECP as Add-on Therapy to Standard Triple Immunosuppression in Heart Transplantation**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Population Description</th>
<th>Key Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rose 1992</td>
<td>4</td>
<td>Elevated levels of non-donor-specific anti-HLA antibodies and at high risk for rejection</td>
<td>ECP reduced high levels of PRA, achieved a low number of rejection episodes and resulted in no infectious complications</td>
</tr>
<tr>
<td>Costanzo-Nordin 1992</td>
<td>16</td>
<td>Moderate rejection</td>
<td>ECP may be efficacious in the treatment of moderate rejection in hemodynamically stable heart transplant patients</td>
</tr>
<tr>
<td>Meiser 1994</td>
<td>15</td>
<td>Preventive RCT</td>
<td>ECP reduces number of rejection episodes and does not increase risk of infection</td>
</tr>
<tr>
<td>Barr 1998</td>
<td>60</td>
<td>Preventive RCT</td>
<td>ECP decreased the risk of acute cardiac rejection without increasing incidence of infection</td>
</tr>
<tr>
<td>Barr 2000</td>
<td>23</td>
<td>Preventive RCT</td>
<td>ECP is capable of decreasing the severity of chronic rejection manifesting as post-transplant graft intimal hyperplasia</td>
</tr>
<tr>
<td>Kirklin 2006</td>
<td>36</td>
<td>HCR with recurrent/recalcitrant rejection, or needing prophylaxis in the presence of DSA</td>
<td>ECP reduces the risk of subsequent hemodynamic compromise rejection and/or death from rejection when initiated for patients with high rejection risk</td>
</tr>
<tr>
<td>Carlo 2014</td>
<td>27</td>
<td>Paediatric-rejection including HCR</td>
<td>Non-compliant patients showed a trend toward lower survival than ECP-compliant patients</td>
</tr>
</tbody>
</table>

ECP for Recurrent or Refractory Cellular and Humoral Rejections in Heart Transplant Patients: Experience from Cedars-Sinai, Los Angeles, USA

In a single centre study, 532 patients were transplanted between May 1994–March 2012 and 13 patients were found to have recurrent/refractory rejections, treated with ECP. The remaining 519 patients were included as controls. Outcomes assessed included: five year survival and five year CAV, defined as ≥30% stenosis.

Of the 13 patients that were included in the analysis, one patient had ACR only, five patients had ACR and antibody mediated rejection (AMR), three patients had AMR only and four patients had presumed rejection without biopsy but with severe left ventricular (LV) dysfunction and hemodynamic compromise. All patients had multiple rejection episodes. In addition to ECP, six patients also received intravenous corticosteroids, nine patients received plasmapheresis, eight patients received muromonab-CD3, 3 patients received cyclophosphamide, 5 patients received prednisone bolus and 4 patients received intravenous immunoglobulins.

Following ECP therapy, the number of recurrent/refractory rejection episodes decreased significantly (p<0.0001), (Figure 2).

Three of the 13 patients treated with ECP died within five years, resulting in an overall five year survival rate of 76.9% for ECP-treated patients, which was comparable to the control group (75.3%, p=0.76). Of the 13 surviving ECP-treated patients, three developed at least one episode of recurrent rejection, all of which were AMR in nature.

More recently, Cedars-Sinai have been exploring the mechanisms that elude to the effect of ECP. Between 2010 and 2011, seven heart transplant patients underwent ECP over a six month course. Six patients had chronic LV dysfunction and one patient had recurrent AMR on heart biopsy. Inflammatory cytokines were assessed before and after ECP and other outcomes included: change in echocardiographic LV dysfunction, follow-up heart biopsy results, and decline in circulating antibodies.

After ECP treatment, all six patients with chronic LV dysfunction experienced an improvement in cardiac function and the patient with recurrent AMR had no further rejection episodes in follow-up biopsies. A benefit was also seen for antibody response; mean peak panel-reactive antibodies (PRA) reduced significantly following ECP (p=0.022).

Session 2: Immunosuppression-Sparing Potential of ECP – Case Series

Massimo Maccherini, MD, University Hospital Siena, Italy
Markus J. Barten, MD, PhD, University Heart Center, Hamburg, Germany
Johannes Gökler, MD, Medical University of Vienna, Austria

Cases 1 and 2: Use of ECP for Heart Transplant Patients with Concurrent Pathology, Dr Maccherini

• Experience from the University Hospital Siena, Italy, suggests that ECP can be used to manage patients with persistent or refractory rejection.

• ECP provides control of complex pathologies to prolong patient survival without the use of immunosuppressive drugs.

Between 1995-2005, two patients with cancer and concomitant infection or renal impairment underwent heart transplantation at the University Hospital Siena, Italy and were treated with ECP. One patient had lung cancer and was subsequently treated with local radiotherapy and ECP. The patient survived in this condition for almost three years. The second patient, also with lung cancer, was treated for over six years with cyclosporine (CSA) and rituximab. Subsequently, the patient was treated with an ECP only regimen for a period of almost three years before cancer relapse that resulted in death.

Cases 3 and 4: ECP Management of ACR After Heart Transplantation in Patients Weaned from Calcineurin Inhibitors Due to Nephrotoxicity, Dr Barten

• Two case studies reported from the University Heart Center, Hamburg, Germany, provide support for the use of ECP for the management of ACR following heart transplantation in patients weaned from calcineurin inhibitor (CNIs) due to nephrotoxicity.
A 70-year-old man underwent heart transplant in 2012 and was stable for nine months when he subsequently presented with heart failure symptoms and biopsy proven acute rejection (BPAR) (GRADE 1B, International Society for Heart and Lung Transplantation [ISHLT] 1990). The patient was converted to a calcineurin inhibitor (CNI)-free regimen and was treated three times with an ECP only regimen. Following ECP treatment, the patient’s kidney and heart function recovered and BPAR improved to Grade 1A (ISHLT 1990).

A second female patient was converted to a CNI-free regimen but in Month nine after heart transplant the patient developed BPAR, Grade 1B (ISHLT 1990). The patient was treated six times only with ECP and at Month 12 post-transplant the patient had only mild BPAR (Grade 1A, ISHLT 1990).

Case 5: ECP Prophylaxis of Rejection in Heart Transplant Patients, Dr. Barten

- The following case report from the University Heart Center, Hamburg, Germany highlights the possibility for CNI-free treatment in low-risk patients achieved using ECP.

A 59-year-old male was transplanted in 2016 and ECP therapy was initiated three months post-transplantation and continued to Month 18. The patient was converted to a CNI-free regimen at Month six and by Month 12, the patient had no ACR or humoral rejection.

Case 6: ECP Treatment of AMR After Heart Transplantation, Dr. Barten

- A case report from the University Heart Center, Hamburg, Germany, demonstrates the efficacy of ECP for the treatment of AMR after heart transplantation.

A 29-year-old male had renal insufficiency post-heart transplantation and subsequent kidney failure. He was subsequently weaned off tacrolimus to a CNI-free regimen. The patient presented at Month 11 with heart failure symptoms and evidence of humoral rejection with hemodynamic compromise. For acute therapy for humoral rejection, tacrolimus was reintroduced and the patient was treated three times over five months with plasmapheresis, IgG and rituximab. Thereafter, the patient received 22 ECP treatments over a period of eight months as chronic therapy for humoral rejection. Post-ECP times over five months with plasmapheresis, IgG and rituximab. Thereafter, the patient received 22 ECP treatments over a period of eight months as chronic therapy for humoral rejection. Post-ECP therapy, no PRA levels were detected and echocardiogram results showed normal left- and right-ventricular function. The patient is currently receiving tacrolimus and low-dose everolimus and is working full time.

Cases, 7, 8 and 9: ECP and CNI Delay After Heart Transplantation, Dr. Gökler

- The three following case studies report the first experiences from the Medical University Vienna, Austria, where ECP administered on Day one post-transplantation has been successfully used in patients with a risk of sepsis or cancer recurrence.

Currently there are no data on treatment with ECP immediately post-operatively in heart transplant patients to achieve CNI delay and avoid the use of induction therapy. An ECP protocol was developed at the Medical University Vienna, Austria (Box 1) and has been used to treat three heart transplant patients.

### Box 1 - ECP Treatment Regimen Used Immediately Post-Heart Transplantation, Medical University Vienna

- Ten ECP treatments within first month; one treatment every two weeks in Months two and three, and one treatment per month until Month six;
- Low maintenance immunosuppression with tacrolimus (target range 7-10 ng/ml in Month one to three, 5-10 ng/ml, >three months);
- Mycophenolate mofetil (MMF; 2 mg/day);
- In cancer patients, switch from MMF to everolimus (3-8 ng/ml), after two to three weeks;
- Steroids (0.2 mg/Kg starting on Day seven, tapering to 0.03 mg/Kg until end of first year).

The three following case studies provide examples of patients treated with the ECP regimen described in Box 1 following heart transplantation.

**Patient 1:** A 46-year-old with cardiac sarcoma and severe cardiac failure required urgent heart transplantation. The patient had a PRA of 7% and unacceptable antigens (A2, A28, B5, B17). Following transplantation, with exception to the first biopsy, all subsequent post-transplantation biopsies showed no evidence for rejection. There were no remarks for the one year post-operative echocardiogram. The patient has a follow-up of one year and seven months with good quality of life.

**Patient 2:** A 43-year-old patient presented with dilative cardiomyopathy and a high risk of cancer recurrence. All biopsies following transplant were negative (n=7) and echocardiograms at six months post-transplantation showed good cardiovascular function. The patient has a follow-up of one year and one month with excellent quality of life.

**Patient 3:** A 33-year-old patient required urgent transplantation due to severe biventricular failure and had a high risk of sepsis. Post-transplantation, all biopsies were negative, with exception to Week three biopsy (1A/1R). Follow-up echocardiogram showed no remarks and the patient has a follow-up of one year with excellent quality of life.

Six patients in total have now been treated with the ECP regimen described in Box 1 at the Medical University Vienna. To date, all patients are alive, no negative side effects have been observed, and only 2/16 biopsies have shown mild signs of ACR. No AMR has been observed nor have there been any cases of infection in the six month follow-up period.
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Therakos would like to thank all speakers and attendees who participated during the meeting, contributing to an atmosphere of lively scientific debate and collaboration.

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Chairs
Andreas Zuckermann, MD, Medical University of Vienna, Austria
Markus Barten, MD PhD, University Hospital Hamburg, Germany

12:50 – 13:20
ECP Immunomodulation in Heart transplant – Single centre data in patients with recurrent or recalcitrant rejection
Jignesh K. Patel, MD PhD, Cedars-Sinai Heart Institute, Beverly Hills, CA, US

13:20 – 13:40
Immunosuppression-sparing potential of ECP – Case series
Massimo Maccherini, MD, University Hospital Siena, Italy
Markus Barten, MD, PhD, University Hospital Hamburg, Germany
Johannes Gökler, MD, Medical University of Vienna, Austria

13:40 – 13:45
Concluding remarks and outlook
Andreas Zuckermann, MD, Medical University of Vienna, Austria

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International Society for Heart and Lung Transplantation (ISHLT)
11 – 14 April 2018, The Acropolis, Nice, France

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