Celebrating 30 Years of Extracorporeal Photopheresis (ECP) in Vienna

Our Vision for the Future

Van Swieten Saal - Medical University of Vienna, Austria, 24th November 2017

On the 24th November 2017, Mallinckrodt Pharmaceuticals hosted Celebrating 30 Years of Extracorporeal Photopheresis (ECP) in Vienna, Our Vision for the Future at the Medical University of Vienna, Austria.

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.
Development of ECP in Cutaneous T Cell Lymphoma (CTCL)

Dr Julia Scarisbrick, Birmingham, United Kingdom

- ECP is an effective and well-tolerated therapy for CTCL and the THERAKOS™ CELLEX™ Photopheresis System is US Food and Drug Administration (FDA)-approved for the palliative treatment of skin manifestations of CTCL that are unresponsive to other forms of treatment.
- A prospective, multi-centre, single-arm cohort study of ECP in the treatment of erythrodermic mycosis fungoides and Sézary syndrome is planned.

Figure 1. ECP with the THERAKOS™ CELLEX™ Photopheresis System

ECP is a cell-based immune modulatory therapy, which takes place outside the body in three phases (Figure 1).

In 1988, the Therakos UVAR™ system for ECP became US FDA-approved for the palliative treatment of skin manifestations of CTCL and data has now been published on over 1,000 CTCL patients treated with ECP from centres worldwide, reporting response rates of around 60% and complete response rates of 14-26.%.

ECP is a well-tolerated procedure and significant reactions are infrequent. ECP may be combined with skin-directed therapy, especially in the first six months of treatment when responses may be slow. Predictors of response to ECP include a response within six months of treatment, the absence of bulky lymphadenopathy, a disease course of less than two years and the patient being chemotherapy-naive.

ECP is recommended as a first-line systemic treatment for erythrodermic Stage III and IV CTCL by a number of groups, including the European Organisation for Research and Treatment of Cancer (EORTC) and the US National Comprehensive Cancer Network (NCCN).

Several consensus statements for proper use of ECP have been published, including those by the European Dermatology Foundation and the UK Photopheresis Society.

There are plans to begin a prospective, multi-centre, single-arm cohort study of ECP in the treatment of erythrodermic mycosis fungoides and Sézary syndrome, as described below in “Developments in CTCL” by Professor Franz Trautinger.

2. Trautinger F, Eder J, Assaf C, et al. European Organisation for Research and Treatment of Cancer (EORTC) and the US National Comprehensive Cancer Network (NCCN). Several consensus statements for proper use of ECP have been published, including those by the European Dermatology Foundation and the UK Photopheresis Society.
ECP in Transplantation
Importance of immunological tolerance in transplantation

Professor Thomas Wekerle, Vienna, Austria

- The major challenge in transplantation medicine remains long-term allograft acceptance, with preserved allograft function under minimal chronic immunosuppression.
- Results from experimental models of transplantation indicate that achieving tolerance in organ transplantation is possible, however, translating the reconstitution of immune tolerance into the clinical setting is a daunting challenge.

The chronic use of immunosuppressive therapy, as is required by many transplant recipients, is associated with significant morbidity.1 While the attrition rate of graft loss within the first year after transplantation has been decreasing since 1989, the rate of graft loss following the first year after transplantation has remained relatively stable.7 A prospective study of 315 kidney allograft recipients who were undergoing biopsies post-transplantation found a high incidence of immune-mediated graft injury in biopsies carried out after the first year post-transplantation (Figure 2).8

Figure 2. Distribution of histologic diagnoses in kidney transplant recipients according to time post-transplantation

- Antibody-mediated rejection
- T cell-mediated rejection
- Borderline
- Glomerular diseases
- Polyoma virus nephropathy
- Atrophy-fibrosis
- No major abnormalities
- Other

Dysregulation of the B cell compartment is a hallmark of cGvHD and levels of B cell activating factor (BAFF) are raised in patients with active cGvHD. Low BAFF levels following one month of ECP predicted three- and six-month skin disease response and persisting high BAFF levels are associated with an increased risk of treatment failure or of a need to re-escalate steroids. An analysis of the response rates of 34 patients with steroid-refractory cGvHD found that reduced CD19+CD21- cells before treatment is a predictive biomarker of response to ECP in cGvHD.

It is not clear whether the mechanism of action of ECP is the same across diseases. In CTCL, the effect of ECP is thought to be mediated via the upregulation of cytotoxic T cells, whereas in GvHD it is thought to be via the “tolerisation” of donor T cells. This difference may be due to ECP modulation of different dendritic cell (DC) populations: ECP is associated with an increase in myeloid type 2 T helper (T2) DCs in CTCL and an increase in plasmacytoid T2 and iDCs in GvHD.

From mice to men – ECP in aGvHD: How early is early?
Professor Hildegard Greinix, Graz, Austria

- ECP is an effective and well-tolerated second-line therapy for aGvHD and has shown efficacy as a first-line therapy, particularly in patients with skin involvement.

aGvHD following allogenic HSCT is the foremost reason for non-relapse mortality (NRM), and is a major determinant of long-term survival.

A pilot study of the safety and efficacy of ECP in addition to cyclosporine and steroids in steroid-refractory aGvHD found that three months after initiation of ECP, 60% of patients achieved a complete resolution of aGvHD and patients with complete response demonstrated higher rates of overall survival (OS) (Figure 3).

ECP was well-tolerated in this study, with adverse events observed during ECP including a decrease in peripheral blood cell counts in the early phase after HSCT. Based on the promising results of this pilot study, a prospective phase II trial was carried out in steroid-refractory aGvHD patients, with a more intensive ECP treatment schedule, in which ECP was started earlier, a median of 41 days following HSCT, in comparison with 43 days in the pilot study, and was administered on two consecutive days per week. Complete resolution of GvHD was achieved in 82% of patients with cutaneous involvement, 61% with liver involvement and 61% with gut involvement. Patients who experienced a complete response to ECP had a significantly higher probability of long-term survival compared to patients who experienced no or a partial response.

A retrospective comparison of ECP and anticytokine therapy as a second-line treatment for steroid-refractory aGvHD found significantly higher overall response and complete response rates with ECP than with anticytokines (66% vs. 32%; p=0.001; 54% vs 20%; p=0.001, respectively).

Multivariate analyses demonstrated that ECP was an independent predictor of response and survival and was associated with superior survival and lower NRM in steroid-refractory Grade II aGvHD.

A Clinical Trials Network survey of HSCT clinicians found that 39.6% of clinicians use ECP in first-line therapy in patients with high-risk aGvHD. Addition of ECP to methylprednisolone as initial therapy for aGvHD results in higher GvHD response and facilitates steroid tapering, with the highest response rates in patients with skin involvement.

Clinical data of ECP in cGvHD
Professor Mauricette Michallet, Lyon, France

- ECP is an effective, well-tolerated and cost-effective second-line therapy for cGvHD, associated with a steroid-sparing effect.

C GVHD can occur more than 100 days after transplantation and can develop following aGvHD or independently. It is the most important cause of late morbidity and mortality following allogenic HSCT and occurs in 60-70% of long-term survivors (from five years post-transplantation). cGvHD can present in the skin, eyes, mouth, gastrointestinal system, liver, musculoskeletal system, lungs and genitourinary system.

The first-line treatment for cGvHD remains as use of corticosteroids, calcineurin inhibitors (CNIs) or their combination. Second-line treatment is less standardised and a 2012 survey by the European Group for Blood and Marrow Transplantation (EBMT) found that ECP was the preferred treatment option, used by 53% of centres, either alone or in combination therapy.

Adapted from Greinix et al. (2000)

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A randomised trial of ECP plus standard therapy versus standard therapy alone in steroid-refractory, -dependent or -intolerant cGvHD found that significantly more patients treated with ECP achieved a greater than 50% reduction in steroid dose, coupled with a greater than 25% reduction in Total Skin Score (TSS) at Week 12. ECP was generally well-tolerated and no serious adverse events were judged by investigators to be related to ECP.

A recent systematic review investigating ECP in steroid-refractory cGvHD, including 18 studies and 595 patients, found the pooled rates of complete response and overall response were 29% (CI: 19-42%) and 64% (CI: 65-82%), respectively. The review found that ECP is an effective therapy for oral, skin and liver steroid-refractory cGvHD with modest activity in lung and gastrointestinal cGvHD. ECP may mediate a significant steroid and immunosuppressant sparing effect which may account, in part, for improved survival in ECP responders. In a prospective study of 25 patients with extensive, steroid-refractory cGvHD, 52% of patients discontinued corticosteroids and 44% had discontinuation of at least one immunosuppressive medication following a median duration of nine months of ECP therapy. In total, 15 patients developed serious adverse events, with one patient discontinuing ECP. In a retrospective analysis of 32 patients with steroid-dependent or steroid-refractory cGvHD there was a 64% steroid-sparing response rate and ECP was well-tolerated, with few major complications observed, usually related to the long-term indwelling central venous catheters catheters. In another retrospective analysis of 71 patients with steroid-refractory cGvHD, 22% discontinued steroids and 10% discontinued all immunosuppressive therapy at one year and only four patients developed toxicity, which did not require discontinuing therapy.

In a more recent review of second-line cGvHD therapies, ECP was reported to have a 65-70% overall response rate (ORR) and a 70-78% survival rate at one year, associated with low toxicity. Second-line rituximab (ORR: 66-86%) was associated with an enhanced infective risk, whilst second-line imatinib (ORR: 22-79%) could result in liver and gastrointestinal toxicities, and syndrome of inappropriate antidiuretic hormone secretion. Other second-line therapies assessed included pentostatin (ORR: 53-56%), mycophenolate (ORR: 26-64%), mTOR inhibitor (ORR: 76%) and interleukin-2 (ORR: 52%) all of which had corresponding toxicities.

A health technology assessment in Italy found that, of the most common second-line treatments for cGvHD, ECP was most cost-effective option due to higher rates of complete and partial responses and fewer serious adverse events.

Close to my heart - Spotlight on ECP in heart transplantation
Dr Markus Barton, Hamburg, Germany

- ECP is effective and well-tolerated as an induction therapy, and for the prevention and treatment of acute and antibody-mediated rejection following heart transplantation.

Between 1982 and 2012, despite an increase in short-term survival following heart transplant, there have been limited changes in long-term survival. Immunosuppressive therapy is associated with nephrotoxicity, infections and malignancies.

In a pilot randomised study, patients who received ECP in addition to triple immunosuppression as induction therapy after cardiac transplantation had a significantly lower rate of acute rejection episodes than patients who received standard therapy alone. Additionally, cytomegalovirus (CMV) DNA was detected significantly less frequently in the ECP group than in the standard therapy group. One patient in the ECP group had bacteremia due to a catheter-related infection which was successfully treated with intravenous antibiotics.

A study of high-risk patients treated with ECP showed that, even after the cessation of treatment, patients were at a reduced risk of rejection.

A more recent single-centre study of 20 heart transplant patients found significant reduction in the number of rejection episodes in the six months after ECP as compared with the six months preceding ECP (p=0.002). One patient developed pneumonia during ECP and post-transplant lymphoproliferative disease 21 months after finishing ECP; no other adverse events or infectious complications associated with ECP were noted.

The efficacy of ECP was described in a case report of a 45-year-old heart transplant recipient who developed cardiac allograft vasculopathy (CAV), which was treated with tacrolimus and everolimus. Ten years after the transplantation, the patient developed diarrhoea, which was treated with ganciclovir and valganciclovir, and biopsy-proven CMV colitis. The patient then began ECP, weekly for the first month, twice weekly for the second and third month and monthly thereafter, resulting in symptom relief.

Keep breathing – ECP in lung transplantation: Where are we now?
Professor Peter Jaksh, Vienna, Austria

- ECP is a well-tolerated and promising therapy for chronic lung allograft dysfunction (CLAD) and response to ECP is a predictor of improved graft survival.

CLAD affects up to 50-60% of patients who survive five years following lung transplantation. The underlying causes of CLAD are allogimmune and non-allogimmune tissue injury. The most common risk factors include severe and/or persistent acute rejection episodes, humoral rejection, gastro-esophageal reflux, viral infection and medication non-compliance.

The most common form of CLAD is bronchiolitis obliterans syndrome (BOS), characterised by progressive airflow obstruction. Restrictive allograft syndrome (RAS), another form of CLAD, is characterised by patchy infiltrates and interstitial changes visible on the chest X-ray and in histological samples. Patients who develop RAS after lung transplantation have a worse prognosis than patients without CLAD or patients who develop BOS (Figure 4).41

Treatment options for patients who have developed CLAD following lung transplantation include increasing or switching immunosuppressive therapy, azithromycin, re-transplantation and ECP. ECP is recommended by the American Society for Apheresis for lung allograft rejection as a second-line therapy, either as monotherapy or in combination.44

Studies find that just over half of patients with CLAD benefit from treatment with ECP. A retrospective analysis of 60 lung allograft recipients with progressive BOS found that six months of ECP treatment reduced the rate of decline in forced expiratory volume in one second (FEV1).45

In another study, 54% of patients treated with ECP for CLAD improved or stabilised. Patients with restrictive graft dysfunction and patients who were rapidly declining were less likely to respond to ECP.46 ECP responders demonstrated improved progression-free survival.46 In a cohort of 106 patients from Vienna, 68% of CLAD patients responded to ECP. Response was associated with a significant increase in graft survival and, consequently, a decreased need for re-transplantation. Therefore, ECP is a well-tolerated and promising therapy for CLAD, however, further studies are necessary to determine subgroups who benefit most, prognostic markers and an ideal treatment paradigm.

ECP from Atopic Dermatitis (AD) to Scleroderma

ECP in AD

Professor Eggert Stockfleth, Bochum, Germany

- ECP can be used to treat selected patients with AD.

AD is a chronic inflammatory, relapsing and pruritic skin disease. AD is estimated to affect up to 25% of children and 2-10% of adults, with the prevalence of the disease having doubled or tripled in industrialised countries over the past 30 years.47 The disease has a considerable impact on the quality of life of both patients and their families due to the psychological and social impact of itching and oozing skin diseases, which is often neglected in studies.

In 2013, the treatment guidelines for mild to moderate AD were updated to recommend topical, non-corticosteroid, anti-inflammatory treatments which do not induce skin atrophy or epidermal barrier dysfunction as topical steroids do.48 However, the frequent use of topical emollients on large areas of skin is not practical for many patients.

At St. Josef Hospital, Bochum, Germany, ECP treatment for AD has been introduced to treat more than 20 AD patients, with an average of 7-8 cycles (2 treatments per cycle) per year.

ECP in systemic sclerosis and morphea

Dr Ulrike Just, Vienna, Austria

- Randomised controlled trials of ECP in systemic sclerosis have demonstrated significant skin and joint improvements. ECP in systemic sclerosis is associated with immunomodulatory effects, including a significant increase in T regulatory cells and IL-10.

- Case studies of ECP in morphea are inconsistent, however, results from Vienna suggest that ECP is a viable treatment option for refractory morphea with no noticeable side effects.

Systemic sclerosis is an autoimmune connective tissue disease characterised by excessive production and abnormal deposition of collagen in skin, subcutaneous tissue and internal organs. The exact cause of systemic sclerosis is unclear, but it is thought to be due to the impact of environmental factors in a genetically primed individual.49

In 1992, Rook et al. demonstrated a significant benefit of ECP compared to D-penicillamine.50 Later, a randomised, triple-blind, multi-centre trial of patients with recent-onset systemic sclerosis, demonstrated statistically significant improvements in skin score and joint involvement at six and 12 months in the ECP group but not in the sham photopheresis group.50 No serious adverse events were reported in the trial and there was no significant difference in overall adverse events between the two study arms.51 The European Dermatology Forum (EDF) guidelines recommend that ECP may be used as a second-line or adjuvant treatment in early progressive disease.52


Localised sclerosis or morphea, is a rare fibrosing disorder of the skin and underlying tissue, which is limited to the skin, subcutaneous tissue and underlying bone.  

Case studies of ECP in morphea have demonstrated inconsistent results.  

In a study of 28 patients with moderately-to-severely active Crohn’s disease, ECP was well tolerated and induced clinical response in 50% of patients and remission in 25%. The effect of ECP was durable, with 75% of patients who entered the extension study maintaining a response at Week 24.  

We are getting there – Technical challenges of venous access  

Professor Nina Worel, Vienna, Austria  

• Venous access required for ECP is associated with many technical challenges; peripheral venous access should be used whenever possible. Options include temporary central venous catheters (CVCs), tunneled CVCs and implantable port systems.

When choosing an appropriate mode of venous access, the duration of the treatment (months to years), the underlying disease and its effects on skin and veins have to be taken into account (Table 1). Whilst the UVAR™ system can handle relatively low flow rates, the resulting long procedural times and possible temperature issues should be taken into account. It is therefore advisable to carefully consider the optimal access for each individual patient. Depending on the skin and vein conditions, a switch from double to single needle mode might be indicated.


Table 1. Advantages and disadvantages of different venous accesses in ECP

<table>
<thead>
<tr>
<th>Venous Access</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Peripheral venous access</td>
<td>• Single needle procedures if indicated</td>
<td>• Underlying disease (condition of skin and veins) can be challenging</td>
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<tr>
<td>(with dialysis cannula or intravenous catheter)</td>
<td>• Low risk of infections</td>
<td>• Repeated skin puncture can be problematic with impaired wound healing</td>
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<td></td>
<td></td>
<td>• Veins with small calibres can be challenging</td>
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<tr>
<td>Temporary central venous catheter (CVC)</td>
<td>• Short-term venous access</td>
<td>• Risk of infections and occlusion (clots)</td>
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<tr>
<td></td>
<td></td>
<td>• Subcutaneous kinking</td>
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<td></td>
<td></td>
<td>• Clamping can lead to bonding</td>
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<tr>
<td>Implantable port systems</td>
<td>• Skin barrier is effective protection against bacterial contamination</td>
<td>• Limited published data</td>
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<td></td>
<td></td>
<td>• Only a few ports are suitable for apheresis (including Titan-Port APH and Vortex TR)</td>
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<td></td>
<td></td>
<td>• Risk of infections and occlusion (clots)</td>
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<tr>
<td>Tunnelled CVC</td>
<td>• Skin barrier is effective protection against bacterial contamination</td>
<td>• Risk of infections and occlusion (clots)</td>
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<tr>
<td></td>
<td>• Can be used in children and low body-weight adults</td>
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<tr>
<td></td>
<td>• Low risk of kinking or collapse of CVC</td>
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<tr>
<td></td>
<td>• Long-term venous access possible</td>
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†Optimal with 16G dialysis needles, with 18G IV catheters as second choice.

ECP – What Will The Future Bring?
Developments in CTCL
Professor Franz Trautinger, St Pölten, Austria

• PROMPT, a multi-centre, single-arm cohort study, aims to address questions of the mechanism of action and optimal treatment schedules of ECP in CTCL.

There are still several open questions surrounding the use of ECP in CTCL (see Key Theme – Open questions surrounding ECP in CTCL). PROMPT, a prospective, multi-centre, single-arm cohort study aims to validate an EDF consensus-based ECP protocol in 43 patients with erythrodermic mycosis fungoides and Sézary syndrome. The translational research programme aims to investigate how ECP affects the number of tumour cells and reactive cells, the cytokine milieu in peripheral blood and the cytotoxic function of natural killer (NK) cells and CD8+ cells. It is anticipated that the first site will be initiated in June 2018.

Key Theme – Open questions surrounding ECP in CTCL

• Mechanism of action
• Role of photosensitised blood components other than peripheral blood mononuclear cells, for example platelets and plasma
• Patient selection
  - Predictive biomarkers?
  - CTCL variants other than Sézary Syndrome
• Optimal treatment combinations
• Optimal treatment schedule

Preventing lung transplant rejection
Professor Peter Jakusch, Vienna, Austria

• ECP treatment is associated with a reduction in levels of donor specific antibodies (DSA) in patients with BOS.

• ECP could be effective in treating antibody-mediated rejection following lung transplantation, in addition to treating CLAD.

\[ T_{reg} \] cell counts in lung transplant recipients progressively decrease according to the severity of CLAD. A long-term study of lung transplant recipients found that patients with higher mean \[ T_{reg} \] counts had a significantly lower risk (OR 0.97, p=0.012) of presenting CLAD or progressing in graft dysfunction.63

In lung transplant recipients with BOS, six months of ECP treatment was associated with a reduction in the levels of circulating DSA (Figure 6), antibodies to lung-associated self-antigens and several pro-inflammatory cytokines. These immunologic changes were associated with a significant 63% reduction in the rate of decline in FEV, over a one-year period. However, no clear correlation between the immunological changes and reduced rate of decline could be established and these results have not been subsequently replicated.

Figure 6. Percentage change in DSA levels following ECP

A case series investigated the effect of combined plasmapheresis, ECP and intravenous immunoglobulin for the treatment of acute antibody-mediated kidney transplant rejection in three patients. In two cases there was immediate restoration of graft function, however, in one case the patient withdrew consent and the graft was lost. Similarly, two case studies from Vienna were presented in which patients with high DSA levels after lung transplant were treated with plasmapheresis to reduce DSA levels and then maintained without any rebound on low level immunosuppression plus ECP.

Pre-emptive use in aGvHD

Dr Francis Ayuk, Hamburg, Germany

- More effective treatments in severe aGvHD are needed.
- TNFR1, ST2 and Reg3a have been identified as early biomarkers for high-risk GvHD patients.
- A study assessing the efficacy of ECP plus steroids as first-line therapy in this patient group is planned to start in Germany.

aGvHD occurs in 50% of recipients of allogenic HSCT, of which 20% have severe aGvHD (Grade III-IV), and is a key driver of NRM. There have been significant advances in HSCT, which has led to significant improvements in treatment-related mortality, progression-free survival and OS in patients with severe aGvHD. However, a study found that these improvements were only significant in the Grade IV, and not Grade III group, suggesting that the effects are mainly due to improved supportive care.

The challenges in aGvHD include identifying patients at risk of a poor outcome in terms of severity of aGvHD, response to treatment and mortality, and employing better treatment strategies to improve outcome in terms of reduced NRM and no increase in relapse of underlying disease. Biomarkers may help identify patients at risk of a poor outcome.

The Mount Sinai Acute GvHD International Consortium (MAGIC) aims to discover and validate biomarkers of aGvHD, perform prospective multi-centre clinical trials and improve patient outcome. Recent multi-centre studies have demonstrated that early biomarkers, including TNFR1, ST2 and Reg3a, can be used to predict patients at risk of lethal GvHD and to guide treatment decisions. If a poor treatment outcome is predicted, treatment options include intensifying immunosuppression or carrying out alternative immunomodulation. A meta-analysis of seven randomised controlled trials comparing steroids with steroids plus additional agents did not find any efficacy signal with increasing generic immunosuppression.

More effective treatments in severe aGvHD are needed. MAGIC is carrying out several phase II studies investigating the addition of alternative therapies to steroids in the treatment of high-risk aGvHD. In Germany, a study of standard steroid treatment plus ECP as first-line therapy is planned to open in 2018.
Upfront use in cGvHD

**Professor Hildegard Greinix, Graz, Austria**

- The latest clinical trial demonstrated that ECP is well-tolerated as first-line therapy for moderate or severe cGvHD.
- A prospective study is planned to investigate the efficacy and safety of first-line ECP therapy in high-risk cGvHD.

Recent studies have examined the use of ECP as first-line therapy in moderate or severe cGvHD. A randomised controlled study of 60 patients treated with standard of care versus standard of care plus ECP demonstrated that ECP was well-tolerated in patients with new-onset moderate to severe cGvHD and was associated with a higher overall response rate. Overall, treatment-emergent adverse events were experienced by 96.6% and 90.3% of patients in the standard of care and ECP arms, respectively, with none of these events considered to be related to UVADEX™ or the ECP instrument. A prospective study of 178 cGvHD patients found that recurrent aGVHD, platelet counts below 100 g/l at diagnosis (thrombocytopenia), progressive onset disease and advanced disease stage prior to HSCT were significantly associated with increased NRM.

Steroids are the standard first-line therapy of cGvHD, however, the role of CNIs in high-risk groups (progressive onset and/or thrombocytopenia) is unclear. A survey of 31 centres performing allogenic HSCT found that the majority of the centres (18 of 31) would increase the steroid dose, continue the CNI and start a new agent (ECP [n=9] or mycophenolate mofetil [n=12]) when treating progressive onset cGvHD in the absence of low platelets.

A prospective study of newly diagnosed, high-risk, cGvHD within the GvHD Consortium is planned to begin in Spring 2018. The study defines high-risk as a platelet count of below 100 g/l or progressive onset type, defined as onset before resolution of prior aGvHD and completion of aGvHD therapy. After diagnosis of high-risk cGvHD, patients will be treated with systemic immunosuppressive therapy and begin ECP treatment within four weeks.

**What research and clinical data would we like to see in the future?**

**Dr Arun Alfred, Rotherham, UK**

- Unanswered questions surrounding ECP include the mechanism of action, prospective biomarkers and optimal treatment schedules. More multi-centre clinical trials are required to address these.

There are several aspects of ECP treatment that still need to be optimised and standardised, including timing, protocols, number of cells, patient selection, frequency of infusion and whether these protocols should vary depending on the affected organ. It must be determined which other immune modulating or suppressing therapies ECP can be used in combination with and which indications ECP is effective in, for example, first-line GvHD, autoimmune diseases, BMT and solid organ transplantation.

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CAUTION: READ THE THERAKOS™ UVAR XTS™ or THERAKOS™ CELLEX™ PHOTOPHERESIS SYSTEMS’ OPERATOR’S MANUAL PRIOR TO PRESCRIBING OR DISPENSING THIS MEDICATION. Do not inject directly into patients.

For the THERAKOS™ Photopheresis Procedure:

INDICATIONS
THERAKOS™ UVAR XTS™ and THERAKOS™ CELLEX™ Photopheresis Systems are indicated for the administration of photopheresis.

CONTRAINDICATIONS
THERAKOS™ Photopheresis is contraindicated in patients possessing a specific history of a light sensitive disease. THERAKOS™ Photopheresis is contraindicated in patients who cannot tolerate extracorporeal volume loss or who have white blood cell counts greater than 25,000 mm$^3$.

THERAKOS™ Photopheresis is contraindicated in patients who have coagulation disorders or who have had previous splenectomy.

Warnings and Precautions
THERAKOS™ Photopheresis treatments should always be performed in locations where standard medical emergency equipment is available. Volume replacement fluids and/or volume expanders should be readily available throughout the procedure. Both men and women should take adequate contraceptive precautions both during and after completion of photopheresis therapy. Safety in children has not been established.

Adverse Events
Hypotension may occur during any treatment involving extracorporeal circulation. Closely monitor the patient during the entire treatment for hypotension. Transient pyretic reactions, 37.7-38.9°C (100-102°F), have been observed in some patients within six to eight hours of reinfusion of the photoactivated leukocyte-enriched blood. A temporary increase in erythodema may accompany the pyretic reaction. Treatment frequency exceeding labeling recommendations may result in anemia. Venous access carries a small risk of infection and pain. Methoxsalen should be used only by physicians who have special competence in the diagnosis and treatment of cutaneous T-cell lymphoma and who have special training and experience with the THERAKOS™ UVAR XTS™ or THERAKOS™ CELLEX™ Photopheresis Systems.

For Additional Safety Information, please refer to our website www.therakos.co.uk
Where: Van Swieten Saal - Medical University of Vienna, Department of Dermatology, Division of General Dermatology, Van-Swieten-Gasse 1a, 1090 Vienna, Austria

9:00  Welcome and Introduction
Professors Hildegard Greinix, Graz, Austria and Robert Knobler, Vienna, Austria

9:10  In the beginning there was light
Chair: Prof Rudolph Stadler
Development of Extracorporeal Photopheresis in CTCL
Dr Julia Scarisbrick, London, UK

9:45  Transplant Session
Chairs: Prof Thomas Wekerle, Prof Peter Kahls and Dr Christian Jantschitsch, Vienna, Austria

9:45  Importance of immunological tolerance in transplantation
Prof Thomas Wekerle, Vienna, Austria

10:00  Induction of tolerance using ECP? Mechanism/s of action
Dr Arun Alfred, Rotherham, UK

10:20  Coffee break

10:50  From mice to men - ECP in acute GvHD: How early is early?
Prof Hildegard Greinix, Graz Austria

11:10  Clinical data of ECP in chronic GvHD
Prof Mauricette Michallet, Lyon, France

11:30  Close to my heart - Spot light on extracorporeal photopheresis in heart transplantation:
Prof Markus Barten, Hamburg, Germany

11:50  Keep breathing, ECP in lung transplantation - where are we now?
Prof Peter Jaksch, Vienna, Austria

12:30–13:30  Lunch break
13:30  ECP from Atopic Dermatitis to Scleroderma
Chairs: Prof Herbert Höenigsmann, Prof Peter Petzelbauer and Prof Ventzislav Petkov, Vienna, Austria

13:30  ECP in atopic dermatitis
Prof Eggert Stockfleth, Bochum, Germany

13:45  Extracorporeal photopheresis in the management of inflammatory bowel disease
Prof. Walter Reinisch, Vienna, Austria

14:00  Extracorporeal photopheresis in Morphea and Systemic Sclerosis
Dr Ulrike Just, Vienna, Austria

14:20  We are getting there – Technical challenges of venous access and regulatory considerations
Prof. Nina Worel, Vienna, Austria

14:40  Patient cases
Chris Lewis, Chronic GvHD, UK; Alois Rossmann, Lung transplant, Austria

15:00-15:30  Coffee break

15:30  ECP – What will the future bring?
Chairs: Professors Robert Knobler, Vienna, Austria and Hildegard Greinix, Graz, Austria

15:30  Developments in CTCL
Prof. Franz Trautinger, St Pölten, Austria

15:40  Preventing lung rejection
Prof. Peter Jaksch, Vienna, Austria

15:50  Challenges of GvHD in pediatric patients
Dr. Anita Lawitschka, Vienna, Austria

16:00  Preemptive use in acute GvHD
Dr. Francis Ayuk, Hamburg, Germany

16:10  Upfront use in chronic GvHD
Prof. Hildegard Greinix, Graz, Austria

16:20  What research and clinical data would we like to see in the future?
Dr Arun Alfred, Rotherham, UK

16:30  Farewell
Professors Robert Knobler and Hildegard Greinix

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