On the 6th July 2017, Mallinckrodt Pharmaceuticals (Commercial) hosted the 2nd Annual Advancing Immunomodulation educational meeting in London, UK. This meeting focused on the current practices and challenges in the management and treatment of acute and chronic graft versus host disease (aGvHD and cGvHD).

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.
An Introduction to Immunomodulation

In the opening session, Professor Krishna Komanduri, of the Sylvester Comprehensive Cancer Center at the University of Miami, Miller School of Medicine, summarised the current understanding of the immune response in graft versus host disease (GvHD) and the concept of immunomodulation in patients following stem cell transplantation.

- Research conducted over two decades has demonstrated that T cell dysfunction, rather than absence, plays a crucial part in cytomegalovirus (CMV) reactivation.
- The aim of immunomodulation is to selectively inhibit the GvHD mediating naïve T cells while sparing pathogen-specific mature T cells. This has been attempted by inhibition of signalling pathways and expansion of regulatory T cells (TREG) using therapies such as extracorporeal photopheresis (ECP).
- Combined methods may be the most effective.

Over the last 20 years, cytokine flow cytometry has allowed investigation of the T cell response at the cellular level, including in relation to CMV reactivation.

In the late 1990s, it was widely believed that pathogen-specific T cell response could not rise above 0.5%-1% of the overall repertoire. However, work by the Gladstone Institute of Virology and Immunology, San Francisco in 1997 demonstrated that in HIV patients with no history of end stage organ disease (EOD) CMV specific T cells made up between 1%-40% of all T cells in circulation. It was also believed that CMV reactivation occurred in the absence of pathogen-specific T cells. This was shown to be true in some cases, but it was also found that patients who experienced CMV reactivation following allogeneic hematopoietic stem cell transplant (allo-HSCT) often had similar or even higher concentrations of CMV specific T cells. It was the active (cytokine-producing) T cell fraction which was significantly reduced in patients with CMV reactivation and those with acute GvHD (25% compared to 65% in patients without CMV reactivation). T cell dysfunction also appeared to be involved in steroid associated CMV reactivation; patients receiving steroid treatment have similarly low rates of active T cells (27%).

Classic immunosuppression works to suppress the activity of a wide range of T cells, whereas the goal of immunomodulation is to selectively inhibit the activity of naïve/early T cells and spare mature T cells (which mediate pathogen-specific immunity). The RAS/MEK/ERK signalling pathway appears to be a good target for differentiation between naïve/early T cells and mature cells, as naïve T cells utilise this pathway more efficiently. There is some evidence from murine models that MEK inhibition, for example using selumetinib or trametinib, may spare CMV immunity while inhibiting GvHD.

Inhibition of naïve T cells may also be achieved through the enrichment of TREG cells, which selectively target naïve T cells over mature T cells. One way TREG cells can be expanded in vivo is through the use of a TLR1/2 agonist fusion protein combined with interleukin-2 (IL2). In MHC mismatch murine models, this treatment dramatically and reversibly increased the expansion of TREG cells, which led to a significant reduction in GvHD related mortality.

The expansion of TREG cells is also one of the proposed mechanisms of action for ECP, suggested to explain the improvements seen in clinical studies. In murine GvHD model, ECP significantly increased the TREG cell count, as well as increasing survival and improving clinical scores. This has also been observed in conditioning/prophylactic settings within these models. Combination approaches are likely to yield the best treatment results.

Immunomodulation and the Management of Acute Graft-versus-Host Disease (aGvHD)

The Current Challenges of aGvHD and the MAGIC Consortium

Dr Francis Ayuk, of the Clinic for Stem Cell Transplantation, University Medical Centre Hamburg-Eppendorf, began the second session by providing an overview of the challenges associated with management of aGvHD.

- Steroids remain the backbone of aGvHD treatment, with little progress made to improve response rates, particularly in patients with severe aGvHD.
- Increased immunosuppression through addition of immunosuppressive agents or increase in steroid dosage has little impact on response and increases the risk of negative outcomes.

- The Mount Sinai Acute GvHD International Consortium (MAGIC) of treating centres are pooling patient level data to identify biomarkers of aGvHD outcomes and confirm findings in multi-centre trials.

Key Theme – Defining Steroid Refractory aGvHD

- Progression after ≥3 days ≥2 mg/kg methylprednisolone (or equivalent)
- No complete or partial remission after ≥7 days of treatment

- A week with persistent, non-improving Grade III aGvHD
- ≥2 weeks with persistent, non-improving Grade II aGvHD

- Dependent: Unable to taper steroid dose (definitions vary, including recurrence of Grade II or higher severity during steroid taper)

Overall, about 50% of recipients of allo-HSCT develop aGvHD, 20% of which is severe (Grade III-IV). aGvHD is a major driver to non-relapse mortality. Steroids have formed the backbone of therapy for the last 20 years, however, patients with the most severe aGvHD have the lowest response rates. Although overall survival of patients with Grade IV aGvHD has increased over time, this appears to be mainly due to improvements in supportive care, including improvements in infection management, as opposed to advances in treatment.
Second-line aGvHD treatment is required when a patient becomes steroid-refractory or is unable to tolerate the required steroid dose. Similar to previous findings, the latest Phase III trial, investigating inolimomab versus standard care in steroid refractory aGvHD, has failed to demonstrate a significant improvement in overall survival. A recent systematic review reported that intensifying immunosuppression through increasing steroid dose or addition of immunosuppressive agents does not improve overall survival and so is not recommended (Figure 1).

Figure 1. Forest plots for overall survival: overall survival (OS) at 100 days (A) and 1 year (B)

A) Study or Subgroup | Experimental Events Total | Control Events Total | Weight | Risk Ratio | M-H, Random, 95% CI | Risk Ratio | M-H, Random, 95% CI
--- | --- | --- | --- | --- | --- | --- | ---
Couriel, 2009 (Daclizumab) | 22 | 29 | 23 | 28 | 21.3% | 0.92 [0.71, 1.21] | 
Cragg, 2000 (ATG) | 30 | 50 | 36 | 46 | 20.6% | 0.77 [0.58, 1.01] | 
Lee, 2004 (Daclizumab) | 41 | 53 | 46 | 49 | 58.2% | 0.82 [0.70, 0.97] | 
Total (95% CI) | 132 | 123 | | | 100% | 0.83 [0.74, 0.94] | 
Total events | 93 | 105 | 
Heterogeneity: Tau² = 0.00; Chi² = 0.95; df=2 (P=0.62); I² = 0%
Test for overall effect: Z=1.92 (P=0.004)

B) Study or Subgroup | Experimental Events Total | Control Events Total | Weight | Risk Ratio | M-H, Random, 95% CI | Risk Ratio | M-H, Random, 95% CI
--- | --- | --- | --- | --- | --- | --- | ---
Balanos-Meade, 2014 (MMF) | 67 | 116 | 77 | 119 | 26.7% | 0.89 [0.73, 1.10] | 
Cahn, 1995 (BT563) | 21 | 32 | 21 | 35 | 18.5% | 1.09 [0.76, 1.58] | 
Cragg, 2000 (ATG) | 22 | 50 | 28 | 46 | 17.6% | 0.72 [0.49, 1.07] | 
Lee, 2004 (Daclizumab) | 15 | 53 | 29 | 49 | 13.9% | 0.48 [0.29, 0.78] | 
Martin, 1996 (CDS immunocon) | 63 | 129 | 51 | 114 | 23.3% | 1.09 [0.83, 1.43] | 
Total (95% CI) | 380 | 363 | | | 100% | 0.86 [0.68, 1.09] | 
Total events | 188 | 206 | 
Heterogeneity: Tau² = 0.04; Chi² = 10.80; df=4 (P=0.03); I² = 63%
Test for overall effect: Z=1.26 (P=0.21)

Survival is considered an event. Size of squares in each panel is proportional to the weight assigned to the corresponding study (studies with larger weights have narrower confidence intervals). Taken from Rashidi et al. 2016.

Following on from previous work to identify biomarkers for transplant related mortality and GvHD, MAGIC was set up with the aim of improving patient outcomes by:

- discovering and validating biomarkers
- conducting prospective multi-centre trials.

To improve consistency, the consortium has produced a standardised framework for clinical data collection in aGvHD. Work by the MAGIC consortium has identified a group of biomarkers which can predict outcomes at GvHD onset, including before clinical symptoms are detected.

Separate patient cohorts (training, testing and validation) were used to develop and test a proposed biomarker algorithm. The initial algorithm was developed using data from patients at the Universities of Michigan and Regensburg, and validated using a cohort recruited from across MAGIC participating centres. Patients categorised as high-risk based on biomarker concentrations on day +7 post H SCT (prior to aGvHD onset) were significantly more likely to experience non-relapse and GvHD related mortality and had significantly lower overall survival compared to patients categorised as low-risk on day +7.

Key Theme – Biomarkers in aGvHD

- A 2 biomarker model using ST2 and REG3a concentrations on day +7 post HSCT has identified patients at high and low risk of aGvHD related mortality and severe gastrointestinal aGvHD.

The Role of Intestinal Microbiota in GvHD

Dr Marcel van den Brink, of the Memorial Sloan Kettering Cancer Center, New York, described what is currently known about the role of the microbiome within aGvHD.

- Although there is currently a lot of interest in the field, it was stressed that the study of gut flora in allograft transplant recipients can be considered in its infancy.
- Many studies have identified associations between changes in the microbiome and clinical outcomes. However, as studies investigating mechanisms of action are still lacking, little can be deduced about the causation of any associations reported.
- The use of broad-spectrum antibiotics, particularly those with a large anaerobic coverage, appears to increase the risk of microbiome domination by bacterial strains associated with lethal aGvHD; however, this has yet to be confirmed by a randomised controlled trial (RCT) in humans (study ongoing in 2017).

A cluster analysis showed that microbiome diversity is lost following allo-HSCT, with many cultures becoming monocultures or dominated (>30%) by a single bacterial taxon. Dominating taxa include Proteobacteria (e.g. E. coli) which is a risk for patients.

Infection is responsible for about 17%-21% of mortalities following allo-HSCT, and this is frequently preceded by monodomination of the gut flora.2 More widely, microbial diversity is a predictor for overall survival,20 which appears to be particularly linked to the incidence of lethal aGvHD.21

GvHD has been associated with overrepresentation of Enterococcus in both mice and allo-HSCT patients;22, 26 expansion of E. coli;26 Bacteroides and Prevotella species;22 and changes in microbiome makeup (more Firmicutes and Proteobacteria and fewer Bacteroidetes) compared to the gut flora of patients without GvHD.27 Similarly, Blautia abundance of over 0.05% is associated with a reduced rate of GvHD-related mortality.27 A recent study has also reported a link between the presence of Eubacterium limosum and reduced rates of relapse following allo-HSCT.28

The choice of antibiotics used to treat febrile neutropenia may impact the risk of GvHD and subsequent mortality. A retrospective clinical analysis identified the administration of broad-spectrum antibiotics with anaerobic coverage (piperacillin-tazobactam, imipenem-clindamycin) to be significantly associated with GvHD-related mortality, compared to antibiotic agents with less anaerobic coverage.22 This finding was also supported by murine GvHD model experiments, where agents with a broad anaerobic coverage led to significantly lower overall survival.22 The link between antibiotic use and GvHD is currently being investigated in a Phase II RCT comparing use of piperacillin-tazobactam versus cefepime + de-escalation to aztreonam + vancomycin for the treatment of neutropenic fever (study ongoing in 2017, NCT03078010).22

Although some associations between changes in the microbiome and clinical outcomes have been suggested, there is not yet a sufficient body of evidence to support the use of microbiota augmentation for aGvHD prevention or treatment. While strategies that spare the biodiversity of the microbiome appear desirable, it is also clear that the microbiome is quite robust and typically recovers rapidly once patients re-enter the community. Given the impact on the environment on the microbiome, it is also likely that gut flora research is highly susceptible to single centre effects, therefore, more multi-centre collaboration is needed.

Management of Steroid Refractory aGvHD: Novel Strategies and Clinical Outcomes

Professor Francesco Dazzi, of King’s College, London, presented an overview of novel management strategies for steroid refractory aGvHD.

- Steroid refractory aGvHD remains a major challenge for management of allo-HSCT recipients, and there is currently no consensus as to the best treatment.

Although steroid therapy is the first line of treatment for aGvHD, durable response occurs only in a minority (24%-40%) of patients, with steroid refractory aGvHD associated with a very poor prognosis.29 There are a number of strategies currently under investigation for disrupting the pathophysiology of aGvHD (Figure 2, Table 1).

**Figure 2. Pathophysiology of aGvHD**

Table 1. State of current research into interruption of the aGvHD pathophysiology

<table>
<thead>
<tr>
<th>Target process</th>
<th>Treatment</th>
<th>Status of research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine response</td>
<td>RCTs of these agents have so far not demonstrated a significant improvement in OS compared to supportive care.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jak1/2 blockade (ruxolitinib)</td>
<td>No prospective trials to date, but has been reported to improve OS in observational studies. Suitability for use in paediatric patients needs further confirmation, due to data showing increased toxicity and no impact on OS.</td>
</tr>
<tr>
<td>Antigen presentation</td>
<td>Investigated in 6 patients with Grade IV gut aGvHD, all responded, 4/6 alive at 10 months. Clinical trial ongoing (NCT02493783).</td>
<td></td>
</tr>
<tr>
<td>T cell trafficking</td>
<td>Single arm observational studies have reported mixed results, with a later, larger study reporting a relatively small response rate (21%).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Widely used for prophylaxis, but mixed results as a treatment, response rates in latest single arm observational studies 26%-47%.</td>
<td></td>
</tr>
<tr>
<td>T cell depletion</td>
<td>Small scale study was promising (50% response rate, 20% OS improvement).</td>
<td></td>
</tr>
</tbody>
</table>

ECP: Aims to re-educate the immune system, positive results in both single arm and comparative studies. Proposed mechanism of action involves apoptotic cells triggering the regulation of GvHD. Discussed in more detail in the following section.

Expanded T REG cells: Have demonstrated good outcomes in the prevention of aGvHD in small scale trials.

Immo-modulation: T REG cells which only recognise the allo antigen and only suppress T cells under aGvHD conditions. These have demonstrated some efficacy as prophylaxis.

CAR alloT REG cells: Have been shown to improve OS in Grade III–IV aGvHD responders.

MSC: Particularly good results in gut/skin aGvHD and in paediatric patients.

Natural killer T cells/myeloid derived suppressor cells: Have both shown promise in pre-clinical trials (murine models) with clinical trials currently being planned.

CAR: Chimeric antigen receptors; ECP: Extracorporeal photopheresis; MMF: Mycophenolate mofetil; MSC: Mesenchymal stem cells; OS: Overall survival; RCT: Randomised controlled trial; T REG cells: Regulatory T cells.

The Unmet Clinical Need of aGvHD - ECP in aGvHD

Professor Hildegard T. Greinix, of the Medical University of Graz, Austria, ended the session by discussing the clinical evidence base for the use of ECP to treat steroid refractory aGvHD, including evidence from Phase II trials.

- In patients who responded, ECP was steroid sparing, associated with improved overall survival, and few patients experienced adverse events.

The use of high intensity ECP (administered on 2 consecutive days every week, steroids tapered once patients start to respond and ECP tapered once complete resolution was achieved) has been investigated in pivotal and Phase II studies. Complete aGvHD resolution was observed in 82%/61%/61% of patients with skin/liver/gut involvement and in 86%/55%/30% of Grade II/III/IV aGvHD, respectively.55 Treatment related mortality was less in patients who were able to taper steroids rapidly, and was significantly more likely if no complete resolution was observed following 3 months of ECP therapy.56

In addition, a retrospective multi-centre analysis of 128 patients found a complete resolution rate of 87%. Two year overall survival was significantly higher and non-relapse mortality was significantly lower in patients with aGvHD Grade II compared to Grades III-IV, and in patients with fewer than 3 organs involved, highlighting the potential benefits of ECP early in the course of the disease.55 In another retrospective comparison of ECP (data from three centres) with anti-cytokine inolimomab and etanercept (data from one centre), ECP was an independent predictor of response (Odds Ratio [OR] 3.42, p=0.007) and survival (Hazard Ratio [HR] 2.12, p=0.018) and was associated with lower non-relapse mortality (HR 0.45, p=0.018) and superior survival in Grade II steroid refractory aGvHD (HR 4.6, p=0.018).55 Further, a systematic review and meta-analysis of prospective studies calculated a combined overall response rate of 69% (84%/65%/55% in skin/gut/liver involvement, respectively).55

ECP has also been included in a number of aGvHD treatment guidelines as a useful second line therapy for aGvHD due to limited toxicity, no known interactions with other medications and no impact on viral reactivation,55,56-57 Early ECP start may be particularly useful in recipients of haploidentical or unrelated donor HCT.51

There is also some evidence of ECP benefit as a first-line therapy, with about 40% of HSCT clinicians stating that ECP is used as first-line treatment in high-risk aGvHD patients. A Phase II RCT of ECP with methotrexate in first-line treatment of aGvHD has demonstrated higher response rates in the ECP treated arm, particularly for skin aGvHD.55

Immunomodulation and the Management of Chronic Graft-versus-Host Disease (cGvHD)

Predicting cGvHD and Mortality on Day +100 after Allo-HSCT

Professor Andrea Bacigalupo of the Institute of Haematology, Policlinico Gemelli, UCSC, Rome started the session by providing an overview of his team’s work to discover biomarkers of cGvHD, enabling the early identification of patients at risk of developing the condition following allo-HSCT.

- The team has identified 5 laboratory variables which are predictive of significantly higher rates of cGvHD and lower survival. It is hoped that early identification of high risk patients may facilitate investigation into cGvHD prevention.

CGvHD develops in about 50% of allo-HSCT recipients (expression of cGvHD in 10% of recipients). Over the last 40 years, 5-year mortality has remained around 24%, with little improvement. At 2 years following onset of cGvHD, the majority of patients experience non-relapse mortality (9%), relapse (14%), or switch to a new systemic treatment (77%). Known risk factors for treatment failure are female donor to male recipient, previous acute aGvHD Grades II–IV, gut GvHD, lung GvHD (bronchiolitis), previous liver disease and gastro-oesophageal reflux. It has become clear that increasing immunosuppression in cGvHD patients does not improve outcomes: addition of a new medication has been associated with an increased risk of overall mortality. At 10 years following allo-HSCT transplant, patients with CGvHD have a 4.3-fold higher rate of somatic distress and a 13-fold higher rate of suicidal ideation, demonstrating that CGvHD has a substantial impact on patients’ physical and mental wellbeing.

Longitudinal studies show that the incidence of minimal cGvHD (50% at 100-200 days post-transplant) decreases over time, with only 30% of transplant recipients experiencing minimal cGvHD at 4 years. However, moderate and severe cGvHD is consistently reported in around 11%-14% and 2%-4% of transplant recipients, respectively, through to 4 years.

A study of patients free from cGvHD at day 100 was undertaken to find biomarkers that would enable patients at risk to be identified prior to cGvHD onset. Data from 1,502 patients was used and a multivariate analysis identified 5 laboratory variables (Key Theme - Biomarkers in cGvHD) with predictive power.

Patients with a high day +100 score had significantly higher rates of CGvHD and treatment-related mortality, and significantly lower overall and disease free survival. It is hoped that early identification of patients at risk will enable trials of cGvHD prophylaxis and prevention.

Key Theme - Biomarkers in cGvHD

- A day +100 score was created using median cut-off values for 5 predictive variables (1 point per variable):
  - Platelet count <10 x 10^9/L
  - Serum cholinesterase <3772 U/L
  - Gamma-glutamyltransferase >65 U/L
  - Serum albumin <3.9 g/L
  - Serum immunoglobulin A <49 mg
- Score 0-2 = low risk
- Score 3-5 = high risk


What is the Evidence Base for our Current cGvHD Treatments?

Professor Stephanie Lee, of the Fred Hutchinson Cancer Research Center, Seattle, provided an overview of the evidence base for treatments currently used in cGvHD.

- The current first-line therapy is 0.5-1 mg/kg/day prednisone, which initially works well for 50% of patients.
- While there are many agents under investigation for the treatment of steroid-refractory cGvHD, there is little evidence to differentiate these agents from each other.
- More well-designed and powered studies are needed to move the field forward.

There is a need for more effective and less toxic treatments for cGvHD; response rates are around 50% for each treatment course, patients experience frequent flares, treatment duration is several years to a lifetime, and 60%-85% of deaths are due to infection. There is also a poor understanding of the underlying mechanisms of treatments and no FDA/EMA approved drugs for cGvHD, which leads to a “try and see” approach to therapy.

Prevention has been investigated in 16 large RCTs, which have found that cGvHD incidence is lower when bone marrow or umbilical cord blood is used for the initial transfusion, and when patients are treated with anti-thymocyte globulin (ATG), ex vivo T cell depletion, post-HSCT cyclophosphamide and rituximab. Of the 8 RCTs investigating initial therapy between 1988-2015, none have demonstrated an improvement over steroids (0.5-1 mg/kg/day, long-term resolution in 30% of patients). Several studies have also shown that there is a significant risk of over-immunosuppression in this setting, with patients receiving additional therapy often experiencing worse outcomes in RCTs. In the steroid-refractory setting 37 agents have reported some activity (Table 2).

Table 2. Agents currently undergoing clinical trials for cGvHD

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory T cells</td>
<td>Infusions ± other agents, IL-2 ± ECP</td>
</tr>
<tr>
<td>B cells/ BCR signalling</td>
<td>Ibrutinib (BTK)</td>
</tr>
<tr>
<td>Co-stimulatory blockade</td>
<td>Abatacept (CTLA4)</td>
</tr>
<tr>
<td>IMiDs</td>
<td>Pomalidomide</td>
</tr>
<tr>
<td>Proteosome inhibition</td>
<td>Bortezomib, carfilzomib, ixazomib</td>
</tr>
<tr>
<td>JAK 1/2 inhibition</td>
<td>Baricitinib, ruxolitinib</td>
</tr>
<tr>
<td>ROCK2 inhibition</td>
<td>XDK25</td>
</tr>
<tr>
<td>Hedgehog inhibition</td>
<td>LDE225, Vismodegib</td>
</tr>
<tr>
<td>Cellular therapy</td>
<td>Mesenchymal stem cells</td>
</tr>
<tr>
<td></td>
<td>Dendritic cells</td>
</tr>
</tbody>
</table>


In the salvage setting, responses have been reported between 20%-82%. ECP is the most extensively studied, having been investigated since 1994 and with data from over 725 patients published. Rituximab, ECP, sirolimus, IL-2, ruxolitinib, ibrutinib and imatinib are still under investigation, with thalidomide, MMF and pentostatin not currently being trialled. There is currently little evidence to differentiate salvage therapies from each other (Table 3).

Although well designed and adequately powered studies are desperately needed, there are a number of challenges to investigating cGvHD, mainly due to the small and heterogeneous nature of the patient population. The initial therapy stage provides the cleanest population; however, prednisone provides an adequate response for 50% of patients, who are generally uninterested in participating in trials at this stage. Steroid refractory patients have the greatest unmet need, and are often very willing to be enrolled in studies; unfortunately, this population is more heterogeneous and there is no clear comparator.

Table 3. Overview of most investigated current treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosing</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECP</td>
<td>1-4 hours, q4-1 weeks</td>
<td>iv access</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>Oral, daily</td>
<td>Cardiac, bleeding</td>
</tr>
<tr>
<td>IL-2</td>
<td>SQ daily</td>
<td>Shots, fatigue</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Oral, daily</td>
<td>Nausea, oedema</td>
</tr>
<tr>
<td>ROCK2 inhibition</td>
<td>Oral, twice daily</td>
<td>Liver</td>
</tr>
<tr>
<td>JAK1/2 inhibition</td>
<td>Oral, twice daily</td>
<td>Thrombocytopenia</td>
</tr>
</tbody>
</table>

The Challenge of cGvHD – ECP in cGvHD

Professor Hildegard T. Greinix, of the Medical University of Graz, Austria, discussed the clinical evidence base for the use of ECP to treat steroid refractory cGvHD.

- ECP treatment in steroid refractory cGvHD resulted in high response rates measured both in a RCT setting and calculated using meta-analyses.
- Overall, ECP has been shown to be steroid sparing with a limited side effect profile. Improvements in quality of life and survival have also been reported without inhibition of the graft-versus-leukaemia (GVL) effect.
- Several studies suggest that ECP could also perform well in the first-line setting, but more trials are needed.

ECP has been recommended for the treatment of steroid refractory cGvHD, as it is both steroid sparing and has limited associated adverse events. ECP is already frequently used as a salvage therapy in cGvHD.17

Key supporting evidence for the use of ECP includes a RCT of ECP in combination with conventional treatment compared to conventional treatment (corticosteroids, calcineurin inhibitor, MMF) alone, which demonstrated a significantly increased ability to taper steroids in the ECP arm, and a suggestion of increased clinical response in this patient group. There was particular improvement in skin manifestations, with more modest improvements observed across extracutaneous manifestations. Meta-analyses calculated an ECP overall response rate of 0.68 (0.62–0.74) and a complete response rate of 0.29 (0.19–0.42).18

Lung cGvHD, characterised by bronchiolitis obliterans syndrome (BOS) is a serious manifestation of cGvHD, which is associated with a significant reduction in overall survival. To date, data from 121 ECP treated cGvHD patients with BOS have been published; the reported response rate (improvement or stabilisation) is 54%. Patients treated early in the course of BOS are more likely to respond to treatment, and work is currently underway to investigate B cell subsets as biomarkers for early BOS diagnosis. A number of small scale observational studies have also reported response rates of 42%-100% in patients with steroid refractory sclerodermatous cGvHD.19,20

The UK Photopheresis Society and Consensus Statement

**The UK Photopheresis Society**

Dr Fiona Dignan, of the Manchester Royal Infirmary, discussed the UK experience of establishing a photopheresis expert group to share knowledge and develop best practice.

- The society has published 2 main consensus statements on the use of ECP (2008 and 2017), and has also undertaken retrospective and prospective studies.

The UK Photopheresis society was established in 2011, at a time when there were only 7 active ECP centres in the UK. The society aims to educate medical and nursing staff, support new ECP centres and share knowledge and experience, as well as producing consensus statements and undertaking research and national audits.

The 2008 consensus statement provided recommendations on the use of ECP for cutaneous T-cell lymphoma (CTCL) and cGvHD, including dosing schedules, treatment duration and patient assessment frequencies. The 2017 consensus statement provided an update, including information about the treatment of cGvHD and solid organ rejection.21

Developing a UK Consensus Statement on the Use of ECP for GvHD

In the last presentation of the day, Dr Arun Alfred, of the Rotherham Foundation Trust, UK, provided an overview of the development of the UK consensus statement.

- The need to involve a wide range of stakeholders was highlighted, particularly nursing team members who often carry out ECP procedures.
- The team met twice over a 1 year period, conducted a review of current literature and sought to reach a consensus on contentious issues.
- Final consensus included recommendations for treatment of adults patients for GvHD, CTCL and organ rejection.

An update to the 2008 consensus statement was proposed following a number of advances in the field; new evidence had been published, improvements in technology facilitated the use of ECP in low weight patients, and there was a need to standardise treatment across the UK, laying the foundations for multi-centre UK trials.

The consensus statement sought input from a wide range of stakeholders, including ECP centres across the UK and nursing staff. Centres were invited to comment on previously published guidelines and a literature search was conducted to inform discussions.

The UK statement recommends use of ECP in patients with steroid-refractory, steroid-dependent or steroid-intolerant aGvHD, with a schedule of one treatment cycle (2 consecutive days) per week for 8 weeks. At 8 weeks ECP should be stopped in patients with a clinical response and tapered steroids, and tapered in those with a slower response. Steroid tapering is recommended from the 2nd week of ECP therapy, with an aim of 50% reduction during the first 4 weeks and a further 50% reduction during the following 4 weeks.14

Patients are considered eligible for cGvHD treatment if they are steroid-refractory, dependent or intolerant and have moderate or severe cGvHD with biopsy confirmation (where possible). The recommendations suggest that ECP should be stopped if patients experience progression or intolerance, or who do not respond after 14 weeks of fortnightly treatment. Patients who experience a response during the first 14 weeks should continue to receive ECP every 4 weeks until maximum response is achieved. Following maximum response, ECP should be tapered gradually.22

The consensus statement enables harmonisation of treatment across the UK centres, as well as facilitating the commissioning of ECP by providing clear guidelines for its use and economic impact.

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INDICATIONS
THERAKOS® Photopheresis is 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 mm³. 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 erythroderma 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 methoxsalen used in conjunction with THERAKOS® Photopheresis:

INDICATIONS
UVADEX™ 20 MICROGRAMS/ML SOLUTION FOR BLOOD FRACTION MODIFICATION is used in conjunction with either the THERAKOS® CELLEX® or the THERAKOS® UVAR XTS® Photopheresis System, in the palliative treatment of the skin manifestations (patch plaque, extensive plaque, erythroderma) of advanced stage (T2 – T4) cutaneous T-cell lymphoma (CTCL), only in patients who have not been responsive to other forms of treatment, (e.g. puvaetherapy, systemic corticosteroids, caryolysin, interferon alpha).

CONTRAINDICATIONS
Methoxsalen is contraindicated in patients exhibiting idiosyncratic or hypersensitivity reactions to methoxsalen, psoralen compounds, or any of the excipients. Methoxsalen is contraindicated in patients with co-existing melanoma, basal cell or squamous cell skin carcinoma. Methoxsalen is contraindicated in sexually active men and women of childbearing potential unless adequate contraception is used during treatment, and during pregnancy and lactation. Methoxsalen is contraindicated in patients with aphakia, because of the significantly increased risk of retinal damage due to the absence of a lens.

Warnings and Precautions
Special care should be exercised in treating patients who are receiving concomitant therapy (either topically or systemically) with known photosensitizing agents. Skin burns or premature aging may occur if protective precautions are not taken. Oral administration of methoxsalen followed by cutaneous UVA exposure (PUVA therapy) is carcinogenic. Because the dose with liquid methoxsalen is about 200 times less than with PUVA therapy and the skin is not exposed to high cumulative doses of UVA light, the risk of developing skin cancer following this therapy may be lower. Patients should be told emphatically to wear UVA absorbing, wrap-around sunglasses for twenty-four (24) hours after methoxsalen treatment. They should wear these glasses any time they are exposed to direct or indirect sunlight, whether they are outdoors or exposed through a window. Safety in children has not been established.

Adverse Events
Side effects of photopheresis were primarily related to hypotension secondary to changes in extracorporeal volume (1%).

For Additional Safety Information please refer to our website www.therakos.co.uk