
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.
Chairs for Sessions 1–4: Professor Marie-Thérèse Rubio, Nancy; Professor Regis Peffault de Latour, Paris

Session 1: Immunomodulation

Improving Immunologic Outcomes of Stem Cell Transplantation

Professor Krishna Komanduri, Sylvester Comprehensive Cancer Centre, Miami, USA

• 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 Graft-vs-Host Disease (GVHD) mediating naïve T cells whilst sparing pathogen-specific mature T cells. This has been attempted by inhibition of signalling pathways and expansion of regulatory T cells ($T_{reg}$) 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 the 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 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 haematopoietic stem cell transplant (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 (aGVHD) (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%). Finally, data published at the recent American Society for Hematology congress illustrate that the risk of development of progressive CMV viraemia is predicted by specific T cell cytokine signatures, and not T cell frequencies.

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 naive/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 naive/early T cells and mature cells, as naive 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 $T_{reg}$ cells, which selectively target naive T cells over mature T cells. One way $T_{reg}$ cells can be expanded in vivo is through the use of a TL1A-Ig fusion protein combined with interleukin-2 (IL-2). In Major Histocompatibility (MHC) mismatch murine models, this treatment dramatically and reversibly increased the expansion of $T_{reg}$ cells, which led to a significant reduction in GVHD-related mortality.

Session 2: The Unmet Needs of aGVHD

Current Status and Recent Clinical Data: An Overview

Professor Gérard Socié, Hôpital Saint-Louis, Paris, France

• Many therapies are currently under investigation for the prophylaxis of GVHD. However, disparate results between and within studies highlights the need for well-designed clinical trials.

• Evidence suggests that 2 mg/kg/day corticosteroids should remain the standard of care for first-line aGVHD treatment.

• There is an unmet need for clinical studies of treatments for steroid-refractory patients.

The longstanding prophylactic treatment for aGVHD is combination treatment with cyclosporine (CSA) and methotrexate (MTX). However, a number of clinical trials have been performed or are in progress to explore new preventative strategies, the results of which are presented in Table 1.

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The universal ‘standard of care’ for first-line treatment of aGvHD is 2 mg/kg/day corticosteroids.21 It has previously been shown that higher doses of methylprednisolone (MP) do not improve response rate in aGvHD.22 In an RCT assessing the efficacy and safety of using a reduced dose of MP 1 mg/kg/day appeared to be effective in patients with Grade IIa manifestations, however, patients presenting with Grade IIb or higher manifestations were at an increased risk of requiring secondary immunosuppressive therapy (41% vs. 7% for doses of 1 and 2 mg/kg/day, respectively).23 Evidence supporting combination treatment of corticosteroids with an additional immunosuppressive therapy is also inconclusive,24,25 again highlighting the need for rigorously-designed clinical trials. The American Society for Blood and Marrow Transplantation have recognised that there is currently an unmet need for clinical studies in patients with steroid-refractory aGvHD; in a comprehensive review of published reports, they were not able to recommend any particular therapy over another.26

### Table 1. Summary of evidence for prophylactic therapies for aGvHD

<table>
<thead>
<tr>
<th>Prophylactic therapy</th>
<th>Evidence</th>
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<tr>
<td><strong>Mycophenolate mofetil (MMF)</strong></td>
<td>Synergistic activity between MMF and calcineurin inhibitors has been demonstrated in non-myeloablative and cord HTSCT, however, MMF is not routinely used after myeloablative transplants. Two randomised controlled trials (RCTs) are in progress in France comparing CsA plus MMF with either CsA plus MTX or CsA alone in acute myeloid leukaemia first remission patients in the myeloablative or reduced intensity condition (RIC) settings, respectively.14</td>
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<tr>
<td><strong>Sirolimus in combination with tacrolimus (SIR/TAC)</strong></td>
<td>A number of clinical trials have been conducted to assess the efficacy of SIR/TAC, however, results have been inconclusive, with early studies suggesting that SIR/TAC is associated with a reduced incidence of aGvHD following HSCT,12,13 yet later study identified no statistically significant difference in Grade II-IV GvHD-free survival.14</td>
</tr>
<tr>
<td><strong>Cyclophosphamide, bortezomib and maraviroc</strong></td>
<td>Phase II trials of cyclophosphamide, bortezomib and maraviroc have been published in high impact journals in the last decade,15,16 and a ‘pick the winner’ study comparing the three treatments is currently in progress. The most effective therapy will progress to a Phase III trial.</td>
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<tr>
<td><strong>Vorinostat</strong></td>
<td>Positive data from well-designed Phase II clinical trials support the use of vorinostat prophylaxis combinations in the sibling donor and unrelated donor HTSCT settings.17,18</td>
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<tr>
<td><strong>Post-transplant cyclophosphamide (Pt-Cy)</strong></td>
<td>A Phase II clinical trial assessing the efficacy of Pt-Cy found the incidence of aGvHD Grades III-IV to be extremely low following HSCT. However, unexpectedly, the incidence of Grades II-IV aGvHD was found to be largely unaffected,20 highlighting the need for prophylactic GvHD therapies to be assessed in well-designed, randomised trials.</td>
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<tr>
<td><strong>Anti-thymocyte globulin-Fresenius (ATG-F)</strong></td>
<td>ATG-F has been evaluated in a number of Phase III clinical trials,21,22 with results demonstrating the effectiveness of this therapy specifically in the matched unrelated donor HTSCT setting,23,24 including up to eight years post-transplant. However, ATG-F appears to be less effective in the matched related donor setting.25</td>
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Management of aGvHD with ECP: The French Touch

Professor Marie-Thérèse Rubio, Hôpital Brabois, Nancy, France

- Effective treatments are necessary to control aGvHD.
- ECP is a cell-based immune modulatory therapy under investigation for GvHD that results in the apoptosis of a subset of T cells and antigen-presenting cells (APCs).
- The underlying mechanism of action behind ECP is incompletely understood, however, apoptotic cells may induce tolerance of the immune system.
- Clinical trials in steroid-refractory or -dependent patients suggest that ECP may generate a superior response in patients with skin involvement and less severe grades of GvHD.
- A prospective randomised trial is planned for ECP in the first-line treatment of Grade II skin GvHD. Effective first-line GvHD treatments are required to control aGvHD, which remains a major cause of morbidity and mortality after allogeneic HSCT. 1, 4 ECP is a cell-based immunomodulatory therapy under investigation for GvHD, which takes place outside the body in three phases (Figure 1). 6

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

The photoactivated white blood cells are returned to the patient

UVA

Photoactivation with UVA light

Methoxalen Sterile Solution

The Therakos Photopheresis instrument draws blood from the patient

Blood is separated by centrifugation and red blood cells and plasma are returned

White blood cells are treated with ex vivo methoxalen and exposed to UVA light

Management of aGvHD Using Janus Kinase Inhibitors: Latest Clinical Update

Professor Robert Zeiser, University of Freiburg, Freiburg, Germany

- Abnormal kinase activity, including increased Janus kinase (JAK) activity, is a hallmark of a number of inflammatory diseases.
- The role of ruxolitinib (Jak 1/2 inhibitor) as a potential GvHD treatment has been examined in mice models and patient cohorts.
- The microRNA 'mir146a' plays a regulatory role in the Jak/Stat signalling pathway, and patients lacking this gene may benefit from Jak 1/2 inhibition therapy

Despite the large number of immunotherapies currently used or under investigation for the prophylaxis of GvHD, there remains a significant unmet need for effective strategies, as evidenced by a mortality rate of approximately 50% at one-year post-onset of severe aGvHD. 25

Research has shown that abnormal kinase activity is the hallmark of a number of inflammatory diseases, including immune thrombocytopenic purpura, 26 rheumatoid arthritis 27 and ulcerative colitis. 28 Similarly, a number of kinases have been indicated to play a role in GvHD, including Jak 1 and 2. 29

In a murine aGvHD model, inhibition of Jak 1/2 signalling through application of ruxolitinib improved survival and reduced expansion of alloreactive T cells, whilst increasing Treg cells. 30 In a cohort of patients with steroid-resistant acute or chronic GvHD who received ruxolitinib as salvage therapy, overall response rate following treatment was 82%, 31 and one-year survival rate after the start of ruxolitinib therapy was 62% and 92% for patients with acute and chronic GvHD, respectively. 32 Ruxolitinib is currently under further investigation in ongoing prospective clinical trials. 33

Combination treatment with ECP and ruxolitinib may improve the condition of steroid-resistant GvHD patients. In a case study of a patient with severe acute liver GvHD unresponsive to corticosteroids, ECP therapy with subsequent concomitant ruxolitinib treatment resulted in resolution of the liver GvHD, and the patient was able to stop steroid therapy (unpublished data).

The microRNA 'mir146a' is known to be involved in the regulation of the immune response. 34 In murine models, there was a statistically significant reduction in survival following allogenic HSCT in mir146a knock-out mice in comparison with wild type mice. 35 In a cohort of allogenic HSCT recipients with a single nucleotide polymorphism resulting in reduced mir146a activity, a greater proportion of patients experienced GvHD Grades III-IV compared to Grades 0-II. 36 Accordingly, mir146a has a potential role in the identification of patients who may benefit from Jak 1/2 inhibition.

The role of ruxolitinib (Jak 1/2 inhibitor) as a potential GvHD treatment has been demonstrated in murine models and human patient cohorts. In a murine aGvHD model, inhibition of Jak 1/2 signalling through application of ruxolitinib improved survival and reduced expansion of alloreactive T cells, whilst increasing Treg cells. In a cohort of patients with steroid-resistant acute or chronic GvHD who received ruxolitinib as salvage therapy, overall response rate was 82%, and one-year survival rate after the start of ruxolitinib therapy was 62% and 92% for patients with acute and chronic GvHD, respectively.

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ECP ultimately results in the apoptosis of a subset of T cells and APCs, however, the precise underlying immunomodulatory mechanisms behind ECP are incompletely understood. It is hypothesised that ECP-induced apoptotic cells induce tolerance of the immune system through release of signals that reverse the pro-inflammatory behaviour of macrophages and APCs, that in turn induce anti-inflammatory signals and activate Treg cells. Bone marrow transplant (BMT) recipients with GvHD who received ECP treatment also had increased levels of MDSCs after treatment, which reduce Th1 and Th2 responses in vitro. Furthermore, patients who sustained MDSC levels were identified as responders to ECP, whereas patients with transiently increased MDSCs were not. The mechanisms of induction of MDSCs by ECP and apoptotic cells need to be explored further.

In a clinical trial of ECP in patients with steroid-refractory aGvHD, a complete response was achieved in more patients with cutaneous involvement in comparison to those with gut or liver involvement. This result was supported by a 2014 meta-analysis, in which skin was found to be the most responsive organ to ECP relative to the gut and liver.

In a multivariate analysis of steroid-refractory or -dependent aGvHD patients treated with ECP, patients with less severe grades of GvHD were statistically significantly more likely to respond to treatment compared to patients with Grades III-IV GvHD. Similarly, amongst 37 patients with steroid-refractory or -dependent aGvHD at Hôpital Brabois, Nancy, a complete response was achieved in 100% of patients with Grades I-II disease, 57% of patients with Grade III (partial response: 28%), and 15% of patients with Grade IV (partial response: 35%).

ECP allows for rapid tapering of steroid therapy, has a good tolerance profile and a low risk of haematological relapse. A prospective randomised study is currently planned to assess the effectiveness of ECP in the first-line treatment of Grade II aGvHD with skin involvement.

Session 3: From GUT feeling to ... Clinical Data, Outcomes and Guidelines

The Eukaryotic Gut Virome in HSCT: New Clues in Enteric GvHD

Dr. Jérôme Le Goff, Hôpital Saint-Louis, Paris, France

• Virome dynamics in allogeneic HSCT and enteric GvHD remain relatively unexplored compared to the bacterial microbiome.

• A six-week longitudinal study to characterise the gut virome of 44 HSCT recipients following transplantation identified an increase in vertebrate viral sequences and an increase in the prevalence of persistent viral families.

• Picobirnaviruses were more prevalent in patients with enteric GvHD, and found to be associated with gut inflammation. They were predictive of the occurrence of enteric GvHD Grade II and above, and any type of GvHD post-HSCT.

The gut is one of the main tissues affected in GvHD, and research has previously been performed to understand the role played by the bacterial microbiome in enteric GvHD. Despite evidence to suggest viruses may be implicated in the pathogenesis of the disease, virome dynamics in allogeneic HSCT and enteric GvHD remain comparatively unexplored.

A six-week longitudinal study used metagenomics and sequencing techniques to characterise the gut virome of 44 HSCT recipients, of whom 38 developed aGvHD (84% with enteric disease and 46.25% with Grade II-IV GvHD). In patients with enteric GvHD, a delayed, but statistically significant increase in persistent DNA viruses was observed over time compared to patients without enteric GvHD (p<0.0001).

A relatively unknown viral family, picobirnaviridae, was detected in 18 individuals more frequently before or within a week after transplant than at later time points (p=0.008). Picobirnaviridae were more prevalent in patients with enteric GvHD, and were found to be associated with gut inflammation. In a time-dependent Cox proportional-hazards model, picobirnaviruses were predictive of the occurrence of enteric GvHD Grades ≥II, as well as any type of GvHD.
A Role for Macrolides in HSCT: The ALLOZITHRO Randomised Clinical Trial

Professor Anne Bergeron, Hôpital Saint-Louis, Paris, France

- In a randomised, placebo-controlled trial of azithromycin for the prevention of Bronchiolitis Obliterans Syndrome (BOS) following HSCT, a higher rate of haematological relapse was detected in the azithromycin arm, resulting in a halt to the trial. 48

- At data analysis, azithromycin was associated with a significantly lower airflow decline-free survival compared to placebo. No significant difference was observed in the cumulative incidence of BOS between arms. 48

- Possible explanations for the increased rate of relapse observed with azithromycin include interference with the ‘graft versus leukaemia’ effect and disturbance of the gut microbiome.

BOS is the most frequently reported lung-related complication following HSCT, occurring in 2%-26% of transplant recipients, and is associated with significant mortality and morbidity. 49 There are currently no curative treatments available, and as such preventative strategies are required. Azithromycin is a macrolide that possesses both antibiotic and immunomodulatory properties, 50 and has been shown to be effective in the treatment of BOS following lung transplantation. 51

To determine the efficacy of azithromycin in the prophylaxis of BOS after HSCT, a randomised, double-blind, placebo-controlled trial was performed at 19 French centres in which patients were allocated to receive azithromycin (n=243) or placebo (n=237), starting at the time of the conditioning regimen. 48 However, the study was prematurely stopped and unblinded following an unanticipated imbalance across the two treatment arms in the number of haematological relapses. 48

At data analysis, the primary endpoint of airflow decline-free survival was significantly lower in the azithromycin arm compared to the placebo group (p=0.03), and there was no significant difference in the incidence of BOS between treatments (p=0.08; Figure 2). Overall survival was significantly worse in the azithromycin group compared to the placebo group, and this was deemed to be due to the increased rate of haematological relapse. 48

Possible explanations for the increased rate of relapse observed with azithromycin include interference with the ‘graft versus leukaemia’ effect and disturbance of the gut microbiome. 46, 51

Figure 2. Airflow decline-free survival and cumulative incidence of bronchiolitis obliterans syndrome

Adapted from Bergeron et al. (2017) 48

Session 4: Chronic GvHD: Where Are We?

Immunosuppressive Therapy Sparing and Its Benefits on Quality of Life

Dr. Arun Alfred, The Rotherham NHS Foundation Trust, Rotherham, UK

- Chronic GvHD (cGvHD) has a significant negative impact on quality of life.52
- Published studies have demonstrated improvements in quality of life in cGvHD patients following ECP treatment,53, 54 and this was mirrored by the experience of Rotherham NHS Foundation Trust (unpublished).
- The National Institutes of Health (NIH) have recognised the importance of quality of life outcomes and recommend their inclusion in clinical trials for cGvHD.55

C GVHD is the leading cause of late non-relapse death, results in significant functional impairment and negatively impacts patients’ quality of life.54, 55 Patients with cGvHD report Short Form-36 (SF-36) Physical Component Scores that are lower than population norms and comparable with scores reported for systemic sclerosis, systemic lupus erythematosus and multiple sclerosis.52

Trials have demonstrated an improvement in quality of life with ECP in patients with cGvHD, which may be due to its steroid-sparing effect. In a prospective trial of 38 patients, statistically significant improvements in quality of life, as measured by the Lee GvHD Symptom Scale and the Dermatology Quality of Life Index, were observed after six months of treatment with ECP.53 Similarly, in an RCT comparing ECP plus conventional treatment to conventional treatment alone, there was a statistically significant difference in Targeted Symptom Assessment after 12 weeks in favour of ECP combination treatment.54

Between 2011 and 2015, a total of 68 adult cGvHD patients were treated with ECP for at least six months at the Rotherham NHS Foundation Trust. At all timepoints measured, an improvement in quality of life was observed compared to baseline, which was sustained between 6 and 18 months, and accompanied by a reduction in steroid use. A subgroup of patients was identified with elevated bilirubin or low platelets upon commencing treatment who did not experience quality of life improvements following ECP. These unpublished data represent the longest follow-up of quality of life improvements in cGvHD patients post-ECP to date (unpublished data).

In a 2014 report, the NIH recognised the importance of including quality of life outcomes in clinical trials for cGvHD and recommended the administration of the SF-36 or the Functional Assessment of Cancer Therapy Bone Marrow Transplant (FACT-BMT).55


Session 5: Centre Experiences and Combinations Strategies

Chair: Professor Jean-Hugues Dalle, Paris

Management of aGvHD: The Experience in Robert Debré Hospital

Dr. Mony Fahd, Hôpital Robert Debré, Paris, France

- Between 2011 and 2016, 332 patients at the Robert Debré Hospital received BMTs for both malignant and non-malignant disease. Among them, 42 patients have been treated with ECP as second-line therapy for aGvHD.
- Two clinical trials are ongoing in this centre: one assessing the safety and efficacy of ruxolitinib in patients with steroid-refractory aGvHD after allogenic HSCT; the second assessing the safety and efficacy of ECP for the treatment of patients with steroid-refractory aGvHD.

Between 2011 and 2016, 332 low-weight patients at the Robert Debré Hospital received BMTs for both malignant and non-malignant disease. Among them, 42 patients have been treated with ECP as second-line therapy for aGvHD.

Figure 3. OS between 2011 and 2016 for BMT recipients with malignant and non-malignant disease

<table>
<thead>
<tr>
<th>Months</th>
<th>Survival</th>
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<tr>
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<td>6</td>
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- OS at 1 y: 93.2% (95% CI: 88.6–97.9) vs (IC95%; 70.5–82)
- OS at 2 y: 92.1% (95% CI: 87–97.1) vs 71.1% (IC95%; 64.8–77.4)
- OS at 5 y: 92.1% (95% CI: 87–97.1) vs 66.1% (IC95%; 59.1–73.1)

Unpublished data. OS: overall survival. y: year
Between 2010 and 2016, 56% of transplanted patients presented with acute GvHD. Of these, 16% were steroid-refractory. A total of 42 patients have been treated with ECP as a second-line treatment. Other second-line treatments used in this centre are: switch from tacrolimus to CsA, monoclonal antibodies, anti-TNF antibodies, and recently, ruxolitinib.

Between January 2007 and October 2012, 23 sequential recipients of allogeneic HSCT were switched from CsA to tacrolimus-based immunosuppression for steroid-refractory acute Grade I-III GvHD. A complete response was seen in eight patients (35%), a partial response was seen in seven patients (30%) and no response was seen in eight patients (35%). This hospital is participating in the international multicentre study assessing the safety and efficacy of ECP in patients with steroid-refractory aGvHD (sponsored by Therakos, NCT02524847). An ongoing study at the hospital is assessing the safety and efficacy of ruxolitinib in patients with steroid-refractory aGvHD after allogenic HSCT. Currently 10 patients have been treated, however, the treatment is associated with risk of infection and ruxolitinib withdrawal syndrome.

Management of aGvHD: The Experience in Saint-Antoine Hospital

Dr. Florent Malard, Hôpital Saint-Antoine, Paris, France

- Development of innovative strategies, such as use of Pt-Cy outside of the haploidentical donor setting is required to improve aGvHD prophylaxis.
- MTX demonstrates efficacy in steroid-refractory aGvHD and may be investigated as a potential novel first-line treatment option.1, 4, 6, 6
- Fecal microbiota transplant (FMT) is a promising novel treatment option for steroid-resistant enteric GvHD.6, 4

A longitudinal study following patients undergoing HSCT between 1983 and 2010 identified that aGvHD incidence has remained stable for a number of decades,6, 46 highlighting the need for innovative strategies. A Phase II randomised controlled trial is currently planned by Saint-Antoine hospital to assess the role of Pt-Cy in GvHD prophylaxis outside of the haploidentical donor setting.64

In this hospital, the second-line therapies used in steroid-refractory aGvHD are: ruxolitinib (investigational use as part of the REACH trial), ECP and MTX in skin-predominant disease, and MTX in gastrointestinal (GI)-predominant disease.

To illustrate St Antoine’s practice, Dr Malard described a case study of GI-predominant steroid-refractory aGvHD that was successfully treated with MTX. This case study brings into light the potential efficacy of MTX in the treatment of aGvHD, and is corroborated by two studies demonstrating the efficacy of methotrexate in steroid-refractory GvHD.65, 66 An RCT protocol is currently in development to assess the efficacy of methotrexate in combination with corticosteroids as a first-line treatment option for an aGvHD.67

Fecal Microbiota Transplantation is a promising treatment for steroid-resident enteric GvHD. Increased bacterial diversity and presence of Blautia bacteria have been associated with improved aGvHD survival,68 and FMT was performed safely in a small pilot study.69 A Phase I/II trial is planned to investigate the efficacy of FMT in steroid-refractory Grade III-IV enteric aGvHD patients.68

Management of cGvHD: The Experience in Lille Hospital

Dr. Leonardo Magro, Hôpital Claude Huriez, Lille, France

- Imatinib and ECP are associated with a severe, long-term impact on quality of life67
- Imatinib and ECP are used separately to treat cGvHD,67 however, experience from the Hôpital Claude Huriez in Lille suggests that the treatments are more effective when used in combination (unpublished).
- Seven patients with severe steroid-refractory sclerotic-type cGvHD have been treated with imatinib with ECP, resulting in an overall response rate of 100% and a complete response rate of 57%.

Chronic cGvHD is associated with a severe, long-term impact on quality of life.67 When imatinib and ECP are used separately to treat cGvHD, patient response is limited,67 however, their respective modest efficacies it was hypothesised that the combination of imatinib with ECP could lead to higher response rates. At the Hôpital Claude Huriez, imatinib with ECP has been used to treat seven patients with severe steroid-refractory sclerotic-type cGvHD. After a median follow-up of 54 months, the overall response rate was 100% and the complete response rate was 57%. The median time of ECP treatment in combination with imatinib was 36 months, and corticosteroids could be discontinued in all patients after a median of eight months. Following treatment of imatinib with ECP, four patients experienced a complete response and could discontinue treatment and three patients received maintenance therapy with ECP alone. None of the patients experienced adverse events related to imatinib or ECP.

Dr. Magro described a case study of a 48-year-old man who developed severe sclerotic GvHD that affected more than 50% of his body surface area (BSA), including “hidebound” sclerotic features. The patient had lichen planus-like features present on his mouth, keratoconjunctivitis and moderate dry eye symptoms, and a forced expiratory volume in one second (FEV1) of 65%. Following no response to treatment with imatinib 400 mg/day, the patient was started on combination therapy with ECP, leading to a partial response within three months, including improvements in his lung, skin and eye symptoms. The patient was later able to discontinue steroid therapy and imatinib, continuing on maintenance ECP. The experience from this hospital suggests that combination therapy significantly improves response in cGvHD compared to the treatments used separately.

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 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 mcg/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. puvatherapy, systemic corticosteroids, carnylosin, 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 (7%).

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

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This information is intended only for healthcare professionals in Europe, the Middle East and Asia Pacific.

08.30 Registration & coffee

09.00 Session 1: Immunomodulation
Chairs: Profs Marie-Therese Rubio (Nancy) and Regis Peffault de Latour (Paris)
- Improving immunologic outcomes of stem cell transplantation
  (Krishna Komanduri / Miami - USA)

09.30 Session 2: The unmet needs of acute GvHD
Chairs: Profs Marie-Therese Rubio (Nancy) and Regis Peffault de Latour (Paris)
- Current status and recent clinical data: an overview
  (Prof. Gérard Socié / Paris - France)
- Management of acute GvHD using Jak inhibitors: latest clinical update
  (Prof. Robert Zeiser / Freiburg - Germany)
- Management of acute GvHD with ECP: The French touch/initiative
  (Prof. Marie-Therese Rubio / Nancy - France)

11.00 Coffee break

11.30 Session 3: From GUT feeling to ... clinical data, outcomes and guidelines: the latest French update and studies
Chairs: Profs Marie-Therese Rubio (Nancy) and Regis Peffault de Latour (Paris)
- The eukaryotic gut virome in hematopoietic stem cell transplantation: new clues in enteric
  Graft-versus-Host Disease (GvHD)
  (Dr. Jerôme Le goff / Paris - France)
- A role for macrolides in HSCT: The ALLOZITHRO Randomized Clinical Trial
  (Dr. Anne Bergeron / Paris - France)

12.30 Morning Q&A
13.00 Lunch

14.00 Session 4: Chronic GvHD: where are we?
Chairs: Profs Marie-Therese Rubio (Nancy) and Regis Peffault de Latour (Paris)
- Immunosuppressive therapy sparing and its benefits on Quality of Life
  (Dr. Arun Alfred / Rotherham - UK)
- Skin as chronic GvHD target: old and new concepts
  (Prof. Jean-David Bouaziz / Paris - France)

15.00 Session 5: Center experiences and combinations strategies
Chairs: Profs Jean-Hugues Dalle (Paris) and Jean-David Bouaziz (Paris)
- Management of acute GvHD: the experience in Robert Debre hospital
  (Dr. Mony Fahd / Paris - France)
- Management of acute GvHD: the experience in St Antoine hospital
  (Dr. Florent Malard / Paris - France)

15.40 Coffee break

16.00 Session 5: Center experiences and combinations strategies (continued)
Chairs: Profs Jean-Hugues Dalle (Paris) and Jean-David Bouaziz (Paris)
- Management of chronic GvHD: the experience in Lille hospital
  (Dr. Leonardo Magro / Lille - France)

16.20 Afternoon Q&A
16.50 Final wrap-up
17.00 Meeting closure

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