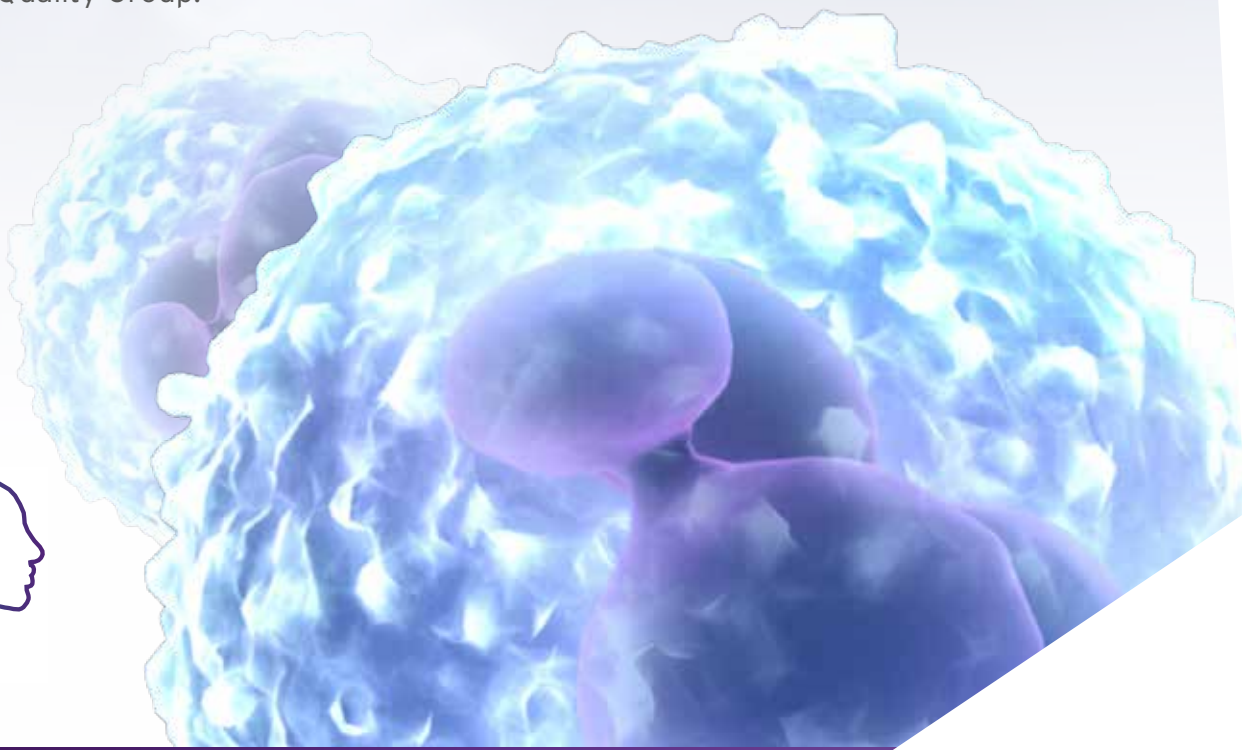
6th Nordic Photopheresis Meeting

Haymarket by Scandic, Hötorget, Stockholm, Sweden, 22nd November 2019

Chair: Professor Gösta Berlin

Department of Clinical Immunology and Transfusion Medicine, Linköping University Hospital, Linköping, Sweden

On the 22nd November 2019, Mallinckrodt Pharmaceuticals hosted the 6th Nordic Photopheresis Meeting in Stockholm, Sweden. Professor Gösta Berlin, Chair of the meeting, welcomed all delegates to this annual gathering, which has now become an established event in the calendar. The distinguished panel of speakers reviewed the latest global scientific and clinical data on the use of extracorporeal photopheresis (ECP) for the management of graft-versus-host disease (GvHD) (including a focus on encouraging data of its use in the treatment of lung GvHD), followed by a panel discussion and chance for delegates to put their key questions to the experts. Professor Berlin also provided an update on ongoing and planned projects within the expanding Nordic ECP Quality Group.



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Disclosure: All speakers received honoraria from Therakos (Mallinckrodt Pharmaceuticals) to attend the meeting. Presentations included discussions of experimental therapies used in clinical practice and clinical trial settings. The meeting purpose was educational; no promotional material was presented during the sessions.

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Contents

Evaluating outcomes of chronic GvHD using real-world data

Professor Jonas Mattsson discussed the value of 'real-world' data in determining the true burden of disease, not only to the individual with GvHD but also to society as a whole.

- *The National Institutes of Health recommendations for diagnosis, severity scoring and management of chronic GvHD (cGvHD) are not always widely implemented in clinical practice, therefore the incidence of the disease may be underestimated.*[1]
- *The use of real-world registry data may help determine the true burden of disease, the impact on clinical outcomes, long-term productivity, and healthcare resource utilisation, as well as the overall cost of management.*

Reports suggest that around 30–50% of haematopoietic stem cell transplant (HSCT) recipients go on to develop cGvHD,[2] however Professor Mattsson suggested that this is likely to be an underestimate of the true figure.

Sweden is noted for its well-established health registries which provide a unique data source for analysis. Professor Mattsson described a recent study undertaken by his team which evaluated data from a range of different national registries in Sweden – including patients, prescriptions, cause of death and cancer, as well as the LISA (longitudinal integration database for health insurance and labour market studies) registry. He stressed the importance of actively treating cGvHD.

Alongside this, better tools are needed to allow precise evaluation of the immunosuppressive status of individuals, so treatment can be tailored appropriately. He recommended considering earlier use of immunomodulatory therapy to avoid the adverse consequences of prolonged immunosuppression.

Combination therapies in GvHD

Professor Francis Ayuk reviewed the latest data on the use of combination therapies for the management of acute GvHD (aGvHD) and cGvHD, and discussed how immunomodulatory therapy with ECP can help minimise the overall burden of chronic immunosuppression.

- *ECP has been used successfully as a second-line treatment for steroid-refractory (SR) aGvHD and has shown promising results in combination with ruxolitinib in this setting.*[3, 4]
- *Positive results have also been obtained with ECP treatment of steroid-resistant (SR) cGvHD and it has been shown to be steroid sparing.*[5]
- *The overall burden of immunosuppression in GvHD is an important consideration in management, as infections are a common cause of non-relapse mortality (NRM).*[6]

Corticosteroids continue to be the standard first-line therapy for aGvHD resulting in complete response (CR) rates of around 48% with overall response rates (ORR) of 64%.[7] A meta-analysis of clinical trials found no improvement in these response rates when corticosteroids were combined with other agents as first-line treatment.[8] However, these studies did not select for high-risk patients, so it is not possible to know for sure whether these patients could benefit from intensified immunosuppression. Several studies in this high-risk patient population are ongoing to evaluate combination therapies: in the USA a Phase II multicentre study of natalizumab plus standard steroid therapy (ClinicalTrials.gov Identifier: NCT02133924) and in Germany a Phase II multicentre study of ECP plus standard steroid therapy (ClinicalTrials.gov Identifier: NCT04291261).

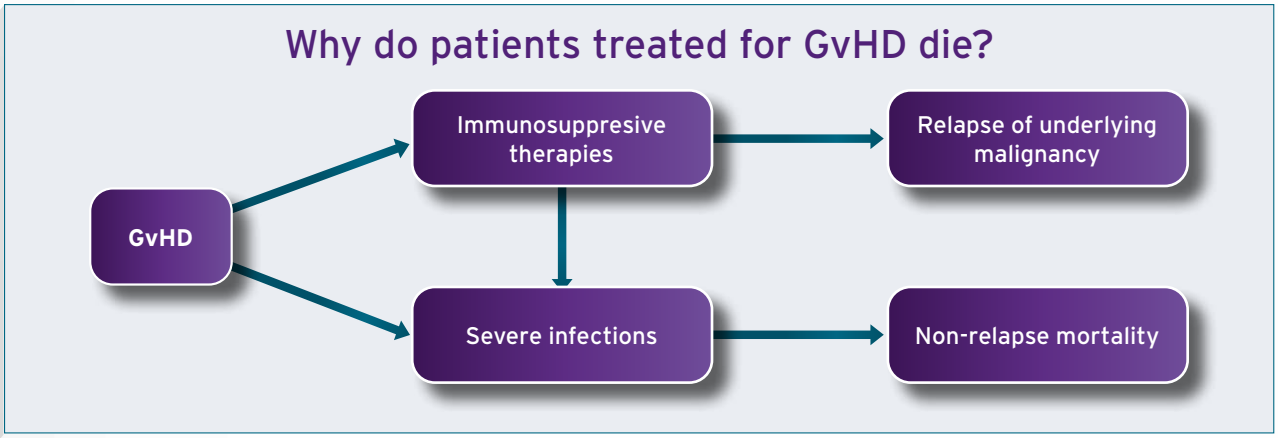
If aGvHD becomes SR or steroid-dependent (SD), second-line treatment options are needed to improve outcomes. A wide range of agents have been evaluated, but analysis of ORR and 6-month survival in these studies does not support the choice of any particular agent over another.[7]

ECP has been used successfully as a second-line treatment for SR aGvHD with a range of retrospective and some prospective studies reporting good ORR (65–100%) and overall survival rates (42–87%) in adult and paediatric patients.[3] Ruxolitinib, a selective Janus-associated tyrosine kinase inhibitor, has also shown promising results as second-line therapy for SR aGvHD.[9,10] In light of these results, a study was undertaken to investigate the combination of ECP and ruxolitinib in SR GvHD.[4] This combination achieved promising results with an ORR of 61% and an estimated 1-year survival of 53.6%.[4] It also allowed rapid tapering of corticosteroids, thereby potentially reducing adverse effects.[4]

Corticosteroids are also the cornerstone of first-line treatment of cGvHD, with the addition of calcineurin inhibitors if needed to allow steroid sparing.[11] In the case of SR cGvHD, various second-line treatment options have been investigated, including ECP.[12] In a prospective, randomised, controlled study of patients with cutaneous manifestations of cGvHD, ECP improved total skin scores, but also had the valuable benefit of allowing a reduction in steroid without any increase in infections.[5*]

Professor Ayuk highlighted the considerable burden of immunosuppression in patients being treated for GvHD, noting that the chronic use of immunosuppressive therapies may lead to a high incidence of NRM as many patients could die of infections (Figure 1).[6] He recommended monitoring the level of immunosuppression and using immunomodulatory therapies where possible.

Figure 1. The burden of immunosuppression and its contribution to non-relapse mortality.



Clinical benefit of ECP-induced immunotolerance

Professor Hildegard Greinix gave an overview of data demonstrating the immunomodulatory effects of ECP in the management of GvHD – an important clinical benefit in this patient group who are susceptible to infectious risks.

- *When selecting an effective therapy for GvHD, clinical response rates should be associated with a good safety profile and minimal toxicity, reflected by a low risk of infections.*
- *The effects of ECP treatment can promote the development of immune tolerance – it has beneficial immunomodulatory, and not immunosuppressive, effects that do not adversely impact the patient's anti-infectious and anti-leukaemic immune responses.*[13]

Following HSCT, the goal is that patients should achieve 'immune homeostasis' – a reconstituted immune system and the development of immune tolerance, namely no immune activity to host tissues while preserving the normal response to foreign antigens, such as invading pathogens (Figure 2).[14] GvHD can result from an imbalance between the immune effector mechanisms that cause inflammation and the

*The Flowers et al 2008 study had several limitations which should be considered when interpreting the data: the primary endpoint did not reach statistical significance.

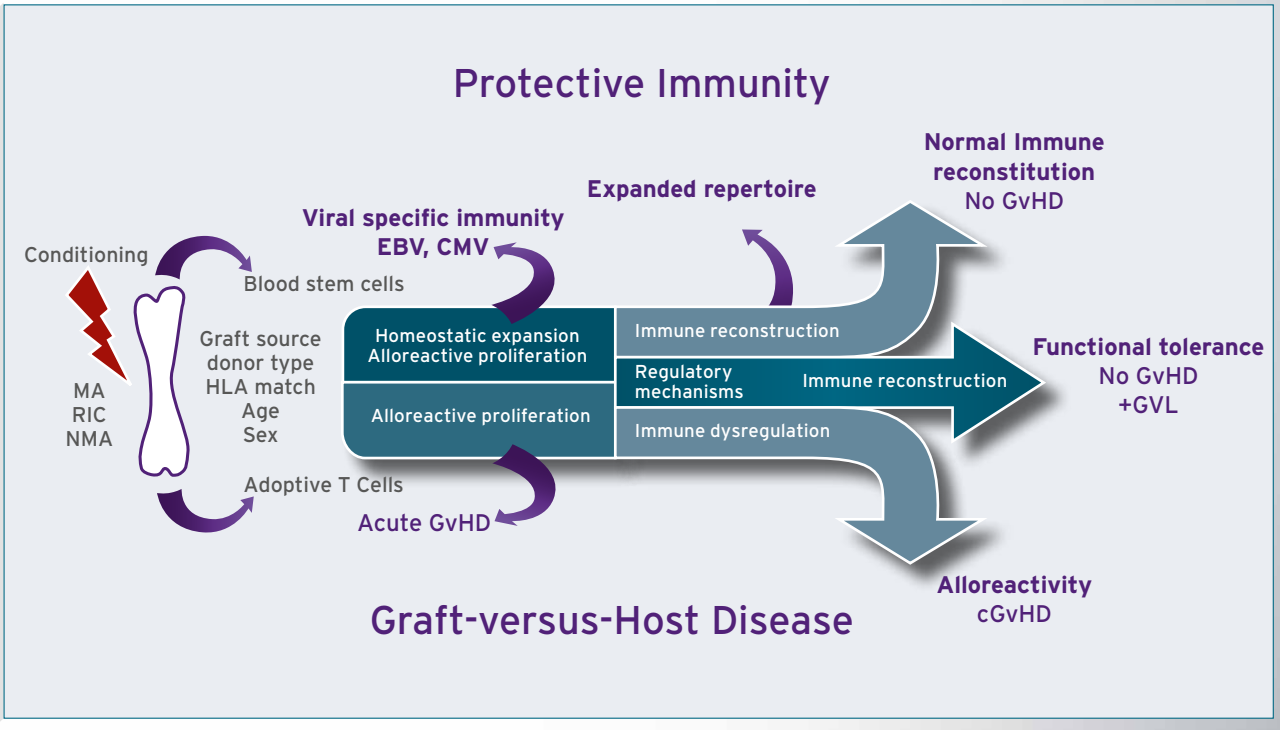
inhibitory (regulatory) mechanisms that may maintain tolerance. Studies have shown that an unbalanced recovery of CD4 regulatory T cells as well as effector CD4 and CD8 T cells following HSCT contributes to cGvHD.[15]

Clinical studies undertaken over several decades have confirmed the effectiveness of ECP as a therapeutic option for the management of aGvHD, including SR disease, achieving sustained ORR and good overall survival rates.[16,17] A systematic review of six prospective studies of ECP in SR GvHD, including 103 patients reported an ORR of 69% (84% for skin manifestations, 65% for gastrointestinal (GI) and 55% for liver).[18] Positive clinical benefits have also been confirmed for ECP in the treatment of SR, SD or steroid-intolerant cGvHD.[5,19] Systematic reviews and meta-analyses of a range of studies of ECP in cGvHD have confirmed good response rates in oral, skin, and liver SR cGvHD, with some activity in lung and GI SR cGVHD.[20,21]

Professor Greinix highlighted that, in addition to its clinical efficacy in SR cGvHD, ECP has also demonstrated an excellent safety profile in clinical studies over many years.[22-24] Notably, these reports suggest that ECP treatment is not associated with any increase in infectious complications or viral reactivation.[7] Infections are known to be a major cause of NRM in GvHD patients, and immunosuppression following HSCT is one of the known risk factors for their development.[25,26]

Professor Greinix highlighted research to date on the mechanisms underlying the immunomodulatory effects of ECP which are thought to result from decrease in pro-inflammatory, and an increase in anti-inflammatory, cytokines, and induction of regulatory T cells.[13] There is a shift from a Th1 to a Th2 cytokine profile and immune phenotype, and induction of tolerogenic dendritic cells (DCs), all of which are thought to contribute to a beneficial increase in immune tolerance.

Figure 2. Pathways to functional immune tolerance or the development of cGvHD.[14] Reproduced with permission.



CMV, cytomegalovirus; EBV, Epstein-Barr virus; GvL, graft-versus-leukemia; MA, myeloablative; NMA, non-meyeloablative; RIC, reduced-intensity conditioning

How to treat lung GvHD using ECP

Professor Hildegard Greinix discussed the pulmonary complications that can arise following HSCT, including bronchiolitis obliterans syndrome (BOS), a serious, non-infectious lung manifestation of GvHD that is often refractory to standard therapies.

- *Pulmonary GvHD is a serious complication in HSCT recipients and is associated with a poor prognosis, therefore early diagnosis and therapeutic intervention are essential.*
- *BOS generally has a poor response to corticosteroids, but studies have shown that ECP can be effective in stabilising or improving lung function, and has survival benefits.*[27,28]

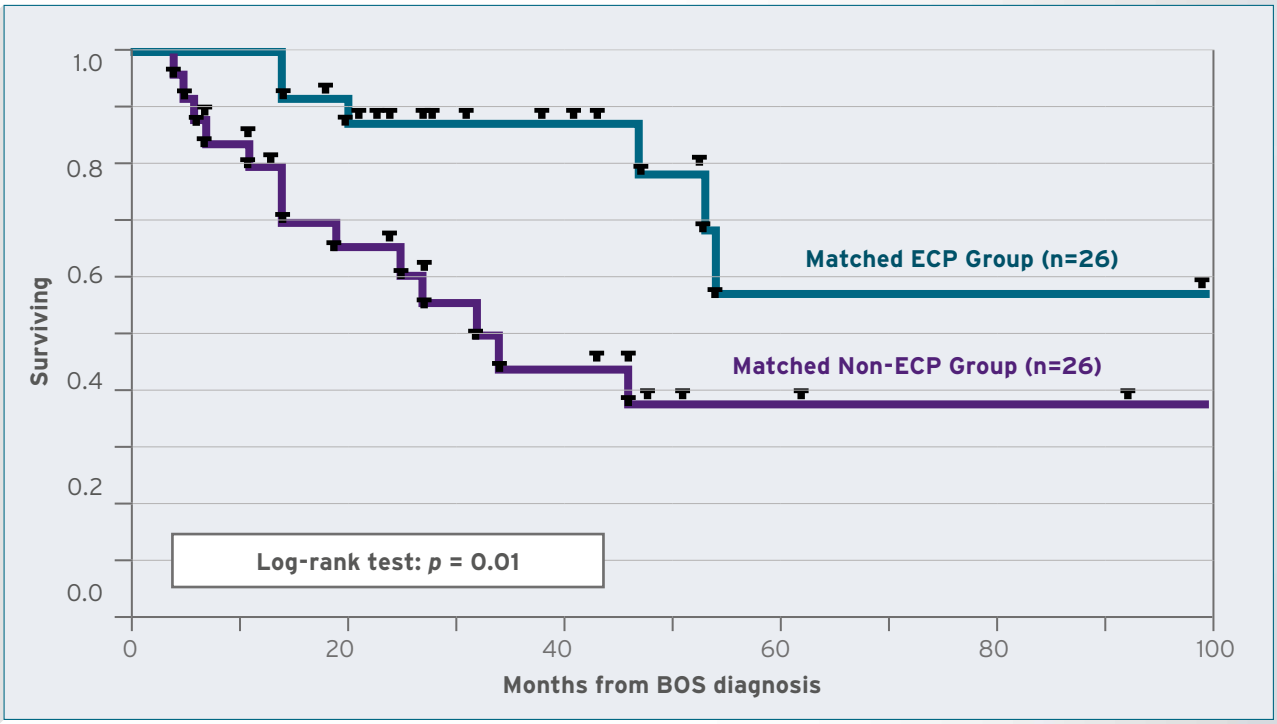
Serious pulmonary complications are reported to occur in 30–60% of HSCT recipients, often requiring hospital admission.[29,30] BOS is a late-stage lung manifestation of GvHD, generally occurring >100 days post-HSCT, characterised by a poor response to corticosteroids and poor overall survival (10–20% at 5 years). According to the NIH criteria for diagnosis and staging of lung GvHD, clinical manifestations can include dyspnoea on exertion, cough, or wheezing, however many patients are asymptomatic early in the disease process, so regular pulmonary function tests are recommended from day 100 post-HSCT.[31] Lung biopsy is required for a definitive diagnosis of BOS.

Initial treatment of lung GvHD includes inhaled steroids plus beta-agonists; early addition of azithromycin is also suggested.[32] First-line systemic therapy comprises corticosteroids alongside other immunosuppressive therapies, but response is often poor. ECP is one of a range of second-line therapies that have been investigated in patients with BOS in whom first-line treatment has failed.

Professor Greinix gave an overview of studies investigating the use of ECP for the treatment of BOS. While these studies are relatively small and non-randomised, they confirm that ECP treatment is associated with sustainable improvements or stabilisation in lung function, and significant decreases in the rate of decline in lung function in BOS patients.[27,28] Adverse event reports show that ECP is generally well tolerated. In a retrospective cohort study of patients who developed BOS following HSCT, 26 who underwent ≥3 months of ECP treatment were matched with another 26 non–ECP-treated patients.[28] ECP-treated patients were found to have significantly better overall survival (hazard ratio 0.1; p=0.001) than non-ECP-treated patients (Figure 3). These positive results for ECP treatment of BOS suggest that further investigation of its efficacy is warranted in prospective, randomised trials.

Biomarkers for the prediction and diagnosis of BOS are also needed to allow early therapeutic intervention and better patient outcomes. A prospective study that evaluated B-cell subpopulations in 136 patients found that elevated levels of $CD19^{+}CD2^{low}$ B cells represent a potential novel biomarker for BOS.[33] Another prospective study is ongoing using B cell subsets as biomarkers to establish a diagnosis of BOS early in the disease course (by screening asymptomatic patients) and then initiating immediate treatment with ECP or standard immunosuppressants if a diagnosis of BOS is confirmed.

Figure 3. Kaplan–Meier survival curves for matched ECP- and non-ECP-treated patients with BOS.[28] Reproduced with permission.



Data on preservation of graft-versus-leukaemia and antiviral effects in ECP-treated patients

Dr Anita Schmitt discussed the factors that need to be considered when selecting a second-line therapy for GvHD and reviewed recent studies of ECP treatment showing it is not associated with viral reactivation and preserves the graft-versus-leukaemia (GvL) effect.[36,37]

- *ECP has been shown in clinical studies and in clinical practice to be an effective and well tolerated treatment for SR aGvHD and cGvHD when standard first-line immunosuppressive therapies fail.*[11,24,34,35]
- *ECP helps restore the dysregulated immune system – studies show that it does not cause viral reactivation but preserves both immunity against infections and the GvL effect, important factors when selecting treatment.*[36,37]

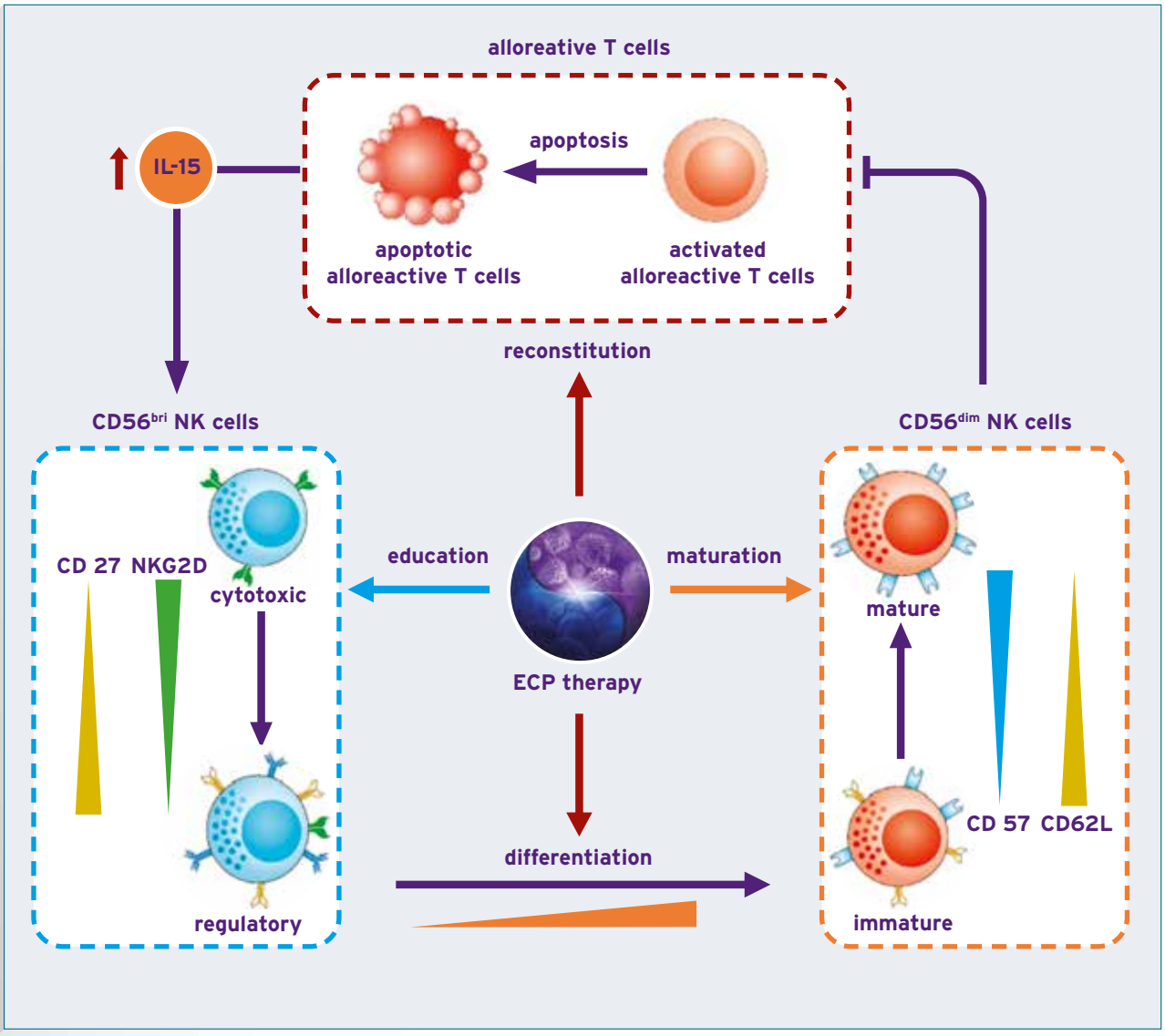
There is currently no standard approach to second-line treatment for either aGvHD or cGvHD once first-line treatment has failed. A range of different therapeutic options have been investigated in this setting and are recommended in EBMT guidelines, including ECP, mycophenolate mofetil, calcineurin inhibitors, mammalian target of rapamycin (mTOR) Inhibitors, and rituximab.[38]

As there are currently no available data demonstrating the superiority of one agent over another, other factors need to be considered when selecting the most appropriate therapy for individual patients. For example, when using agents that cause depression of T-cell function (e.g. anti-thymocyte globulin or pentostatin) it is important that strategies are in place for surveillance and prophylaxis against opportunistic infections, and patients who are seropositive for cytomegalovirus (CMV) will require monitoring for CMV reactivation.

ECP is known to induce apoptosis in neutrophils and DCs[39,40] and results in a reduction in pro-inflammatory cytokines.[36] In patients with aGvHD, ECP treatment has also been shown to promote the maturation and differentiation of subsets of NK cells which are known to play an important role in the pathogenesis of GvHD (Figure 4).[36,37] Studies in aGvHD patients who achieved CR to ECP treatment found a significant decrease in $CD56^{bri}CD16^{-}$ NK cells with long-term treatment and a shift from cytotoxic to regulatory NK subsets.[36,37] Importantly, anti-viral and anti-leukemic effects were preserved in all patients following ECP treatment due to the maintenance of specialised antiviral/leukemic NK cells $CD57^{+}NKG2C^{+}CD56^{dim}$.[36,37] In addition, ECP treatment did not have any negative impact on the proliferative function of these NK cells or the quality or quantity of cytokine release.[37]

Dr Schmitt highlighted how the immunomodulatory properties of ECP may induce cellular changes that help restore the dysregulated immune system in GvHD patients. She considered that ECP may be a valuable second-line treatment option in SR disease as it preserves immunity against infections as well as maintaining the quality and quantity of effector cells to ensure a good GvL effect.[36,37]

Figure 4. Proposed mechanism of action of ECP on NK cells in GvHD.[37] Reproduced with permission.



Update from the Nordic ECP Quality Group

Professor Gösta Berlin provided an update on progress within the expanding Nordic ECP Quality Group (NEQG). He reviewed the group's achievements since its inception in 2016 as well as the future plans for the network.

- *The fundamental aims of the NEQG are to create a network of ECP centres in the Nordic region that will allow an exchange of ideas and experience, and promote research and other projects relating to ECP treatment.*
- *The NEQG has recently published guidelines for the use, and standardised follow-up, of ECP in the treatment of GvHD which will hopefully be implemented in clinical practice in the near future.*[41]

The NEQG held its first meeting in Oslo in 2016 with representatives from just five centres. It has since expanded considerably and now includes clinicians and nurses from all centres undertaking ECP in the Nordic countries (Denmark, Sweden, Norway and Finland) who meet twice a year to exchange ideas, share best practices, and collaborate on projects.

Within the Nordic region in 2018, a total of 361 patients underwent 6,602 ECP treatments. Norway undertook the most treatments (mainly at the Oslo centre) followed by Denmark, Sweden and then Finland. The predominant use for ECP was cGvHD but it was also used to treat aGvHD, cutaneous T cell lymphoma and a few patients with rejection following solid organ transplantation.

Professor Berlin commented that individual centres generally had only a small number of patients and undertook a limited number of ECP treatments either in apheresis units, haematology or dermatology departments – this highlighted the need for cooperation between centres in the Nordic region to improve experience and clinical practice.

Since its inception in 2016, the NEQG had been actively developing guidelines for the use of ECP in the treatment of both aGvHD and cGvHD, which include recommendations for assessment and treatment schedules, as well as follow-up and response assessment. These have recently been published[41] and Professor Berlin hoped that the guidelines would be adopted into routine clinical practice at all ECP centres in the Nordic region.

Future plans for the NEQG are to facilitate and promote research projects in the field of ECP in the Nordic region. Professor Berlin summarised some of their key activities and encouraged delegates to get in touch with the group with any further suggestions for collaboration (gosta.berlin@regionostergotland.se).

Follow-up on the Oslo cost-effectiveness study

Alba Pons, RN, gave an overview of the results of a cost-effectiveness analysis undertaken at Oslo University Hospital, Norway, of ECP and other second-line treatment of patients with SR aGvHD.

- *ECP is one of several possible second-line therapies for the management of SR aGvHD but cost effectiveness data are lacking.*
- *A small study has been undertaken at Oslo University Hospital to compare the impact of second-line treatment of aGvHD with or without ECP on patient outcomes and costs in a 'real-world' setting.*

Oslo University Hospital in Norway has recently started using ECP for the management of HSCT recipients who have developed SR aGvHD and initiated a retrospective analysis to compare the costs of ECP with other second-line therapies. Patients with SR aGvHD were identified who had been treated with either:

- ECP monotherapy (n=5) or ECP combined with another agent (n=7)
- No ECP treatment; patients given other second-line agents, either as monotherapy or in combination (n=18)

Data were collected on patient demographics (gender, age, transplant type, conditioning regimen, onset of aGvHD, dose and days of prednisone prior to second-line treatment), hospitalisation time, medication and parenteral nutrition use, and outcomes (mortality, hospital discharge).

Patients included in the analysis had predominantly experienced gut aGvHD and therefore had a high requirement for parenteral nutrition.

Once all the data have been consolidated and fully analysed, it is hoped that the findings will be published.

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Therakos would like to thank all speakers and attendees who participated during the meeting, contributing to an atmosphere of lively scientific debate and collaboration.

CAUTION: READ THE THERAKOS™ CELLEX™ PHOTOPHERESIS SYSTEM OPERATOR'S MANUAL PRIOR TO PRESCRIBING OR DISPENSING THIS MEDICATION.

Do not inject directly into patients.

IMPORTANT SAFETY INFORMATION FOR THE THERAKOS™ PHOTOPHERESIS PROCEDURE

Indications

The THERAKOS™ CELLEX™ Photopheresis System is indicated for the administration of photopheresis. Please refer to the appropriate product labelling for a complete list of warnings and precautions.

Contraindications

THERAKOS™ Photopheresis is contraindicated in:

- Patients possessing a specific history of a light sensitive disease
- Patients who cannot tolerate extracorporeal volume loss or who have white blood cell counts greater than 25,000 / mm^3
- Patients who have coagulation disorders or who have previously had a 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. Safety in children has not been established.

- Do not expose the device to a magnetic resonance (MR) environment. The device may present a risk of projectile injury, and thermal injury and burns may occur. The device may generate artifacts in the MR image, or may not function properly.
- Thromboembolic events, including pulmonary embolism and deep vein thrombosis, have been reported in the treatment of Graft versus Host Disease (GvHD). Special attention to adequate anticoagulation is advised when treating patients with GvHD.
- When prescribing and administering THERAKOS™ Photopheresis for patients receiving concomitant therapy, exercise caution when changing treatment schedules to avoid increased disease activity that may be caused by abrupt withdrawal of previous therapy.

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 labelling recommendations may result in anaemia.
- Venous access carries a small risk of infection and pain.

Please refer to the THERAKOS™ CELLEX™ Photopheresis System Operator Manual for a complete list of warnings and precautions.

IMPORTANT SAFETY INFORMATION FOR METHOXSALEN USED IN CONJUNCTION WITH THERAKOS™ PHOTOPHERESIS

Contraindications

Methoxsalen is contraindicated in:

- Patients exhibiting idiosyncratic or hypersensitivity reactions to methoxsalen, psoralen compounds, or any of the excipients
- Patients with co-existing melanoma, basal cell or squamous cell skin carcinoma
- Patients who are pregnant, and sexually active men and women of childbearing potential unless adequate contraception is used during treatment
- 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.
- Oral administration of methoxsalen followed by cutaneous UVA exposure (PUVA therapy) is carcinogenic.
- 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.

Refer to the package insert for methoxsalen sterile solution (20 micrograms / mL) or the oral 8-methoxypsoralen dosage formulation for a list of all warnings and precautions.

Please refer to the THERAKOS™ CELLEX™ Photopheresis System Operator Manual for a complete list of warnings, precautions and adverse events.

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