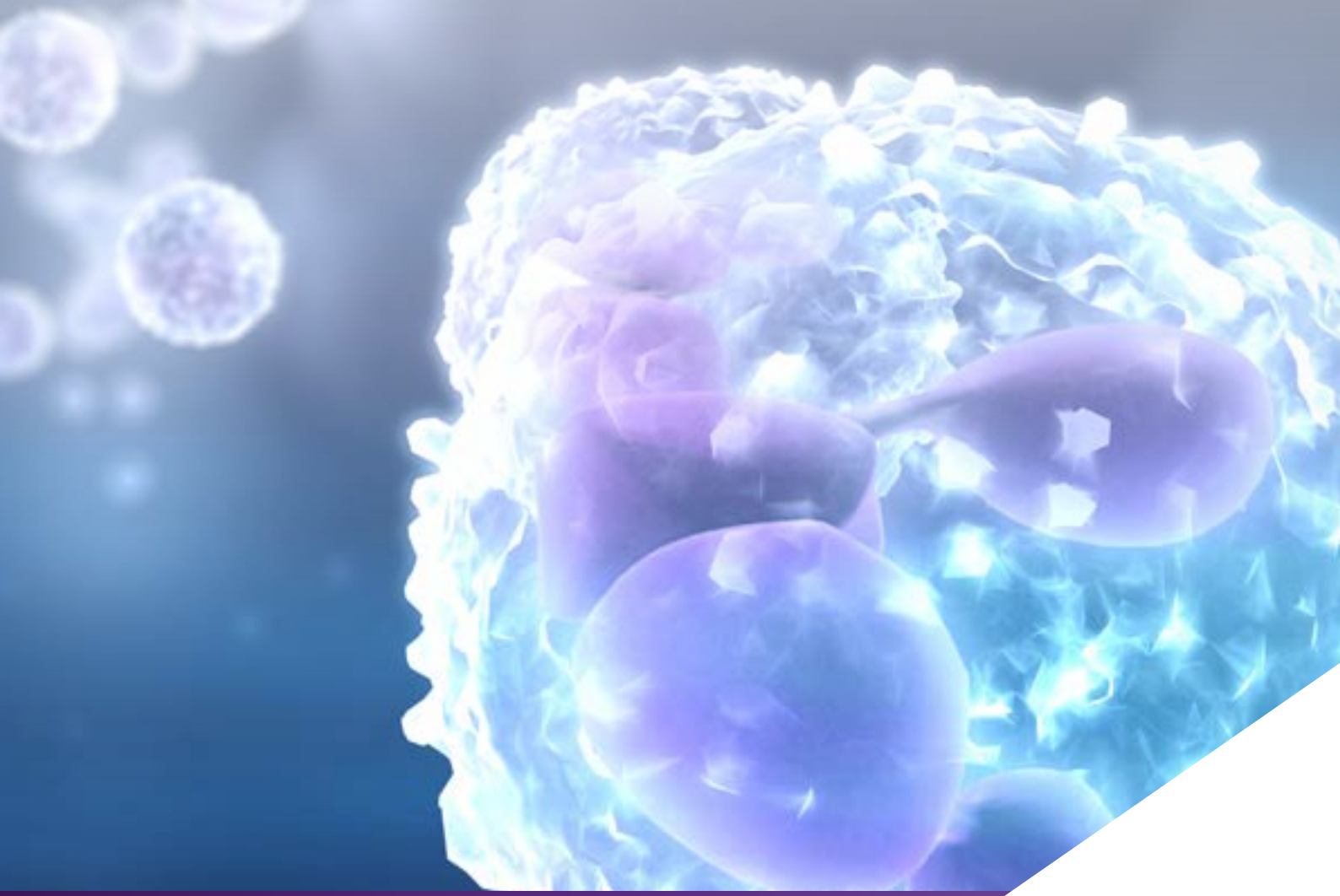
# 2nd Annual Advancing Immunomodulation Meeting

## One Great George Street, London, UK, 6th July 2017

Chair: Professor Jane Apperley, Department of Haematology and Professor of Haemato-oncology, Faculty of Medicine, Imperial College, London

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.

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## 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 ($T_{REG}$) 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 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.[1]

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,[2] 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.[3] 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).[3] 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%).[3]

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.[4] There is some evidence from murine models that MEK inhibition, for example using selumetinib or trametinib, may spare CMV immunity while inhibiting GvHD.[4, 5]

Inhibition of naïve T cells may also be achieved through the enrichment of $T_{REG}$ cells, which selectively target naïve 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[6] combined with interleukin-2 (IL-2). In 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.[7]

The expansion of $T_{REG}$ cells is also one of the proposed mechanisms of action for ECP, suggested to explain the improvements seen in clinical studies.[8] In murine GvHD models, ECP significantly increases the $T_{REG}$ cell count, as well as increasing survival and improving clinical scores.[9] This has also been observed in conditioning/prophylactic settings within these models.[10] 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
  - >1 week with persistent, non-improving Grade III aGvHD
  - >2 weeks with persistent, non-improving Grade II aGvHD[11]
- Dependent: Unable to taper steroid dose (definitions vary, including recurrence of Grade II or higher severity during steroid taper)[11]

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.[12] 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.[13]

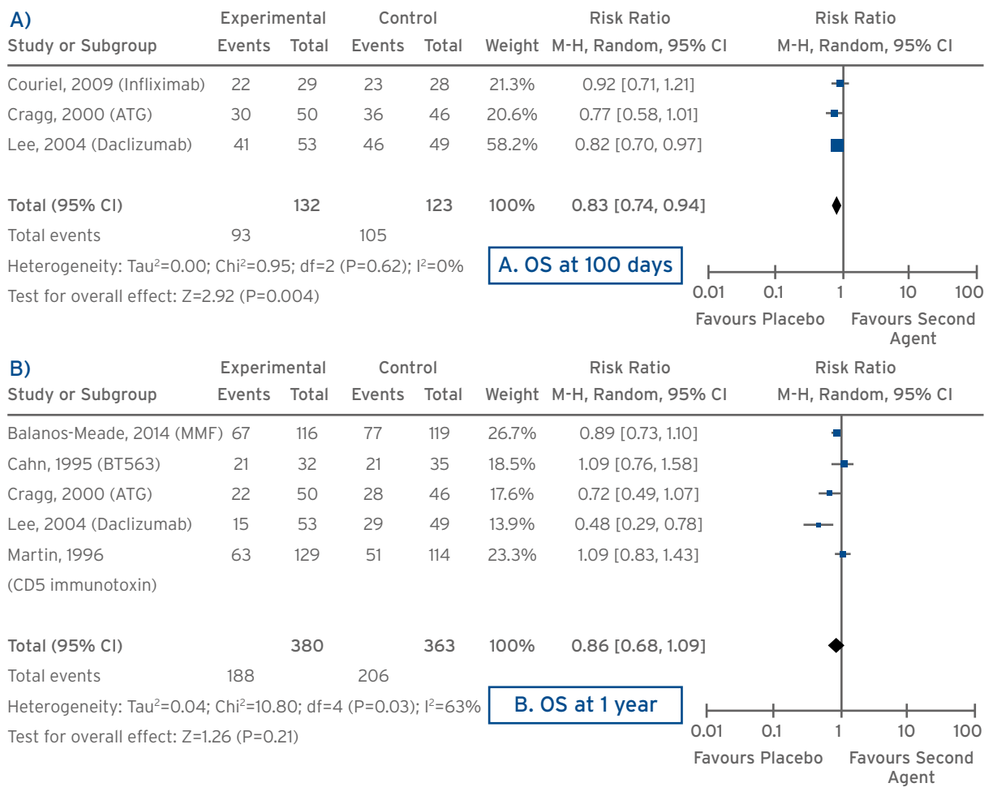
1. Komanduri KV, Viswanathan MN, Wieder ED, *et al.* Restoration of cytomegalovirus-specific CD4+ T-lymphocyte responses after ganciclovir and highly active antiretroviral therapy in individuals infected with HIV-1. Nat Med 1998;4:953–6; 2. De Lima M, St John LS, Wieder ED, *et al.* Double-chimaerism after transplantation of two human leucocyte antigen mismatched, unrelated cord blood units. Br J Haematol 2002;119:773–6; 3. Ozdemir E, St John LS, Gillespie G, *et al.* Cytomegalovirus reactivation following allogeneic stem cell transplantation is associated with the presence of dysfunctional antigen-specific CD8+ T cells. Blood 2002;100:3690–7; 4. Shindo T, Kim TK, Benjamin CL, Wieder ED, Levy RB, Komanduri KV. MEK inhibitors selectively suppress alloreactivity and graft-versus-host disease in a memory stage-dependent manner. Blood 2013;121:4617–26; 5. Itamura H, Shindo T, Tawara I, *et al.* The MEK inhibitor trametinib separates murine graft-versus-host disease from graft-versus-tumor effects. JCI Insight 2016;1:e86331.

6. Khan SQ, Tsai MS, Schreiber TH, Wolf D, Deyev VV, Podack ER. Cloning, expression, and functional characterization of TL1A-Ig. J Immunol 2013;190:1540–50; 7. Wolf D, Barreras H, Bader CS, *et al.* Marked in Vivo Donor Regulatory T Cell Expansion via Interleukin-2 and TL1A-Ig Stimulation Ameliorates Graft-versus-Host Disease but Preserves Graft-versus-Leukemia in Recipients after Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant 2017;23:757–66; 8. Flowers ME, Apperley JF, van Besien K, *et al.* A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease. Blood 2008;112:2667–74; 9. Gatza E, Rogers CE, Clouthier SG, *et al.* Extracorporeal photopheresis reverses experimental graft-versus-host disease through regulatory T cells. Blood 2008;112:1515–21; 10. Florek M, Sega EI, Leveson-Gower DB, *et al.* Autologous apoptotic cells preceding transplantation enhance survival in lethal murine graft-versus-host models. Blood 2014;124:1832–42; 11. Martin PJ, Rizzo JD, Wingard JR, *et al.* First- and second-line systemic treatment of acute graft-versus-host disease: recommendations of the American Society of Blood and Marrow Transplantation. Biol Blood Marrow Transplant 2012;18:1150–63; 12. MacMillan ML, Weisdorf DJ, Wagner JE, *et al.* Response of 443 patients to steroids as primary therapy for acute graft-versus-host disease: comparison of grading systems. Biol Blood Marrow Transplant 2002;8:387–94; 13. El-Jawahri A, Li S, Antin JH, *et al.* Improved Treatment-Related Mortality and Overall Survival of Patients with Grade IV Acute GVHD in the Modern Years. Biol Blood Marrow Transplant 2016;22:910–8.

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 of care in steroid refractory aGvHD, has failed to demonstrate a significant improvement in overall survival.[14] 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)**.[15]

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




Survival is considered 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[15]

Following on from previous work to identify biomarkers for transplant related mortality and GvHD,[16, 17] MAGIC was set up to 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.[18] Work by the MAGIC consortium has identified a group of biomarkers which can predict outcomes at GvHD onset,[19] including before clinical symptoms are detected.[20]

### Key Theme – Biomarkers in aGvHD

- A 2-biomarker model using ST2 and REG3α concentrations on day +7 post HSCT has identified patients at high and low risk of aGvHD related mortality and severe gastrointestinal aGvHD.[19]

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 HSCT (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.[20]


14. Socie G, Vigouroux S, Yakoub-Agha I, *et al.* A phase 3 randomized trial comparing inolimomab vs usual care in steroid-resistant acute GVHD. Blood 2017;129:643–9; 15. Rashidi A, DiPersio JF, Sandmaier BM, Colditz GA, Weisdorf DJ. Steroids Versus Steroids Plus Additional Agent in Frontline Treatment of Acute Graft-versus-Host Disease: A Systematic Review and Meta-Analysis of Randomized Trials. Biol Blood Marrow Transplant 2016;22:1133–7; 16. Sormani MP, Oneto R, Bruno B, *et al.* A revised day +7 predictive score for transplant-related mortality: serum cholinesterase, total protein, blood urea nitrogen, gamma glutamyl transferase, donor type and cell dose. Bone Marrow Transplant 2003;32:205–11; 17. Ayuk F, Bussmann L, Zabelina T, *et al.* Serum albumin level predicts survival of patients with gastrointestinal acute graft-versus-host disease after allogeneic stem cell transplantation. Ann Hematol 2014;93:855–61.

18. Harris AC, Young R, Devine S, *et al.* International, Multicenter Standardization of Acute Graft-versus-Host Disease Clinical Data Collection: A Report from the Mount Sinai Acute GVHD International Consortium. Biol Blood Marrow Transplant 2016;22:4–10; 19. Levine JE, Braun TM, Harris AC, *et al.* A prognostic score for acute graft-versus-host disease based on biomarkers: a multi-centre study Lancet Haematol 2015; 2:e21–9; 20. Hartwell MJ, Ozbek U, Holler E, *et al.* An early-biomarker algorithm predicts lethal graft-versus-host disease and survival. JCI Insight 2017;2:e89798.

## 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 allotransplant 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.[21] More widely, microbial diversity is a predictor for overall survival,[22] which appears to be particularly linked to the incidence of lethal aGvHD.[23] GvHD has been associated with overrepresentation of Enterococcus in both mice and allo-HSCT patients;[24, 25] expansion of *E. coli*,[25] Bacteroides and Prevotella species;[24] and changes in microbiome make up (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.[23] 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-cilastatin) to be significantly associated with GvHD-related mortality, compared to antibiotic agents with less anaerobic coverage.[29] This finding was also supported by murine GvHD model experiments, where agents with a broad anaerobic coverage led to significantly lower overall survival.[29] 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[30]).

21. Taur Y, Xavier JB, Lipuma L, *et al.* Intestinal domination and the risk of bacteremia in patients undergoing allogeneic hematopoietic stem cell transplantation. Clin Infect Dis 2012;55:905–14; 22. Taur Y, Jenq RR, Perales MA, *et al.* The effects of intestinal tract bacterial diversity on mortality following allogeneic hematopoietic stem cell transplantation. Blood 2014;124:1174–82; 23. Jenq RR, Taur Y, Devlin SM, *et al.* Intestinal Blautia Is Associated with Reduced Death from Graft-versus-Host Disease. Biol Blood Marrow Transplant 2015;21:1373–83; 24. Heimesaat MM, Nogai A, Bereswill S, *et al.* MyD88/TLR9 mediated immunopathology and gut microbiota dynamics in a novel murine model of intestinal graft-versus-host disease. Gut 2010;59:1079–87; 25. Holler E, Butzhammer P, Schmid K, *et al.* Metagenomic analysis of the stool microbiome in patients receiving allogeneic stem cell transplantation: loss of diversity is associated with use of systemic antibiotics and more pronounced in gastrointestinal graft-versus-host disease. Biol Blood Marrow Transplant 2014;20:640–5; 26. Eriguchi Y, Takashima S, Oka H, *et al.* Graft-versus-host disease disrupts intestinal microbial ecology by inhibiting Paneth cell production of alpha-defensins. Blood 2012;120:223–31; 27. Chiusolo P, Metafuni E, Paroni Sterbini F, *et al.* Gut Microbiome Changes after Stem Cell Transplantation. Blood 2015;126:1953. 28. Peled JU, Devlin SM, Staffas A, *et al.* Intestinal Microbiota and Relapse After Hematopoietic-Cell Transplantation. J Clin Oncol 2017;35:1650–9. 29. Shono Y, Docampo MD, Peled JU, *et al.* Increased GVHD-related mortality with broad-spectrum antibiotic use after allogeneic hematopoietic stem cell transplantation in human patients and mice. Sci Transl Med 2016;8:339ra71. 30. Memorial Sloan Kettering Cancer Center: Choosing the Best Antibiotic to Protect Friendly Gut Bacteria During the Course of Stem Cell Transplant; clinicaltrials.gov; 2017.

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 of 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.

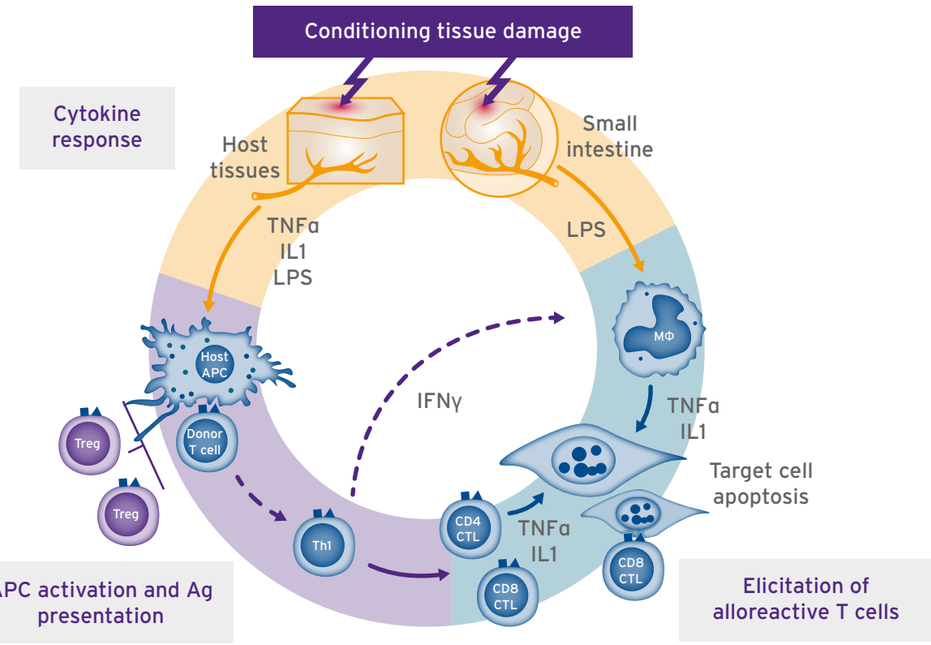
## Management of Steroid Refractory aGvHD: Novel Strategies and Clinical Outcomes

*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.[31] There are a number of strategies currently under investigation for disrupting the pathophysiology of aGvHD **(Figure 2, Table 1)**.

### Figure 2. Pathophysiology of aGvHD[32]




31. Calmettes C, Vigouroux S, Labopin M, *et al.* Risk Factors for Steroid-Refractory Acute Graft-versus-Host Disease after Allogeneic Stem Cell Transplantation from Matched Related or Unrelated Donors. Biol Blood Marrow Transplant 2015; 21:860–5; 32. Ferrara JL, Levine JE, Reddy P, Holler E. Graft-versus-host disease. Lancet 2009;373:1550–61.

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

| Target process | Treatment | Status of research |
|---|---|---|
| Cytokine response | Anti-IL-2<br>Anti-TNFα | RCTs of these agents have so far not demonstrated a significant improvement in OS compared to supportive care. |
| | Jak1/2 blockade (ruxolitinib) | No prospective trials to date, but has been reported to improve OS in observational studies.[33]<br>Suitability for use in paediatric patients needs further confirmation, due to data showing increased toxicity and no impact on OS.[34] |
| Antigen presentation | Anti-CD26 (begelomab) | Has been shown to improve response at day 28 and incidence of Grade II–IV gut GvHD, but not 1 year OS (31% control vs. 50% begelomab, p=0.06) in a small dose-escalation study.[35]<br>Clinical trial ongoing (NCT02411084).[36] |
| T cell trafficking | Vedolizumab | Investigated in 6 patients with Grade IV gut aGvHD, all responded, 4/6 alive at 10 months.[37]<br>Clinical trial ongoing (NCT02993783).[38] |
| T cell depletion | Pentostatin | Single arm observational studies have reported mixed results, with a later, larger study reporting a relatively small response rate (21%).[39] |
| | MMF | Widely used for prophylaxis, but mixed results as a treatment, response rates in latest single arm observational studies 26%–47%.[40, 41] |
| | Alemtuzumab | Small scale study was promising (50% response rate, 20% OS improvement).[42] |
| | Suicide gene approach | Novel approach: transduction of a suicide gene, activated by a specific drug, into donor T cells. T cell suicide is induced to stop aGvHD progression. An elegant but expensive approach – still highly experimental. |
| Immuno-modulation | 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.[10] 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.[43–45] |
| | CAR allo$T_{REG}$ cells | $T_{REG}$ cells which only recognise the allo antigen and only suppress T cells under aGvHD conditions. These have demonstrated some efficacy as prophylaxis.[46] |
| | MSC | Have been shown to improve OS in Grade III–IV aGvHD responders.[47, 48]<br>Particularly good results in gut/skin aGvHD and in paediatric patients.[49] |
| | Natural killer T cells/ Myeloid derived suppressor cells | Have both shown promise in pre-clinical trials (murine models)[50, 51] with clinical trials currently being planned. |

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


33. Zeiser R, Burchert A, Lengerke C, *et al.* Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey. Leukemia 2015;29:2062–8; 34. Khandelwal P, Teusink-Cross A, Davies SM, *et al.* Ruxolitinib as Salvage Therapy in Steroid-Refractory Acute Graft-versus-Host Disease in Pediatric Hematopoietic Stem Cell Transplant Patients. Biol Blood Marrow Transplant 2017;23:1122–7; 35. Bacigalupo A, Deeg HJ, Caballero D, *et al.* 671 Treatment of Patients with Steroid Refractory Acute Graft vs Host Disease (SR-GvHD): A Matched Paired Analysis of Anti-CD26 (Begelomab) Compared to Other Treatment. ASH 58th Annual Meeting & Exposition. San Diego, CA; 2016; 36. Adienne SA. Study of BEGEDINA® vs "Conventional Treatment" for Treating Steroid-Resistant Acute GvHD. clinicaltrials.gov; 2015; 37. Fløisand Y, Lundin KEA, Lazarevic V, *et al.* Targeting Integrin α4β7 in Steroid-Refractory Intestinal Graft-versus-Host Disease. Biology of Blood and Marrow Transplantation 2017;23:172–5; 38. Millennium Pharmaceuticals Inc. A Dose-Finding Study of Vedolizumab for Treatment of Steroid-Refractory Acute Intestinal Graft-Versus-Host Disease (GvHD) in Participants Who Have Undergone Allogeneic Hematopoietic Stem Cell Transplantation (Allo-HSCT). clinicaltrials.gov; 2016; 39. Schmitt T, Luft T, Hegenbart U, Tran TH, Ho AD, Dreger P. Pentostatin for treatment of steroid-refractory acute GVHD: a retrospective single-center analysis. Bone Marrow Transplant 2011;46:580–5; 40. Furlong T, Martin P, Flowers ME, *et al.* Therapy with mycophenolate mofetil for refractory acute and chronic GVHD. Bone Marrow Transplant 2009;44:739–48; 41. Pidala J, Kim J, Perkins J, *et al.* Mycophenolate mofetil for the management of steroid-refractory acute graft vs host disease. Bone Marrow Transplant 2010;45:919–24; 42. Khandelwal P, Emoto C, Fukuda T, *et al.* A Prospective Study of Alemtuzumab as a Second-Line Agent for Steroid-Refractory Acute Graft-versus-Host Disease in Pediatric and Young Adult Allogeneic Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant 2016;22:2220–5; 43. Di Ianni M, Falzetti F, Carotti A, *et al.* Immunoselection and clinical use of T regulatory cells in HLA-haploidentical stem cell transplantation. Best Pract Res Clin Haematol 2011;24:459–66. 44. Brunstein CG, Miller JS, Cao Q, *et al.* Infusion of *ex vivo* expanded T regulatory cells in adults transplanted with umbilical cord blood: safety profile and detection kinetics. Blood 2011;117:1061–70; 45. Brunstein CG, Miller JS, McKenna DH, *et al.* Umbilical cord blood-derived T regulatory cells to prevent GVHD: kinetics, toxicity profile, and clinical effect. Blood 2016;127:1044–51; 46. Brudno JN, Somerville RP, Shi V, *et al.* Allogeneic T Cells That Express an Anti-CD19 Chimeric Antigen Receptor Induce Remissions of B-Cell Malignancies That Progress After Allogeneic Hematopoietic Stem-Cell Transplantation Without Causing Graft-Versus-Host Disease. J Clin Oncol 2016;34:1112–21; 47. Le Blanc K, Frassoni F, Ball L, *et al.* Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study. Lancet 2008;371:1579–86; 48. von Dalowski F, Kramer M, Wermke M, *et al.* Mesenchymal Stromal Cells for Treatment of Acute Steroid-Refractory Graft Versus Host Disease: Clinical Responses and Long-Term Outcome. Stem Cells 2016;34:357–66; 49. Galleu A, Deplano S, Szydlo R, *et al.* Mesenchymal stromal cells for the treatment of steroidresistant acute graft versus host disease: factors influencing clinical responses. European Hematology Association. Madrid, Spain: EHA Learning Center; 2017; 50. Chaidos A, Patterson S, Szydlo R, *et al.* Graft invariant natural killer T-cell dose predicts risk of acute graft-versus-host disease in allogeneic hematopoietic stem cell transplantation. Blood 2012;119:5030–6; 51. Highfill SL, Rodriguez PC, Zhou Q, *et al.* Bone marrow myeloid-derived suppressor cells (MDSCs) inhibit graft-versus-host disease (GVHD) via an arginase-1-dependent mechanism that is up-regulated by interleukin-13. Blood 2010;116:5738–47.

## 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 (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.[52] Treatment related mortality was less likely 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.[52]

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.[53] In another retrospective comparison of ECP (data from three centres) with anti-cytokines 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=0.016).[54] 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 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.[11, 56-57] Early ECP start may be particularly useful in recipients of haploidentical or unrelated donor HSCT.[58]

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.[59] A Phase II RCT of ECP with methylprednisolone versus methylprednisolone alone in first-line aGvHD has demonstrated higher response rates in the ECP treated arm, particularly for skin aGvHD.[60]

52. Greinix HT, Knobler RM, Worel N, *et al.* The effect of intensified extracorporeal photochemotherapy on long-term survival in patients with severe acute graft-versus-host disease. Haematologica 2006;91:405–8; 53. Das-Gupta E, Greinix H, Jacobs R, *et al.* Extracorporeal photopheresis as second-line treatment for acute graft-versus-host disease: impact on six-month freedom from treatment failure. Haematologica 2014;99:1746–52; 54. Jagasia M, Greinix H, Robin M, *et al.* Extracorporeal photopheresis versus anticytokine therapy as a second-line treatment for steroid-refractory acute GVHD: a multicenter comparative analysis. Biol Blood Marrow Transplant 2013;19:1129–33; 55. Abu-Dalle I, Reljic T, Nishihori T, *et al.* Extracorporeal photopheresis in steroid-refractory acute or chronic graft-versus-host disease: results of a systematic review of prospective studies. Biol Blood Marrow Transplant 2014;20:1677–86; 56. Dignan FL, Clark A, Amrolia P, *et al.* Diagnosis and management of acute graft-versus-host disease. Br J Haematol 2012;158:30–45; 57. Alfred A, Taylor PC, Dignan F, *et al.* The role of extracorporeal photopheresis in the management of cutaneous T-cell lymphoma, graft-versus-host disease and organ transplant rejection: a consensus statement update from the UK Photopheresis Society. Br J Haematol 2017;177:287–310; 58. Pierelli L, Perseghin P, Marchetti M, *et al.* Extracorporeal photopheresis for the treatment of acute and chronic graft-versus-host disease in adults and children: best practice recommendations from an Italian Society of Hemapheresis and Cell Manipulation (SIdEM) and Italian Group for Bone Marrow Transplantation (GITMO) consensus process. Transfusion 2013;53:2340–52; 59. Wood WA, McGinn MK, Wilson D, *et al.* Practice Patterns and Preferences Among Hematopoietic Cell Transplantation Clinicians. Biol Blood Marrow Transplant 2016;22:2092–9; 60. Alousi AM, Bassett R, Chen J, *et al.* A Bayesian, Phase II Randomized Trial of Extracorporeal Photopheresis (ECP) Plus Steroids Versus Steroids-Alone in Patients with Newly Diagnosed Acute Graft Vs. Host Disease (GVHD): The Addition of ECP Improves Gvhd Response and the Ability to Taper Steroids. Blood 2015;126:854.

# 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 (extensive cGvHD in 10% of recipients).[61] Over the last 40 years, 5-year mortality has remained around 24%, with little improvement.[62] 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%).[63] 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.[63] 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.[63] At 10 years following allo-HSCT transplant, patients with cGvHD have a 4.5-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.[64]

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.

### 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 <110 x $10^9$/L
  - Serum cholinesterase <3772 IU/l
  - Gamma-glutamyltransferase ≥56 IU/l
  - Serum albumin <3.9%
  - Serum Immunoglobulin A <49 mg
- Score 0–2 = low risk
- Score 3–5 = high risk

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.

61. Lee SJ, Vogelsang G, Gilman A, *et al.* A survey of diagnosis, management, and grading of chronic GVHD. Biol Blood Marrow Transplant 2002;8:32–9; 62. Goerner M, Gooley T, Flowers ME, *et al.* Morbidity and mortality of chronic GVHD after hematopoietic stem cell transplantation from HLA-identical siblings for patients with aplastic or refractory anemias. Biol Blood Marrow Transplant 2002;8:47–56; 63. Palmer J, Chai X, Martin PJ, *et al.* Failure-free survival in a prospective cohort of patients with chronic graft-versus-host disease. Haematologica 2015;100:690–5; 64. Sun CL, Kersey JH, Francisco L, *et al.* Burden of morbidity in 10+ year survivors of hematopoietic cell transplantation: report from the bone marrow transplantation survivor study. Biol Blood Marrow Transplant 2013;19:1073–80.

## 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[64]). 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.[65] In the steroid-refractory setting 37 agents have reported some activity **(Table 2)**.

### Table 2. Agents currently undergoing clinical trials for cGvHD

| Mechanism | Agent |
|---|---|
| Regulatory T cells | Infusions ± other agents, IL-2 ± ECP |
| B cells/BCR signalling | Ibrutinib (BTK)<br>Entospletinib, Fostamatinib (SYK) Ofatumumab (CD20) |
| Co-stimulatory blockade | Abatacept (CTLA4Ig) |
| IMIDs | Pomalidomide |
| Proteosome inhibition | Bortezomib, carfilzomib, ixazomib |
| JAK 1/2 inhibition | Baricitinib, ruxolitinib |
| ROCK2 inhibition | KD025 |
| Hedgehog inhibition | LDE225, Vismodegib |
| Cellular therapy | Mesenchymal stem cells<br>Dendritic cells |

*Correct at the time of meeting. Ibrutinib was approved for the 2nd line treatment of adults with cGvHD by the FDA in August 2017 (Pharmacyclics LLC (2017). IMBRUVICA® [ibrutinib]: Full Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205552s017lbl.pd. Accessed: 2 Oct 2017).

64. Flowers ME, Parker PM, Johnston LJ, *et al.* Comparison of chronic graft-versus-host disease after transplantation of peripheral blood stem cells versus bone marrow in allogeneic recipients: long-term follow-up of a randomized trial. Blood 2002;100:415–9;
65. Martin PJ, Storer BE, Rowley SD, *et al.* Evaluation of mycophenolate mofetil for initial treatment of chronic graft-versus-host disease. Blood 2009;113:5074–82.

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,[66] ECP, sirolimus, IL-2,[67] ruxolitinib,[66] ibrutinib and imatinib[68, 69] 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.

### Key Theme – Defining Steroid Refractory cGvHD

- Progression despite ≥1 mg/kg/day prednisone for 1 week
- Persistence despite ≥0.5 mg/kg/day or 1 mg/kg/qod prednisone for 4 week
- Steroid dependent: need for >0.25 mg/kg/day or >0.5 mg/kg/qod to control manifestations, shown by 2 taper failures >8 weeks apart

### Table 3. Overview of most investigated current treatments

| Treatment | Dosing | Disadvantages |
|---|---|---|
| ECP | 1–4 hours, q1–4 weeks | iv access |
| Ibrutinib | Oral, daily | Cardiac, bleeding[70] |
| IL-2 | SQ daily | Shots, fatigue[67] |
| Imatinib | Oral, daily | Nausea, oedema[68, 69] |
| ROCK2 inhibition | Oral, twice daily | Liver[71] |
| JAK1/2 inhibition | Oral, twice daily | Thrombocytopenia[66] |

## 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.

66. Arai S, Pidala J, Pusic I, *et al.* A Randomized Phase II Crossover Study of Imatinib or Rituximab for Cutaneous Sclerosis after Hematopoietic Cell Transplantation. Clin Cancer Res 2016;22:319–27; 67. Koreth J, Matsuoka K, Kim HT, *et al.* Interleukin-2 and regulatory T cells in graft-versus-host disease. N Engl J Med 2011;365:2055–66; 68. Olivieri A, Locatelli F, Zecca M, *et al.* Imatinib for refractory chronic graft-versus-host disease with fibrotic features. Blood 2009;114:709-18; 69. Olivieri A, Cimminiello M, Corradini P, *et al.* Long-term outcome and prospective validation of NIH response criteria in 39 patients receiving imatinib for steroid-refractory chronic GVHD. Blood 2013;122:4111–8; 70. Ryan CE, Sahaf B, Logan AC *et al.* Ibrutinib efficacy and tolerability in patients with relapsed chronic lymphocytic leukemia following allogeneic HCT. Blood. 2016;128(25):2899-2908; 71. Flynn R, Paz K, Du J, *et al.* Targeted Rho-associated kinase 2 inhibition suppresses murine and human chronic GVHD through a Stat3-dependent mechanism. Blood. 2016; 127(17):2144-21542908

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ECP has been recommended for the treatment of steroid refractory cGvHD, as it is both steroid sparing and has limited associated adverse events.[72] ECP is already frequently used as a salvage therapy in cGvHD.[72]

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.[8] There was particular improvement in skin manifestations, with more modest improvements observed across extracutaneous manifestations.[8] Meta-analyses calculated an ECP overall response rate of 0.68 (0.62–0.74)[73] and a complete response rate of 0.29 (0.19–0.42).[74]

Lung cGvHD, characterised by bronchiolitis obliterans syndrome (BOS) is a serious manifestation of cGvHD, which is associated with a significant reduction in overall survival.[75] 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.[76-78]

# 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.[79] The 2017 consensus statement provided an update, including information about the treatment of aGvHD and solid organ rejection.[56]

72. Wolff D, Schleuning M, von Harsdorf S, *et al.* Consensus Conference on Clinical Practice in Chronic GVHD: Second-Line Treatment of Chronic Graft-versus-Host Disease. Biol Blood Marrow Transplant 2011;17:1–17; 73. Olivieri J, Manfredi L, Postacchini L, *et al.* Consensus recommendations for improvement of unmet clinical needs—the example of chronic graft-versus-host disease: a systematic review and meta-analysis. Lancet Haematol 2015;2:e297–305; 74. Malik MI, Litzow M, Hogan W, *et al.* Extracorporeal photopheresis for chronic graft-versus-host disease: a systematic review and meta-analysis. Blood Res 2014;49:100–6; 75. Palmer J, Williams K, Inamoto Y, *et al.* Pulmonary symptoms measured by the national institutes of health lung score predict overall survival, nonrelapse mortality, and patient-reported outcomes in chronic graft-versus-host disease. Biol Blood Marrow Transplant 2014;20:337–44; 76. Greinix HT, Volc-Platzer B, Rabitsch W, *et al.* Successful use of extracorporeal photochemotherapy in the treatment of severe acute and chronic graft-versus-host disease. Blood 1998;92:3098–104; 77. Bisaccia E, Palangio M, Gonzalez J, *et al.* Treatment of extensive chronic graft-versus-host disease with extracorporeal photochemotherapy. J Clin Apher 2006;21:181–7; 78. Couriel DR, Hosing C, Saliba R, *et al.* Extracorporeal photochemotherapy for the treatment of steroid-resistant chronic GVHD. Blood 2006;107:3074–80.

The group is currently undertaking prospective trials, including POSTAGE (NCT02151539),[80] and a prospective data collection study. The society plans to build a GvHD registry, host annual education meetings, provide a network for discussion and support, and facilitate collaborative research and audits.

## 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[79] 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 2$^{nd}$ 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.[56]

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.[56]

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.

79. Scarisbrick JJ, Taylor P, Holtick U, *et al.* U.K. consensus statement on the use of extracorporeal photopheresis for treatment of cutaneous T-cell lymphoma and chronic graft-versus-host disease. Br J Dermatol 2008;158:659–78; 80. Vanderbilt-Ingram Cancer Center. Prospective Outcomes of Second-Line Therapy in Acute Graft-Versus-Host Study Including ECP (POSTAGE) (POSTAGE). clinicaltrials.gov; 2014.

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

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**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**

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