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Treatment patterns of extracorporeal photopheresis in steroid-refractory graft versus host disease: A delphi study

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Steroid-refractory GvHD (SR-GvHD) following allogeneic transplant is a major clinical challenge and is associated with substantial mortality [1]. While the European Society for Bone and Marrow Transplantation (EBMT) recommends ruxolitinib for second-line treatment of GvHD [2], some patients may experience side effects or refractoriness, and therefore require alternative treatment options [2]. However, there are no standardized treatment recommendations for SR-GvHD beyond ruxolitinib in Europe [2]. Extracorporeal photopheresis (ECP), a cell-based, immunomodulatory therapy, is quoted as a potential treatment option beyond second-line, in the EBMT guidelines [2]. ECP has been shown to be an effective and well-tolerated treatment for SR-GvHD [3]. Clinical evidence has limitations though, including few randomized studies and a lack of consensus on optimal treatment schedule [3, 4]. A Delphi study was thus carried out to provide a descriptive account of clinical practice regarding ECP treatment patterns in SR-GvHD.

Seventeen GvHD experts were invited by Therakos UK Limited (Staines, United Kingdom) to participate in a Delphi panel; of which, 11 agreed. All panelists had extensive experience in GvHD treatment and prescribed ECP or ruxolitinib at their centers.

The Delphi study consisted of three rounds of online questionnaires conducted in 2023 (February 20th–March 13th; May 31st–June 23rd; August 4th–24th), assessing 62 statements. A description of the Delphi questionnaire, the development and scoring processes and a list of the consensus statements are provided in the Appendix. The main findings are summarized in Table 1.

Experts were asked the main reasons for choosing ECP, but not ruxolitinib, in SR-GvHD. For steroid refractory acute graft-versus-host disease (SR-aGvHD), experts reached consensus (100% agreement for all) on (1) contraindication and safety profile of ruxolitinib (2), ruxolitinib failure, and (3) safety profile and high efficacy of ECP (especially in patients with skin involvement). For steroid refractory chronic graft-versus-host disease (SR-cGvHD), experts reached consensus on (1) contraindication to ruxolitinib (100% agreement) (2), ruxolitinib failure (91% agreement) (3) efficacy, especially in patients with skin involvement and for steroid-sparing effect (91% agreement), and (4) safety profile (100% agreement). Expert consensus aligned with published clinical evidence, which has shown ECP to be well-tolerated and associated with high response rates [3, 5], whereas ruxolitinib, whilst efficacious, has been associated with the incidence of cytopenia and infection [6]. For patients with contraindications to ruxolitinib or who become refractory, ECP may, therefore, provide a suitable alternative.

Experts were asked the main reasons for selecting ruxolitinib, but not ECP, in SR-GvHD. For SR-aGvHD, experts reached

consensus on (1) high efficacy, especially in patients with gastrointestinal involvement (100% agreement) (2), regulatory reasons (91% agreement), and (3) venous access not being necessary (91% agreement). For SR-cGvHD, experts reached consensus on (1) high efficacy, especially in patients with gastrointestinal involvement (100% agreement) (2), regulatory reasons (91% agreement) and patient preferences (82% agreement). These results are largely consistent with published literature, which shows ruxolitinib to be highly effective [6], and long-term vascular access, as required by ECP, to be associated with an increased risk of complications (e.g. bacteremia) [7]. Moreover, compared to ruxolitinib, the administration of ECP may be more challenging for patients who live far from ECP centers and for hospitals with limited capacity. However, lack of access to ruxolitinib in some countries such as the UK may limit patient access [8]. In which case, ECP may provide an alternative treatment option for these patients.

Expert consensus for the definition of ruxolitinib refractoriness (Appendix Table 2), a common challenge during GvHD treatment [9, 10], was reached and broadly aligned with the criteria proposed by Mohty et al. for aGvHD [11]. For cGvHD, the following definition reached consensus: progression of GvHD after 1–2 weeks of treatment, lack of improvement in GvHD after 2–3 months of treatment and loss of response, defined as objective worsening of GvHD. Given the importance of ruxolitinib refractoriness as a selection factor and limited literature on the positioning of ECP following EBMT's ruxolitinib recommendation, the Delphi study's proposed definition of ruxolitinib refractoriness offers an opportunity for standardization of the rationale for selecting ECP over ruxolitinib.

Experts agreed that there were no obstacles to combining ECP with any other guideline-recommended therapy for aGvHD (100%) and cGvHD (91%), respectively. The clinical evidence for combination therapy is, however, limited to retrospective studies on combined ECP and ruxolitinib treatment [3]. Future research on ECP combination therapy may, therefore, offer valuable insights into its use in SR-GvHD and expand treatment options for patients. In line with this, ECP combination therapy in GvHD was identified as a research priority in the 2024 EBMT guidelines [2].

All experts agreed that, in 50% of aGvHD and 60% of cGvHD patients treated with ECP, steroids could be reduced by ≥50%. All experts agreed that in 80% of aGvHD and cGvHD patients treated with the combination of ECP and ruxolitinib, steroids could also be reduced by ≥50%. 91% of experts agreed that an average of ~29 days and ~56 days is required to implement a 50% steroid reduction in aGvHD and cGvHD patients treated with ECP, respectively. All experts agreed that steroid treatment could be stopped in 50% of aGvHD and ~40% of cGvHD patients treated with ECP. All experts agreed that an average of 2–3 months and 5.5 months is required to stop steroid treatment in aGvHD and cGvHD patients treated with ECP, respectively. This potential steroid-sparing effect of ECP, as evidenced in multiple studies [3],

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Table 1. Summary of key Delphi study results.

Topic	Question to the experts	Results	Agreement %	Agreement %
Reasons for selecting ECP	Which factors influence you to select ECP as a treatment in SR-GvHD patients?	aGvHD	cGvHD	Agreement %
		Rank 1: Efficacy of ECP	Rank 1: Efficacy of ECP	100
		Rank 2: Safety profile	Rank 2: Safety profile	100
		Rank 3: Steroid-sparing effect	Rank 3: Steroid-sparing effect	100
		Rank 1: Severe cases	Rank 1: Increased efficacy	100
Combination of ECP with other GvHD therapies	What are the main reasons for choosing the combination therapy of ECP and ruxolitinib in SR-GvHD patients?	Rank 2: Increased efficacy	Rank 2: Severe cases	100
		Proportion of patients treated with ECP: 50%	Proportion of patients treated with ECP: 60%	100
		Proportion of patients treated with ruxolitinib: 53%	Proportion of patients treated with ruxolitinib: 65%	91
		Proportion of patients treated with ECP-ruxolitinib: 50%	Proportion of patients treated with ECP-ruxolitinib: 50%	100
		Proportion of patients treated with ECP: 50%	Proportion of patients treated with ECP: 41%	100
Stopping steroid treatment	Depending on the applied treatment: What is the percentage of SR-GvHD patients in your practice where steroid treatment could be stopped completely? Do you agree on these percentages, resulting from round 1?	Proportion of patients treated with ruxolitinib: 51%	Proportion of patients treated with ruxolitinib: 40%	91
		Proportion of patients treated with ECP-ruxolitinib: 70%	Proportion of patients treated with ECP-ruxolitinib: 60%	100
		Rank 1: Low risk (e.g. skin involvement only or upper GI only)	Rank 1: Low risk (e.g. skin involvement only or upper GI only)	91
		Rank 2: Contraindication for Ruxolitinib (e.g. thrombocytopenia)	Rank 2: Contraindication for Ruxolitinib (e.g. thrombocytopenia)	91
		ECP: 4 to 6 months	ECP: 10 to 12 months	91
Treatment duration of ECP/ruxolitinib	What is the average treatment duration of ECP/ruxolitinib in SR-GvHD in the following scenarios?	Ruxolitinib: 3 to 5 months	Ruxolitinib: 10 to 12 months	100
		ECP in combination with ruxolitinib: 4 to 6 months	ECP in combination with ruxolitinib: 8 to 10 months	91
		Ruxolitinib in combination with ECP: 3 to 5 months	Ruxolitinib in combination with ECP: 8 to 10 months	91
		Treatment schedule 1: 2 – 3 ECP procedures on consecutive days weekly for 4 weeks	Treatment schedule 1: 2 ECP procedures per week for approximately 9 weeks	55
		Treatment schedule 2: 2 ECP procedures per week at least every two weeks for approximately 8 weeks (2 months)	Treatment schedule 2: 2 ECP procedures per week, at least every two weeks for approximately 10 weeks	64
Treatment schedules of ECP	When treating SR-GvHD patients with ECP alone but not with ruxolitinib - which treatment schedules do you apply?	Treatment schedule 3: 2 ECP procedures per week at least every month for approximately 8 weeks (2 months)	Treatment schedule 3: 1 – 2 ECP procedures per week at least monthly for approximately 20 weeks (5 months)	73
		36		

aGvHD acute graft-versus-host disease, cGvHD chronic graft-versus-host disease, ECP extracorporeal photopheresis, GI gastrointestinal, SR-GvHD steroid-refractory graft-versus-host disease.

may help circumvent the significant toxicity and mortality associated with long-term steroid use, notably in cGvHD [12], and improve patients' health-related quality of life.

Experts were asked to estimate the average treatment duration and frequency of ECP in SR-GvHD but reached partial and no consensus for SR-aGvHD and SR-cGvHD, respectively. For SR-aGvHD, 91% of experts agreed that the average duration of ECP is approximately 4 to 6 months, while the highest level of agreement (91%) for treatment frequency was 2 to 3 ECP procedures on consecutive days weekly for 4 weeks. Published ECP treatment recommendations for SR-aGvHD mostly suggest weekly treatment with varying tapering regimens [4]. For SR-cGvHD, the highest level of agreement for treatment duration was reached for 10 to 12 months (91%), and for a treatment frequency of 1 to 2 ECP procedures per week at least monthly for approximately 20 weeks (73%). ECP treatment recommendations for SR-cGvHD in the literature are more varied than SR-aGvHD, with studies suggesting weekly and biweekly treatment regimens [4]. This variation may be due to patient-specific factors or differences in center-specific immunosuppression regimens [4].

This Delphi study combined the views of multiple international experts in the field of GvHD and use of ECP, and offers insights into real-world ECP treatment patterns. However, expert opinions are subject to their respective clinical experience, which may not reflect country-wide clinical practice. While the selection of experts with experience in ECP by Therakos ensured that the results were valid, the small sample size ($n = 11$) may not reflect country-specific nuances and resources which may influence treatment patterns. The results should therefore be interpreted with these limitations in mind.

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REFERENCES

- Axt L, Naumann A, Toennies J, Haen SP, Vogel W, Schneidawind D, et al. Retrospective single center analysis of outcome, risk factors and therapy in steroid refractory graft-versus-host disease after allogeneic hematopoietic cell transplantation. *Bone Marrow Transpl.* 2019;54:1805–14.
- Penack O, Marchetti M, Aljurf M, Arat M, Bonifazi F, Duarte RF, et al. Prophylaxis and management of graft-versus-host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation. *Lancet Haematol.* 2024;11:e147–e59.
- Greinix HT, Ayuk F, Zeiser R. Extracorporeal photopheresis in acute and chronic steroid-refractory graft-versus-host disease: an evolving treatment landscape. *Leukemia.* 2022;36:2558–66.
- Drexler B, Buser A, Infanti L, Stehle G, Halter J, Holbro A. Extracorporeal photopheresis in graft-versus-host disease. *Transfus Med Hemother.* 2020;47:214–25.

- Niittyvuopio R, Juvonen E, Heiskanen J, Lindström V, Nihtinen A, Sahlstedt L, et al. Extracorporeal photopheresis in the treatment of acute graft-versus-host disease: a single-center experience. *Transfusion.* 2018;58:1973–9.
- Fan S, Huo WX, Yang Y, Shen MZ, Mo XD. Efficacy and safety of ruxolitinib in steroid-refractory graft-versus-host disease: A meta-analysis. *Front Immunol.* 2022;13:954268.
- Adamski J. Vascular access considerations for extracorporeal photopheresis. *Transfusion.* 2018;58:590–7.
- National Institute for Health and Care Excellence. TA840: Ruxolitinib for treating chronic graft versus host disease refractory to corticosteroids (terminated appraisal). Available at: <https://www.nice.org.uk/guidance/ta840>. [Last accessed: 19/02/24]. 2022].
- Abedin S, Rashid N, Schroeder M, Romee R, Nauffal M, Alhaj Moustafa M, et al. Ruxolitinib resistance or intolerance in steroid-refractory acute graft-versus-host disease – a real-world outcomes analysis. *Br J Haematol.* 2021;195:429–32.
- Wu H, Shi J, Luo Y, Tan Y, Zhang M, Lai X, et al. Evaluation of ruxolitinib for steroid-refractory chronic graft-vs-host disease after allogeneic hematopoietic stem cell transplantation. *JAMA Netw Open.* 2021;4:e2034750.
- Mohty M, Holler E, Jagasia M, Jenq R, Malard F, Martin P, et al. Refractory acute graft-versus-host disease: a new working definition beyond corticosteroid refractoriness. *Blood.* 2020;136:1903–6.
- DeFilipp Z, Alousi AM, Pidala JA, Carpenter PA, Onstad LE, Arai S, et al. Nonrelapse mortality among patients diagnosed with chronic GVHD: an updated analysis from the Chronic GVHD Consortium. *Blood Adv.* 2021;5:4278–84.

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Substantial contributions to study conception and design: OP, FM, DM, CS, RZ, DW, ES, HG, ZP, EG, AB, AO; substantial contributions to analysis and interpretation of the data: OP, FM, DM, CS, RZ, DW, ES, HG, ZP, EG, AB, AO; drafting the article or revising it critically for important intellectual content: OP, FM, DM, CS, RZ, DW, ES, HG, ZP, EG, AB, AO; final approval of the version of the article to be published: OP, FM, DM, CS, RZ, DW, ES, HG, ZP, EG, AB, AO. Authors (FM, DM, CS, RZ, DW, ES, HG, ZP, EG, AB, AO) received an honorarium from Therakos for their participation in the Delphi panel. OP contributed to the development of the Delphi questionnaire, analyzed data and edited the manuscript. He did not participate in the Delphi panel study. OP has received an honorarium from Therakos for his involvement in this project. OP: OP has received honoraria or travel support from Gilead, Jazz, MSD, Neovii, Novartis, Pfizer and Therakos. He has received research support from Incyte and Priothera. He is member of advisory boards to Equilibrium Bio, Jazz, Gilead, Novartis, MSD, Omeros, Orca Bio, Priothera, Sanofi, Shionogi and SOBI. FM: FM has received honoraria from BMS, Therakos, Sanofi, JAZZ Pharmaceuticals, Gilead, Novartis, AstraZeneca and MSD. DM: DM has received honoraria from Jazz, Novartis, Incyte, Sanofi, Therakos for consulting, and research grants from Novartis and CSL Behring. CS: CS has received honoraria or travel support from Gilead, Jazz, MSD, Novartis, Pfizer and Therakos. He has received research support from Pfizer. RZ: RZ has received honoraria from Novartis, Incyte, Sanofi and Therakos. DW: DW has received research support from Novartis and honoraria from Incyte, Sanofi, Therakos Neovii, Behring, Takeda and Novartis. ES: ES has received honoraria for consulting activities or travel support from Gilead, Jazz, MSD, Neovii, Novartis, Priothera, MSD and Therakos. HG: HG has received honoraria from Gilead, Neovii, Takeda, Stemline, Novartis, Sanofi and Therakos for presentations in scientific meetings and consultations. ZP: ZP has received honoraria from Therakos. EG: EG has received honoraria from Amgen, AstraZeneca, Jazz, Novartis, Omeros, Sanofi, Sobi, Therakos. AB: AB has received honoraria from being a part of the Speakers Bureau for Jazz, Adienne, Sanofi, Pfizer, Novartis, Therakos. AO: AO has received honoraria from Therakos, Jazz, Novartis, Incyte and Sanofi in the last 3 years.

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ADDITIONAL INFORMATION

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