Systematic Review and Meta-Analysis of Extracorporeal Photopheresis for the Treatment of Steroid-Refractory Chronic Graft-Versus-Host Disease

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Objectives

To evaluate the clinical efficacy and safety of extracorporeal photopheresis for the treatment of steroid-refractory chronic graft-versus-host disease.



Background

- Chronic graft-versus-host disease (cGvHD) is associated with substantial morbidity and non-relapse mortality in hematopoietic cell transplant (HCT) recipients.¹
- Extracorporeal photopheresis (ECP), which mediates an anti-GvHD effect via immunomodulation, is recommended as a treatment option for steroid refractory cGvHD (SR-cGvHD).2-4

Methods

- ► A systematic literature review (SLR) was conducted according to PRISMA guidelines.
- ► MEDLINE, Embase, Cochrane, DARE and relevant conference proceedings were searched to 19 October 2022 for studies of patients with SR-cGvHD receiving ECP and reporting on efficacy, safety or health-related quality of life (HRQoL) outcomes.
- ► A feasibility assessment (FA) was conducted to assess sources of potential between-study heterogeneity in the meta-analyses (MA).
- Random-effects MAs were performed for long- and short-term efficacy outcomes including overall survival (OS) and failure-free survival (FFS), and overall response rate (ORR) and skin-specific response, respectively.
- ► Timepoint windows were used for ORR (Months 3–4 and Months 6-8) and skin-specific response (Months 2-3and Months 4-6).
- Insufficient safety and HRQoL data precluded further analysis.
- ► A subgroup analysis for ORR only was conducted to explore the effect of outcome assessment criteria (National Institutes of Health [NIH] vs non-NIH/unknown).

ABBREVIATIONS: CI: confidence interval; cGvHD: chronic graft-versus-host disease; ECP: extracorporeal photopheresis; FA: feasibility assessment; FFS: failure-free survival; HCT: hematopoietic cell transplantation; HRQoL: health-related quality of life; MA: meta-analyses; NIH: National Institutes of Health; ORR: overall response rate; OS: overall survival; **SLR:** systematic literature review: **SR-cGVHD:** steroid refractory cGvHD.

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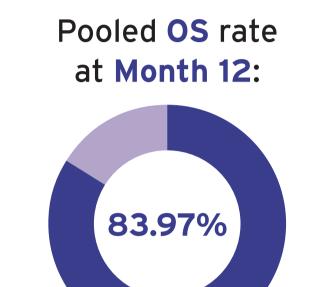
REFERENCES: ¹Grube M. Biol Blood Marrow Transplant 2016;22(10):1781–91; ²Greinix HT. Leukemia 2022;36(11):2558–66; ³Drexler B. Transfus Med Hemother 2020;47(3):214−25; ⁴Nygaard M. Eur. J. Haematol 2020;104(5):361−75. **AUTHOR DISCLOSURES: ZD:** Research support from Incyte, Regimmune and Taiho Oncology; consulting fees from Incyte, Inhibrx, MorphoSys, Ono Pharmaceutical, PharmaBiome and Sanofi. LF: Travel fees from Sanofi. TH: Honoraria from Amgen, Bristol-Myers-Squibb, GlaxoSmithKline and Jazz; consulting or advisory role for Amgen, Bristol-Myers-Squibb, GlaxoSmithKline, Jazz, Kite/Gilead, Novartis, Pfizer and Sanofi; travel/accommodation/expenses from AbbVie Amgen, Astellas, BeiGene, Bristol-Myers-Squibb, GlaxoSmithKline, Immatics, Janssen, Jazz, Kite/Gilead, Neovii and Sanof **DK:** Research grant from Novartis; honoraria from Novartis and Sanofi; advisory boards for Novartis and Sanofi. VM: Research grants from Gilead, MSD and Pfizer; advisory boards for Allovir, Gilead, Mundipharma, Pfzier and Sanofi; honoraria from Cidara, Gilead, Novartis, Pfizer, Sanofi and Therakos. **DM:** Research grant from CSL Behring; honoraria from Incyte, Jazz, Novartis and Mallinckrodt. Al: Employee of Therakos UK. AP: Employee of Costello Medical Consulting **AK:** Employee of Costello Medical Consulting.

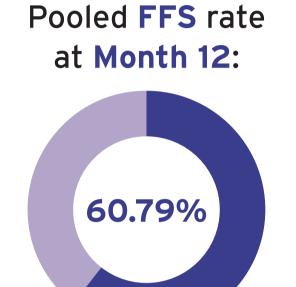
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Summary

An SLR and MA was conducted to evaluate the clinical efficacy of ECP used in the treatment of SR-cGvHD The SLR identified 621 records, of which 47 unique studies reporting on Therakos ECP machines were included

The MA found favorable outcomes with ECP in SR-cGvHD,





including OS, FFS and ORR

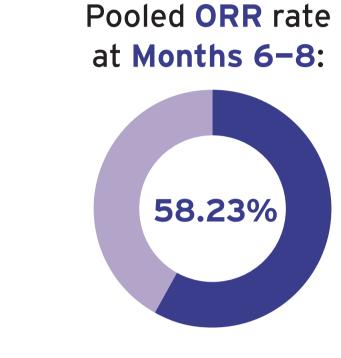
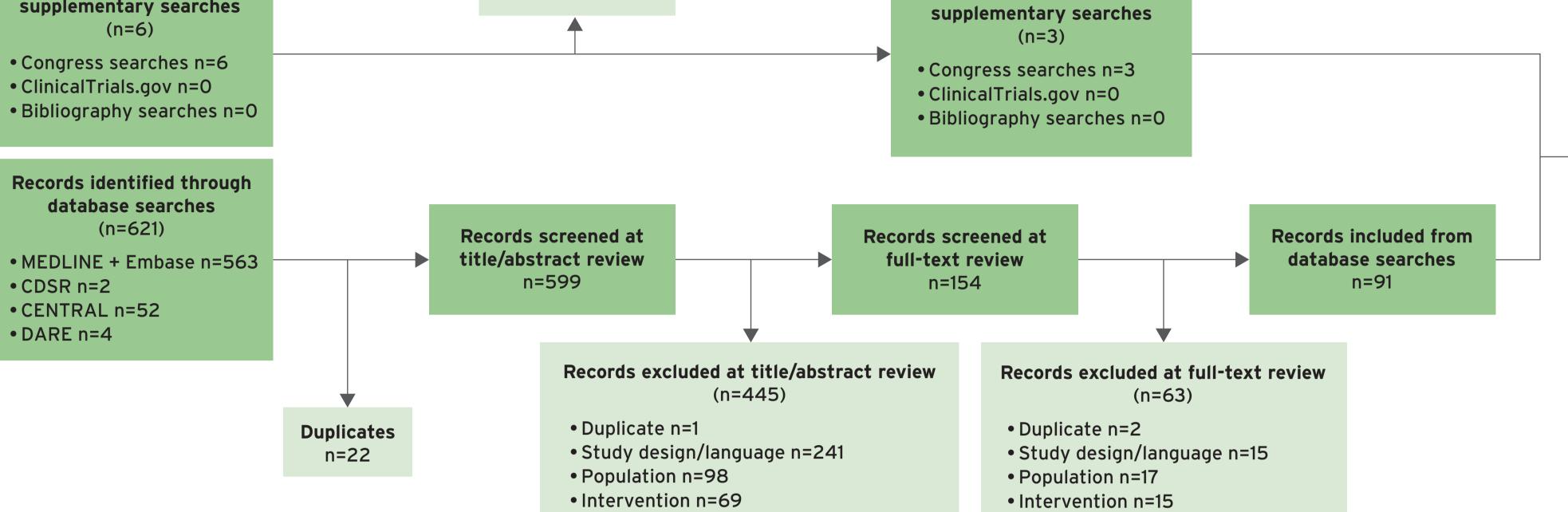


FIGURE 1. PRISMA Diagram Records identified through supplementary searches



CDSR: Cochrane Database of Systematic Reviews; CENTRAL: The Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effect.

• Outcomes n=36

FIGURE 2. Pooled OS rate at Month 12

Study	Events	Total Patients	Events per 100 Observations	Proportion	95% CI
Akhtari 2010	18	25		72.00	[50.61; 87.93]
Amat 2021	22	25		88.00	[68.78; 97.45]
Belizaire 2019	20	25		80.00	[59.30; 93.17]
Bisaccia 2006	14	14	:	100.00	[76.84; 100.00]
Couriel 2006	38	71		53.52	[41.29; 65.45]
Dignan 2012	66	82	 :	80.49	[70.26; 88.42]
Jagasia 2009	23	31		74.19	[55.39; 88.14]
Kansu 2022	45	53		84.91	[72.41; 93.25]
Linn 2021	64	75		85.33	[75.27; 92.44]
Messina 2003	40	44		90.91	[78.33; 97.47]
Motolese 2007	21	24		87.50	[67.64; 97.34]
Nygaard 2019	51	54		94.44	[84.61; 98.84]
Sakellari 2018	69	82		84.15	[74.42; 91.28]
Whittle 2017	86	99		86.87	[78.59; 92.82]
			: : :		
Pooled Proportion	n	_		83.97	[77.33; 88.94]
Heterogeneity: /²	=72%, p < 0	0.01	40 60 00 100		
			40 60 80 100		
			Proportion of Patients		

CI: confidence interval; OS: overall survival

CI: confidence interval; FFS: failure-free survival

FIGURE 4. Pooled ORR at Months 6-8

Study	Events	Total Patients	Events per 100 Observations	Proportion	95% CI
Outcome Asessm	ent Criteri	a = NIH			
Dignan 2012	65	82		79.27	[68.89; 87.43]
Dignan 2014	19	27		70.37	[49.82; 86.25]
Gandelman 2018	20	49	- 1	40.82	[27:00; 55.79]
Jagasia 2019	21	29		72.41	[52.76; 87.27]
Linn 2021	36	63		57.14	[44.05; 69.54]
Nygaard 2019	16	53		30.19	[18.34; 44.34]
Whittle 2011	20	39		51.28	[34.78; 67.58]
Zeiser 2021	16	55		29.09	[17.63; 42.90]
Pooled Proportion	1	_		54.06	[37.51; 69.75]
Heterogeneity: /2:	=87%, p < 0	0.01			
Outcome Assessr	nent Criteı	ria = non-NIH			
Couriel 2006	28	44		63.64	[47.77; 77.59]
De Novellis 2021	13	13		100.00	[75.29; 100.00]
Flowers 2008	19	48		39.58	[25.77; 54.73]
Okamoto 2018	8	15		53.33	[26.59; 78.73]
Piccirillo 2021	16	23		69.57	[47.08; 86.79]
Pooled Proportion	1	_		66.26	[34.55; 87.96]
Heterogeneity: /2:	=48%, p=0	.10			
Pooled Proportion	1	_		58.23	[45.04; 70.35]
Heterogeneity: /2:	=80%, p < 0	0.01			
Test for subgroup	difference	s:	0 20 40 60 80 100		
$x^2/_1 = 0.86$, df = 1	(p = 0.35)		Proportion of Patients		

• Outcomes n=14

CI: confidence interval; NIH: National Institutes of Health; ORR: overall response rate.

CI: confidence interval

FIGURE 3. Pooled FFS rate at Month 12

Study	Events	Total Patients	Events per 100 Observations	Proportion	95% CI
Belizaire 2019	19	25	: +	76.00	[54.87; 90.64]
Jagasia 2019	10	18		55.56	[30.76; 78.47]
Linn 2021	51	75		68.00	[56.22; 78.31]
Nygaard 2019	22	51		43.14	[29.35; 57.75]
Pooled Proportion		-		60.79	[38.94; 79.03]
Heterogeneity: /²=71%, <i>p</i> < 0.01		.01	20 40 60 80 100 Proportion of Patients		

FIGURE 5. Pooled skin-specific response at Months 4–6

Study	Events	Total Patients	Events per 100 Observations	Proportion	95% CI
Belizaire 2019	9	19		47.37	[24.45; 71.14]
Gandelman 2018	36	65		55.38	[42.53; 67.73]
Okamoto 2018	3	11		27.27	[6.02; 60.97]
Seaton 2003	10	21		47.62	[25.71; 70.22]
Whittle 2017	54	75		72.00	[60.44; 81.76]
Pooled Proportion	า	_		54.22	[35.67; 71.67]
Heterogeneity: /2=65%, p=0.02		.02	0 20 40 60 80 100 Proportion of Patients		

Results

Records prioritized

for extraction

47 unique studies

(54 publications)

- ► The SLR identified 621 records, of which 47 unique studies reporting on Therakos ECP machines (inline; CELLEX™ or UVAR-XTS™) were included; Figure 1.
- ► In general, reporting of study characteristics and outcomes was inconsistent.
- The majority of studies (n=28) reported on adult only populations (≥18 years). Lines of therapy were poorly reported (n=15) and ranged from 0 to ≥4 lines of previous treatment. Most studies (n=27) used a retrospective case series study design.
- For long-term efficacy, the pooled OS rate at Month 12 was 83.97% (95% confidence interval [CI]: 77.33-88.94; 14 studies, 704 patients; **Figure 2**).
- ► At Month 60, the pooled OS rate was 57.96% (95% CI: 35.48-77.56; 8 studies, 431 patients).
- Results from four studies (169 patients) indicated a pooled FFS rate of 60.79% at Month 12 (95% CI: 38.94-79.03; Figure 3).
- ► For short-term efficacy, the pooled ORR was 45.34% (95% CI: 26.64-65.45) at Months 3-4 (7 studies; 293 patients) and 58.23% (95% CI: 45.04-70.35) at Months 6-8 (13 studies; 540 patients; Figure 4).
- Subgroup analyses showed no significant difference in ORR between studies utilizing NIH criteria and those utilizing non-NIH criteria.
- ► The pooled skin-specific response was 34.86% (95% CI: 13.26–65.21) at Months 2–3 and 54.22% (95% CI: 35.67-71.67) at Months 4-6; **Figure 5**.
- ► There was considerable heterogeneity across all analyses, with I² values ranging from 65% to 91%.

Discussion

- ► An important limitation of this study was the inconsistency of reporting across the literature which resulted in high heterogeneity.
- ► This highlights the need for consistent study reporting in the field; future primary research should aim to harmonize diagnostic and outcome criteria, including timepoints for response measurement, as well as consistency in reporting baseline characteristics of patients.
- ► However, due to the relative rarity of cGvHD, patient recruitment can be challenging, limiting the size and quality of potential studies.

This recent systematic review and MA indicated that ECP results in favorable clincial outcomes in SR-cGvHD, including OS, FFS and ORR.