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Review

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

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A B S T R A C T

The objective of this meta-analysis (MA) was to evaluate the efficacy and safety of extracorporeal photopheresis (ECP) for the treatment of steroid-refractory chronic graft-versus-host disease (SR-cGvHD). A systematic literature review (SLR) was conducted according to PRISMA guidelines, followed by a feasibility assessment (FA) to assess potential between-study heterogeneity in the meta-analysis (MA). Random-effects MAs were performed for overall survival (OS), failure-free survival (FFS), overall response rate (ORR) and skin-specific response. A subgroup analysis was conducted to explore the effect of NIH assessment criteria. The SLR identified 627 records; 45 unique studies were ultimately included in the MA. For patients treated with ECP, at Month 12, the pooled OS rate was 83.97% and the pooled FFS rate was 60.79%. ORR was 45.34% at Months 3 to 4 and 58.23% at Months 6 to 8. Subgroup analyses showed no significant difference in ORR between studies utilizing NIH criteria and those utilizing non-NIH criteria. Skin-specific response was 34.86% at Months 2 to 3 and 54.22% at Months 4 to 6. There was considerable heterogeneity across all analyses, with I^2 values ranging from 65% to 91%. This SLR and MA indicates that ECP results in favorable outcomes in the treatment of SR-cGvHD, including OS, FFS and ORR.

INTRODUCTION

Extracorporeal photopheresis (ECP) is recommended as a second line or beyond treatment option for steroid refractory cGvHD (SR-cGvHD) [1–7]. The procedure itself involves exposing a portion of the patient's circulating leucocytes to a photoactive compound (8-MOP) and ultraviolet A (UVA) radiation, before reinfusing the treated

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leukocytes back into the patient [8]. ECP does not have an immunosuppressive effect [8]; instead, it has specific immunomodulatory effects, including inducing a switch from pro- to anti-inflammatory cytokine production [9]. ECP has also been shown to increase donor T regulatory cell (Treg) activity, improving peripheral tolerance and in turn helping to suppress GvHD [10,11]. A number of studies and reviews have demonstrated the safe and effective use of ECP in patients with SR-cGvHD [2,12–19]. However, despite the advantages of ECP, the treatment can be relatively time-consuming, taking between one and a half and 3 h per treatment, depending on the type of machine used [8,9]. It also requires venous access, which can cause administration-related infections [2,3]. A previous systemic literature review (SLR) and meta-analysis (MA) of outcomes of ECP in cGvHD was conducted by Malik et al. in 2014, however it did not analyze outcomes at reported timepoints or discuss variation in clinically relevant patient characteristics [20].

The objective of this SLR/MA was to evaluate evidence on the efficacy and safety of ECP for the treatment of cGvHD, by synthesizing reported estimates to quantify clinically relevant endpoints for ECP. This would provide a comprehensive understanding of both short- and long-term outcomes, including survival and treatment response. Within the literature, we aimed to take greater consideration of heterogeneity of the studies, including variations in the use of National Institutes of Health (NIH) criteria for diagnosis and/or outcome measurement [21], and what effect this might have on response-driven outcomes.

METHODS

Systematic Literature Review

Search Strategy

A systematic search of various electronic databases (summarized in Table 1) was conducted in October 2022, in compliance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Supplementary searches were also conducted to ensure that no relevant studies were missed (Table 2). Search terms are summarized in the Supplementary Methods—Table 1, Table 2, Table 3.

Study Selection

Studies were included if they reported on: patients diagnosed with steroid-refractory cGvHD, including steroid-dependent and steroid-intolerant patients, following HCT from any source; inline ECP as the intervention and any/no comparator; efficacy outcomes, including by not limited to, overall response rate (ORR), response (complete, partial, organ specific), duration of response (DOR), overall survival (OS), failure-free survival (FFS), relapse, mortality and steroid-sparing effect; safety outcomes, including but not limited to, adverse events (AEs), infection rate and discontinuation due to AEs; or health-related quality of life (HRQoL). Due to the volume of studies identified, a prioritization strategy was implemented at the full-text stage to ensure that only the most relevant data were extracted; inline ECP machines were prioritized to minimise heterogeneity. A full list of the eligibility criteria are summarized in the Supplementary Methods—Table 4.

In addition, the most stringent record screening process, as recommended by the Cochrane Collaboration, was followed [22]. The study selection and data collection processes are summarized in the Supplementary Methods.

Data Extraction and Quality Assessment

Publications suitable for inclusion were extracted into a predefined extraction grid configured for the subsequent feasibility assessment (FA) and MA. The quality of all extracted studies was assessed using the Joanna Briggs Institute critical appraisal tools for case series, cohort studies, randomized controlled trials, quasi-experimental studies or cross-sectional studies, dependent on the study design. Data extraction and quality control processes are summarized in the Supplementary Methods.

Meta-Analysis

Details of the FA, which was conducted to assess potential between-study heterogeneity in the MA, are provided in the Supplementary Methods.

Software Implementation, Data Preparation and Cleaning, Handling of Missing Data and Publication Bias

Primary and secondary MAs were conducted using the *meta* package (version 6.2–1) of statistical software R, version 4.2.2 or later [23,24]. The studies included for each MA consisted of all eligible studies with useable data as determined by the FA, ensuring there were no missing study-level data. Methods for data preparation and cleaning are summarized in the Supplementary Methods. For analyses which only contained a small number of studies (2 to 4), the approach suggested by Bender et al. 2018 was used, in

Table 1
Electronic Databases Searched

Platform	Database (Period Searched)
Ovid SP Platform*	MEDLINE (1946 to October 2022) • MEDLINE In-Process • MEDLINE Daily • MEDLINE Epub Ahead of Print Embase (1974 to October 2022)
Wiley Online Platform	The Cochrane Library (database inception to October) • Cochrane Database of Systematic Reviews (CDSR) • The Cochrane Central Register of Controlled Trials (CENTRAL)
University of York Centre for Reviews and Dissemination (CRD) Platform	Database of Abstracts of Reviews of Effect (DARE; database inception to October 2022)

*MEDLINE and Embase were searched simultaneously.
CDSR indicates Cochrane Database of Systematic Reviews; CENTRAL, The Cochrane Central Register of Controlled Trials; CRD, Centre for Reviews and Dissemination; DARE, Database of Abstracts of Reviews of Effect.

Table 2
Additional Literature Searched

Search Strategy	Literature Source (Period Searched)
Congress Searches	European Society for Blood and Marrow Transplantation (EBMT; 2021 to 2022) American Society of Hematology (ASH; 2021 to 2022) European Hematology Association (EHA; 2021 to 2022) American Society for Transplantation and Cellular Therapy (ASTCT; 2021 to 2022) American Transplant Congress (ATC; 2021 to 2022)
Grey Literature	PubMed/Google Scholar ClinicalTrials.gov
Bibliography Searches	Bibliographies of all SLRs and NMAs identified as part of database searches

ASH indicates American Society of Hematology; ASTCT, American Society for Transplantation and Cellular Therapy; ATC, American Transplant Congress; EBMT, European Society for Blood and Marrow Transplantation; EHA, European Hematology Association; NMA, network meta-analysis; SLR, systematic literature review.

which the estimator for the between-study variance may have differed from the default of the *meta* package [25]. A funnel plot was generated and inspected for each MA to assess small study effects and provide insight into whether publication bias may have been present. Funnel plots for the primary outcomes of interest, are provided in the Supplementary Results (Figures 5-7).

Given that clinical variation was identified in several patient characteristics, random-effects MAs were conducted to allow between-study heterogeneity to be modelled, following Cochrane recommendations [22].

Primary Analyses

MAs were conducted according to a prespecified analysis protocol to synthesize estimates of treatment effects reported across studies and pooled estimates were obtained for each outcome at the specified timepoints. MAs were performed for clinically relevant, well-reported outcomes and timepoints identified in the SLR. Long-term survival outcomes included OS at Month 12 and Month 60, and FFS at Month 12. Short-term response outcomes included ORR at Months 3 to 4 and Months 6 to 8 and skin-specific response at Months 2 to 3 and Months 4 to 6. The definition of how skin-specific response was measured varied between studies. Timepoint ranges were used for these response outcomes to capture as much reported data as possible at similar timepoints. Ideally, meta-analysis of time-to-event outcomes such as OS and FFS would pool reported hazard ratios, which account for censoring of patients. However, these were typically less well reported across studies compared to survival rates provided as a binary outcome, likely due to small sample sizes, and so meta-analyses focused instead on survival rates at specified timepoints.

Secondary Analyses

Secondary analyses were conducted to investigate the effect of cGvHD assessment criteria on efficacy outcomes; given insufficient data availability for other outcomes, only ORR was assessed. Between-subgroup differences in ORR Months 3 to 4 and Months 6 to 8 were assessed for the following subgroups: patients assessed using NIH criteria and patients assessed using non-NIH or unknown criteria. Studies using unknown criteria are referred to as non-NIH from hereon.

Results Output

Results are presented as forest plots, and a table of point estimates, 95% confidence intervals (CI) and estimates of heterogeneity (I^2). *P*-values, based on a test for subgroup differences, are also reported for the secondary analyses [24].

RESULTS

Systematic Literature Review

The database search yielded 621 records, of which 91 full texts were included (Figure 1). After prioritizing studies reporting on Therakos ECP machines (inline; CELLEX or UVAR-XTS), or a combination of Therakos and non-Therakos (offline) ECP machines, and with a sample size of ≥10 cGvHD patients, 54 publications reporting on 47 unique studies were ultimately included and underwent data extraction [3,14–16,26–72].

Throughout these studies, 2 361 patients received ECP, with 39/47 studies reporting on data for inline ECP machines only; the remaining studies reported on data for mixed in line and offline ECP machines. Most included studies were retrospective case series (n = 27), followed by prospective case series (n = 6), retrospective cohort studies (n = 4), randomized controlled trials (RCT; n = 3), non-RCTs (n = 3), prospective cohort studies (n = 2), a RCT crossover (n = 1) and a cross-sectional study (n = 1). Of the 47 included studies, 19 reported using NIH criteria for cGvHD diagnosis, with 11/19 using the 2005 NIH criteria and 6/19 using the 2014 NIH criteria; 1 study did not specify the date of the NIH criteria used and another study used both non-NIH and 2005 NIH criteria for diagnosis. Of the 47 included studies, 8 studies used non-NIH criteria (e.g. Seattle Criteria) for cGvHD diagnosis. Overall, 16 of the 47 included studies reported using the NIH criteria for outcome measurement. Three studies used non-NIH criteria, however, the majority of studies (28/47) did not report the criteria used for outcome measurement and were assumed to be non-NIH criteria.

In general, reporting of study characteristics and outcomes was inconsistent. Most studies included adults only (≥ 18 yr; n = 28 studies), followed by patients ≥ 12 yr (n = 8 studies), mixed (all ages; n = 7 studies) and pediatrics only (≤ 18 yr; n = 3 studies). One study did not report the age of patients. The severity of patients' cGvHD was reported in 33 studies; 29 studies included patients with severe cGvHD, 19 studies included patients with moderate cGvHD and 11 studies included patients with mild cGvHD. Number of treatment lines for cGvHD was also poorly reported (n = 15 studies), with previous lines of treatment ranging from 0 to ≥ 4. The duration of treatment with ECP was not reported in 43/47 studies. However, the administration schedule of ECP was well reported (n = 43 studies), although it was variable between the studies. Concomitant therapies were well reported across the studies (n = 36 studies); 5 studies included in the MA reported on patients receiving both ruxolitinib and ECP treatment, and 2 studies reported on patients receiving both ibrutinib and ECP treatment. A full breakdown of study characteristics can be found in the Supplementary Material—Table 5.

With regards to prespecified efficacy/effectiveness outcomes, the most commonly reported were OS (n = 30 studies), ORR (n = 28 studies) and organ specific response (n = 21 studies), with DOR (n = 3 studies), FFS (n = 4 studies), relapse (n = 11 studies) and nonrelapse mortality (n = 4 studies) being inconsistently reported across the included studies. In general, the reporting of safety outcomes was poor and inconsistent, with infections (n = 9 studies) among the most reported, and secondary malignancies reported in none of the studies. HRQoL was reported in only 5 studies, none of which used a directly comparable instrument to measure quality of life.

Feasibility Assessment

In total, 47 unique studies were considered in the FA; 2 studies did not report cGvHD specific outcomes or had a crossover design and were subsequently excluded, leaving 45 unique studies.

Patient characteristics and lack of reporting of timepoints were noted as the main inconsistencies across studies; ultimately, given that outcomes were not consistently reported across the included studies, no studies were excluded to ensure sufficient data were available to analyze. Further details regarding patient characteristics can be found in the Supplementary Material, with a full list of baseline characteristics located in the

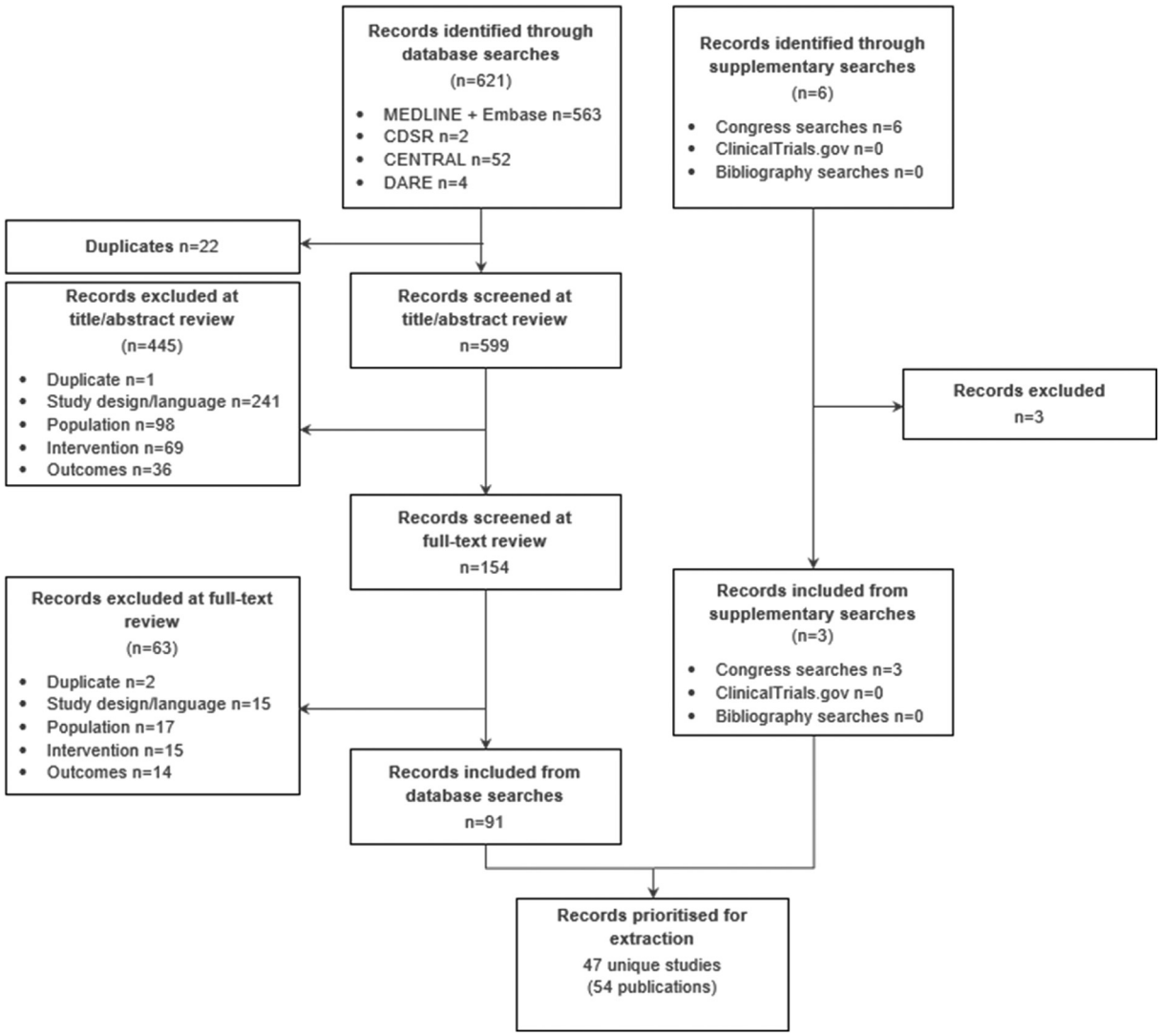

Figure 1. PRISMA diagram (SLR).
CDSR indicates Cochrane Database of Systematic Reviews; CENTRAL, The Cochrane Central Register of Controlled Trials; DARE, Database of Abstracts of Reviews of Effect.

Supplementary Material—Table 6. Response rate (ORR), OS, FFS and skin-specific response were ultimately identified as outcomes of primary interest; insufficient safety and HRQoL data precluded further analysis.

Meta-Analysis

Only studies which were deemed eligible, as determined by the FA, such as those that reported outcomes of interest at relevant timepoints and provided useable data, were analyzed. Out of the 45 eligible studies identified from the FA, 21 studies did not report useable data for any analysis. Therefore, MAs were conducted across combinations of the remaining 24 unique studies which reported useable data for at least 1 analysis, leading to analyses that included between 4 and 14 studies (with 169 to 704 patients per analysis). The pooled estimates and their confidence intervals from the random-effects MAs describe the average effect of ECP treatment on the outcome being analyzed and the uncertainty in locating this average in the underlying distribution of individual study effects.

For long-term efficacy, the pooled OS rate was 83.97% (95% CI: 77.33, 88.94) at Month 12, across 14 studies including 704 patients (Figure 2). The corresponding funnel plot (Supplementary Figure 5), visually indicates slight asymmetry, suggesting the presence of publication bias. At Month 60, the pooled OS rate was 57.96% (CI: 35.48, 77.56%; 8 studies, 431 patients; [Supplementary Figure 1]).

Results from 4 studies (169 patients) led to a pooled FFS estimate of 60.79% at Month 12 (95% CI: 38.94, 79.03; Figure 3). The corresponding

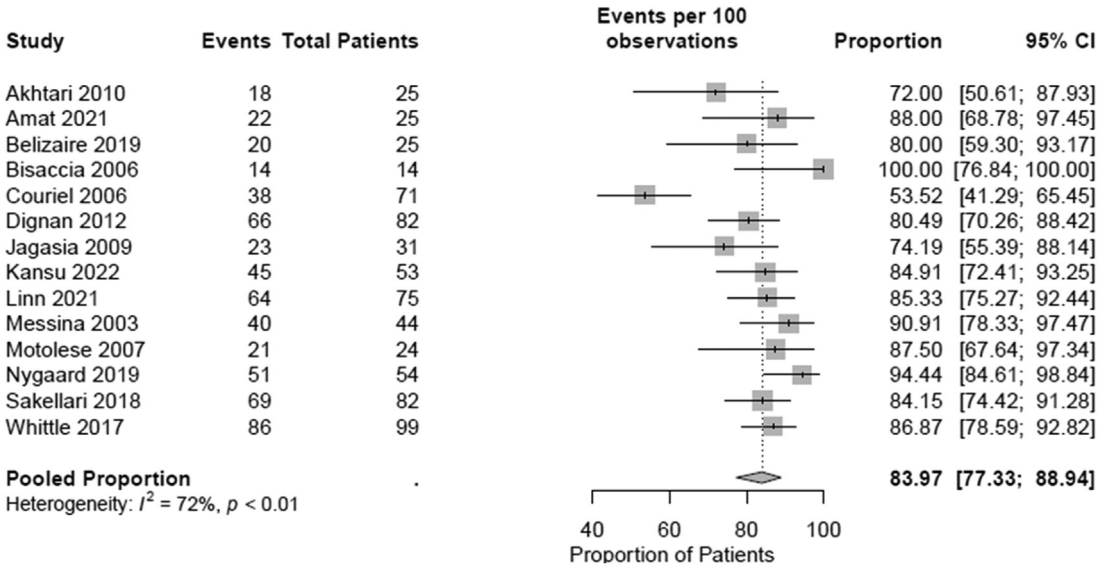

Figure 2. Pooled OS rate at month 12.

OS data for Akhtari 2010, Amat 2021, Bisaccia 2006, Dignan 2012, Jagasia 2009, Kansu 2022, Messina 2003 and Sakellari 2018 were estimated following digitization of Kaplan–Meier curves in the publications.

CI indicates confidence interval; OS, overall survival.

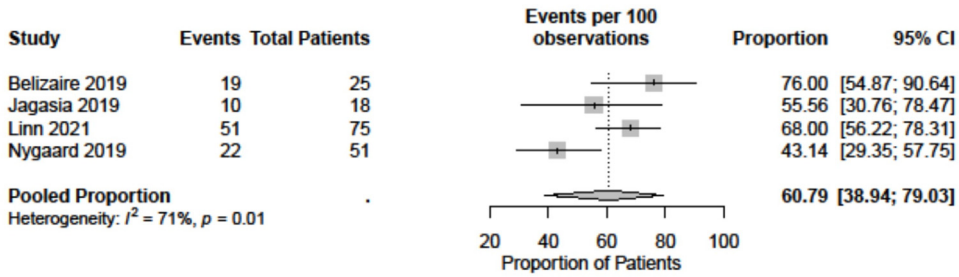

Figure 3. Pooled FFS rate at month 12.

FFS data for Jagasia 2019 were estimated following digitization of Kaplan–Meier curves in the publication.

CI indicates confidence interval; FFS, failure-free survival.

funnel plot (Supplementary Figure 6), visually indicates there are no strong concerns about asymmetry, however, it is difficult to assess with few studies. For short-term efficacy, pooled ORR was 45.34% (95% CI: 26.64, 65.45) at Months 3 to 4 (7 studies; 293 patients; [Supplementary Figure 2]) and 58.23% (95% CI: 45.04, 70.35) at Months 6 to 8 (13 studies; 540 patients; Figure 4). Inspection of the forest plots for pooled ORR showed large variation in study responses.

Subgroup analyses showed no significant difference in ORR between studies utilizing the NIH criteria and those using non-NIH criteria, at either timepoint; Months 3 to 4: NIH criteria (4 studies; 208 patients; 38.33% [95% CI: 19.36, 61.67]) vs non-NIH criteria (3 studies; 85 patients; 56.74% [95% CI: 6.57, 96.08]; P = .31; [Supplementary Figure 2]); Months 6 to 8: NIH criteria (8 studies; 397 patients; 54.06% [95% CI: 37.51, 69.75]) vs non-NIH criteria (5 studies; 143 patients; 66.26% [95% CI: 34.55, 87.96]; P = .35; Figure 4). The corresponding funnel plot (Supplementary Figure 7), visually, is relatively symmetric, indicating no publication bias. Overall, the pooled rates for the NIH criteria were numerically lower than for the non-NIH criteria.

When analyzing the organ-specific response, skin-specific response was 34.86% (95% CI: 13.26, 65.21) at Months 2 to 3 (5 studies; 177 patients) and 54.22% (95% CI: 35.67, 71.67) at Months 4 to 6 (5 studies; 191 patients) [Supplementary Figure 3 and 4]. Other organ-specific responses could not be included in the MA due to inconsistencies across studies in reporting at different timepoints. However, when analyzing the studies included in the SLR, liver-specific responses for patients with

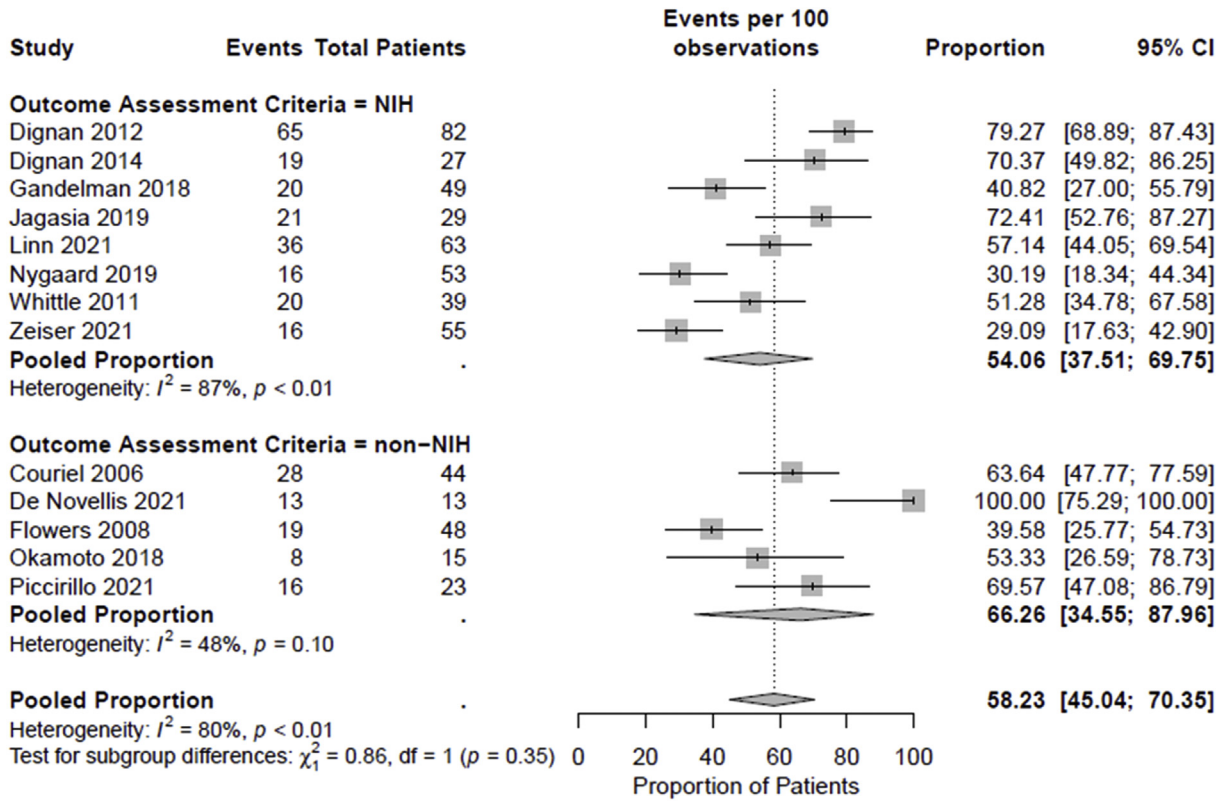

Figure 4. ORR at months 6 to 8.
Abbreviations: CI, confidence interval; NIH, National Institutes of Health; ORR, overall response rate.

cGvHD varied from 21% to 100% (11 studies) and lung-specific responses for patients with cGvHD ranged from 0% to 100% (11 studies). A full list of organ-specific responses can be found in the Supplementary Material—Table 7.

There was "substantial" to "considerable" heterogeneity across all primary analyses with I^2 values ranging from 65% and 91%; 95% CIs were wide, with the exception of 12-month pooled OS rate where more studies reported this outcome [22].

DISCUSSION

A systematic search of the literature for recent evidence on ECP treatment outcomes in patients with cGvHD was performed, allowing for MA of both short- and long-term, clinically relevant outcomes. Findings from this MA support the clinical effectiveness of ECP for the treatment of cGvHD, particularly for pooled OS and FFS rates at Month 12 and pooled ORR at Months 6 to 8.

The pooled OS rates found in this study support the long-term effectiveness of ECP. However, at Month 12 and Month 60, there were 1 and 2 clear outliers, respectively. The majority of patients in both studies presented with severe cGvHD; in 1 study, 42/53 (93.3%) patients had severe cGvHD, and 71/71 (100%) patients had severe cGvHD in the other [37,50]. The high proportion of patients with severe disease may therefore be expected to result in worse survival outcomes, compared to those with mild or moderate disease, thus affecting the pooled OS estimates and interpretation of long-term efficacy.

FFS is a composite measure where events comprise initiation of a new systemic cGvHD treatment, recurrent malignancy and/or death [73]. It is an objective and clinically meaningful tool to assess treatment success, and is increasingly being used as a secondary endpoint in clinical trials for cGvHD [73]. Out of the 4 studies that analyzed FFS, only 2 provided a definition of the outcome. One study defined FFS as the absence of GvHD recurrence, new immunosuppressive therapy, relapse, or death from any cause. The other study described FFS as the patient being alive without the need for additional cGvHD therapy or experiencing a relapse [48,72]. The pooled FFS rates observed after 12 months of treatment with ECP are indicative of an extended time on treatment and acceptable toxicity due to lower rates of treatment switching and/or discontinuation, as well as clinical efficacy. While FFS is a useful surrogate for response in real-world clinical practice,

there are limitations to its use. One significant risk is that patients may continue a treatment despite not deriving any benefit, for example, in patients who have exhausted available treatment options [74–76]. Additionally, treatment changes can occur for reasons unrelated to clinical response, such as patient preference, which does not necessarily reflect clinical efficacy [73]. Regular and predetermined assessments may help overcome the potential bias of incorporating initiation of new treatment within a composite measure [77]. However, implementing fixed time-point assessments may not be feasible in many clinical trials due to logistical or financial constraints.

The lack of significant difference in outcomes between the NIH and non-NIH criteria subgroups in ORR may be due to inconsistencies in the implementation of the NIH criteria as well as the subjective nature and poor reporting of criteria used for cGvHD diagnosis/outcome assessment (NIH or non-NIH) [78]. It is important to note that many of the studies, including some of the randomized controlled trials, were conducted prior to the NIH guidance and therefore could not implement the criteria. The reluctance to utilize validated endpoints in routine clinical practice presents significant barriers to consistent evaluation of optimal care for cGvHD patients. As such, a more consistent application of the NIH response criteria should be used in future studies to evaluate the efficacy of ECP treatment and to ensure a fair comparison of study results. Furthermore, in addition to ORR, when outcomes and response assessments are reported in a standardized fashion, future studies should consider using FFS to help characterize clinical outcomes. Patient-reported outcomes, such as the Lee Symptom Scale, can also provide valuable insights into clinical response, from the patient's perspective [79]. Although the scale is less commonly used in clinical practice, it can detect changes in symptoms that might not be captured by NIH response criteria. Consequently, the Lee Symptom Scale, and other PROs, can serve as a useful supplement to physician-assessed response criteria, including NIH criteria, and enable a more comprehensive understanding of treatment effects [80].

Skin-specific response was poorly reported across the included studies; however, the improved response rates observed after a longer duration of treatment (4 to 6 months compared to 2 to 3 months), support the long-term clinical effectiveness of ECP. Additionally, in one of the included randomized controlled trials, complete or partial skin response was observed in 17 ECP patients (40%) compared to 4 patients treated with the standard of care (10%), at Wk 12 (P = .002). To fully understand the extent of ECP effectiveness, better reporting of skin-specific response, including standardized definitions, needs to be implemented in future studies.

An important limitation of this study was the widespread clinical variation in patient characteristics such as underlying treatment malignancy, concomitant therapies, and previous treatment lines. When analyzing the forest plots for the analyses there are clear outlying studies, however there is uncertainty regarding the source of this heterogeneity. Clinical variation also existed in outcome reporting across studies as identified in the FA and demonstrated by the I^2 values, indicating substantial or considerable heterogeneity in most analyses. For example, I^2 values for OS at Month 12 and FFS at Month 12 were 72% and 71%, respectively, suggesting substantial heterogeneity [22]. Heterogeneity was high due to small samples, combined with the need to include studies with varying baseline patient characteristics due to poor data availability and high inconsistency of reporting in the literature. This highlights the need for improved study reporting in the field, in particular more detailed reporting of patient baseline characteristics and time-points at which efficacy outcomes are assessed. However, it should be noted that, due to the relative rarity of cGvHD, patient recruitment can be challenging, limiting the size and quality of potential studies [81].

Challenges surrounding heterogeneity have been noted in previous meta-analyses [20,82]. Studies included in this MA of ECP did not consistently report patient characteristics such as disease severity, treatment line and previous treatment history, and therefore these factors could not be accounted for in the MA, making methods to adjust for these characteristics in the MA inappropriate [83].

An additional limitation of this study is the potential presence of publication bias. When analyzing the funnel plots for the primary outcomes of interest, in particular OS at Month 12 and FFS at Month 12, they were slightly asymmetric, suggesting the presence of publication bias. However, given the small number of studies included in the analyses, it was difficult to conclusively assess.

Patients treated with ECP are often treated with other concomitant therapies [19,84]. This was reflected in the publications included in this MA; patients were reported to have received multiple

concomitant therapies, including but not limited to ruxolitinib, ibrutinib, methotrexate, prednisone, calcineurin inhibitors, steroids and cyclosporin. Most of the studies included in the MA were conducted before ibrutinib, ruxolitinib and belumosudil started to be used more frequently in clinical practice. Five studies included in the MA reported on patients receiving both ruxolitinib and ECP treatment; 1 study reported an ORR of 74% (17/23), although the timepoint was not stated [34,53,63,72,85]. One of these studies analysed patients who received ruxolitinib and ECP combination treatment, therefore, it is important to acknowledge that the observed treatment effects may not solely be due to the effect of ECP, as with any combination [53]. While the published data clearly demonstrates the clinical efficacy of ECP, many questions remain regarding its positioning within the current treatment landscape and whether treatment line impacts clinical outcomes. Therefore, future analysis on the potential synergistic effects of combination strategies would be valuable, to better inform treatment consensus.

CONCLUSION

This systematic review and MA, conducted according to PRISMA guidelines, indicated that ECP results in favorable outcomes, both long- and short- term, in cGvHD, including OS, FFS and ORR. Future primary research should aim to harmonize diagnostic and outcome criteria, including timepoints for measurement, as well as consistency in reporting baseline characteristics of patients.

DATA SHARING STATEMENT

Authors had access to the report of all datasets generated during and/or analyzed during the current study. The data that support the findings of this study are available from Therakos, a Mallinckrodt Pharmaceuticals company, upon reasonable request.

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Authorship Statement: Substantial contributions to study conception and design: ZD, LF, TH, DK, VM, DM, AP, AK; substantial contributions to analysis and interpretation of the data: ZD, LF, TH, DK, VM, DM, AP, AK; drafting the article or revising it critically for important intellectual content: ZD, LF, TH, DK, VM, DM, AP, AK; final approval of the version of the article to be published: ZD, LF, TH, DK, VM, DM, AP, AK.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2024.11.004.

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