Received: 18 October 2019 | Revised: 30 December 2019 | Accepted: 1 January 2020

DOI: 10.1111/ejh.13381

REVIEW ARTICLE

European Journal of Haematology | WILEY

Extracorporeal photopheresis for graft-vs-host disease: A literature review and treatment guidelines proposed by the Nordic ECP Quality Group

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Abstract

Extracorporeal photopheresis (ECP) is one of the most used and established therapies for steroid-refractory graft-vs-host disease (GvHD), with a good effect to side effect profile. In this review, we present a summary of present literature and provide evidence-based treatment guidelines for ECP in GvHD. The guidelines constitute a consensus statement formed by the Nordic ECP Quality Group representing all ECP centres in the Nordic countries, and aims to facilitate harmonisation and evidence-based practice. In developing the guidelines, we firstly conducted a thorough literature search of original articles and existing guidelines. In total, we identified 26 studies for ECP use in acute GvHD and 36 in chronic GvHD. The studies were generally small, retrospective and heterogeneous regarding patient characteristics, treatment schedule and outcome assessment. In general, a majority of patients achieved partial response or better, but response rates varied by the organs affected. Head-to-head comparisons to other treatment modalities were lacking. Overall, we consider the quality of evidence to be low–moderate (GRADE) and encourage future prospective multi-armed trials to strengthen the present recommendations. However, despite limitations in evidence strength, standardised treatment schedules and regular follow-up are imperative to ensure the best possible patient outcome.

KEYWORDS

graft-vs-host disease, hematologic neoplasms, hematopoietic stem cell transplantation, immune tolerance, immunomodulation, photopheresis

1 | INTRODUCTION

Extracorporeal photopheresis (ECP) was originally used in the treatment of cutaneous T-cell lymphomas and received US Food and Drug Administration (FDA) approval for the indication in the late 1980s. Since the 1990s, ECP has been increasingly used for treating graft-vs-host disease (GvHD).[1] GvHD is a common and potentially severe complication after allogeneic hematopoietic stem cell transplantation (HSCT) where the donor immune cells interfere with the recipients' healthy tissues as these are recognised as foreign. There is an acute form of GvHD, which is characterised by inflammation and mainly affects the skin, the gastrointestinal tract and the liver. There is also a chronic form, which can affect almost any organ and resembles systemic autoimmune diseases.

The first ECP for GvHD was reported in 1994,[2] and through the 1990s, several case reports/series were published on the use of ECP in primarily chronic GvHD (cGvHD).[3-7]

ECP consists of an apheresis procedure, where mononuclear cells are collected, and thereafter a photo-activation procedure, where the collected cells are treated with a psoralen compound (methoxsalen) and then exposed to ultraviolet light. The treated cells are eventually returned to the patient.

The mechanism of action is not fully elucidated. Treatment with ECP causes the DNA strands in the treated cells to crosslink, and eventually, the cells undergo apoptosis. This occurs after the cells have been returned to the patient again.[8] Only 5%-10% of the total amount of lymphocytes are treated; therefore, the effect is not caused by direct killing of alloreactive T cells.[9] Instead, ECP is considered an immunomodulatory treatment, where the apoptotic surface markers of the treated lymphocytes are recognised by antigen-presenting cells. The recognition of apoptotic cells modifies the response of the antigen-presenting cells, which now produce more anti-inflammatory cytokines that favours the development of regulatory T cells. These events lead to a down-regulation of the active cellular immune response and induction of tolerance.[10]

There are overall two techniques for performing ECP: an "off-line" system where the apheresis, photo-activation and re-infusion procedures are performed in different devices, or an "in-line" system, where the procedures are integrated. In the Nordic ECP centres, both systems are used, but the in-line system is the most common.

ECP treatment is traditionally administered on two consecutive days, and this entity is often referred to as a cycle or a session, which is then repeated with different intervals according to severity of disease symptoms. In the following, we will refer to the ECP treatment entity as a "sequence." The sequence-based approach is the only one described in the literature, and thus, head-to-head comparisons to other potential alternatives are lacking. High-quality data on the amount of whole blood that should be processed or whether collection of a certain cell number is needed for response are also absent.

There have been no indications that choice of anticoagulation (commonly heparin or acid citrate dextrose solution A (ACD-A)) effects treatment outcome, and in most patients, there appears to be no reason to recommend one over the other.[11] However, in patients with risk of haemorrhage, ACD-A may be preferred over heparin.

To facilitate best practice care in both adult and paediatric patients considered for ECP treatment within the Nordic countries, we provide these guidelines together with an overview of existing literature on ECP for GvHD. In accordance with current literature, we summarise, how and when this therapy can be used and suggest clinically useful tools to enable adequate treatment evaluation and comparison of results and experiences. These guidelines contain treatment schedules and recommendations on appropriate time points for evaluation of GvHD activity and decision support on whether treatment should be continued or not. Furthermore, a standardised referral form for documentation on baseline assessment data and a standardised form for response assessment are included. The guidelines are written in accordance with the requirements set by the JACIE standards.

2 | METHODS

We searched PubMed (1 June 2018) for reports on ECP treatment in GvHD using the search terms "extracorporeal photopheresis," "extracorporeal photochemotherapy," "graft vs host disease." Furthermore, the reference lists from the relevant reports were searched for additional relevant reports. We reviewed the reports on treatment effect of ECP in both acute and chronic GvHD with emphasis on which patients could be treated, contraindications to ECP, the treatment schedule and duration of ECP. Reports on both adult and paediatric patients were included. Also, we reviewed existing guidelines on ECP treatment for GvHD and general recommendations on how to evaluate treatment effect in GvHD. The recommendations constitute a consensus of the Nordic ECP Quality group and are based on the existing reports and guidelines and the experience from the Nordic ECP centres.

3 | CURRENT LITERATURE ON ECP IN ACUTE AND CHRONIC GVHD

3.1 | Acute GvHD

The best treatment for aGvHD that does not respond sufficiently to first-line treatment with glucocorticoid remains unknown. Both ECP and other treatments have been investigated but there are few studies directly comparing the outcome of available second-line treatments.[12] ECP has emerged as a first choice among second-line treatments as it is not broadly immunosuppressive and does not seem to affect the graft-vs-leukaemia effect. The main potential drawbacks are that the treatment is time-consuming, is costly, requires venous access and can only be given where the equipment for ECP is available. Several papers have been published reporting on the results from ECP treatment of aGvHD, and these are listed below in Table 1.

Only a few of the above-described studies were prospective, and few of them had an adequate control group. All the studies describe patients who were steroid-refractory, steroid-dependent or steroid-intolerant, and these patients are known to have a dismal prognosis. Comparison both within these ECP-treated patients and patients treated with other second- or further-line treatment is difficult because treatment regimens vary and response is defined and assessed in different ways.[13] Furthermore, the timing of response assessment varied substantially.

Jagasia et al[14] compared two retrospective groups from different centres where one group was treated with ECP and the other with anti-cytokine therapy. They found ECP to be predictive of response to treatment and associated with superior survival.

The rate of complete response (CR) in the different organs varies between studies, but encouragingly, it was possible in general to achieve CR in a substantial fraction of these otherwise treatment-refractory patients.

It has been shown that early initiation of ECP leads to better response.[15,16] However, as shown in Table 1, there is often a considerable delay before ECP is initiated. Hautmann et al[17] retrospectively evaluated 30 patients who primarily received ECP as third- or fourth-line treatment and could show that some patients

TABLE 1 Summary of studies (including > 6 patients) in acute graft-vs-host disease

Authors	N	aGvHD severity	Method	Treatment regimen	Duration ECP (median and range)	Time to start of ECP (median and range)	CR skin N (%)	CR liver N (%)	CR GI N (%)	Survival
Greinix et al[25]	21	10 II; 3 III 8 IV	In-line	2 × ECP every 1-2 wk > response > twice every 2-4 wk > maximal response > individual tapering	–	–	13/21	8/12	0/4	57% 25 mo after HSCT (median)
Salvaneschi et al[48]	9[a]	1 II; 7 III 1 IV	Off-line	3 × ECP weekly > clinical improvement > twice every 2 wk for 3 mo > individual tapering	5.4 mo (0.5-13.4)	From aGvHD 22 d (9-47)	6/9 (67)	1/3 (33)	3/5 (60)	67% (median follow-up of 11 mo)
Dall'Amico et al[49]	76[b]	–		Variable	1-24 mo	From HSCT 9-124 d	39/59	18/49	15/28	47% died during ECP
Messina et al [20]	33[a]	2 I: 11 II 13 III 7 IV	In-line	2 × ECP weekly for 1 mo > twice monthly for 2 mo > monthly for at least 3 more months. In 9 patients 3 × ECP weekly > improvement > individual tapering	74 d (8-467) 8 cycles (2-20)	From HSCT 45 d (13-98)	25/33 (76)	9/15 (60)	15/20 (75)	58% overall
Garban et al[50]	12	II-IV	Off-line	6 × ECP in 3 wk > CR or NR—stop, PR—1 × ECP weekly until CR	–	–	8/12 (67)	0/2 (0)	2/5 (40)	–
Greinix et al[15]	59	36 II; 13 III 10 IV	In-line	As Greinix (25) or 2 × ECP weekly > maximal response > stop ECP without tapering	–	From HSCT 37 d 14-70)	47/57 (82)	14/23 (61)	9/15 (60)	47% median observation time of 52 mo
Berger et al[21]	15[a]	7 II; 4III 4 IV	In-line + off-line	2 × ECP weekly for 1 mo > every second week for 2 mo > monthly for 3 mo	12 procedures (4-21)	From HSCT 28 d (15-97). From aGvHD 25 d (13-55)	8/13 (62)	3/7 (43)	4/10 (40)	67% alive
Kanold et al[51]	12[a]	3 II; 6 III 3 IV	Off-line	3 × ECP weekly for 3 wk > individual tapering	24.5 procedures (10-56)	From aGvHD 19 d (6-50)	9/10 (90)	5/9 (55.5)	5/6 (83)	67%—median 8.5 mo follow-up (1-40)
Calore et al[22]	15[a]	7 II; 4 III 4 IV	Off-line	2 × ECP weekly for 1 mo > every 2 wk for 2 mo > monthly for at least another 3 mo	171 d (35-311)	From HSCT 43 d (13-85)	12/13 (92)	1/1 (100)	10/14 (71)	85% 2 y OS
Perfetti et al[16]	23	10 II; 7 III 6 IV	Off-line	2 × ECP weekly for 1 mo > every second week for 2 mo > twice monthly until CR or stabilisation	9.9 cycles (1-25)	From aGvHD 63 d (14-148)	15/23 (66)	3/11 (27)	8/20 (40)	45% at 4 y
Gonzalez-vicent et al[52]	8[a]	3 II; 2 III 3 IV	Off-line	2 × ECP weekly until clinical improvement	8 cycles (2-19) 67 d (1-267)	From HSCT 191 d (12-1635) Includes cGvHD	8/8 (100)	2/2 (100)	4/7 (57)	38% median follow-up of 6.7 mo (2-14)
Perotti et al[53]	50[a]	31 II 14 III 5 IV	Off-line	2-3 × ECP weekly until improvement > twice weekly for 2 wk > twice biweekly 3 times > twice a month until clinical improvement or tapering of immunosuppression	18 procedures (IQR 12-24)	From aGvHD median 9 d (6-20)	39/47 (83)	16/24 (67)	8/11 (73)	44% median follow-up of 23.7 mo (incl. cGvHD)
Hautmann et al[17]	30[b]	9 I; 10 II 10 III; 1 IV	Off-line	2-3 × ECP weekly until PR or CR, then twice every second week and then twice every month if continuous improvement	7 (1-45) 50 d (5-604)	From aGvHD 28 d (3-144)	4/15 (27)	3/11 (27)	2/4 (50) at 3 mo	30% median follow-up of 23 mo (3-125)

(Continues)

TABLE 1 (Continued)

Authors	N	aGvHD severity	Method	Treatment regimen	Duration ECP (median and range)	Time to start of ECP (median and range)	CR skin N (%)	CR liver N (%)	CR GI N (%)	Survival
Merlin et al[54]	12[a]	2 II; 7 III 3 IV	Off-line	3 × ECP weekly for 3 we > taper	22 sessions 810-56) 3.8 mo (0.7-9)	From HSCT 37 (18-78)	Overall CR in 6/8 (75%)	Overall CR in 6/8 (75%)	Overall CR in 6/8 (75%)	57% at 5 y
Rubegni et al[55]	9	5 II 4 III	In-line	2 × ECP weekly until improvement > every 2 wk > individual tapering	–	From aGvHD 46.3 d (10-70)	6/9 (67)	3/4 (75)	4/4 (100)	100% alive after 90 d
Ussowicz et al[56]	8	All III-IV	In-line	2 × ECP weekly up to 8 wk	8.6 procedures (1-32)	From HSCT 3.6 mo (1.8-6.9)	ORR 3/8 (38)	ORR 3/8 (38)	ORR 3/8 (38)	0%, observation mean 1.3 mo (0.5-17.1)
Jagasia et al[14]	57	41 II 16 III-IV	???	2-3 × ECP weekly or biweekly until maximal response > discontinued or tapered	12 treatments (2-45) 45 d (14-293)	Mean steroid use for 19.3 d (4-82)	Overall CR 31/57 (54)	Overall CR 31/57 (54)	Overall CR 31/57 (54)	59% at 2 y
Berger et al[23]	34[b]	16 II; 12 III 6 IV	In-line and off-line	2 × ECP weekly for 1 mo > twice every second week for 2 mo > twice monthly for 3 mo	11 cycles (8-25)	From HSCT 38 d (15-97)	ORR 65%	ORR 65%	ORR 65%	68%. Median follow-up of 4 y (2 mo-12 y) for survivors
Das Gupta et al[40]	128	90 II 38 III-IV	Unknown	2-3 × ECP weekly for 4-6 wk > every other week. Stopped after maximal response or gradually tapered	11 ECP treatments (2-24) 60 d (2-324)	From HSCT 42 d (17-121)	ORR 77% CR total 61%	ORR 77% CR total 61%	ORR 77% CR total 61%	2-y OS 56% median follow-up of 23.3 mo (0.6-41.4)
Calore et al[24]	72[a]	8 I; 29 II 17 III 18 IV	In-line and off-line	2 × ECP weekly for 1 mo > twice every 2 wk for 2 mo > twice monthly for 3 mo > individual tapering or discontinuation	18 procedures (8-90) 4 mo (1.1-10.2)	From aGvHD 22 d (4-81)	26/64 (41%)	6/12 (50%)	29/55(53%)	5-y OS 71% median follow-up of 5 y (0.18-17.6)
Malagola et al[57]	45	36 II 8 III 1 IV	Off-line	2 × ECP weekly for 4 wk > every 2 wk for 4 wk > monthly until IS discontinuation without GvHD.	77 d (28-1112) or 194 d (30-933)	5-7 d after starting 2 mg/kg steroid for aGvHD	Overall CR in 91%	Overall CR in 91%	Overall CR in 91%	64% alive at last follow-up
Niittyvuopio et al[58]	56	3 I; 7 II 34 III; 8 IV	In-line	2 × ECP weekly until maximum response, no maintenance	6 cycles (2-21)	From aGvHD 11 d (2-102)	77%	33%	34%	33% alive at time of analysis
Worel et al[59]	99	13 I; 48 II 23 III; 12 IV	In-line	2-3 × ECP weekly or biweekly > stop if CR or steroid dose <0.5 mg/kg	5 cycles (1-16) 1 mo (0.25-5)	From aGvHD 11 d (1-105)	ORR 75% at 1 mo	ORR 75% at 1 mo	ORR 75% at 1 mo	1-y OS 69%
Nygaard et al[41]	38	3 I; 12 II 13 III; 10 IV	In-line	2 × ECP weekly until CR > stop ECP after 2 wks with CR or individual taper in patients with steroid-dependent aGvHD	9.5 cycles (2-65)	From aGvHD 37 d (3-190)	ORR 82%	ORR 82%	ORR 82%	47% at 1 y

Abbreviations: aGvHD, acute graft-vs-host disease; CR, complete response; ECP, extracorporeal photopheresis; GI, gastrointestinal; HSCT, hematopoietic stem cell transplantation; ORR, overall response rate; OS, overall survival.

[a]Only children.

[b]Both adults and children.

still achieved CR or partial response (PR), though in lower percentages (CR skin = 27%, CR liver = 27%, CR gut = 25%, overall survival 30%).

ECP has recently been proposed for prophylaxis or first-line treatment. Michallet et al[18] treated 20 patients with ECP from day 21 after HSCT and showed subsequent low GvHD rates. Castagna et al[19] reported good results in a small uncontrolled study of 7 patients treated with ECP as first-line treatment for skin aGvHD (grade II and one grade IV). Six patients achieved CR and one PR. However, evidence on ECP as prophylaxis or first-line treatment is limited.

The regimen most often reported in the above studies follows a predefined schedule with two weekly procedures for 4 weeks followed by reduction to two procedures every second week for the next 2 months and then two procedures monthly. This regimen is reported in six studies from mainly Italian centres.[16,20-24] In the remaining studies, ECP is mostly performed two or three times weekly until response and then tapered according to response. In the majority of studies, ECP is tapered, but Greinix et al[15] have shown that ECP may be stopped without tapering after maximal response is achieved. Greinix et al[25] found that maximal response occurs within 3 months (median 4 sequences, range 1-13 sequences or median 2 months, range 0.5-6 months). Messina et al[20] found maximal response after 8 weeks.

There are several reviews and guidelines available on ECP for aGvHD. See Table 2 for overview of the recommendations. There is agreement that ECP should be provided intensely with weekly treatments, but the tapering recommendations differ.

Compared with other second-line treatments for aGvHD, ECP is less toxic and has little or no immunosuppressive effect.[1,12,26] Because of this excellent tolerability, it is reasonable to use ECP early in the treatment of steroid-refractory aGvHD. It can be provided as second-line treatment alone or along with other treatment options.

3.2 | Chronic graft-vs-host disease

In a review of 60 studies on treatment of cGvHD, Martin et al[27] reported that ECP is the most commonly evaluated among 17 different treatment options for cGvHD. Table 3 shows an overview of results from studies on ECP as second-line treatment for cGvHD.

As it is the case with reports on ECP in aGvHD, the reports on cGvHD were mainly small, uncontrolled, retrospective and used different endpoints and treatment regimens. Only the study by Flowers et al[28] was randomised and had a control group. This study used a more intensive treatment regimen with weekly ECP for 12 weeks, whereas most others used weekly treatments for 4 weeks or start with biweekly treatments. Tapering schedules and duration of treatment varied between studies. See Table 4 for an overview of treatment schedules and duration in cGvHD.

In the study by Flowers et al,[28] there was no significant difference in total skin score after 3 months, but there were significantly more patients in the ECP group with more than 50% reduction in steroid dose and at least a 25% reduction in total skin score by week 12. It was suggested by the authors that 3 months may be too soon to capture the full effect of ECP.

Twenty-nine patients from the non-ECP arm of Flowers' study were subsequently treated with ECP in 12 weeks. In this period, they achieved significantly higher response rates in skin, oral mucosa and eyes than in the preceding 12 weeks with standard cGvHD treatment.[29] In all the studies, a substantial proportion of the patients saw improvements in their cGvHD, and improvement could be seen in all organs.

The steroid-sparing effect of ECP has been observed in several studies as shown in Table 3.

The importance of starting ECP early is unclear as some studies found better response if started early, and some found no differences. Some found ECP effective even after a long period with severe cGvHD.[7,20,30,31] However, it is often recommended to start ECP early to prevent irreversible tissue damage and prolonged immunosuppression, especially considering the beneficial safety profile of ECP.[32-34] As for aGvHD, ECP may be provided as second-line treatment alone or along with other treatment options.

Comparative studies to determine the most efficient treatment schedule and how and when to discontinue ECP are lacking. This is also reflected in existing guidelines (Table 2) where the recommendations on intensity in the beginning of ECP treatment vary. Also, duration of ECP is not strictly specified, but should be guided by response. The effect of ECP in cGvHD seems to be slow, and it is recommended in some studies that ECP is continued for at least 6 months.[28,29,35] Especially, in cutaneous cGvHD prolonged ECP may be beneficial.[29] In some of the existing guidelines, it is recommended to consider stopping ECP after 3 months if there is progression or no change in cGvHD.[36,37]

Evidence on effect of different second-line treatments for cGvHD is sparse with most studies being phase II clinical studies or small case series with inhomogeneous inclusion criteria, lack of documentation for severity of cGvHD and insufficient response assessment.[38] As with aGvHD, the excellent safety profile of ECP and lack of evidently more effective treatment options make ECP a reasonable choice for second- or further-line treatment in cGvHD. Especially, the fact that ECP, as far as we know, does not seem to affect the defence against infections or the graft-vs-leukaemia effect is of great importance in cGvHD.

4 | NORDIC GUIDELINES FOR THE USE OF ECP

4.1 | Considerations before starting ECP

ECP is a treatment with low toxicity, no reported general immunosuppressive effect and thereby no reported increased risk of infections or relapse. In relation to other treatment options, ECP is therefore particularly well suited for patients at elevated risk of infection.

TABLE 2 Summary of existing guidelines for the use on ECP in acute and chronic GvHD

Author	Schedule	Assessment
Scarisbrick et al[60]	cGvHD: two procedures on consecutive days. Evaluation after 3 mo and if PR reduction to every 4 wk. If no response, stop ECP. If some improvement and/or reduction in IS, continue every 2 wk until PR. Possible to re-intensify ECP in case of progression	NIH criteria for evaluation every 3 mo
Pierelli et al[61]	aGvHD and cGvHD: Two procedures weekly until maximum response and then tapering tailored to the individual patient	Weekly assessment of clinical response in aGvHD and every 8-12 wk in cGvHD
Das-Gupta et al[26]	aGvHD: one cycle (two procedures on consecutive days) weekly for minimum of 8 wk. Patients with grade III-IV may benefit from three treatments per week for the first 4 wk After 8 wk—if CR and <20 mg methylprednisolone/25 mg prednisolone (adults) or <0.5 mg/kg (children), discontinue ECP After 8 wk—if PR or >20 mg methylprednisolone/25 mg prednisolone (adults) or >0.5 mg/kg (children), continue weekly cycles with weekly assessments. Stop if there is no further response but consider tapering for patients with aGvHD in lower GI tract After 8 wk—if less than PR, consider alternative therapy	Weekly assessment of clinical response and staging of cutaneous, hepatic and gut GvHD
Knobler et al[1]	aGvHD: two-three procedures weekly until CR, then ECP can be discontinued cGvHD: No general recommendation made due to lack of evidence, but it is common to use 1 cycle weekly or biweekly for 12 wk and then taper with 1 wk every 3 mo according to response. If progression of cGvHD, consider other treatment options	Acute GvHD activity every 7 d with staging according to modified Glucksberg criteria (62) Preferably assessment of quality of life Chronic GVHD should be assessed by NIH criteria
Howell et al[62]	All indications: two consecutive treatments for at least 3 mo before evaluation	No recommendations
Schwartz et al[63]	aGvHD: two-three procedures every week until response and then taper to every other week before discontinuation cGvHD: one cycle weekly (or biweekly if only mucocutaneous cGvHD) until response or for 8-12 wk and then taper to every 2-4 wk until maximal response	No recommendations
Alfred et al[36]	aGvHD: 2 procedures on consecutive days weekly for minimum 8 wk. Some patients with grade III-IV aGvHD may benefit from 3 procedures a week for the first 4 wk – If CR after 8 wk and <20 mg/d methylprednisolone or <25 mg prednisolone or <0.5 mg/kg for children, ECP can be stopped. Taper is recommended if lower GI-aGvHD – If PR with >20 mg/d methylprednisolone or >25 mg prednisolone or >0.5 mg/kg for children, ECP should be continued until maximal response and then either stop or taper – Patients without CR/PR after 8 wk should be considered for other treatment options cGvHD: 1 cycle every 2 wk for at least uninterrupted 6 cycles (=3 mo) – If CR or PR after 3 mo, reduce to every 4 wk and continue until maximal response – If minimal response, continue one cycle biweekly – If progression, consider other treatment options and stop ECP After 6 mo – If CR, taper/stop ECP – If PR, continue one cycle monthly until maximal response or stopped corticosteroid, and then taper/stop – If minimal response, consider reduction to one cycle monthly for 3 mo, and if no further response or PD, taper/stop ECP	Acute GvHD: Weekly assessment and staging Chronic GvHD: NIH consensus criteria for response assessment every 3 mo

Abbreviations: aGvHD, acute graft-vs-host disease; cGvHD, chronic graft-vs-host disease; CR, complete response; ECP, extracorporeal photopheresis; NIH, National Institute of Health; PD, progressive disease; PR, partial response.

Upon considering ECP, we recommend assessing the patients' peripheral veins. If a peripheral venous access for ECP is not possible, the entailed risks of inserting a central venous catheter must also be considered when weighting pros and cons against other treatment options.

Furthermore, ECP requires a long-term patient commitment. If the patient lives far from the ECP centre, the commute time may be a factor to consider when weighting against pharmaceutical treatments that may be administered closer to home.

TABLE 3 Summary of studies (including > 6 patients) in chronic graft-vs-host disease

Authors	N	Method	CR/PR skin %	CR/PR liver %	CR/PR oral %	CR/PR lung %	CR/PR ocular %	CR/PR GI %	ORR %	Steroid sparing	OS n (%)
Rossetti et al[64]	8[b]	In-line	–	–	–	–	–	–	50	Yes	100% alive at follow-up
Smith et al[65]	18[b]	In-line	–	–	–	–	–	–	33	–	7/18 alive (39)
Greinix et al[6]	15	In-line	100	90	100	–	80	–	93	Yes	14/15 (93)
Child et al[7]	11	In-line	100	17	50	40	50	–	–	Yes	9/11 (82)
Salvaneschi et al[48]	14[a]	Off-line	93	67	67	–	–	–	64	Yes	11/14 (79)
Halle et al[66]	8[a]	Off-line	88	100	100	–	–	100	100	Yes	100% alive at follow-up
Seaton et al[67]	28	In-line	48	32	21	–	–	–	36	No	24/28 (86)
Apisarnthanarax et al[30]	32[b]	In-line	56	–	–	–	–	–	56	Yes	(65)
Messina et al[20]	44[a]	In-line	57	60	–	43	–	47	59	Yes	(77)
Ilhan et al[68]	8	In-line	100	80	100	67	50	67	75	Yes	100% alive at follow-up
Foss et al[31]	25	In-line	64	0	46	–	–	–	64	Yes	Median 51 mo
Rubegni et al[69]	32	In-line	81	77	92	40	94	–	69	–	–
Garban et al[50]	15	Off-line	100	33	–	100	–	77	87	–	–
Bisaccia et al[70]	14	In-line	50	60	43	33	40	–	–	Yes	(77) (5 y)
Couriel et al[71]	71[b]	In-line	57	71	78	54	67	–	61	Yes	(53) (1 y)
Kanold et al[51]	15[a]	Off-line	75	82	86	–	–	–	73	Yes	(67)
Motolese et al[72]	24	In-line	78	–	–	–	81		81	Yes	–
Duzovali et al[73]	7[a]	In-line	100	40	0	50	50	0	43	–	57% alive at follow-up
Berger et al[21]	10[a]	Both in- and off-line	90	50	33	–	–	–	50	–	80% alive at last follow-up
Perseghin et al[74]	25[b]	Off-line	84	67	78	–	100	50	80	Yes	(76)
Flowers et al[28]	48	In-line	40	29	53	–	30	–	–	Yes	(98)
Jagasia et al[75]	43	???	–	–	–	–	–	–	65	Yes	–
Perotti et al[53]	23	Off-line	96	100	80	67	50	75	69.5	Yes	(78) (HCT)
Dignan et al[76]	82	In-line	92	–	91	–	–	–	79	Yes	(69) (3 y)
Greinix et al[29]	29	In-line	31	50	70	57	–	–	31	Yes	(100)
Del Fante et al[77]	102	Off-line	–	–	–	–	–	–	53	Yes	(78)
Ussowicz et al[56]	13[b]	In-line	67	89	86	0	80	100	69	Yes	(68) (4 y)
Hautmann et al[17]	32[b]	Off-line	59	100	60	25	33	0	44	Yes	21/32 (66)
Dignan et al[78]	38	In-line	65	–	29	50	55	100	50	Yes	(94)
Berger et al[23]	37[b]	Both in- and off-line	–	–	–	–	–	–	82	Yes	(73)
Brownback et al[79]	8	In-line	–	–	–	Reduced IS + slow decline in PFT	–	–	0	Yes	63% alive at follow-up
Malagola et al[57]	49	Off-line	–	–	–	–	–	–	80	–	(90)
Nygaard et. al[80]	54	In-line	–	–	–	–	–	–	61	Yes	(94%) 1 y

Abbreviations: cGvHD, chronic graft-vs-host disease; CR, complete response; ECP, extracorporeal photopheresis; GI, gastrointestinal; HSCT, hematopoietic stem cell transplantation; IS, immunosuppression; ORR, overall response rate; OS, overall survival; PFT, progression-free survival; PR, partial response.

[a]Only children.

[b]Both adults and children.

TABLE 4 Summary of treatment schedules and duration of ECP in cGvHD

Author	Treatment schedules in cGvHD	Time to start ECP (median and range)	Duration ECP (median and range)
Smith et al[65]	Every 3 wk but later increased to 2-3 pr week. Tapering according to response	From HSCT 539 d (58-1414)	22 procedures (6-48)
Greinix et al[6]	Every 2 wk for 3 mo, then every month until resolution	From HSCT 12 mo (3-44)	17 cycles 87-47)
Child et al[7]	Every 2 wk for 4 mo, then monthly for 3 mo, if response, monthly	From cGvHD 17 mo (5-59)	Not defined
Salvaneschi et al[48]	Every 2 wk for 3 mo. If improvement, twice every 3 wk for 3 mo	From cGvHD 12 mo (1-110)	16 mo (1-32)
Halle et al[66]	Weekly (2 d apart) for 2 wk, then 1 a week or two every 2 wk, individual taper	From HSCT 707 d (162-2616)	31 procedures (10-66)
Seaton et al[67]	Every 2 wk for 4 mo and then monthly until 6 mo—decision—stop or continue	From cGvHD 23 mo (2-164)	6 mo (1-58)
Apisarnthanarax et al[30]	Varying schedules. Median 6 sequences pr month (2-17)	From cGvHD 19 mo (0.3-62.5)	34 sessions (12-98)
Messina et al[20]	Weekly the first month, every 2 wk for 2 mo, monthly intervals for 3 mo	From cGvHD 8.9 mo (0.4-109)	Not defined
Foss et al[31]	Every 2 wk to 17 patients and weekly for patients who lived far away (?)	From HSCT 790 d (242-2928)	9 mo (3-24)
Rubegni et al[69]	???	From HSCT 11 mo (1-56)	A total of 1128 cycles
Garban et al[50]	6 procedures for 3 wk, if CR, stop; if PR, 1 procedure per week until CR. If NR, stop	From HSCT 16 mo (3-110)	15 cycles (4-37)
Bisaccia et al[70]	3 × weekly, decreased by 1 pr week depending upon response until 1 every 2 wk	From cGvHD 9 mo (1-26)	17 mo (3-44)
Couriel et al[71]	2 to 4 procedures per week, decreased by 1 per week if response, then every 2 wk	From cGvHD 512 d (23-1537 de novo), 263 (1-1205 relapsing) or 90 (4-1351 progressive)	32 procedures (1-259)
Kanold et al[51]	3 times a week for 3 wk, then gradually reduced for stabilised or improved patients	From cGvHD 19 (6-50)	23 procedures (10-68)
Motolese et al[72]	Every 2 wk for 3 mo, every 3 wk for 3 mo, every 4 wk for 6 mo	From HSCT 13.5 mo (2-56)	Scheduled for 16 cycles
Duzovali et al[73]	3-5 times a week based on severity and tolerance and individual taper	From cGvHD 349 d (2-1191)	19 procedures (3-31)
Berger et al[21]	Weekly for 4 wk, then every 2 wk for 2 mo and then monthly for 3 mo	From cGvHD 650 d (21-3455)	22 procedures (10-98)
Perseghin et al[74]	Weekly for 3 wk, then every 2 wk for 1 mo, then monthly until 6 mo	From c GvHD 2 mo (0.5-28.6)	177 d (28-454)
Flowers et al[28]	3 times in week 1, then weekly for 11 wk. Responders every 4 wk until week 24	From cGvHD 569 d (35-2743)	Scheduled for 15 cycles
Jagasia et al[75]	Weekly for 3-4 wk, every second-third week and then every 4 wk	From HSCT 228 (39-2943)	12 cycles (1-83)
Perotti et al[53]	Weekly for 2 wk, then every 2 wk for 3 times and then monthly until improvement	From cGvHD 42 d (17-220)	34 sessions (16-43)
Dignan et al[76]	Every 2 wk until > PR, then monthly	From HSCT 28 mo (6-120)	15 cycles (1.5-32)
Greinix et al[29]	3 in week one, then twice weekly until week 12, followed by monthly until week 24	From cGvHD 26 mo (4-79)	Not defined
Del Fante et al[77]	Weekly for 3 wk, every 2 wk for 2 wks, monthly until improvement or IS tapering	From cGvHD 130 d (102-287)	8-130 procedures
Ussowicz et al[56]	Every 2 wk for 14 wk, then monthly for up to 30 procedures	From HSCT 26.2 mo (8.5-77.7)	28 procedures (5-46)
Hautmann et al[17]	Weekly until improvement, every other week for 3-4 wk, one cycle monthly if remission	From cGvHD 310 d (39-1447)	12 cycles (3-60)

(Continues)

TABLE 4 (Continued)

Author	Treatment schedules in cGvHD	Time to start ECP (median and range)	Duration ECP (median and range)
Dignan et al[78]	Every 2 wk until PR and then reduced to monthly	From HSCT 19 mo (3-93)	27 patients > 6 mo
Berger et al[23]	Weekly for 4 wk, then every 2 wk for 2 mo, monthly for 3 mo	From HSCT 193 d (10-5681)	20 cycles (8-77)
Brownback et al[79]	Weekly for 4 wk, then every 2 wk for 3 mo and then monthly for at least 1 y	From HSCT 21.1 mo (7.1-62.5)	92 treatments (21- 221)
Malagola et al[57]	Weekly for 4 wk, every 2 wk for 4 wk, monthly until IS discontinuation and CR	From cGvHD 247 d (24-3221)	276 d (29-2861)
Nygaard et al[80]	Every 2 wk > individual tapering according to response	From cGvHD 559 d (11-2760)	20 cycles (8-61)

Abbreviations: cGvHD, chronic graft-vs-host disease; CR, complete response; ECP, extracorporeal photopheresis; HSCT, hematopoietic stem cell transplantation; IS, immunosuppressive therapy; PR, partial response.

4.1.1 | Contraindications

These conditions constitute at least relative contraindications to provide ECP:

- unstable circulatory or respiratory condition
- known sensitivity to psoralen compounds
- known photosensitivity
- aphakia (absence of lens in the eye)
- pregnancy
- low white blood cell count (<1 × 10^9/L)

Precautions should be taken in patients with:

- low haematocrit
- low platelet count
- active bleeding or risk of bleeding
- active infection
- low body weight

We recommend having an up-to-date complete blood count, but in stable patients, fresh sampling in conjunction with treatment may not be necessary. Additional pretreatment blood test may be considered on an individual basis or be taken as part of a standardised ECP routine. We propose to at the minimum consider the following tests:

- Complete blood count
- In patients where ACD-A is used also Ca^{++} and K^+
- In patients treated with warfarin also INR

Other blood tests may be taken concomitantly for general assessment of the patient and/or the status of their GvHD.

Transfusion prior to ECP may be indicated as guided by local or manufacturer's recommendations.

4.1.2 | Vascular access

The vascular access for ECP should be safe and efficient to allow a successful procedure and minimise risk of infection and other complications including minimal interference with the patients' daily life. Temporary, peripheral venous access should always be the first choice. In case of difficult venous access, technical support through ultrasound guidance or nervous stimulation is highly encouraged. An already existing central venous catheter may be used, but often these do not provide adequate blood flow. In these cases, an apheresis-compatible central venous device with double lumen/chamber may be required.

Suggestion of devices for vascular access:

Peripheral: Steel dialysis needle ≥16 G or peripheral venous catheter (≥18 G for collection and ≥20 G for return).

Central: Central venous lines should be tunnelled to allow for long-term treatment. Dialysis catheters with 2 lumens (10-13,5 Fr) are preferred. When using CVCs made from more flexible material, the lumen may collapse during the negative pressure applied during collection phases. For smaller children, it may be necessary to insert two single lumen CVCs to achieve sufficient lumen diameter.

Venous access ports can also be used, and special large volume ports are particularly suited for apheresis purposes.

4.1.3 | Special considerations for treating children

High extracorporeal to total blood volume poses a risk for hypotension, particularly in children. Blood prime significantly reduces this risk and is recommended in subjects with low body weight. A standard operating procedure should be available at each centre when treating these patients, and additional staff may be needed for appropriate supervision.

The treatment schedules and assessment of GvHD for children do not differ from our recommendations for adults.

4.1.4 | Referral and assessments

We recommend using the Referral and Baseline Assessment Forms (Appendix S1). These forms will facilitate adequate, qualitative follow-up. Photo documentation and quality-of-life assessment may bring additional value. Furthermore, it is encouraged to determine pretreatment what will be considered a successful ECP result for the individual patient.

It is also recommended to use the Evaluation and End-of-Treatment Forms (Appendix S1) for aGvHD and cGvHD, respectively, at the below proposed time points. It is desirable to have the same physician repeating the assessments for the individual patient.

4.2 | Acute GvHD

ECP can be used for patients with aGvHD if they are as follows:

1. Steroid-refractory (SR), defined as worsening of aGvHD after 3 days with high-dose methylprednisolone or prednisolone with a minimum dose of 2 mg/kg/d or no improvement after 5-7 days with a dose of prednisolone of at least 1 mg/kg/d.
2. Steroid-dependent (SD), defined as inability to reduce the corticosteroid dose (to a dose less than 0.5 mg/kg/d) without recurrence of grade II or worse GvHD, or
3. Steroid-intolerant (SI), defined as inability to tolerate the side effects of adequate doses of corticosteroids.

ECP can be used for all organ manifestations of aGvHD but with better-expected results for cutaneous > gastrointestinal > hepatic involvement.[39] According to clinical experience, it is possible to combine ECP with other second-line therapies like infliximab and ruxolitinib.

We recommend the following ECP schedule in aGvHD: one sequence of ECP (one treatment on two consecutive days) weekly for 4 weeks. If possible, intensify to three treatments a week during the first 1 or 2 weeks. Evidence is lacking whether ECP is more efficient when provided on one or more consecutive days. We propose the sequence-based regimen as this is the only one in which outcome data are available.

After the first 4 weeks, we propose to distinguish between SR and SD/SI patients. In the SR patient, where aGvHD cannot be controlled by conventional therapy, there is no need for prolonged ECP treatment after complete remission on ECP is achieved. This has been shown by Greinix et al[15] and Das Gupta et al.[40]

In SD/SI aGvHD, the symptoms can be controlled with high doses of steroids but tapering or tolerating this first-line treatment has failed. According to our experience, these patients could often achieve CR quickly on treatment with ECP but reducing or stopping ECP early will mean the patient once again has only the steroids and/or other systemic immunosuppression to control aGvHD. In a recent study, patients with SD aGvHD were more likely to have recurrent aGvHD.[41] Therefore, we recommend a more cautious and prolonged period of tapering of ECP and concomitant immunosuppressive therapy including steroids for these patients. See Figure 1 for an overview of the proposed treatment schedule for aGvHD.

4.2.1 | Treatment evaluation

Response evaluation and dose adjustment of concomitant immunosuppressive therapy should be performed weekly. For documentation, we recommend using the form: "Evaluation or End-of-Treatment Form for aGvHD" (Appendix S1). At 4-week intervals, we recommend adjusting the ECP schedule according to the proposed algorithm (Figure 1).

For response evaluation, we recommend repeated grading of aGvHD in accordance with EBMT-NIH-CIBMTR Task Force position statement on standardised terminology and guidance for graft-vs-host assessment[42] or the updated criteria according to Harris et al.[43]

4.2.2 | Definition of response

CR (complete response) is defined as a complete resolution of aGvHD manifestations in all organs with a prednisolone dose of ≤0.25 mg/kg/d.

PR (partial response) is defined as decrease in stage of originally involved organ/organs without worsening in other organs and/or ≥50% reduction in dose of immunosuppressive drugs.

NC (no change) is defined as the same severity of aGvHD in all originally involved organs with <50% reduction in dose of immunosuppressive drugs.

PD (progressive disease) is defined as worsening in at least one organ regardless of improvement in other organs. Requirement of additional therapy is considered PD.

Temporary flares in aGvHD activity should be noted in the records but is not considered PD if it resolves again without additional therapy.

The response assessment is a clinical assessment. Patients who have not achieved at least a partial response after 8 weekly sequences of ECP should be considered for other treatment. In case of progression, additional or alternative treatments should be considered earlier.

4.3 | Chronic GvHD

ECP is recommended for patients with cGvHD, who are refractory, dependent or intolerant to corticosteroids.

There are no well-established criteria for steroid-refractoriness or steroid-dependency in cGvHD, but recently the following definitions were suggested by a task force from EBMT, NIH and CIBMTR[42]:

Steroid-refractory cGvHD: Progression of cGvHD despite prednisolone ≥1 mg/kg/d for 1-2 weeks OR stable cGvHD for 1-2 months while on ≥0.5 mg/kg/d

Steroid-dependent cGvHD: Two unsuccessful attempts, separated by at least 8 weeks in time, to taper steroids.

Steroid-intolerant cGvHD: Unacceptable toxicity due to the use of steroids.

All organ manifestations of cGvHD can be treated with ECP, but expected better results for cutaneous > gastrointestinal > hepatic > ocular/oral mucosa > pulmonary involvement.[39] Other therapies for cGvHD can be used concomitantly.

We recommend the following schedule in cGvHD: one sequence of ECP every second week for the first 12 weeks. Initial biweekly sequences are recommended because there is no firm evidence of

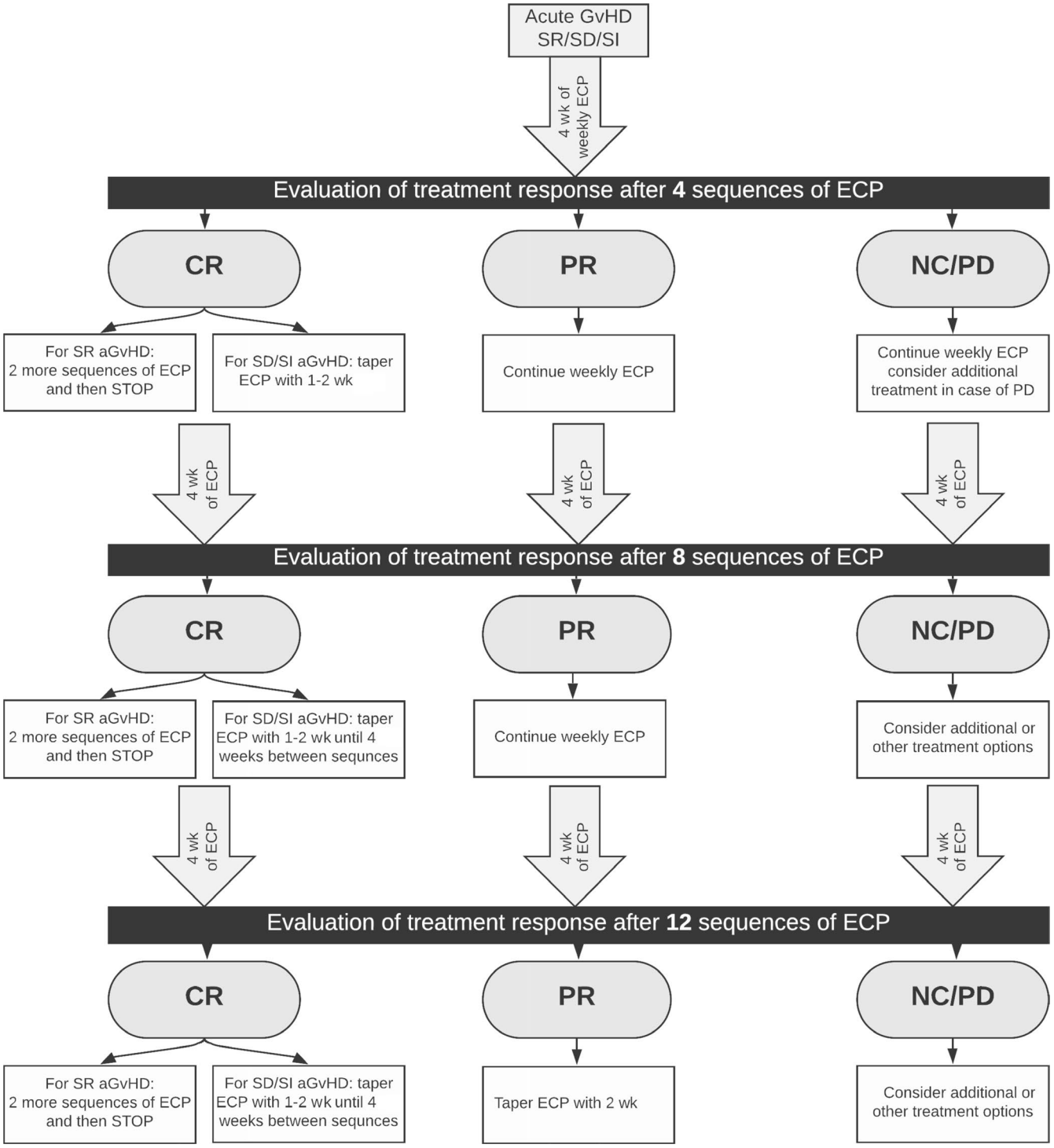

FIGURE 1 Recommendations of treatment intensity and response assessment in acute graft-vs-host disease. A sequence refers to two extracorporeal photopheresis treatment procedures on consecutive days. aGvHD, acute graft-vs-host disease; CR, complete remission; ECP, extracorporeal photopheresis; NC, no change; PD, progressive disease; PR, partial remission; SD, steroid-dependent; SI, steroid-intolerant; SR, steroid-refractory

superior treatment effect using initial weekly sequences.[31] As for aGvHD, we recommend paired treatment on consecutive days due to the lack of studies on single-day ECP.

Subsequent treatment strategy depends on the response where treatment intensity can be reduced to every 4 weeks in case of a positive response. In patients with progression of symptoms, physicians should consider to end ECP or add additional therapies. When no cGvHD symptoms remain or the intended treatment goal has been reached, ECP can be stopped. This is illustrated in Figure 2.

For patients with cGvHD with pulmonary involvement or scleroderma, the expected treatment response is slow and we recommend continued ECP for at least 6 months.[29,44]

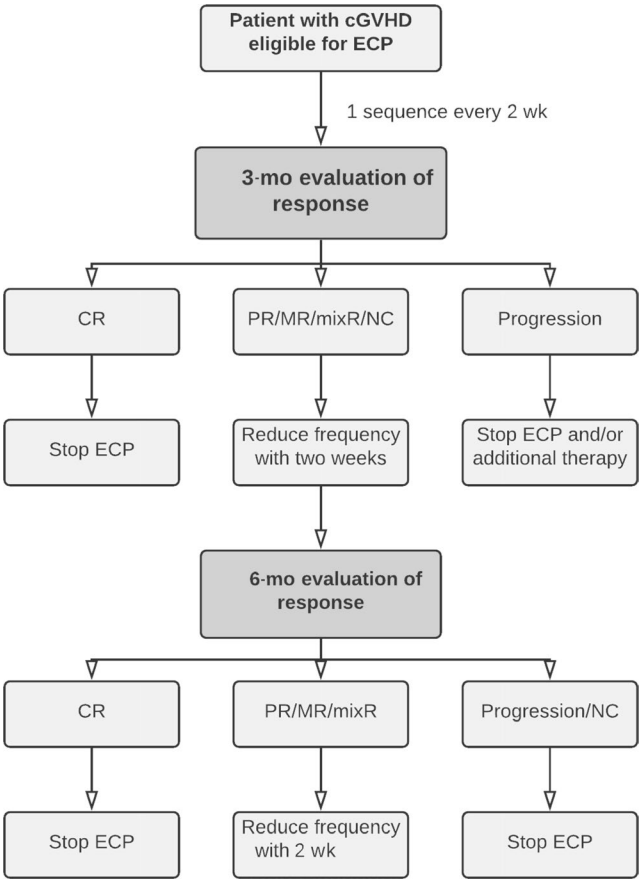

FIGURE 2 Recommendations of treatment and response assessment in chronic graft-vs-host disease. A sequence refers to two extracorporeal photopheresis treatment procedures on consecutive days. cGvHD, chronic graft-vs-host disease; CR, complete remission; ECP, extracorporeal photopheresis; mixR, mixed response; MR, minimal response; NC, no change; PR, partial remission

As ECP has proven steroid sparing, we encourage the treating physician to actively contemplate steroid tapering throughout the ECP treatment.

We recommend that reduction in immunosuppression is not done at the same time as reducing ECP.

4.3.1 | Treatment evaluation

Response evaluation should be performed every 3 months (12 weeks). The evaluation should be performed after 3 full months of treatment, for example the first evaluation before sequence 7. We recommend repeated grading of cGvHD according to NIH 2014[45] and to use the "Referral and Baseline Assessment Form for cGvHD" before starting and the "Evaluation or End-of-Treatment Form for cGvHD" (Appendix S1) at the 3-month evaluations or whenever making the decision to discontinue treatment. If ECP treatment exceeds 1 year and has long intervals between sequences, evaluation may potentially be done less frequently.

For assessment of treatment response, we recommend repeated scoring of cGvHD severity in all affected organs as defined in the NIH response criteria from 2014.[46]

Responses are defined as described below:

Complete response (CR)—no sign of active chronic GvHD without immunosuppression.

CR with residual immunosuppression (CR-IS)—no sign of active chronic GvHD with a low residual dose of immunosuppression (prednisolone <10 mg/d).

Partial response (PR)—partial organ response in accordance with the NIH criteria[47] and/or >50% reduction in dose of immunosuppressive drugs.

Minimal response (MR)—less than a partial organ response in accordance with the NIH criteria, but no signs of progression, and ability to reduce the dose of immunosuppressive drugs with at least 25%. For patients who before start of ECP had a progressive disease, a stable or unchanged cGvHD might be considered a minimal response as well as an improved Karnofsky score.

Mixed response (MixR)—decrease in organ-specific NIH score in one or more organs but with increase in another organ score or increased systemic immunosuppression.

No change (NC)—no changes in organ-specific NIH scores and no change in systemic immunosuppression.

Progressive disease (PD)—increase in organ-specific scores and/or increase in systemic immunosuppression with stable symptoms.

As steroid-dependency is a common indication for ECP, ability to reduce the dose of corticosteroids, even without major organ response, is considered to be a treatment response. In case of aggravated cGvHD after tapering or cessation, ECP treatment can be resumed.

We recommend including patient self-assessment and/or quality-of-life measures in the evaluation of treatment response concomitant to response assessment.

5 | QUALITY ASSURANCE

In order to fulfil the requirements of JACIE (C8.17), the following items are recommended:

1. The requirement for a therapy plan and an order from the transplant physician specifying the patient's diagnosis, GvHD grade, involved organs, indication and timing of the ECP could be fulfilled by the referral form.
2. The requirement for a "proposed regimen" could be fulfilled by adherence to the recommended ECP schedules for aGvHD and cGvHD in these guidelines.
3. A documented agreement between the transplant physician and the apheresis physician regarding the therapy plan is required—this could be fulfilled by both parts signing the referral form, manually or electronically.

4. Upon completion of a series of ECP, a final report should be provided to the clinical programme—this can be provided/documented in the suggested assessment form, for example number of ECP cycles and adverse reactions.

The information provided to the patient about ECP and the patient's consent to ECP treatment should be documented.

ACKNOWLEDGEMENTS

The authors want to thank the members of the Nordic ECP Quality Group for fruitful discussions and input to the guidelines: Riitta Niittyvuopio (Finland); Dag Heldal, Jörn Dehli Kristiansen, Pål Tore Bentsen and Emadoldin Feyzi (Norway); Betina Samuelsen Sørensen, Johanne Hjort Baatrup, Britt Storm Tråsdahl and Annika Rewes (Denmark); and Ulla Axdorph Nygell, Josefina Dykes, Krista Vaht, Elisabeth Ejerblad, Gabriel Afram and Torsten Eich (Sweden).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Nygaard M, Wichert S, Berlin G, Toss F. Extracorporeal photopheresis for graft-vs-host disease: A literature review and treatment guidelines proposed by the Nordic ECP Quality Group. *Eur J Haematol*. 2020;104:361–375. https://doi.org/10.1111/ejh.13381