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# Extracorporeal photopheresis in the treatment of acute and chronic graft-versus-host disease: A position statement from the Turkish Society of Apheresis (TSA)

Leylagul Kaynar [a,*], Emre Tekgunduz [b], Ilknur Kozanoglu [c], Hasan Atilla Ozkan [d], Salih Aksu [e], Fahir Ozkalemkas [f], Fatih Demirkan [g]

[a] Istanbul Medipol University Medical School, Department of Hematology and BMT, Istanbul, Turkey
[b] Memorial Bahcelievler Hospital Adult Hematology and BMT Clinic, Istanbul, Turkey
[c] Baskent University, Dr. Turgut Noyan Teaching and Medical Research Center, Apheresis Unit, Adana, Turkey
[d] Yeditepe University Faculty of Medicine, Department of Internal Medicine Division of Hematology, Istanbul, Turkey
[e] Hacettepe University, Department of Hematology, Ankara, Turkey
[f] Bursa Uludag University Medical School, Department of Internal Medicine, Division of Hematology, Bursa, Turkey
[g] Dokuz Eylul University Medical School, Department of Internal Medicine, Division of Hematology, Izmir, Turkey

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ABSTRACT

Graft versus host disease (GVHD) is still the most important cause of mortality and morbidity after allogeneic stem cell transplantation. Though perfect response rates are not achieved, steroids are still the first-line treatment. In the face of the presence of the drugs approved by FDA in recent years for acute and chronic GVHD as second-line therapy in the steroid-refractory group, there exists no standard approach.

Extracorporeal photopheresis (ECP) with an immunomodulatory effect, is favored in the treatment of both acute and chronic steroid refractory GVHD as it does not increase the risk of relapses or infections. Having a low profile of side effects, ECP is also generally well-tolerated by patients. Being a time requiring procedure, the fact is that it is not able to be practiced in all health centers and requires central venous catheters in patients unfit for venous access may be enumerated among its shortcomings.

No complete standard is available with respect to ECP application frequency-time; it varies from one center to another. The Turkish Society of Apheresis established the Turkish ECP (TECP) group and sought some answers to the questions regarding the use of ECP in the treatment of GVHD, and issued a position statement.

## 1. Introduction

ASCT (Allogeneic Stem Cell Transplantation) provides an efficacious treatment in a number of benign as well as malign hematological diseases. Graft versus host disease is one of the most important factors with an effect on the morbidity and mortality occurring in the aftermath of allogeneic stem cell transplantation and accounts for 15 % of the deaths [1].

A transplantation recipient's antigens are presented to the donor cells following the allogeneic stem cell transplantation. Upon recognition of these antigens as foreign, alloreactive cells become activated and the inflammatory cascade caused by cytokine storm results in tissue damage [2]. Whereas acute GVHD may be outlined this way, chronic GVHD occurs subsequent to a process that is somewhat more complex; following the acute inflammation, chronic changes such as fibrosis are also involved therein and mimic autoimmune diseases [3].

Much as corticosteroids are the only preferred option as the first-line therapy in treatment of both acute GVHD and chronic GVHD, a standard approach is yet to be available for second-line therapy. Second-line therapy preferences generally depend on the institutional standard operating procedures, the physician's preference and regular practice as well as availability of the treatment and patients' preferences [1,4–7].

The efficacy of ECP therapy used for the first time in treatment of cutaneous T-cell lymphoma was first demonstrated in 1990s in chronic

*Abbreviations:* aGVHD, Acute graft versus host disease; cGVHD, Chronic graft versus host disease; ECP, Extracorporeal photopheresis; ASCT, Allogeneic stem cell transplantation; TECP working group, Turkish Extracorporeal Photopheresis working group.

* Corresponding author at: Istanbul Medipol University Medical School, Department of Hematology and BMT, Istanbul, Turkey.
*E-mail address:* drleylagul@gmail.com (L. Kaynar).

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GVHD in the first place, followed by demonstration thereof in acute GVHD [8–13]. Nowadays, it is included in GVHD treatment guidelines among treatment options available for GVHD patients unresponsive to corticosteroid treatment [1,4,5,13,14].

In published studies, ECP was used especially in combination with corticosteroids and other immunosuppressive drugs in the treatment of GVHD and the treatment response was assessed according to reduction of immunosuppressives (in particular the steroid sparing effect) as well as clinical improvements achieved via the treatment.

Even though administration by combination renders the assessment of photopheresis' efficacy difficult, ECP's efficacy was reported in the literature as being in the vicinity of 70–80 % in acute and chronic GVHD [15–18]. A great many of the responses elicited were partial, nevertheless the highest rate of success was obtained in skin GVHD.

In the literature, ECP therapy has been used in the treatment of GVHD, especially in combination with corticosteroids and other immunosuppressive drugs. Although these forms of administration make it difficult to evaluate the efficacy of ECP, the treatment response to ECP has been evaluated according to the reduction of other immunosuppressives (especially steroid sparing effect) and clinical improvements [10–12,15–18].

Activating the immune response against malignant cells in cutaneous T cell lymphomas, ECP induces immunotolerance in GVHD [19]. Although the mechanism of action thereof cannot be fully revealed, it is considered to be effective with ECP immunomodulation (apoptosis induction of T lymphocytes, activated monocytes to differentiate to immature plasmacytoid dendritic cells, changes in the action and the maturation of dendritic cells, and alterations in lymphocyte subpopulations and T cell responses) [20,21]. Since no immunosuppressive effect is expected, there is no expectation of an increase in the risk of viral infections or relapses [20,21].

Despite the current data and information available, it is not yet clear as to what order the administration should be initiated in steroid refractory / dependent patient groups in order to obtain an optimal response with ECP, what the optimal administration and tapering schedule, should be combinations with other possible anti-GVHD therapies, how the treatment responses may be assessed and its place in up-front treatment.

Here the position statement of Turkish Society of Apheresis regarding extracorporeal photopheresis treatment strategies in adult patients with GVHD is reported. In addition, both basic information and data with regard to ECP as well as answers to some of the aforementioned questions are given.

## 2. Methods

A working group named the "Turkish ECP" composed of experts from the field of adult hematopoietic stem cell transplantation or therapeutic apheresis was established with a view to determining the state of use of extracorporeal photopheresis in GVHD treatment and preparing a national common guide. This group has examined and assessed the clinical trials, meta-analyses, reviews and current national and international guidelines relating to the use of ECP in treatment of GVHD.

A core group of experts prepared a draft containing the most up-to-date data on ECP in GVHD and also based on the current status of daily practice and local regulations in Turkey. This draft was extensively evaluated by all members of the working group to finalize the article/statement. The objective of this position statement was to present recommendations that would shed a light on and elucidate the frequently asked questions about the use of ECP therapy in GVHD rather than to serve as a guide.

Recommendations of the working group are given in the boxes under the relevant subject titles.

## 3. Photopheresis indications in GVHD:

### 3.1. ECP in GVHD prophylaxis:

There are few data that show the place of ECP in GVHD.

Miller et al. used ECP together with pentostatin as part of a RIC preparation regime for GVHD prophylaxis and reported very low rates of GVHD (9% grade II aGVHD and 43 % chronic GVHD with extensive in 12 % and limited in 31 %.), however subsequently this effect could not be demonstrated in animal models [22,23].

Shaughnessy et al. used ECP as a part of myeloablative regime and prior to transplantation, and they reported some decline in aGVHD rates and an advantage of survival (83 % versus 67 % relative risk 0.44; 95 % CI, 0.24–0.80, P=0.007) according to a historical control [23].

Though Kitko et al. could not reveal in a prospective phase 2 study that contribution of administration of ECP along with post-RIC allo-HSCT Etanercept, tacrolimus and MMF to the development of GVHD, encouraging rates of aGVHD (30 % in matched related donor, 40 % in unrelated donors) and survival (83 % in one year) were reported in another prospective phase 2 study comprising the use of prophylactic following RIC allo-HSCT [24,78].

There is no strong evidence to support the pre- and post-transplant use of ECP for the sake of GVHD prophylaxis.

### 3.2. ECP in first-line acute GVHD treatment:

Standard first-line treatment in patients with acute GVHD is administration of 1−2 mg/kg of prednisone. About a half of patients do not respond to this treatment or no reduction may be performed in the dose of prednisone [25]. In patients with a failed first line treatment, NRM rate is higher, whereas OS is shorter [26]. Therefore, other agents were included in corticosteroid treatment in order to improve the results of the first-line treatment, however none of them alone were demonstrated to prove superior to the steroid treatment [27–32]. In literature, there is limited evidence or there exist a small number of studies on use of ECP as a first-line therapy in treatment of aGVHD. Furthermore, these studies have a small number of patients, and they are retrospective and observational studies where a significant number of patients only have grade I aGVHD [33–35]. Thus, it will contribute to the literature to present results from studies that cover a patient profile of severe aGVHD regarding the use of ECP as a first-line therapy in treatment of aGVHD.

There is not sufficient evidence to support the addition of ECP to corticosteroid therapy or use of ECP alone in up-front GVHD treatment in patients found to have acute GVHD.

### 3.3. Treatment of steroid-resistant acute GVHD:

Upon a literature screening, we found that there are no randomized, controlled studies on efficacy of ECP in steroid-refractory acute GVHD. When we look at prospective studies, however, high rates of responses have been reported in aGVHD [15,36–42].

When reviewed in terms of organ-specific responses, the highest rate of responses were elicited in skin GVHD (n = 103, 0.84 95 %CI = 0.75−0.92), followed by the gastrointestinal (n = 45, 0.65 95 %CI = 0.52−0.78), and thereafter followed by the liver aGVHD (n = 38, 0.55 95 %CI = 0.35, 0.74) [42]. Moreover, retrospective and observational studies repeatedly support efficacy of ECP in steroid-refractory aGVHD as well although organ-specific response rates vary in the obtained data.

Currently available guidelines recommend use of ECP in general for steroid-resistant or steroid-dependent or steroid-intolerant aGVHD patients for treatment of aGVHD [1,4,5,44].

Overall, provided that there is a marked progression in aGVHD 3–5 days after the use of corticosteroids at an appropriate dose (1−2 mg/kg)

or no response can be elicited on the 5–7 t h day of the treatment, it is considered a steroid-resistant aGVHD, or if there occurs a re- activation of aGVHD in the event of inability to reduce dose of steroid or during reduction thereof, then it is considered steroid-dependent GVHD [45, 46]. Days and steroid doses indicated in these specifications may differ from one center to another. In the presence of serious toxicities such as avascular necrosis associated with steroids, a steroid intolerance is thought to be involved [44,46]. It would be appropriate to consider second-line GVHD treatment alternatives in the case of steroid resistance, steroid dependence and steroid intolerance. No criteria have been defined for addition of a new treatment or switching to another treatment modality during use of second and subsequent line treatments.

The Turkish ECP working group recommendation is that ECP therapy, as described below, may be administered to steroid-resistant, steroid-dependent and steroid-intolerant patients with grade II-IV acute GVHD in second line or subsequent lines of therapy.

1-Steroid-resistant aGVHD: Progression in GVHD after at least 3 days of 1 mg/kg dose of methyl prednisone or lack of response following a 7-day treatment, or lack of absence recovery after a 28-day steroid treatment.

2-Steroid-dependent aGVHD: aGVHD (Grade II or above) exacerbation during reduction of steroid therapy dose or before reaching 50 % of steroid starting dose.

3-Steroid-intolerant aGVHD: Intolerance of steroid at the dose required for treatment due to serious side effects.

Due to the excellent safety profile and lack of a generalized immunosuppressive efficacy of ECP, it is recommended to initiate its early use during aGVHD treatment, particularly in case of necessity of graft versus tumor effect.

The absence of of significant toxicity of ECP with other agents, the lack of reports of interactions with other agents, and the theoretical potential to synergize its immune effect constitute the basis of combination therapies.

2-year OS rates were reported as 25 % in patients with steroid-resistant stage 3 and 4 Lower GI Tract GVHD [47]. Ruxolitinib, which is the only agent approved by the FDA in 2019 for the treatment of steroid refractor aGVHD, as well as the ECP combination therapy were used in 18 patients with lower GI Tract GVHD. In this retrospective study, Modemann et al. reported a complete response at a rate of 44 % and a 2-year OS at a rate of 56 % in the poor prognostic patient group [48].

Although the results are promising, prospective and randomized studies are needed to shed light on the unknown aspects such as the algorithm, combination therapies as well as the place and efficacy of ECP, ruxolitinib and other subsequent line anti-GHVD therapies.

### 3.3.1. *ECP therapy schedule in acute GVHD:*

Although the suggested indications for the ECP indications recommended in the treatment of aGVHD are similar, the treatment schedules and treatment durations are different from each other [13,49–51]. Response rates in steroid-resistant aGVHD were reported as 86 % in the skin, 60 % in the liver, and 68 % in the GI tract in a meta-analysis evaluating prospective studies [52].

For ECP indications and therapy schedules included in guidelines published in recent years, see Table 1.

Recommendations related to ECP schedule by TECP working group in GHVD treatment are as follows.

ECP **Schedule** recommended for aGVHD treatment;

One cycle is two consecutive days of treatment.

Duration of treatment should be a minimum of 8 consecutive weeks with one cycle a week.

Treatment response should be assessed after 8 weeks;

If **CR** is achieved, tapered with 2 more administrations once every 2 weeks and then stopped.

If **PR** is achieved, it is recommended to continue with the weekly treatment and assess weekly. It should be stopped when no further response is produced.

**In case of stable disease or progressive disease or no response at all**, treatment should be stopped.

(*continued on next column*)

**Table 1**
ECP indication and therapy schedule for aGVHD treatment in current guidelines.

| Guidelines | Acute GVHD |
|---|---|
| **The UK Photopheresis Society (2017)** | **Indication:** Steroid-refractory, dependent or intolerant Grade II-IV aGvHD<br>**Schedule***:*<br>One cycle (two consecutive days) minimum for 8 weeks. 3 days per week for the first 4 weeks may be benefit at advanced stage.<br>Lower GI aGVHD often takes longer time to respond.<br>If complete response is obtained with low dose steroid (<20mg methylprednisolone), ECP treatment can be stopped without tapering after 8 weeks.<br>If there is no at least a PR after 8 weeks, consider for alternative therapy.<br>If a PR is achieved after 8 weeks but still requiring steroid doses of >20 mg/day methylprednisolone, continue with weekly cycles and weekly response evaluation and stop when no further response is received. |
| **ASFA (2019)** | **Indication**: Salvage treatment after failure of first-line therapy<br>**Schedule:** One cycle (2-3 treatments) performed weekly until disease response and then tapered to every-other-week before discontinuation. |
| **European dermatology forum (2020)** | **Indication**: aGVHD but not responding to first-line corticosteroid therapy<br>**Schedule:**<br>One cycle (2-3 treatments) every week until achieving CR and no benefit of maintenance.<br>Asses weekly |
| **Nordic ECP Quality Group (2020)** | **Indication:** *: Steroid-refractory, dependent or intolerant aGVHD*<br>**Schedule:**<br>One sequence (one treatment on two consecutive days) weekly for 4 weeks.<br>Asses the treatment response at 4-week intervals<br>**If CR is achieved:**<br>Steroid refractor aGVHD: 2 more sequences of ECP and stop<br>Steroid-dependent/intolerant aGVHD: taper ECP with 1-2 week<br>**If PR is achieved:** continue weekly ECP<br>**If no change or progressive disease:** consider additional or other treatment options. |

(*continued*)

In Lower GIS GVHDs, it may take a little longer to respond and duration of treatment may be extended.

In presence of Grade III-IV aGVHD, addition to ECP therapy of other agents that might have a faster impact should be considered.

Although there is no standardized international criterion for the evaluation of response to second and subsequent lines of treatment in aGVHD, adapted criteria in the ECP guidelines can be used [49,50].

Adapted response criteria for second-line and subsequent lines of treatment recommended by the Turkish ECP working group in treat of aGVHD:

Complete response: resolution of all manifestations related to acute GVHD.

Partial response: reduction in aGVHD stages of all pre-treatment affected organs without a newly affected organ

Progressive disease: more than 50 % less than full response in organ involvements

Stable disease: less than 50 % response in GVHD organ involvements

Progressive disease: deterioration of GVHD in any organ

### 3.4. *ECP in first-line chronic GVHD treatment:*

As in aGVHD, first-line therapy in cGVHD is steroids and approximately half of the patients will not respond [1]. We have limited data on the first line use of ECP in the treatment of cGVHD.

A recent phase 1 pilot study evaluated the efficacy of first-line ECP therapy in moderate to severe cGVHD. Sixty patients were randomized

and conventional treatment was given alone in one arm, while ECP treatment was added to conventional treatment in the other arm. Conventional treatment plus the ECP arm showed encouraging results without impairing the patients' quality of life (ORR of 74.1 % at week 28 in the conventional arm compared with 60.9 % in the Conventional + ECP arm) [53].

There is not sufficient evidence to support the addition of ECP to corticosteroid therapy or its use alone in the treatment of chronic GVHD.

### 3.5. Treatment of steroid-resistant chronic GVHD:

While there is no standard treatment approach in the treatment of steroid-resistant, dependent, and intolerant chronic GVHD patients, we have two FDA-approved agents, ruxolinitib and ibrutinib, in the treatment of cGVHD [54,55]. However, the algorithm at this stage is not clear in the guidelines in steroid-refractory cGVHD. ECP is among the second-line treatment alternatives [1,43]. However, its use with other agents, its role of other in the presence of new agents and the results of combination with them are still unclear.

There are several randomized controlled studies in the literature on the use of cGVHD in ECP. Firstly, in the phase 2 study conducted by Flowers et al., conventional treatment alone (n = 47) or ECP treatment in conventional treatment (n = 48) was applied to cases with skin GVHD that could not be controlled with standard corticosteroid treatment. In conclusion, the steroid dose-reducing effect of adding ECP to conventional therapy at the end of the 3rd month has been demonstrated [56]. ECP was applied to 29 patients in the control group who did not show adequate response and could not undergo steroid dose reduction (non-ECP), and 42 –100 % response (partial and complete) was obtained after week 24 in extracutaneous cGVHD with the highest response in oral mucosa with 70 % [57].

Apart from these, many observational, prospective and retrospective studies support the early use of cGVHD in post-steroid treatments, due to the excellent safety profile of ECP and its graft versus leukemia effect being unaffected by ECP [58–60].

However, although there are differences in the literature between the definitions of steroid resistance and dependence, the definition made by the TECP group and the recommendations for the use of ECP in cGVHD are given below.

The recommendation of the TECP working group is that ECP therapy can be administered as second-line or following lines of treatment to patients with steroid-resistant, steroid-dependent, and steroid-intolerant chronic GVHD as described below.

1-Steroid-resistant cGVHD: progression under prednisone at ≥1 mg/kg/day for 1week.

2-Steroid-dependent aGVHD: in two failed attempts made 8 weeks apart, inability to reduce prednisone dose below 0.25 mg/kg/day or stable GVHD on ≥0.5 mg/kg/day of prednisone for 1–2 months

3-Steroid-intolerant aGVHD: intolerance to the steroid at the dose required for treatment due to serious side effects.

#### 3.5.1. ECP treatment schedule in chronic GVHD:

In the treatment of cGVHD, ECP is widely used alone or in combination with other therapies. The pooled response rates in the meta-analysis of Malik et al. are 74 % in the skin, 68 % in the liver, 60 % in the eyes, 72 % in the mouth, 48 % in the lung, 53 % in the GI and 64 % in the musculoskeletal system [61].

The ECP treatment schedules used in the treatment of cGVHD in studies are different from one another and it is recommended that the treatment durations be adapted according to the responses obtained [13, 49–51]. See Table 2 for ECP indications and treatment schedules in cGVHD in current international guidelines.

ECP schedule recommendations for the treatment of GHVD by the ECP working group are given below.

**Table 2**
ECP indications and treatment schedules in cGVHD in current guidelines:

| Guidelines | Chronic GVHD |
|---|---|
| **The UK Photopheresis Society (2017)** | **Indication:** Steroid-refractory, dependent or intolerant GVHD.<br>**Schedule:**<br>One cycle (two treatments on consecutive days) every 2 weeks.<br>After completion of the initial 6 uninterrupted treatments cycles, assess to determine the further treatment.<br>If PR is achieved, taper 4 weekly treatment and continue till maximal response. |
| **ASFA (2019)** | **Indication**: Steroid-refractory or dependent extensive cGVHD<br>**Schedule**:<br>One cycle (2 treatments) weekly for 4 weeks (or consider biweekly if treating only mucocutaneous cGVHD) and then one cycle every 2 weeks or for at least 8 weeks (assess at 2-3 monthly intervals), continue to maximum response every 2-4 weeks with taper. |
| **European dermatology forum (2020)** | **Indication: S**econd-line therapy in patients with steroid-dependent, intolerant or resistant cGvHD and recurrent infections or a high risk of relapse of their underlying disease.<br>**Schedule:**<br>One cycle (two treatments) weekly for the first 3 months (or until GVHD stabilizes) followed by one cycle twice per month and then tapered depending on clinical response.<br>The time schedule is largely dependent on the severity of cGVHD and the response. |
| **Nordic ECP Quality Group (2020)** | **Indication:** Steroid-refractory, dependent or intolerant cGVHD<br>**Schedule:**<br>One sequence (two consecutive days) every second week for the first 12 weeks.<br>Asses the treatment response every 3 months.<br>**If CR is achieved:** Stop ECP<br>**If progressive disease:** Stop ECP and/or additional therapy<br>For the other responses (partial, minimal, mixed or no change): reduce frequency to every 4 weeks. |

ECP **Schedule** recommended by the TECP working group in cGVHD treatment:

One cycle is two consecutive days of treatment.

One cycle weekly (biweekly if treating only mucocutaneous cGVHD) for the first 2−3 months followed by one cycle twice per month for 2 months and then tapered depending on clinical response.

Assesses the treatment response every 2−3 months.

If response is CR, stop ECP,

If response is PR, continue until you achieve the maximum response.

If treatment response is progressive, mixed or stable disease, stop treatment or include additional agents to treatment.

## 4. Technical considerations on ECP:

The ECP is a leukapheresis-based therapy. The leukocyte-rich buffy coat collected from the patient by centrifugal separation is exposed to the photosensitizing agent 8-methoxypsoralen (8-MOP) ex vivo. Immediately thereafter, the product is illuminated with ultraviolet A (UVA; 352 nm wavelength) light and infused into the patient. This process can be carried out by two different methods, these being offline and inline. In the inline method, all steps are performed in a closed system in approximately 1.5−2 hours. In the offline method, the leukoapheresis, illumination and re-infusion of buffy coat steps are performed separately and last for 3−4 hours [19].

With the new generation devices used offline, better lymphocyte collection efficiency can be achieved in a shorter time [61].

While it was performed by the inline method in a shorter processing

time, a higher mononuclear cell ratio was detected in the obtained product, but no difference could be shown between the two methods in terms of GVHD response [62,63].

Although both methods are available in Turkey, centers mainly prefer the offline method due to its cost advantage.

Initially, 8-MOP, which was given orally to the patient before the procedure, was replaced over time by the pre-UVA application of 8-MOP to the buffy coat that was collected. Thus, 8-MOP is given only to the product to be irradiated, instead of the whole body, and 0.25 % of the orally administered dose is used. Thus, gastrointestinal side effects that may be caused by oral 8-MOP are prevented and the posttreatment risk from photosensitization caused by photosensitization is decreased [19,64].

While the UV-A dose used in the inline method is 1.2 j/cm$^2$, it is 2 j/cm$^2$ in the offline method [61]. The irritation time is automatically adjusted according to the volume of the product to be irritated by the illumination device used, the hematocrit (which determines the optical density) and the residual luminosity of the UVA lamp [19].

Centers may prefer the offline or inline method according to their own experience or preferences.

## 5. Quality management of ECP:

Centers with ECP should provide quality management of the process and should prepare standard operating procedures and training programs related to the process. It should perform the validation of the device and procedures used in the process [65].

The Italian group recommends using a functional test that demonstrates apoptosis of lymphocytes to validate the ECP process. They recommend that this test be performed during the two procedures in the first cycle in each patient unless there is a change in any equipment, drug, disposable set, machine used during the ECP procedure.

Validation of the procedure is done by evaluating apoptotic lymphocytes (which are 7-aminoactinomycin (7-AAD)-positive CD3+cells) by flowcytometry 72−96 hours after the completion of the procedure [66].

There are no cut-off values determined for the amount of cells to be photoactivated and the rate of apoptotic cells.

Centers should provide quality management in accordance with national and international guidelines.

## 6. Vascular access:

In order for the leukopheresis to be performed effectively, it is necessary to provide a good vascular access to effectively provide extracorporeal circulation [67]. A blood flow of 50-100 mL/minute is needed for apheresis devices working with the centrifuge method [68]. With this blood flow rate, the processing of 1.5 blood volumes in an average individual is completed in 2−3 hours. The peripheral vein can provide blood flow up to 60−80 ml/min., and this flow can be reached from the peripheral venous inlet with 2 large 16–18 gauge needles [69,70]. Therefore, if the patient's peripheral veins are suitable, this can be preferred primarily [68,70].

However, at least 11.5-French central venous catheters can be used in cases where there is no appropriate peripheral venous access due to reasons such as skin GVHD in the arms [71]. The Nordic ECP Quality Group recommends dialysis catheters with a width of 10−13Fr [50]. While temporary central venous catheters can be used for short-term apheresis procedures, tunneled catheters can be preferred in order to minimize the risk of infection, since ECP therapy is a repetitive and long-term treatment extending from weeks to months [72].

Most of the serious apheresis complications are related to catheters and these include infection, bleeding, pneumothorax, and catheter-related thrombosis [73]. Similarly, local hematoma, phlebitis and scarring may occur due to recurrent venous punctures.

If the peripheral blood veins of patients not currently having a central venous catheter are suitable, then their antecubital veins should be preferred, or else tunneled dialysis catheters fit for the procedure of apheresis should be inserted.

## 7. Safety:

Regardless of the method used, ECP has an excellent safety profile with minimal side effects without causing generalized immunosuppression and without interfering the graft versus leukemia effect, and World Health Organization grade III–IV side-effects have not been reported [74]. No increased risk of ECP-related disease relapse or opportunistic infection has been reported [75].

Especially in patients who do not need a central venous catheter, the complication rate is very low and they are usually manageable apheresis complications such as hypotension and mild complications such as mild anemia and mild thrombocytopenia [73–75].

See "Vascular Access" section for side effects related to venous access.

Due to increased photosensitivity, it is recommended that patients take protective measures against UVA rays for the skin and eyes for 24−48 hours after the procedure [62].

## 8. Patient groups to be carefully considered for ECP:

ECP is considered to be contraindicated in patients with susceptibility to psoralen products, known photosensitivity, aphakia (increased risk of retinal damage), pregnancy, hemodynamic instability, respiratory instability, low white blood cell counts ($<1 \times 10^9$/L despite G-CSF injection), low platelet counts ($<20 \times 10^9$ /L despite platelet transfusion support), uncontrolled infection and active bleeding [4,50,76,77].

However, in patients with low blood values (low hematocrit, platelet and leucocyte count), as well as in patients with low body weight, apheresis should be performed after taking necessary precautions [4,50,76,77].

## 9. Conclusion:

Although ASCT is still the only curative treatment method for many diseases, GVHD is still the most important cause of morbidity and mortality. Especially in the treatment of steroid refractory GVHD, two FDA-approved agents, ruxolitinib and ibrutinib, have been widely used in recent years. However, there is still no complete standardization in the guidelines for the treatment of steroid refractory GHVD.

ECP, which is still one of the important options in the guidelines of the related art, is a procedure that requires experience and cannot be performed in every center, making the accessibility of the procedure difficult. Cost is another issue that needs to be taken into account, as it is a repetitive and long-term treatment. Despite all this, the procedure continues to be a widely preferred treatment method in the treatment of steroid-resistant GVHD, although its ideal place and role in the treatment has not been fully determined, due to the good response rates, immunregulatuar effecacy without generalized immunosuppression, no increased risk of infection and relapse, and the absence of the risk of serious complications. Randomized, prospective, multicenter studies using common definitions, grading and response criteria are needed to eliminate existing question marks.

## Conflict of interest statement:

All authors declare that they do not have any potential conflict of interest that could inappropriately influence this manuscript.

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