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European Guidelines (S1) on the Use of Extracorporeal Photopheresis – Update 2020

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Updated Guidelines on the Use of Extracorporeal Photopheresis 2020

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I. INTRODUCTION

Extracorporeal photopheresis (ECP, also known as extracorporeal photochemotherapy, extracorporeal photoimmunotherapy, or just photopheresis) is a leukapheresis-based therapy that is available at more than 200 centres worldwide.(1, 2) During ECP, the patient's whole blood is processed outside the body: blood is collected via an antecubital vein, or a permanent catheter if vein access is cumbersome; white blood cells are then separated from red blood cells and plasma by centrifugation in a device that is specially constructed for this procedure. White blood cells are exposed to ultraviolet A (UVA) light in a separate plastic chamber and then returned to the patient.(3) In the past, patients treated with ECP were given oral 8-methoxypsoralen (8-MOP; methoxsalen) before the blood was leukapheresed.(1) Thus, during the ECP treatment, patients typically experienced untoward gastrointestinal effects such as nausea and vomiting, or the visual side effects of psoralen. Moreover, differences in gastrointestinal absorption due to individual variability resulted in unpredictable blood concentrations of 8-MOP.(1, 4) To avoid the problems of oral 8-MOP administration, a liquid formulation of 8-MOP (UVADEX®, Therakos®) that is added directly to the buffy-coat/blood fraction was developed. This method of dosing circumvents the potential side effects of systemic 8-MOP administration and eliminates the need to measure for target blood levels.(5)

The first investigational study of ECP in patients with cutaneous T-cell lymphoma (CTCL) was completed in 1983. The first ECP apparatus that was approved by the United States Food and Drug Administration in 1988 was a closed system (UVAR®; Therakos®). National approvals in Europe and elsewhere followed. Although ECP was initially developed for use in CTCL patients, it has also shown promising efficacy in a number of other severe and difficult-to-treat clinical conditions such as graft-*versus*-host disease (GvHD), Crohn's disease, systemic sclerosis and for the prevention and treatment of rejection in solid organ transplantation, particularly in the areas of lung and heart transplantation.(6)

Several closed and open ECP apparatuses are currently available for clinical use and are compared in Table 1.(7) Their clinical efficacy in the treatment of a variety of T-cell mediated diseases is well established. However, the two techniques have not been directly compared in a clinical setting. In a closed ECP apparatus (one-step method), the blood cell separation, drug photoactivation, and reinfusion stages are fully integrated and automated, and all elements are approved for their combined use, including methoxsalen, a photoactivating agent (Table 2). There is no risk of improper re-infusion when used according to the labelling, and the risk of infection and contamination associated with the medical device itself is very low.

From a technical aspect, an open apparatus is any disconnected process using a cell separator in combination with a lightbox and a drug. Although the individual components may be Communauté Européenne (CE) marked, they are not explicitly approved for use together in the process of photopheresis. To obtain proper CE marking for photopheresis use, all the components of an apparatus must undergo a validation process prior to being used together in controlled clinical trials and routine therapy. This technology falls under the regulations of cell therapy according to the federal agency *L'Agence Nationale de Sécurité du Médicament* (ANSM) in France.(8) Open apparatuses can only be used by centres that are certified for cell therapy. To obtain the certificate, ANSM requires the filing of a record of authorisation describing the entire ECP procedure, including the drug and material to be used, transport, quality controls, traceability, the structure of cell manipulation and much more. Closed apparatuses do not have these restrictions. A closed apparatus is a one-step method (UVAR-XTS® and CELLEX®; Therakos®). Critical steps, such as cell separation, drug photoactivation, and reinfusion, are fully integrated and automated processes. All the components are validated for their combined use, including the use with 8-methoxypsoralen Table 2. Components of closed ECP apparatuses are approved and certified as one functional unit, which may be operated by a single trained person.

One of the critical elements of both open and closed ECP apparatuses is the photoactivation chamber. Closed photopheresis apparatuses are equipped with

a microprocessor that allows for a dynamic recirculation of photoactivated cells. All photoactivation elements have a fixed thickness and are tested by UV spectrophotometry to ensure the retention of photodynamic properties (optimal UV transmittance). Adsorption of 8-methoxypsoralen to the disposable plastic kit is measured and compensated for to ensure proper dosing. Components that are used in open ECP apparatuses are not designed or manufactured for the process of photopheresis, and, therefore, need to be certified prior to their use.

Inconsistent light exposure to targeted cells because of non-validated plastic films, variation in the fluidity of the solution in the treatment bag, unknown or variable drug adsorption onto plastic components, or stasis of the cells during UVA irradiation could cause partial DNA damage to the cells.

Regardless of the apparatus used, ECP is usually well-tolerated. There are no reports of grade III-IV side effects (as rated by the World Health Organisation (WHO)) following treatment. Transient hypotension or mild anaemia (after multiple treatments) may occur, and thrombocytopenia has also been reported. ECP should not be used as a therapy in patients with a known sensitivity to psoralen compounds such as methoxsalen, or comorbidities, including photosensitivity, a history of heparin-induced thrombocytopenia, cardio-circulatory failure, or a low haematocrit. It is also contraindicated in pregnancy. Methoxsalen containing ready-to-use sterile solutions are contraindicated in patients with aphakia because of the significantly increased risk of retinal damage. In patients with low body weight, children, and those with problematic venous access, implantable venous access devices with a proper blood flow per minute should be used. In this regard, peripheral venous catheters appear to be advantageous over central venous devices.(9)

Ideally, ECP should be initiated as soon as clinically indicated, which in most cases is as a second-line therapy when other first-line therapies have failed. In general, currently, many centres in Europe perform ECP treatment as inpatient therapy. Monitoring of efficacy before and during ECP treatment should be based on the standards of care for each indication. The use of either heparin or acid citrate dextrose as anticoagulation during ECP depends on the preference

of different centres. While the use of UVA protective glassware is recommended during PUVA in combination with oral methoxsalen, it may be unnecessary during ECP therapy due to the very low doses of psoralen used.

II. MODE OF ACTION

Although ECP has been in clinical use for more than thirty-five years, its mode of action remains elusive. Current doses and treatment intervals remain almost identical to regimens used in the 1980s. Early studies indicated that ECP induced lymphocyte apoptosis contributed to the therapeutic effect.(10, 11) More recent studies have shown that the mechanism of action of ECP is primarily due to an immunomodulatory effect. The principal mechanisms of action comprise of the modulation of dendritic cells, alteration of the cytokine profiles, and induction of particular T-cell subpopulations.(12, 13) ECP, like psoralen plus UVA (PUVA), induces psoralen-mediated DNA crosslinks that cause apoptosis in lymphoid cells, particularly in natural killer (NK) cells and T-cells.(14)

However, the therapeutic effect of ECP in Sézary syndrome (SS) cannot be explained by the depletion of malignant cells, as only a relatively low proportion of the entire lymphocyte pool is treated in a photopheresis cycle. Monocytes, which appear to be more resistant to apoptosis, undergo a differentiation process within two days, and express surface markers such as CD83, X-11, α-V, beta- V, or CD1a that are characteristic of immature dendritic cells.(15-17) This differentiation process appears to be independent of the psoralen-induced photoactivation and is mostly driven by direct contact of the cells with plastic and other synthetic materials during the passage through the ECP apparatus. Apoptotic lymphocytes are phagocytosed and eliminated by immature dendritic cells, which subsequently undergo maturation and present antigenic peptides — a process that has been designated transimmunisation.(18) Thus, it has been suggested that transimmunisation may induce an immune response against lymphoma cells, which might explain the beneficial effects of ECP observed in the therapy of SS.

The ECP-initiated cellular mechanisms of differentiation are associated with the release of a variety of cytokines including tumour necrosis factor (TNF) and interleukin (IL)-6, which induce the activation of CD36-positive macrophages.(19)

Long-term, beneficial immunologic alterations can be gained through the use of continuous ECP. The severity of CTCL is directly related to the imbalance of the ratio of T-helper cells 1 to T-helper cells 2 (Th1/Th2), which leads to the increased release of IL-4 and IL-5, the reduced activity of NK cells, and the diminished cytotoxic activity of CD8-positive T-cells. In a study performed in patients with early-stage CTCL (stage IB) undergoing ECP therapy for one year, Di Renzo et al. observed not only an increase in CD36-positive monocytes in the blood but also a change in the cytokine reaction profile of peripheral blood lymphocytes upon stimulation with phytohaemagglutinin.(20) Both observations imply that ECP reverses the pathologic shift towards a Th2 immune response and restores the Th1/Th2 balance in CTCL patients. Also, anti-inflammatory cytokines appear to be induced by ECP, whereas blood levels of pro-inflammatory cytokines are lowered.(21)

In relation to neutrophils, these also undergo apoptosis resulting in mobilisation of neutrophilic myeloid-derived suppressor cells (MDSC) into the circulation which can dampen Th1 and Th17 responses.(22)

Over the last two decades, ECP has been shown to be beneficial in patients with CTCL, GvHD, transplant rejection, and various autoimmune diseases. The findings mentioned above, however, cannot explain the effects of ECP in these patients, and because these conditions respond to immunosuppressive therapies, it was surmised that ECP might also exert immunosuppressive effects. Furthermore, in patients with GvHD, ECP was shown to induce IL-10 via the modulation of arginine metabolism.(23) In contrast to classic immunosuppressive therapy, ECP is not associated with significant side effects such as opportunistic infections. It has been postulated that the therapeutic effect of ECP is due to the induction of regulatory T (T-reg) cells, without causing general immunosuppression. Using a murine contact hypersensitivity model, Maeda et al. demonstrated that T-reg cells could be induced

successfully by an ECP-like procedure (intravenous injection of leukocytes exposed to 8-MOP and UVA *in vitro*).(24) T-reg cells induced by the combination of 8-MOP and UVA express CD4, CD25, CTLA-4, and the transcription factor Foxp3, similar to T-reg cells induced by UVB. Foxp3 suppresses the activity of other lymphocytes.(25) Furthermore, the release of IL-10 appears to be involved in this process.(26) The levels of serum B-cell activating factor (BAFF) were measured in a recent study of forty-six patients with chronic GvHD (cGvHD). Serum levels of BAFF determined at one month after the start of ECP therapy were predictive of the three-month and six-month skin responses. Serum levels of BAFF lower than 4 ng/ml were associated with a significant improvement of the skin.(27) In addition, monocytes showed immunoregulatory capacity on CD4+ T cells in a human in-vitro model of ECP. Reduced proliferation rates of T cells after co-culture with ECP-treated monocytes was dependent on cell-contact between monocytes and T cells.(28) Also, there is evidence that infusion of lymphocytes treated with 8-MOP and UVA light induces CD19+IL-10+ regulatory B cells and thereby promotes skin allograft survival.(29)

The manifestation of acute GvHD (aGvHD) in patients with allogeneic grafts was associated with a low number of T-reg cells.(30, 31) Hence, several research groups have studied the effects of ECP on counts of T-reg cells. In a model of murine GvHD, regulatory T-cells were shown to be induced by ECP.(32) In the majority of CTCL and GvHD patients, an increase in T-reg cells was observed after ECP therapy. Also, T-reg cells showed an enhanced immunosuppressive activity.(33-38) These findings could explain, at least in part, the beneficial effects of ECP detected in GvHD and autoimmune diseases. In patients with SS, however, reduced counts of T-reg cells have been reported, and their suppressive activity appears to be impaired.(36, 39, 40) These observations have led to the notion that T-reg cells could exert a suppressive impact on CD4-positive tumour cells in patients with SS.

ECP slightly increases or stabilises counts of peripheral CD4+CD25+FoxP3+ T-reg cells in lung transplant recipients.(41) Overall, the reinfusion of ECP-treated leukocytes induced suppression of the humoral and cellular immune

responses, and thereby improved and extended the tolerance and survival of transplanted tissues and organs. The mechanism by which ECP counteracts cardiac transplant rejection was studied using a murine model of ECP.(41) Splenocytes exposed to the combination of 8-MOP and UVA were injected into syngeneic mice before and after heterotopic cardiac allograft transplantation. None of the mice received immunosuppressive agents. The treatment group showed extended cardiac allograft survival and increased counts of FoxP3-expressing CD4+CD25+ T-cells when compared to controls. The authors concluded that the murine model of ECP extends graft survival in fully histoincompatible strain combinations with no immunosuppressive agent added.(41)

In Crohn's disease, reinfusion of ECP-treated apoptotic leukocytes to the patient is hypothesised to induce a tolerogenic response via T-reg cells. Indeed, recirculation of DNA-adduct-positive cells to the intestinal mucosa has been described following ECP.(26, 42) Murine models of inflammatory bowel disease have provided information on the potential therapeutic role of T-reg cells in overcoming inflammation in the intestine in humans.(43)

The effects of ECP on the immune system were studied in a randomised, double-blind, placebo-controlled trial in children with type 1 diabetes.(44) No significant effects of ECP on lymphocyte populations were observed. However, in the placebo group, the proportions of activated CD4+ (T-helper cells) and CD8+ cells increased over time, whereas such changes were not seen in the ECP-treated group. These findings probably reflect the activation of lymphocytes as a part of the natural course of type 1 diabetes and suggest that ECP may exert immunosuppressive effects by preventing lymphocyte activation.(45, 46) Patients treated with placebo showed reduced T-reg cell-associated activity, which seems to be counteracted by ECP because ECP treated patients showed preserved T-reg cell activity. These data indicate that ECP may help maintain T-reg cell-associated activity in recent-onset type 1 diabetes.(47)

Although distinct aspects of the mode of ECP action, such as the induction of T-reg-cells, are well understood today, we are still far from a complete

understanding of how ECP works. Animal models help us to optimise currently used treatment regimens with respect to the number of cycles, concentrations of 8-MOP, doses of UVA, and the number of cells treated in one clinical setting. Also, an enhanced understanding of the mechanism of action will finally enable ECP therapy to be directed towards those patients who will most benefit from it.

III. METHODS

The present updated guidelines on the use of ECP were developed based on best medical practices, web review of relevant medical databases and literature, and collected expert opinions on the appropriate use of ECP.

In general, ECP is employed for the therapy of severe refractory disease courses or in situations in which other treatments have failed. However, ECP availability is limited, and evidence for its efficacy is derived from retrospective data, and small cohort or case-controlled studies. There is a lack of randomised, controlled clinical trials in the literature. Double-blind trials are challenging to perform and using sham photopheresis may be unethical for patients with severe diseases.

The present guidelines were drawn up to display the indications for which ECP is currently considered useful, as well as other indications where studies have shown promising results. For the main indications of ECP, namely CTCL and GvHD, the recommendations were developed by peers and leaders in the respective diseases. For minor indications, members of expert committees collaborated to examine all available evidence and to make appropriate recommendations. The aim was to answer clinical questions as follows:

- What are the potential indications for the treatment with ECP?
- Are there currently any guidelines/consensus statements on the use of ECP in this indication?
- Which patients should be considered for ECP treatment?

- What is the optimal treatment schedule, and how long should ECP treatment be continued?
- How can therapeutic efficacy be assessed?

For these recommendations, the individual experts in their area of expertise were consulted for their written contribution by email. In addition, individual co-authors were personally contacted during meetings (St. Gallen, Switzerland, January 26, 2018; Lisbon, Portugal, March 19, 2018; Vienna, Austria, March 22, 2018; Orlando, USA, May 17, 2018; Paris, France, September 15, 2018; St. Gallen, Switzerland, September 28, 2018; Montreux, Switzerland, January 25, 2019) or by email if a meeting in person was not feasible. The document was circulated among all members of the Guidelines Subcommittee before it was submitted to the Guidelines Committee for final approval according to the standard operating procedures of the European Dermatology Forum (EDF).

IV. CUTANEOUS T-CELL LYMPHOMA

CTCL describes a heterogeneous group of rare lymphoproliferative disorders that are characterised by the accumulation of malignant T-cell clones that are localised to the skin.(48) The most common variants are mycosis fungoides (MF), which accounts for about 60% of CTCL cases, and Sézary syndrome (SS), which accounts for 5% of cases. MF is characterised by the presence of a clonal T-cell population in the cutaneous environment and, in the early stages of the disease, presents as scaly patches or plaques, which may resemble eczema or psoriasis in appearance and are often associated with pruritus. As the disease progresses, patients may experience the growth of nodular lesions and large tumours, also with severe pruritus, which may ulcerate and result in chronic septicaemia, thrombosis, and pain.

SS is the "leukaemic" form of CTCL, in which the dominant T-cell population also circulates in the peripheral blood and may affect internal organs such as the lungs and spleen. MF/SS is classified into clinical stages from IA (the earliest stage) to IVB according to the degree of skin, lymph node, peripheral blood, and visceral organ involvement.(49, 50)

Curative therapies are not available, and treatment is usually directed towards palliation and the induction of long-term remissions. The aim is to reduce or clear skin lesions, including tumours, and reduce pruritus, thereby providing symptom relief and improving patient quality of life.(48) In the early stages of MF, treatment usually involves skin-directed therapies such as topical corticosteroids, topical chemotherapy (nitrogen mustard or bis-chloronitrosourea), or phototherapy (narrow-band UVB or PUVA). Systemic therapies, including chemotherapy and biological response modifiers (interferon [IFN]-α, bexarotene), brentuximab vedotin or mogamulizumab, are used if the disease progresses or for those who present with more advanced-stage disease, often in combination with skin-directed therapies.(51)

PUVA, in which patients take an oral formulation of 8-MOP to induce photoactivation followed by exposure of their skin to UVA radiation, is a widely used and effective skin-directed therapy for early-stage, skin-localised CTCL, which can produce relatively long-lasting remissions.(51) It is, however, associated with the short-term side effects of oral psoralen intake and possible long-term complications such as photosensitivity and the potential for the development of skin cancer.(4) ECP has enabled the safety profile of PUVA to be improved, avoiding the potential complications associated with long-term skin exposure to UVA. Thus, the benefits of ECP therapy can be extended to patient populations with more advanced disease stages, including those patients with malignant clones in the peripheral blood.(4) Many studies have demonstrated that ECP is of significant value for the treatment of CTCL.(52)

However, due to the low prevalence of CTCL and the fact that ECP therapy is only available in specialised centres, there are no prospective, placebo-controlled, randomised clinical trials that evaluate the impact of ECP treatment on survival available in the literature. Thus, comparisons are usually made with historical controls. The initial ECP study in patients with CTCL resistant to other treatments was reported by Edelson et al. in 1987 and showed it to be a promising therapy.(2) Among thirty-seven patients, twenty-seven (73%) responded to treatment, with an average decrease of 64% in cutaneous involvement; nine of these patients had a complete response (CR). Data from

this study have recently been reanalysed using currently accepted international criteria. The skin overall response rate was 74%; 33% of patients were achieving ≥50% partial skin response, and 41% of patients were achieving ≥90% improvement.(53) An update on the overall survival (OS) of these patients was also provided. Overall survival times were 9.2 years and 6.6 years from disease onset and initiation of ECP, respectively.

Since 1987, numerous studies employing ECP have been conducted. A meta-analysis of nineteen studies covering more than 400 patients at all stages of CTCL reported a combined overall response (OR) rate of 56% for ECP monotherapy and 56% when used in combination with other agents, and a CR rate of 15% and 18%, respectively.(54) For erythrodermic disease, the OR rate was 58%, and the CR rate was 15%. Importantly, ECP was effective in SS, showing an OR rate of 43%, with a CR rate of 10%. Table 3, adapted from the UK consensus statement on the use of ECP for the treatment of CTCL and GvHD, provides a summary of the published response rates with ECP in the treatment of CTCL from 1987 to 2011.(55) Based on the thirty separate studies in 689 patients published from 1987 to mid-2007 that were analysed in the UK consensus statement, the mean OR rate in the studies was 63% (range 33%-100%), and response rates were generally higher among patients with erythrodermic CTCL.(55) The CR rates, where recorded, ranged from 0% to 62% (mean 20%). More recent studies published from late 2007 to 2011 report OR rates ranging from 42% to 80%, with CR rates ranging from 0% to 30%.(56-62)

ECP is beneficial in the treatment of CTCL.(52) However, it is also apparent that there are considerable differences in response rates between centres. Differences in the selection of patients, stage of the disease, prior treatments, treatment schedule of ECP, and the definition of response used might explain the large variability in the study results.(55) Similar considerations apply to studies reporting on survival rates of patients with CTCL treated with ECP. Variable median survival data have been reported for SS, ranging from 30 to 60 months. Much longer median survival times for CTCL patients treated with ECP have been reported, but not all patients in these studies had the

erythrodermic disease, or they had received other therapies in combination.(63-66)

In most case series, ECP was used as monotherapy or in conjunction with other treatments. Such combination therapies have been investigated to further improve response rates, particularly in patients with a high tumour burden. Raphael et al. published the most extensive case series of CTCL patients treated with ECP.(61) The group reported on their twenty-five-year experience from a total of ninety-eight erythrodermic CTCL patients treated with ECP for a minimum of three months. A significant clinical improvement was obtained in 75% of patients with a multimodality therapy; 30% achieved CR. Previously, Suchin et al. reported on forty-seven patients who had received at least six cycles of ECP. In these patients, stage III or IV CTCL was diagnosed in 68%, and malignant T-cells were detected in the blood of 89%.(67) Thirty-one patients received treatment with ECP plus other drugs, including IFN-α, IFN-ɣ, granulocyte-macrophage colony-stimulating factor (GM-CSF; sargramostim) or systemic retinoids for three months at least. Overall, 79% of the patients responded well to therapy; 26% were achieving CR. Among patients receiving combination therapy, 84% responded well to therapy, and 20% were attaining CR; the OR rate with ECP monotherapy was 74% (CR rate was 38%). The median survival times were seventy-four months for the combination therapy and sixty-six months for ECP monotherapy; the difference was not statistically significant.

A prospective observational study of forty-eight patients with erythrodermic CTCL (thirty-six with SS) reported a response rate of 58% for ECP alone, compared with 64% for combination therapy in patients with more adverse prognostic factors.(62) Similarly, Duvic et al. reported on a slightly higher response rate among thirty-two patients treated with ECP in combination with IFN-α, bexarotene, or GM-CSF compared with 54% for ECP monotherapy.(68) A number of other studies with ECP plus IFN-α have been published that report an increased response rate compared with ECP monotherapy.(65, 69) However, none of these studies was controlled or randomised, making it difficult

to assess how much of the clinical benefit is due to IFN-α and ECP and what the magnitude of potential synergistic effects is.

In the USCLC review of the thirty-four patients presenting with SS treated with ECP, IFN, and bexarotene, thirty patients (88.2%) responded to the combined therapy, including eleven patients with CR (32.4%).(70) Bexarotene oral dosages ranged from 75 to 450 mg per day. Subcutaneous dosages of IFN-α and IFN-γ ranged from 1.5 to 6 MU given three times a week and 40 to 100 µg given five times a week, respectively.

A total of 97 CTCL patients included in five UK sites (2010-2015) were investigated.(71) Patients tended to be treated early in the course of their disease (median time from diagnosis of CTCL to ECP therapy was 4.6 months). In 45.4% of cases, ECP was used as first-line systemic therapy. Most patients had advanced disease stage IIIA-IVA2 at the start of treatment, but three had early-stage MF (treated for 2, 34 and 148 cycles, respectively). The intention to treat response rate at six months was 61.2% (60/97 patients). The median duration of ECP therapy was nine months (range 1-118 months), and the median number of treatments was 16 cycles (range 1-148). Most patients (72%) were receiving concurrent systemic therapy at the start of treatment. The authors concluded that distinct long term responders might have improved survival. However, these results may be confounded by other prognostic factors.

ECP has also been used in combination with total skin electron beam (TSEB) therapy. A retrospective study of forty-four patients with erythrodermic MF/SS treated with TSEB with or without ECP reported an overall CR rate of 73%; the three-year disease-free survival rate was 63%.(72) Among those patients who were receiving TSEB plus ECP, the three-year disease-free survival rate was 81% compared to 49% for TSEB monotherapy. Based on these data, further studies using the combination of TSEB and ECP are warranted.

Most of the studies with ECP in CTCL have primarily included patients with advanced stages of the disease. Recent guidelines recommend ECP as first- or second-line therapy for erythrodermic MF and SS.(51, 55, 73-76) Its use in

early stages of CTCL is controversial but warrants further investigation. A literature review of data from sixteen studies with ECP or ECP plus adjuvant therapy performed between 1987 and 2007 included a total of 124 patients with early-stage CTCL (stage IA, IB, IIA). This study revealed that response rates ranged from 33% to 88% for ECP monotherapy and 50%-60% for ECP plus adjuvant therapy.(77) Furthermore, many early-stage patients treated with ECP achieved long-lasting regression of the disease. In a recent prospective clinical trial, 19 patients with early-stage MF were treated with one ECP cycle every four weeks for six months.(60) Patients with a partial response (PR) continued with ECP monotherapy for another six months, whereas non-responders were allowed to receive additional therapy with oral bexarotene and/or IFN-α. The OR rate for ECP monotherapy was 42% (8/19, including 1 CR; 7 PRs), with an overall duration of response of 6.5 months (range 1-48). Seven patients with stable disease at three months received additional bexarotene and/or IFN-α, and four of these patients (57%) responded to therapy. For all 19 patients, the OR rate was 63% (2 CRs, 10 PRs). Most guidelines do not indicate the use of ECP in early-stage disease, but the National Comprehensive Cancer Network (NCCN) Guidelines recommend ECP in patients with stage IA, IB, and IIA refractory disease.(76)

In summary, ECP administered as monotherapy or in combination with other immunotherapies can be alternative treatment options that have proven effective and might beneficially impact survival rates in patients with advanced CTCL, i.e., a patient population who is typically resistant to conventional treatments and, therefore, shows poor prognosis. Given the favourable side effect profile of ECP compared with other therapies and its demonstrated efficacy in late-stage CTCL, this treatment modality might also be useful in earlier stages of the disease as recently suggested by Talpur et al. and others.(52, 60) However, there is substantial intersubject variability in response to ECP therapy in CTCL disease. Therefore, attempts have been made to characterise and identify those patients who are most likely to respond to therapy.

Baseline predictors of response to photopheresis have recently been summarised (see Table 4).(78) Although these criteria are useful in identifying responders to ECP, these criteria consistently need to be adapted and improved.(79) A critical factor for the success of ECP therapy is that the patient's immune system must be capable of responding appropriately to malignant cells that have undergone photoactivation.(80, 81)

Existing clinical guidelines

Several professional organisations have set up guidelines on the management of CTCL and the use of ECP. In 2006, the European Organisation for Research and Treatment of Cancer (EORTC) recommended ECP for the first-line treatment of SS and MF stage III with a C-strength of recommendation (on a scale from A to D).(51, 73) In MF, the level of evidence was rated 4 (evidence from case series, poor-quality cohort or case-control studies), and in SS, 2b (evidence from individual cohort study or poor-quality, randomised, controlled trial). Although not recommended by EORTC, it was mentioned that ECP treatment is usually performed on two consecutive days at four-week intervals, continued for up to six months, and followed by maintenance therapy.

The UK Photopheresis Expert Group consensus statement recommends ECP for the treatment of patients with CTCL if they fulfill the criteria of erythroderma and stage III or stage IVA CTCL and at least one of the minor criteria, which are: i) circulating clonal disease (circulating T-cell clone proven by polymerase chain reaction or Southern blot analysis), ii) evidence of circulating Sézary cells (>10% of circulating lymphocytes), and iii) a CD4/CD8 ratio higher than 10.(55) The recommended ECP treatment schedule is one cycle on two consecutive days every 2 to 4 weeks. It may be administered more frequently in symptomatic patients and those with a high blood tumour burden. At the maximum clinical response, ECP treatment should be tapered to one cycle every 6 to 12 weeks before it is completely stopped. However, in a very recent update from 2017, the UK Photopheresis Expert Group revised its recommendations and suggested continuing with ECP treatment in patients with complete, partial, or minimal clinical response.(82) This revised recommendation is in keeping with other treatments for advanced MF/SS,

which should be continued as long as a clinical benefit is detectable. Unfortunately, there are no curative therapies currently available for CTCL. However, in some patients, a durable response of more than five years has been observed with ECP, which is markedly better than conventional therapy with a median survival time of about three years in advanced-stage patients.(82)

Guidance on the monitoring of treatment success is also provided. Assessments at three-month intervals will allow nonresponders to be offered a combinatory or alternative therapy to ensure that ECP treatment is not unnecessarily prolonged.

In 2006, the British Photodermatology Group and the UK Skin Lymphoma Group reported on the use of ECP in a variety of clinical conditions based on data that were derived between 1987 and 2001.(83). These groups concluded that there is i) 'fair' evidence of the clinical benefit of ECP in patients with erythrodermic MF/SS (stage III/IVA/B1/0), with a strength of recommendation B (on a scale from A to E) based on a level of evidence of II1 (i.e., derived from well-designed, non-randomised, controlled trials); ii) 'fair' evidence that support the use of TSEB plus ECP for erythrodermic MF/SS patients, with a strength of recommendation B, level of evidence II2 (i.e., well-designed cohort or case-control studies); and iii) 'poor' evidence that support the use of IFN-α plus ECP for erythrodermic MF/SS, with a strength of recommendation C, level of evidence II2. Per standard protocol, ECP treatments should be performed on two consecutive days per month, continued for up to six months, and followed by tapering or maintenance treatment in those patients who have adequately responded. The treatment intervals can be shortened to biweekly cycles in poor responders, or ECP can be combined with other therapeutic agents such as IFN-α. Recommended time points on patient assessments and appropriate efficacy parameters are also listed. These recommendations have also been updated and adopted in the 2018 British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas.(84)

The US National Cancer Institute recommends ECP for the therapy of MF and SS.(75) ECP is offered as an option for the treatment of stage III MF/SS and, either alone or in combination with TSEB, for the treatment of stage IV MF/SS. For patients with recurrent MF/SS, it is noted that ECP has produced tumour regression in those patients who were resistant to other therapies. No information was given on the appropriate monitoring of therapy or outcomes.

In 2012, the NCCN clinical guidelines on MF/SS stated that their recommendations are all based on category 2A evidence (lower level evidence). ECP was recommended as first-line therapy for stage IV SS alone, or in combination with interferon or bexarotene. The guidelines also suggest that ECP may be used in relapsed or refractory stage III disease, and stages IA, IB-IIA, which are refractory to skin-directed therapy.(76)

The United States Cutaneous Lymphoma Consortium (USCLC) reviewed available therapeutic options for SS.(70) Based on level II2 evidence, ECP was classified as category A systemic monotherapy. Level II2 evidence means that information was obtained from at least one prospective, well-designed cohort or a case-control study, preferably from more than one centre or research group. Similarly, TSEB plus ECP, alone and in combination with IFN-α, IFN-γ, or bexarotene and ECP plus bexarotene, IFN-α, IFN-γ, or low-dose methotrexate alone or in combination are alternative therapeutic options.

Finally, the German Association of the Scientific Medical Societies (AWMF) provides guidance on the staging, assessment, diagnosis, and therapy of cutaneous lymphomas.(85, 86) ECP was recommended as first-line therapy for stage III erythrodermic MF and for SS. Their guidelines stated that ECP could be combined with IFN-α, methotrexate, bexarotene, or PUVA. The AWMF also commented on the excellent safety profile of ECP. No rating of the grade of recommendation or level of evidence was given, and no information was provided on how these guidelines were prepared.

Recommendations

Patient selection

ECP should be considered as first-line therapy for patients with MF/SS as follows:

- Erythrodermic MF stages IIIA or IIIB (B0 or B1) according to the revised International Society for Cutaneous Lymphomas (ISCL) / EORTC classification).(49)

Even though case series have suggested that there is a potential benefit of ECP in patients with early-stage disease (stage IA, IB, IIA), the consensus decision was that this application should only be considered for clinical trial purposes, as a variety of other effective, safe, and easily accessible treatment options are available for use at these stages.(60)

- MF/SS Stage IVA1 (T1-T4, N0-2, M0, B2)
- MF/SS Stage IVA2 (T1-T4, N3, M0, B0-2)

Treatment schedule

The recommended ECP treatment schedule is one cycle (i.e., one ECP procedure per day on two consecutive days) every two weeks for the first three months followed by an ECP cycle every 3 to 4 weeks. However, there is no optimal therapy, and other published guidelines have recommended one cycle every 2 to 4 weeks followed by tapering after the maximum response has been achieved.(55)

Currently, there are no data in the literature that support the concept of increased clinical efficacy if the frequency of ECP cycles rises. However, based on common clinical experience, it is assumed that an initially higher frequency of ECP treatments may result in a significant improvement of subjective symptoms, particularly in CTCL patients suffering from itchiness and those with B2 staging. Based on the patient´s compliance, a standard treatment regimen could also be performed, according to the policies and possibilities at the centre. Treatment of CTCL patients should be continued for six months at minimum

before the response to ECP is evaluated. At maximum response, treatment should slowly be tapered to one treatment cycle every 4 to 8 weeks for maintenance therapy. In patients with a favourable response or disease stabilisation and good quality of life, ECP treatment should be extended to more than two years. Treatment intervals should be progressively prolonged to up to eight weeks. Patients who do not respond to ECP as first-line therapy should be considered for combination therapies (i.e., ECP plus other drugs or interventions). IFN and/or bexarotene should be used in combination with ECP. Skincare and topical medications, including topical steroids and emollients, should also be prescribed to help alleviate ongoing symptoms.

In CTCL, patients with leukaemic involvement and high white blood cell counts (i.e., >20,000 mm^3), a cytoreductive treatment (debulking chemotherapy or alemtuzumab) aimed at decreasing the number of leukaemic peripheral cells can be performed prior to the start of ECP therapy. Also, local radiotherapy can be performed either before or during ECP to treat localised infiltrated skin lesions. While the combination of ECP with histone deacetylase inhibitors appears potentially useful, there are no published data available which support this approach at present.

Systemic concurrent therapies can be initiated at any time point. However, the consensus is that ECP monotherapy should be continued for at least three months before another drug or therapy is added. If patients are already on other therapies (bexarotene and/or IFN), ECP can be added without the withdrawal of the previous treatment.

Response assessment

Response assessments should be performed every three months according to the ISCL/EORTC/USCLC consensus statements.(49, 70, 87) Based on clinical experience, responses to ECP therapy are not immediate and may take 3-6 months before a clinical response is observed. Thus, it was agreed that there should be at least six months of treatment and evaluation of the response to ECP before conclusions on its efficacy are being drawn. If CR is observed in CTCL patients, ECP treatment should not be stopped. Instead, ECP intervals

should be extended to up to eight weeks. If PR or stable disease is observed, the consensus statement suggests that the efficacy of combining ECP therapy with other treatments or increasing the frequency of ECP treatments should be evaluated. Similar recommendations are made for the case of progressive CTCL disease. Alternatively, ECP may be stopped in favour of other CTCL therapies.

V. CHRONIC GRAFT-VERSUS-HOST DISEASE

Chronic GvHD (cGvHD) is a multisystem disorder occurring in the range of 30 to 50% of patients after allogeneic transplant.(88)

The likelihood of cGvHD rises with the use of unrelated, mismatched, older, or multiparous donors, in older recipients, and with the application of reduced-intensity conditioning (RIC). RIC transplants are recognised for having haematological malignancies; notably, due to myeloid leukaemia, the number of patients with cGvHD has increased in recent years.(89) Non-myeloablative and RIC treatment regimens enable older patients or comorbid patients presenting with myeloid malignancies to be treated by allogeneic haematopoietic cell transplantation (HCT). This approach allows for the essential immunosuppression of allogeneic cells, while malignant cells are eliminated.

The difficulty of finding the optimal treatment versus risk balance between cGvHD relapse, significant morbidity, and non-relapse mortality has been addressed by Kuzmina et al.(90) The first report on the successful treatment of cGvHD by use of ECP was published in 1994.(91) A more recent prospective multicentre study by Arora et al. performed between 2011 and 2014 at thirteen locations in the US reports on a cohort of 911 HCT patients (55% RIC). The authors of this study detected an incidence of 47% (95% confidence interval [CI]: 44%-51%) for cGvHD two years after the start of HCT.(92) The median time to the onset of cGvHD was 7.4 months or 222 days (range: 0.8-45.1 months). Oral mucosa was the most common site involved (59%), followed by skin (57%) and liver (56%). According to the National Institutes of Health (NIH)

Consensus Conference, cGvHD symptoms were classified as mild in 19%, moderate in 53%, and severe in 28% of the patients. Among the 428 cGvHD patients, non-relapse mortality was 12% (95% CI: 9%-16%). The probability of overall survival was 81% (95% CI: 76%-85%) two years after the diagnosis of cGvHD. The two-year non-relapse mortality was 11% (95% CI: 5%-24%) for mild, 8% (95% CI: 5%-13%) for moderate, and 18% (95% CI: 12%-28%) for severe cGvHD. Among all patients with cGvHD, only 11% (95% CI: 8%-16%) were able to discontinue the entire immunosuppression one year after cGvHD diagnosis. Patients with severe GvHD were less likely (9%) to discontinue immunosuppression as compared to those with moderate (12%) or mild GvHD (18%).

The pathogenesis of cGvHD remains poorly understood. cGvHD is an immune-mediated disease resulting from the interactions between the donor graft and the recipient's immune system. The donor T-cells are the primary aggressors causing antibody-mediated damage. There is increasing recognition that B-cells may have a role in the initiation and progression of cGvHD pathogenesis by altered B-cell homeostasis and disruption of tolerance mechanisms.(93) Cytokine dysregulation is implicated with high levels of IL-6, IFN-γ, TNF-α, IL-12, IL-17, and low levels of IL-10.(94)

The varied manifestations of cGvHD make the diagnosis and monitoring of the multisystem disorder difficult and comparing different clinical studies can be challenging. Criteria for the diagnosis and staging of clinical trials in cGvHD have recently been updated by Jagasia et al. to standardise diagnosis and assessment of response to treatment. Established first-line treatment of cGvHD is with glucocorticosteroids (~1 mg/kg body weight of prednisone equivalent).(95) An established first-line treatment of cGvHD uses the administration of glucocorticosteroids (~1 mg/kg body weight of prednisone equivalent). The addition of a calcineurin inhibitor may be considered, if appropriate.(96) In some patients, second-line therapy must be initiated. However, the choice of second-line agent varies considerably between centres and are often selected on an individual patient basis. Second-line treatment

options include the administration of ECP, mycophenolate mofetil, mTOR inhibitors, methotrexate, imatinib, rituximab, and ruxolitinib.(97)

ECP is an attractive treatment option exerting glucocorticosteroid-sparing effects and showing response rates of approximately 60% in cGvHD patients.(82) In 2008, Scarisbrick et al. reviewed twenty-three studies, including a total of 633 patients presenting with cGvHD who underwent ECP treatment between 1987 and 2001.(55) Response rates were determined based on organ involvement. The mean response rate was 68% (range, 29%-100%) in cutaneous cGvHD as derived from eighteen studies (patients evidencing CR were included in this analysis). In patients with hepatic involvement, the mean response rate was 63% (10 studies). Likewise, the mean response rate was 63% (9 studies) in patients presenting with mucosal involvement. An updated review of the literature reveals that thirteen additional investigations, comprising a total of 492 patients, are available for the analysis of response rates of the skin, liver, and oral manifestations in cGvHD patients. Response rate ranges were 31%-93% for the skin, 29%-100% for the liver, 21%-100% for oral disease, resulting in an overall response rate ranging from 36% to 83% (Table 5).

These data suggest that ECP is an effective treatment option for patients with cGvHD affecting skin, liver or oral mucosa. However, differences in the selection criteria of patients, and the use of different first-line therapies, and second-line treatment combinations may be the reason for the large variability in reported response rates. Alfred et al. investigated the results of 725 adult patients with either steroid-resistant, steroid-intolerant, or steroid-dependent cGvHD.(82) Response rates for cutaneous cGvHD were available from twenty-three studies showing a mean response rate of 74%. Response rates for hepatic cGvHD were available from fifteen studies that resulted in a mean response rate of 62%. Also, another twelve studies reported on mucosal cGvHD response rates resulting in a mean value of 62%. Response rates for pulmonary, ocular, and gastrointestinal involvement were 46%, 60%, and 46%, respectively. The overall response rate from a cross-section of fourteen studies was 68%.

Jagasia et al. recently reported on a randomised, prospective study investigating ECP use as first-line therapy in cGvHD, based on the 2015 NIH consensus criteria for diagnosis and response assessment. The addition of ECP to standard of care was compared to standard of care alone. ORR at week 28 was 74.1% (ECP arm) versus 60.9% (control arm). Patients in the ECP arm tolerated the treatment well whilst maintaining quality of life (QoL).(98) QOL is an important facet of survival post-HSCT, and scores in cGvHD are comparable to other chronic conditions such as multiple sclerosis and scleroderma.(99) Maintaining or improving QoL has also been demonstrated in other ECP studies of cGvHD.(100-103) There is also emerging evidence to suggest that ECP helps maintain response to viral infections whilst also not increasing the risk of relapse, which is of clinical importance in this group of patients.(104, 105)

Flowers and colleagues published the first multicentre, randomised, controlled, prospective phase II trial of ECP in 95 patients with steroid-refractory/-dependent/-intolerant cGvHD.(103) The primary efficacy end-point of the study was a blinded quantitative comparison of percentage change from baseline in Total Skin Score (TSS) of 10 body regions at week twelve. The median percentage improvement in TSS at week twelve was 15% for the ECP arm compared with 9% for the control arm - a non-significant difference. However, significantly more patients in the ECP arm had a complete or partial skin response, as assessed by the clinical investigators ($p<0.001$). At week twelve, the proportion of patients who had at least a 50% reduction in steroid dose and at least a 25% decrease in TSS was 8% in the ECP arm *versus* 0% in the control arm ($p=0.04$).

The safety profile of ECP is excellent, with only minimal side effects and no long-term complications. When compared to other immunosuppressive therapies currently available for the treatment of cGvHD, ECP is not associated with organ toxicities, the occurrence of opportunistic infections, treatment-emergent adverse events or underlying disease relapse.(97, 98, 104, 105)

Review of recent guidelines

ECP is recommended as second-line therapy for steroid-intolerant, steroid-refractory, or steroid-dependent cGvHD including but not limited to skin, oral mucosa, and liver involvement.(55, 97, 106, 107) ECP should be performed every two weeks for a minimum of three months. The updated NIH criteria for measuring response in cGvHD patients should be used, and treatment should be tapered in responders.(82, 108)

In 2013, an update of the ECP guidelines was provided by the *Societa Italiana di Emaferesi e Manipolazione Cellulare* (SIdEM) and the *Gruppo Italiano Trapianto Midollo Osseo* (GITMO) for both adult patients and paediatric patients with steroid-resistant or steroid-dependent cGvHD, irrespective of the extent and severity of the disease.(101) Also, it was noted that ECP might exert a potentially steroid-sparing effect and improve the quality of life in responding patients. SIdEM and GITMO recently published a review article on the assessment of best practices among twenty-four Italian centres investigated.(100)

In 2017, the UK Photopheresis Society published an update of its 2008 Guidelines.(82) For cGvHD of the skin, liver, and oral mucosa, they recommend ECP as second-line therapy in steroid-refractory, steroid-intolerant, or steroid-dependent patients. Two treatments per week (one cycle) performed at two-week intervals and a monitoring schedule according to the updated NIH criteria are stipulated.(108)

The American Society for Apheresis recommends ECP for second-line therapy of cutaneous and non-cutaneous cGvHD (level of evidence cII), either as monotherapy or in conjunction with other therapies.(109)

Recommendations

Patient Selection

ECP should be considered as second-line therapy in patients with steroid-dependent, steroid intolerant or steroid-resistant cGvHD and those with recurrent infections or a high risk of relapse of their underlying disease.

Patients ineligible for ECP include those with leucocyte counts below 1.0 G/L, intolerance to methoxsalen, heparin, or citrate products, and haemodynamic instability due to life-threatening infections.

Treatment Schedule

ECP cycles are weekly (two treatments; one cycle) for three months followed by one cycle once per month and then tapered depending on clinical response. The time schedule is largely dependent on the severity of cGvHD and the documented response. If cGvHD progresses, a change in the treatment strategy should be considered.

Response Assessment

Serial response assessments should be carried out using NIH assessment criteria and performed by appropriately trained staff.(108) .

Serial quality of life assessments, in addition to clinical response criteria, are recommended. Concurrent steroid and other immunosuppressive drug doses should be recorded at each assessment.

VI. ACUTE GRAFT-VERSUS-HOST DISEASE

Acute GvHD is a serious complication of allogeneic Haematopoietic Stem Cell Transplantation (HSCT) and a fundamental cause of transplant-related morbidity and mortality, mainly due to severe infections and organ toxicities.(110) Furthermore, aGvHD is an important risk factor and determinant for the development of cGvHD. Currently, the standard first-line therapy comprises the application of corticosteroids. However, less than 50% of patients respond to corticosteroid therapy, and thus a substantial proportion of patients presenting with aGvHD require salvage treatment.(110-113) So far, not a single immunosuppressive agent has been approved by regulatory agencies

for the treatment of steroid-refractory aGvHD; as a consequence, there is large variation in its management and treatment. Martin et al. published recommendations by the American Society of Blood and Marrow Transplantation (ASBMT) for the treatment of aGvHD based on a comprehensive and critical review of published reports.(110) Across the sixty-seven studies selected, a total of nineteen different agents or medical devices were investigated. Besides horse anti-thymocyte globulin (ATG), ECP was the most frequently studied therapeutic intervention. ECP was applied in approximately 300 patients with steroid-refractory aGvHD, and these numbers have been increasing over time.(114-135)

Overall, the median rates for CR and PR of cutaneous manifestations of patients are 75% each (range 50%-100%). Accordingly, the median rates for CR and PR of patients with hepatic involvement are 47% each (range 0%-100%), while the median rates for CR and PR of gastrointestinal manifestations are 58% each (range 0%-100%). ECP was tolerated excellently as the side effects observed were only mild in severity, consisting primarily of reversible, temporal drops in peripheral blood cell counts after the first courses of ECP.

The results of studies that employed ECP as second-line treatment of aGvHD are summarised in able 7. (114-119, 122, 126-128, 130) Promising first results from a preliminary study were confirmed by a pilot study performed on twenty-one aGvHD patients.(119, 136). Subsequently, Greinix et al. conducted a phase II study on ECP in fifty-nine steroid-refractory or steroid-dependent adult patients with severe aGvHD.(126)

In contrast to the pilot study, an intensified schedule of ECP was applied in the respective phase II study, consisting of 2 to 3 treatments per week until a maximum response was observed.(125, 126) By using this “intensified” ECP schedule, CR rates improved in patients with grade IV aGvHD (60% vs 12%) and gastrointestinal involvement (73% vs 25%) compared to results from the pilot study.(125, 126, 136). The best response rates to ECP were observed after a median treatment duration of 1.3 months (range 0.5-6), and no flare-ups were detected after tapering and discontinuation of corticosteroid therapy. In ECP-responders, corticosteroid therapy was discontinued after a median of

fifty-five days (range 17-284 days) after the start of ECP. In subsequent univariate analyses, the following parameters were identified as significantly affecting the outcome of aGvHD patients treated with ECP: i) the grade of aGvHD, ii) the number of organs involved at the start of ECP and first-line therapy with corticosteroids, and iii) the cumulative corticosteroid dose given prior to ECP. However, in logistic regression analyses, a low grade of aGvHD at the start of ECP therapy and the late onset of corticosteroid drugs after HSCT were the only variables that affected CR outcomes positively. Three months after the start of ECP, the cumulative incidence of transplant-related mortality at four years was 14% in patients achieving CR of steroid-refractory aGvHD, compared to 73% in patients without CR ($p<0.0001$). Patients with CR of steroid-refractory aGvHD with ECP had a significantly improved OS rate of 59%, compared to 11% in patients without CR ($p<0.0001$). The cumulative incidence of relapse at four years was 28%, which was thus not increased when compared with HSCT patients not receiving ECP. In general, treatment with ECP was well tolerated.

Perotti et al. recently reported on excellent response rates in fifty patients with steroid-refractory aGvHD and confirmed the corticosteroid-sparing effect of ECP.(118) There was a policy of early intervention in place in patients with aGvHD, so the median time from onset of symptoms to the start of ECP therapy was only nine days. The OR rate was 68% (32% CR and 36% PR), with almost similar response rates for skin (83%), liver (67%), and gastrointestinal tract (73%). Furthermore, the survival of ECP-responders was significantly improved (62% vs 6%) in aGvHD patients compared to ECP non-responders ($p<0.001$). The ability to decrease the corticosteroid dose thirty days after the start of ECP therapy was associated with a significantly reduced mortality rate, confirming the importance of sparing corticosteroid doses in aGvHD patients. Other authors have noted that the decrease of dose of corticosteroids after 30 days of therapy reflects a major advantage of ECP in the prevention of long-term complications in children.(115, 116)

Several ECP studies conducted in paediatric patients with aGvHD have shown similar results to those obtained in adults. For instance, in a large, multicentre,

retrospective study of thirty-three paediatric patients with steroid-refractory aGvHD, the overall rates were 54% for CR and 21% for PR.(115) The CR rates were 76% for skin symptoms, 75% for gastrointestinal manifestations, and 60% for liver involvement. The five-year OS rate was significantly better for responders than for nonresponders (69% vs 12%; p=0.001). Due to ECP therapy, immunosuppressive treatment was discontinued in eight out of nineteen survivors (42%) and reduced in another seven patients (36%). The median Karnofsky performance score improved significantly from 60% before ECP therapy to 100% (range 80%-100%) after the completion of ECP therapy.

Supportive data were derived from subsequent small studies using a twice-weekly ECP treatment regimen.(117, 137) In fifteen paediatric patients with steroid-refractory aGvHD, the strongest predictor of response to ECP treatment was the stage of the disease itself: there was a 100% response rate for stage II, 75% for stage III, and 0% for stage IV. The stage of aGvHD and the response to ECP therapy both turned out to be significant predictors of transplant-related mortality. A direct comparison of ECP and steroid therapy also showed somewhat better results for ECP in paediatric patients.(130) Following ECP treatment, 73% of fifteen patients showed CR; the remaining 27% showed PR. CR was recorded in 92% of patients with skin manifestations, 71% with gastrointestinal tract manifestations, and 100% with liver disease. In comparison, 56% of the sixteen patients receiving steroid therapy showed CR and 31% had PR; two patients had persistent cGvHD after one year. CR rates were 46% for skin, 57% for gastrointestinal tract, and 67% for liver. Transplant-related mortality at day 100 of treatment was 6% for steroid therapy, but no patient died in the ECP group, and the two-year OS rates were numerically, but not significantly, higher in the ECP groups (85%) as compared to the steroid therapy group (57%).(130)

Several authors have pointed out that the use of ECP in children might be challenging because of low body weight, difficult vascular access, high extracorporeal volume, metabolic and haematological problems, and psychological intolerance.(115, 116, 131) Nevertheless, Messina et al. were able to treat patients with body weights as low as 10 kg without detecting

significant side effects.(115) Kanold et al. reported on the follow-up with paediatric patients diagnosed with GvHD. The authors put particular emphasis on the technical aspects of the ECP therapy.(116) The efficacy results were similar to those from other studies (7/12 patients [58%] with aGvHD showed CR, and 3/12 [25%] showed PR). They observed good tolerability of the treatment in patients with low body weight and emphasised the importance of a dedicated paediatric environment and care team to manage challenges such as difficult vascular access and psychological intolerance.(116)

Calore et al. consecutively treated seventy-two paediatric patients (twenty-one steroid-refractory, forty-two steroid-dependent, nine steroid-naïve) between 1997 and 2013, achieving CR in 72% and PR in 11% of the patients.(133) Transplantation-related mortality was 3% and 20% among responders and non-responders to ECP ($p<0.0001$), respectively. The five-year overall survival showed a significant difference between responders and non-responders (78% vs 30%, $p=0.0004$).(133)

The challenge of treating paediatric patients of low-body-weight (as low as 15 kg) was addressed in a study of patients presenting with aGvHD or cGvHD.(131) In contrast to many groups that have used an ‘offline’ two-stage technique for mononuclear cell collection and irradiation, this group reported on the use of a sterile, closed-loop procedure in which patients received fluid boluses of normal saline or 5% albumin to boost blood volume before and, if needed, during the ECP treatment.(116-118) This procedure allows for the use of continuous flow ECP even in patients with low body weight.

In a retrospective analysis of 128 patients with steroid-refractory or steroid-dependent aGvHD treated with ECP as second-line therapy on a weekly basis, Das-Gupta et al. reported six-month freedom from treatment failure of 77.3% and a two-year survival rate of 56%.(138) Higher grades of aGvHD (grade 2 vs grades 3-4) at the start of ECP were predictive of poor clinical outcome as determined by survival analysis (hazard ratio [HR] 2.78, $p<0.001$); non-relapse mortality (HR 2.78, $p=0.001$); and six-month freedom from treatment failure (HR 3.05, $p<0.002$). Jagasia et al. compared ECP versus anti-cytokine therapy as second-line treatment for steroid-refractory aGvHD in a retrospective

analysis.(139) Overall response rates were 66% and 32% in the ECP and the anti-cytokine cohort, respectively. The respective rates for CR were 54% and 20%. ECP was an independent predictor of response (HR 3.42, p=0.007) and survival (HR 2.12, p=0.018). In patients with steroid-refractory aGvHD grade II, the use of ECP was associated with superior survival rates (HR 4.6, p=0.016). Furthermore, the administration of ECP was associated with lower non-relapse mortality (HR 0.45, p=0.018). These promising results warrant confirmation in a prospective clinical study.

In a systematic review of six prospective studies including a total of 103 patients with steroid-refractory aGvHD given ECP as salvage therapy, Abu-Dalle et al. reported an overall response rate of 69%, including 84% for cutaneous, 65% for gastrointestinal, and 55% for hepatic manifestations.(140) In a meta-analysis of seven prospective studies on ECP treatment in patients with steroid-refractory aGvHD, Zhang et al. included a total of 121 patients. The reported overall response rate was 71%, and the CR rate was 71%.(141) The efficacy rates of ECP on the skin, liver, and gut manifestations of aGvHD were 86%, 60%, and 68%, respectively.

To reduce the incidence of aGvHD, several studies investigated the use of ECP as part of the myeloablative conditioning regimen prior to HSCT. For instance, Miller et al. showed an unexpectedly low incidence of severe aGvHD if ECP was used as part of a novel ‘reduced-intensity’ conditioning regimen. No disease relapse or negative effects on the engraftment were observed.(142) However, the results from a phase II study revealed that after the addition of ECP to cyclosporine and methotrexate (all given as aGvHD prophylaxis as part of a standard myeloablative regimen), the incidence of aGvHD was similar to that found by other studies.(143) The comparison of the ECP-treated group to historical controls indicated a somewhat lower incidence of aGvHD grades II-IV and improved OS of patients when ECP was introduced during the conditioning phase.(143)

Recently, Michallet et al. performed a prospective multicentre phase II study to evaluate the safety and efficacy of prophylactic ECP soon after the start of reduced-intensity conditioning (RIC)-HCT in twenty adult patients with

haematological malignancies.(144) ECP was started on day twenty-one and was given twice per week for the first two weeks and then once per week for the following four weeks for a total of eight ECP courses. The cumulative incidence of aGvHD grades II-IV on day 100 was 15%. The two-year OS and progression-free survival (PFS) were 84% and 74%, respectively. ECP was tolerated well, and no adverse effects related to ECP were reported.

Kitko et al. investigated the combination of etanercept and ECP for GvHD prophylaxis in a prospective phase II study in forty-eight patients undergoing RIC-HCT.(145) The cumulative incidence of aGvHD grades II-IV was 46% on day 100. The one-year OS was 73% because of low rates of non-relapse mortality (21%) and relapse (19%). However, this strategy was ineffective in preventing chronic GvHD and late deaths. Therefore, the two-year survival probability declined to 56%. The preventive use of ECP may have some benefits, but data from more patients with a longer duration of follow-up are needed for confirmation.

In conclusion, ECP is well-tolerated, shows an excellent safety profile in children and adults, and is highly effective in aGvHD. The early start and use of an intensified ECP schedule consisting of 2 to 3 treatments per week and rapid tapering of corticosteroids in steroid-refractory patients are necessary actions that might exert a significant impact on the patients' survival rate. However, more prospective clinical studies are warranted, including those studies investigating the use of ECP for prophylactic purposes.

Existing clinical guidelines

The American Society for Apheresis (ASFA) reviewed available data on ECP in aGvHD patients and concluded that OR rates for steroid-refractory aGvHD in paediatric and adult patients range from 52% to100%. Corresponding response rates for the skin, gastrointestinal tract and liver were ranging from 66% to 100%, 40% to 83%, and 27% to 71%, respectively.(146) ASFA recommends that ECP be used weekly on two consecutive days (one series) until disease response is maximised and then be tapered to every other week before discontinuation.

A joint working group established by the haemato-oncology subgroup of the British Committee for Standards in Haematology (BCSH) and the British Society for Blood and Marrow Transplantation (BSBMT) provided guidelines on the diagnosis and management of aGvHD.(113) Based on the findings of this group, ECP is recommended as second-line therapy for the treatment of steroid-refractory aGvHD (level of evidence 2C). The BCSH/BSBMT commented on the excellent tolerability of ECP but concluded that the optimal treatment schedule and duration have not yet been established. However, Das-Gupta et al. reported on a regimen of weekly ECP cycles for a minimum of eight weeks continued until maximum response or CR is observed.(147) Of note, no other immunosuppressive agent recommended by the BCSH/BSBMT obtained a higher level of evidence.

In a recent update of a consensus statement from the UK Photopheresis Society, the promising role of ECP in the treatment of steroid-refractory aGvHD was confirmed (82). Based on expert opinions, analyses of current practices and published results, in 2007, Kanold et al. released clinical practice guidelines for physicians caring for children with aGvHD.(116) In this guideline article, ECP is recommended for paediatric aGvHD patients who are unresponsive to corticosteroids as defined by the absence of clinical and biologic improvement after one week of corticosteroid therapy (prednisolone or methylprednisolone up to 2-5 mg/kg/day). However, the authors commented that they were considering ECP as early as forty-eight hours after the initiation of corticosteroid therapy in severe cases of aGvHD. Thus, ECP was suggested as second-line therapy of aGvHD in paediatric patients presenting either with steroid-intolerant, steroid-refractory or steroid-dependent severe aGvHD. In detail, given the excellent safety profile of ECP, Kanold et al. considered ECP as first-line therapy for paediatric patients with grade IV aGvHD (in combination with conventional immunosuppressive therapies) and as second-line therapy in steroid-refractory aGvHD grades II-III. The authors recommended that ECP therapy be started at three times a week until a maximum response has been achieved, followed by individual progressive tapering of immunosuppressive treatment. Recommendations on vascular access and ECP technique in children were also provided.

Martin et al. published the recommendations of the American Society of Blood and Marrow Transplantation (ASBMT) for the treatment of aGvHD based on a comprehensive and critical review of published reports.(110) In total, data from sixty-seven reports on six-month survival, CR, and PR of aGvHD have been reviewed. Among the five studies with outliers in the six-month survival rate, the clinical trial by Messina et al. was particularly prominent. Since only children were treated (median age of 9.6 years), Martin et al. concluded that these outliers could be the result of age differences between patient cohorts, as the benchmark study had used horse ATG and included patients with a median age of twenty-seven years.(148) In conclusion, no specific agent was recommended or suggested to be avoided in the second-line therapy of steroid-refractory aGvHD.

The ASBMT reported on blood loss, hypocalcaemia, mild cytopenia, and catheter-associated bacteraemia due to ECP therapy but did not identify an increased risk of infections compared to other treatments. In particular, the ASBMT stated that there are no concerns about viral reactivations during ECP treatment. A typical ECP treatment schedule consists of three administrations during the first week followed by two administrations per week thereafter. According to ASBMT, the appropriate choice of second-line treatment regimens should be guided by factors such as the potential toxicity of drugs, drug interactions, the experience of the physician with the agents, tolerability, and drug costs. Due to the excellent safety profile of ECP and the lack of interactions with other agents, ECP compares favourably to alternative immunosuppressive strategies, supporting the concept of its frequent use as second-line therapy of steroid-refractory aGvHD.

The Italian Society of Hemapheresis and Cell Manipulation (SIdEM) and the Italian Group for Bone Marrow Transplantation (GITMO) stated that ECP is a valuable option for patients with aGvHD who are unresponsive to steroids and calcineurin inhibitors.(101) GITMO and SIdEM recommend the use of ECP in both adults and children. The early start of ECP therapy, particularly in children and recipients of haploidentical or unrelated donor HCTs is suggested. In a recent survey of twenty-four Italian HCT centres, more than 85% of these

GITMO accredited centres agreed with best practice recommendations including the use of ECP.(100)

Recommendations

Patient selection

Patients presenting with aGvHD but not responding to first-line therapy with corticosteroids at 2 mg/kg/day (progression of aGvHD after ≥3 days or lack of response after ≥7 days of corticosteroid treatment) should receive adjunct ECP as second-line therapy.

Treatment schedule

Patients should undergo ECP cycles every week, comprising 2 to 3 treatments per week. At present, there is no evidence that maintenance ECP therapy is necessary. Thus, as soon as patients achieve CR, ECP should be discontinued.

Response assessment

The activity of aGvHD should be assessed at seven-day intervals with staging according to published criteria.(149, 150) Clinical assessments should relate to organ involvement, and data on the quality of life should also be collected.

VII. SCLERODERMA

Scleroderma (systemic sclerosis [SSc]) is a multisystemic connective tissue disease characterised by humoral and cellular immune abnormalities and fibroblast activation. These changes are associated with excessive deposition of collagen and obliterative vasculopathy primarily within the skin and frequently within visceral organs such as the kidneys, heart, lungs, and digestive tract.(151, 152) The prognosis of SSc has been shown to vary depending on both the extent of skin thickening and its rate of progression. Cases restricted to the hands have a ten-year survival above 70%, whereas cases with proximal involvement including the trunk have a ten-year survival rate of only approximately 20%.(153) On average, female patients have a significantly

higher mortality rate than male patients, and primary heart disease, interstitial lung disease, pulmonary arterial hypertension, cancer and infection are the major causes of SSc-related death.(153-156)

Although the aetiology and pathogenesis of SSc are at present unknown, evidence suggests that certain environmental agents (organic solvents, specific tryptophan-containing products, adulterated oils), genetic backgrounds (specific HLA alleles such as DRspecific human leukocyte antigen alleles such as DR-5), and/or viruses (retroviruses, cytomegalovirus [CMV]) may be associated with the development of SSc.(157)

Interestingly, it has been shown that foetal CD3+ T-cells from prior pregnancies are detectable in blood and lesional skin of females with SSc.(158) This observation suggests that in distinct cases, T-cell microchimerism may be directly involved in the pathogenesis of SSc by initiating a graft-versus-host-like response. Furthermore, clonal T-cell populations have been identified in the blood and skin of patients with SSc.(159-161)

The therapeutic management of SSc is challenging. The low prevalence (240 cases per million population) and a variable prognosis of SSc make the evaluation of therapeutic response difficult and may explain why many of the treatments currently in use have not been assessed in randomised, controlled trials.(152) Skin thickening can be treated in various manners (D-penicillamine, interferon-gamma, methotrexate, mycophenolate mofetil, photopheresis, UVA1 phototherapy, allogeneic bone marrow transplantation methotrexate, cyclophosphamide, autologous bone marrow ECP, transplantation), but the US Food and Drug Administration has not approved any therapy for cutaneous involvement in SSc, to date. No placebo-controlled clinical trials exist showing the clear superiority of one treatment to another for cutaneous involvement. In September 2019, the FDA approved nintedanib (Ofev®) for the treatment of SSc interstitial lung disease.

ECP has been evaluated for SSc in three randomised clinical trials, seven open trials, prospective or retrospective series, and several case reports. In the first multicentre trial, seventy-nine patients with SSc of recent onset (mean symptom duration 1.83 years) and progressive skin involvement entered into a randomised, parallel-group, single-blind clinical trial comparing the efficacy of ECP therapy (given on two consecutive days per month) with conventional treatment using D-penicillamine at a maximum dose of 750 mg/day.(162) At both the six-month and ten-month evaluation time points, the mean skin severity score, the mean percentage of skin involvement, and the mean oral aperture measurements were significantly improved from baseline in ECP patients (n=31). In comparison, in patients treated with D-penicillamine (n=25), none of these parameters had significantly improved after six months of therapy. However, in those individuals in whom ECP treatment was continued, the mean skin severity score and the mean percentage of skin involvement were improved after ten months.

In a crossover trial reported by Enomoto in 1999, nineteen patients with progressive SSc of less than five years' duration were randomly assigned to one of two groups: Group A (n=10) received ECP according to the standard protocol for one year, and group B (n=9) received no treatment.(163) The main outcome parameter was the skin score after one year of treatment compared with that of the control group. The results obtained could not show a statistically significant effect of ECP in this relatively small patient population, although the average skin score improved by 5.4% (standard error [SE] 20.8%) in group A (ECP) and deteriorated by 4.5% (SE 13.8%) in group B (sham; not significant; p=0.71). Approximately one year after crossover, the skin scores reversed to what would have been expected, with an average increase of 5.3% per year.

In a randomised, double-blind, placebo-controlled, multicentre clinical trial reported by Knobler et al. in 2006, a total of sixty-four patients with SSc received monthly either active (n=27) or sham (n=37) ECP therapy on two consecutive days for twelve months, and the severity of both skin and joint involvement were assessed.(164) A statistically significant improvement in skin scores compared with baseline was observed at six (p=0.0024) and twelve months (p=0.008)

among patients who were on active ECP therapy but not those on sham ECP treatment. The skin scores were not significantly different between the two study arms, maybe due to the small sample size of the cohorts. Joint involvement was significantly improved after six (p=0.002) and twelve months (p=0.001) of active ECP therapy when compared with baseline. However, the study lacked statistical power to reveal a significant difference in skin and joint manifestations between the active and sham ECP arms.

A single-centre, open trial of ECP in eleven women with progressive SSc of recent onset who were treated for 16 to 57 months revealed an overall improvement and/or stabilisation of skin changes and physical performance in five of the eleven patients (45%).(165) Extracutaneous manifestations deteriorated in ten of the eleven patients (91%; p<0.05) and quality of life worsened in nine of the eleven patients (82%; p<0.05). This small, open, single-centre trial suggested that ECP does have a small impact on skin changes but does not improve extracutaneous manifestations or quality of life in this subset of SSc patients.

The immunomodulatory effects of ECP were assessed in nine patients with diffuse cutaneous SSc in a long-term follow-up study. In this study, each patient was treated every six weeks, receiving a total of 24 ECP procedures (twelve ECP cycles). The modified Rodnan score for skin thickness and the values of Tr1 and CD4+CD25bright T-reg cells increased, while percentages of Th17 cells decreased under ECP therapy.(166) However, this improvement in laboratory parameters diminished at the end of the 12-month follow-up period, indicating that potential immunomodulatory effects of ECP may only last for one year. In the case of effective ECP therapy during the first twelve cycles, the 6-week ECP treatment schedule should be continued without interruptions.(167) Absolute numbers and percentages of CD4+CD25+ T-reg cells, and in vitro suppressor T cell activity improved significantly after ECP treatment in a previous experimental study. However, neither the number nor the activity of CD4+CD25+ T-reg cells correlate with amelioration of skin symptoms in the nineteen SSc patients included in the study.(168)

Finally, a retrospective study by Topuzoglu et al. evaluated the incidence of lung cancer in 71 SSc patients treated with ECP between 1991 and 2013.(169) Confirming larger meta-analyses, the risk for lung cancer in SSc patients was increased by 2.34 [95% confidence interval (CI) 1.63-2.49.(170, 171) However, ECP therapy did not affect the risk of lung cancer in patients with SSc.(169)

Taken together, ECP performed on two consecutive days at monthly intervals is well tolerated in SSc and may have beneficial therapeutic effects on skin involvement that remain undetectable in small trials. Two prospective trials report beneficial effects of ECP on the skin, whereas one of two smaller studies doubts such effects. Caution: The effect of ECP on SSc is probably modest.

Existing clinical guidelines

None.

Recommendations

Grade of evidence 2b, Strength of recommendation B

Patient selection

By its safety profile, ECP should be used in SSc as second-line or adjuvant therapy in mono- or combination therapy, and it is recommended that it should be applied in early progressive disease. In the case of aggressive advancement of the disease, ECP should be considered as an approach to treat skin, but not an organ involvement.

Treatment schedule

In the randomised, double-blind, placebo-controlled trial of ECP in patients with SSc published by Knobler et al., ECP treatment was performed on two consecutive days (one treatment cycle) every four weeks for twelve months.(164)

Maintenance should only consist of one treatment cycle per month for skin symptoms of SSc. Before stopping ECP, treatment intervals can be prolonged by 1 to 2 weeks every three months. Based on the clinical course over a

reasonably long period, individual centres must make a clinical judgement on whether a patient is responsive to ECP therapy or not. If no response is noted, then a pause should be introduced to follow the course of the disease without ECP.

Response assessment

The response should be assessed clinically and photographically, using validated scoring systems for SSc.

VIII. SOLID ORGAN TRANSPLANTATION

Lung transplantation

Based on the recent ISHLT registry data, more than 4,000 lung transplantations were performed in 2015.(172) Despite a shift towards more potent immunosuppressive regimens, the development of acute and chronic allograft rejection continues to impact the long-term survival of lung transplant recipients negatively. Acute rejection of the transplanted lung occurs in more than 30%-50% of recipients, and it is a significant risk factor for chronic rejection, which remains the most common cause of death after the first year.

Chronic lung allograft dysfunction (CLAD) represents chronic allograft rejection and occurs in more than 60% of lung transplant survivors 5-10 years after the transplant.(173) Bronchiolitis obliterans syndrome (BOS) is the most common form of CLAD. BOS is a pathological process that affects small airways. It can be challenging to diagnose BOS by transbronchial biopsy, and, thus, diagnosis is typically made by graft deterioration due to persistent airflow obstruction rather than by histological confirmation. BOS is characterised clinically by progressive dyspnoea and airflow limitation with a decline of the forced expiratory volume in one second (FEV1) that cannot be explained by other causes such as acute rejection or infection. According to the ISHLT staging algorithm for BOS, stage 0 shows no significant abnormality and an FEV1 of >90% of the best postoperative value, while stage 3, which is at the other end

of the severity scale, signifies severe BOS with an FEV1 of ≤50%.(174) Potential BOS (0-p), defined as an FEV1 between 81% and 90%, was added to be able to detect early changes in graft function that might predict the onset of BOS stage 1.

BOS is a significant factor limiting long-term survival after lung transplantation, which is approximately 50% at five years. The most precipitous decline of airflow typically occurs in the first six months following the diagnosis of BOS, although the time of onset of BOS and the rate of decline of FEV1 are highly variable.

Today, many transplant centres employ an induction regimen that includes the infusion of an antibody targeting activated host lymphocytes at the time of transplantation. Such agents include polyclonal anti-T-cell products, such as ATG, or monoclonal agents targeting lymphocyte surface molecules, such as the IL-2 receptor/CD25 (daclizumab, basiliximab) or, less commonly, CD52 alone (alemtuzumab).(175). Maintenance immunosuppressive therapy after lung transplantation typically comprises a three-drug regimen including calcineurin inhibitors such as cyclosporine or tacrolimus, antimetabolites (azathioprine or mycophenolate mofetil), and steroids. Short courses of intravenously pulsed corticosteroids followed by a temporary increase in maintenance doses for a few weeks is the preferred treatment regimen for uncomplicated acute rejection. The initial treatment of BOS usually consists of repeated pulses of high-dose methylprednisolone. Additional therapeutic options are an augmentation of existing regimens and/or a switch within classes of drugs. Successful treatment of BOS is usually defined as the ‘stabilisation’ or ‘slowing’ of the decline of FEV1 rather than the real improvement or normalisation of airflow. For patients presenting with unresponsive BOS, salvage immunosuppressive regimens include ATG, alemtuzumab, and the addition of agents such as methotrexate, cyclophosphamide, inhaled cyclosporine, sirolimus, or interventions such as total lymphoid irradiation. In some cases, surgical treatment of gastro-oesophageal reflux disease is necessary. Also, the azalide antibiotic azithromycin is efficient in improving FEV1 in lung transplant recipients suffering from BOS.(176)

ECP is utilised as salvage therapy for the treatment of lung transplant rejection when conventional therapies result in an inadequate clinical response.(177) Importantly, ECP is not associated with an increased risk of infection, which, however, frequently occurs with immunosuppressive drugs.(148) The first introduction of ECP to human lung transplantation was performed in 1995 for an acute rejection episode occurring in severely infected patients. These patients improved clinically after three weeks and histologically after four weeks of ECP therapy.(178) In the same year, ECP was used in three patients presenting with chronic lung rejection refractory to steroid treatment. In this small cohort of patients, ECP stabilised the decline of pulmonary function.(179) ECP was performed at monthly intervals without the detection of significant complications. Then, ECP was implemented in the therapy of refractory BOS. ECP stabilised pulmonary function and improved survival after monthly treatment cycles, each performed on two consecutive days.(180, 181) Villanueva et al. reported on their experiences with ECP in fourteen lung transplant patients—all were diagnosed with BOS and received 3 to 13 (median 6) ECP treatments.(181) In three patients, acute organ rejection was concurrent, and ECP led to the resolution of this complication. Out of the eight patients with BOS grade 1, four patients improved or remained stable, while two patients progressed to grade 2, and the last patient died from lung cancer. Those patients with BOS grades 2-3 did not improve with ECP treatment (five patients died, and one patient was re-transplanted).(181)

O'Hagan et al. described five patients with severe BOS refractory to augmented immunosuppression, such as methotrexate, ATG, and OKT3. Temporary stabilisation of the airflow obstruction was observed in three patients during ECP therapy. However, a high rate of drug-related complications was reported as an indirect consequence of augmented immunosuppression: one patient developed a lymphoproliferative disease; others suffered from opportunistic infections that resulted in two deaths.(180) A similar experience was reported by Salerno et al. in eight patients, including seven patients with BOS. Five patients improved on ECP, with a histological reversal of rejection in two patients. After a follow-up period of thirty-six months, four patients remained in

stable clinical condition without the occurrence of any ECP-related complication.(182)

Benden et al. reported on their single-centre experience with ECP in twelve patients with BOS and another twelve patients with recurrent acute organ rejection after lung transplantation.(183) In transplant recipients with BOS, the decline in FEV1 was 112 mL/month before ECP was started, but only 12 mL/month after twelve ECP-cycles, with a mean change in the rate of decline of 100 mL/month (28-171 mL/month; 95% confidence interval; P<0.011). Thus, ECP reduced the rate of decline of lung function in transplant recipients with BOS and was well tolerated. Lung transplant recipients with recurrent acute rejection experienced clinical stabilisation.

In another single-centre study, Morrell et al. analysed the efficacy and safety of ECP in patients with progressive chronic rejection of the lung transplant.(184) A total of sixty lung allograft recipients treated with ECP for BOS showed a significant reduction in the rate of decline of lung function.

Jaksch et al. performed a prospective interventional study that included fifty-one patients with BOS treated with ECP between 2001 and 2011.(185) A total of thirty-one (61%) patients responded to the ECP therapy and showed continued stabilisation of lung function (FEV1 range -5% to +5% compared with baseline at the start of ECP) over six months. Responders to ECP showed significantly better survival probabilities and less need for re-transplantation than ECP non-responders (p=0.0001). Factors associated with inferior treatment response were cystic fibrosis as underlying lung disease and a shorter time between transplantation and the development of BOS. Compared with non-ECP-treated patients, those responding to ECP showed improved graft survival (p=0.05).

Greer et al. performed a single-centre retrospective analysis with the primary goal of identifying factors predictive of treatment response in patients treated with ECP for CLAD.(186) Out of a total of sixty-five patients treated with ECP, sixty-four had deteriorated clinically despite treatment with azithromycin. The median follow-up period after starting ECP was 503 days. At the start of ECP

therapy, all patients were categorised into the following clinical phenotypes: restrictive allograft syndrome (RAS), neutrophilic CLAD (nCLAD), and 'rapid decliners'. At follow-up, 12.3% had a ≥10% improvement in FEV1, 41.5% had stabilised, and 46.2% had a ≥10% decline of FEV1. Patients meeting the criteria of 'rapid decliners' (32.3%, p=0.005), RAS (33.8%, p=0.002), and those not exhibiting neutrophilia in bronchoalveolar lavage (67.7%, p=0.01) showed poorer outcomes. ECP was an effective treatment in approximately 54% of patients with CLAD who had failed to respond to azithromycin, and those who responded were found to have a statistically improved progression-free survival time (median 401 vs 133 days).

A possible biomarker for ECP response could be the blood level of T-reg-cells, which increases after photopheresis. It is interesting to note that after ECP for lung transplantation, the levels of T-reg-cells did not correlate with the number of ECP treatments but rather with lung function itself.(187)

A recently published paper tested the association between the dynamics of T-reg-cells and the development of CLAD or the progression of graft dysfunction after lung transplant.(188) The authors found an inverse correlation between restrictive allograft dysfunction and T-reg-cell counts. Furthermore, patients with higher mean T-reg-cell counts had a significantly lower risk (OR 0.97; p=0.012) of presenting with CLAD or progressing in graft dysfunction. These data confirm the influence of T-reg-cells on CLAD development and the possible effect of ECP on T-reg-cell counts.

A new argument for ECP after lung transplant could be to reduce circulating donor-specific antibodies (DSA) and non-HLA antibodies. A paper by the St. Louis group analysed DSAs in CLAD patients before and after ECP.(189) ECP was associated with a significant decline in DSA levels and antibodies against lung-associated self-antigens (SAg) such as Kα1-tubulin (Kα1T), collagen I and V, and circulating levels of pro-inflammatory and anti-inflammatory cytokines. ECP also reduced circulating levels of pro-inflammatory cytokines and increased levels of anti-inflammatory cytokines. These immunologic changes were associated with a significant reduction of 63% in the rate of decline in the forced expiratory volume in one second over one year. Though statistically

insignificant, a higher percentage of clearance of antibodies against lung-associated SAg was strongly associated with improved response to ECP.

Currently, ECP is being tested for efficacy in the treatment of BOS in Medicare-eligible lung transplant recipients in an observational cohort study (ClinicalTrials.gov Identifier: NCT02181257) in the US.(190) This registry study plans to enrol 160 patients from multiple centres across the US to confirm that ECP significantly reduces the rate of decline of FEV1 in patients presenting with BOS considered refractory to standard immunosuppressive drug therapy. Also, this study aims to capture and assess prognostic patient demographics and treatment-, diagnostic-, function-, and comorbidity-related variables that may be predictive of outcome after ECP therapy.

In summary, only a few retrospective investigations and one prospective study on the use of ECP in lung transplant recipients have been reported thus far. ECP has largely been used in patients with BOS, but it has also been employed in a small number of cases with acute and/or recurrent/ongoing rejection episodes of the lung transplant. Furthermore, in several reports on case series with ECP, lung transplant recipients who were unresponsive to standard immunosuppressive therapy and showed deteriorated graft function due to refractory BOS or persistent acute rejection experienced stabilisation of lung function.(179, 180, 183, 187, 191). To date, there is no study available that has addressed the prophylactic use of ECP in lung transplantation.

Existing clinical guidelines

The European Dermatology Forum and guidelines on the Use of Extracorporeal Photopheresis (192) noted the following:

- ECP has been used in lung transplant recipients with a low complication rate.
- ECP was used in patients with CLAD/BOS inducing stabilization of lung function in more than 60%.
- ECP was used in patients with acute recurrent/ongoing cellular rejection episodes.

- No guidelines or recommendations exist for early prophylactic use of ECP.

Recommendations

Patient selection

The main indication for ECP after lung transplantation is chronic lung allograft dysfunction (CLAD). Patients with an obstructive CLAD (former bronchiolitis obliterans syndrome/BOS) seem to respond better than patients with a restrictive form of CLAD. Patients with an earlier onset of CLAD (within the first 3 postTX years) respond better to ECP treatment. In contrast patients with a rapid decrease in lung function in the course of CLAD responded worse to ECP. The use of prophylactic early postTX ECP is recently under investigation. The use of ECP in patients with recurrent cellular rejections or as a second line treatment for humoral rejection seems to be promising but up to the present prospective randomized studies have not been performed in this specific field.

Treatment schedule

Patients are treated every 2 weeks on 2 consecutive days for 3 months. If spirometry improves or stabilizes, treatment intervals are expanded to 1-2 months for the next 6-12 months. Following the treatment efficacy will be reevaluated. In cases of further decrease of lung function ECP therapy will be stopped.

Response assessment

The efficacy of ECP is routinely monitored by measuring the lung function (main parameter FEV1 and MEF 50/25-75 values) and the blood gases (pO2 and pCO2).

Cardiac transplantation

Based on recent ISHLT registry data, more than 5,000 cardiac transplantation procedures were performed in 2015.(193) It has been estimated that acute

rejection of a transplanted heart occurs in 13%-25% of recipients within the first year and approximately 2%-4% will result in severe haemodynamic compromise.(193) Although significant improvements have been made in the prevention and treatment of acute transplant rejection, accelerated cardiac allograft vasculopathy (CAV) still limits the long-term success of heart transplantation.(194) After the first year, CAV is the second most common cause of death (the first is malignancy). Its pathogenesis, although not fully understood, is characterised by a fibroproliferative process that affects all cardiac arteries and results in concentric narrowing, obliteration, and ultimately allograft failure.(194) CAV is detectable by angiography in 8% of survivors within the first year and in more than 30% within the first five years.(193) Patient survival rates tend to diminish significantly after the detection of CAV; CAV and graft failure (most likely undetected CAV) are, in addition to malignancy, the most prevalent causes of death in patients who survive the first year after transplantation.(194)

The first reports on ECP therapy for cardiac transplant rejection surfaced in 1992. These early reports showed a rapid biopsy-proven reversal of acute cardiac rejection after 2 to 4 ECP treatments. In 1998, the first multicentre randomised clinical trial of cardiac transplant recipients receiving ECP was published.(195) In this study, sixty patients were randomised posttransplant to receive either standard triple immunosuppressive therapy or standard triple immunosuppressive therapy plus ECP started within thirty hours after transplant surgery. After six months of follow-up, the addition of ECP (ten treatments in the first month, four treatments in the second and third months, and two treatments each in the fourth, fifth, and sixth months) resulted in significantly fewer cardiac rejection episodes ($p=0.03$). There were no significant differences in the time to the first episode of rejection, the incidence of rejection associated with haemodynamic compromise, or survival rates at six and twelve months. Interestingly, cytomegalovirus DNA titres in the plasma were significantly reduced in the ECP cohort ($p=0.036$).(195)

In 2000, a prospective randomised pilot study tested whether the addition of prophylactic ECP to a triple immunosuppressive treatment regimen would result

in decreased levels of a panel of reactive antibodies and CAV in cardiac transplant recipients.(196) Twenty-three cardiac transplant recipients received either standard triple immunosuppressive therapy or standard triple immunosuppressive therapy plus ECP. ECP was started during the first month after transplantation (two treatments every 2 weeks for months 1-3, two treatments every 3 weeks for months 4-8, two treatments per month 9-12, two treatments every 6 to 8 weeks during months 12-24). Although, there were no differences between the two groups in the rates of infection or acute rejection, a significant reduction in the levels of the panel of reactive antibodies and intimal proliferation (a surrogate for CAV) at twelve and twenty-four months was detected in the ECP group.(196)

New standard protocols, including drugs such as tacrolimus, mycophenolate mofetil, and rapamycin, replaced established treatment protocols in maintenance immunosuppression strategies. These protocols are associated with a lower rate of acute organ rejections in the first year.(193) However, some patients still experience severe organ rejection and steroid-resistant and/or recurrent rejection episodes.

Dall'Amico investigated eleven patients with recurrent acute cardiac rejection who received ECP therapy for three months. In general, patients responded well and showed a significant reduction in acute rejection episodes and the severity of rejection grades.(197) However, six patients suffered from chronic organ rejections in the first five years after the start of treatment. In another study, Lehrer published a report on four patients presenting with severe organ rejections (ISHLT R3).(198) These patients were successfully treated with ECP. Cardiac rejection resolved in two patients after two therapies (on two consecutive days), whereas the other two patients needed to undergo a second course of ECP treatment.

In 2006, Kirklin et al. published the most extensive series of ECP on complex problems with organ rejection.(199) In this retrospective analysis, thirty-six patients receiving ECP therapy for at least three months due to organ rejection with hemodynamic compromise were compared to 307 patients who did not

receive ECP. Survival and risk factors were examined by use of multivariate hazard function analyses. After three months of ECP therapy, the risk of organ rejection and the hazard ratios for subsequent organ rejection with hemodynamic compromise or death from organ rejection were significantly reduced in the ECP group compared to non-ECP patients. These findings suggest that ECP reduces the rate of organ rejection with hemodynamic compromise and death in high-risk patients.(199)

In 2014, Dieterlen et al. published the first report on immunological parameters in cardiac transplant patients undergoing ECP.(200) The authors investigated nine patients undergoing prophylactic ECP, nine patients undergoing ECP who had acute cardiac rejection, and seven heart transplant patients who served as controls. Almost 80% of the patients responded to ECP treatment with an increase of T-reg-cells and plasmacytoid dendritic cells.

The first experience with ECP in a paediatric cardiac transplant population was reported by Carlo in 2014.(201) The study group consisted of twenty patients with a median age of 15.3 years. ECP was started, due to rejection complications, 1.4 years after transplantation. Patients underwent ECP for six months. Overall survival rates were 84% in the first year after ECP and 53% after three years. The authors suggested that nonadherence to medication in 55% of patients is associated with worse outcome (adherent: three-year survival rate is 53%; nonadherent: three-year survival rate is 18%, p=0.06).(201)

Currently, Savignano et al. described a low response rate of 37.5% to ECP therapy in eight patients with severe and complicated cardiac rejection episodes. The authors speculated that this low response rate could be associated with the high-risk subset of patients investigated.(202)

There is circumstantial evidence from a body of studies showing that ECP is a valuable adjunct to standard immunosuppression in cardiac transplantation. However, there are no clear guidelines or recommendations available on the use of ECP in this clinical indication. Furthermore, there are still several questions that need to be addressed, such as how potential responders should

be identified, what the best timing for ECP is (when to start, when to stop), and how response should best be monitored. Although studies consistently report a beneficial effect of ECP on cardiac transplant patients, the protocols used in these investigations varied considerably, and thus, there are only limited data providing information on the appropriate timing and clinical conditions that should govern the application of the ECP technique. Also, the adjuvant immunosuppressive protocols used in these studies varied significantly and may have had a considerable impact on the outcome. Therefore, a prospective randomised multicentre trial is essential to clarify the role of ECP in cardiac transplantation in the future.(203)

Existing clinical guidelines

The UK Photopheresis Society noted the following (82):

- ECP has been used safely in heart transplant recipients with very few complications and is well tolerated.
- ECP reduces the risk of acute cardiac rejection and can be used as an adjunct to standard immunosuppression. Data on the cost-effectiveness of the use of routine ECP and its effects on long-term outcomes in heart transplantation is not yet available.
- ECP can be used in adult and paediatric heart transplant recipients with recurrent acute rejection or severe rejection with haemodynamic compromise.

- In 2016, the ASFA published guidelines on the use of therapeutic apheresis in clinical practice.(109) For cellular/recurrent allograft rejection, ECP therapy was rated category II, evidence 1B (strong recommendation, second-line therapy), and ECP as rejection prophylaxis was rated category II, evidence 2A (weak recommendation, but high-quality evidence, second-line therapy).
- Lastly, the ISHLT published treatment guidelines for heart transplant patients. ECP was rated class IIb, level of evidence B (usefulness/efficacy is less well established by evidence/opinion; data were derived from one or more randomised trials or meta-analysis of

such studies) for the treatment of recurrent or resistant acute cellular rejection.(204)

Recommendations

Patient selection

For patients undergoing heart transplantation, data exist from small prospective studies showing the protective effects of ECP against heart rejection and (less robust) graft vasculopathy. However, these results were obtained from immunosuppressive protocols that are rarely used today. Data based on prospective randomised trials using the current immunosuppressive protocols (tacrolimus, mycophenolate-mofetil) are still missing.

Nevertheless, ECP appears to be a promising strategy for patients in treatment-resistant and treatment recurrent rejection episodes.

Treatment schedule

In general, patients should initially be treated with two ECP treatments back to back every two weeks for a minimum of three months and then tapered according to the clinical and laboratory responses to treatment. If there is organ rejection clearly until the clinical/laboratory response improves significantly to clinically acceptable levels before one stops. Treatments can be repeated at regular intervals if the parameters or antibody titer to the transplanted heart rises.

Response assessment

The efficacy of ECP is routinely monitored by the use of endomyocardial biopsies after the end of ECP treatment. Echocardiographic examinations should be performed to monitor graft function before, in the course of (weekly to monthly), and after the end of ECP treatment.

Other organ transplantation

ECP has, over the years, been used to control rejection following face, liver, and kidney transplantation.(205-218) In 2007, Urbani et al. published a prospective study in thirty-six liver transplant recipients where ECP was used to delay calcineurin inhibitor use in patients considered to be at high risk of renal and neurological complications post-transplantation.(219) ECP was administered at day two and day six posttransplant, then weekly in the first month, followed by weekly or monthly treatments depending on the results of liver function tests. No significant differences in the rates of biopsy-proven acute rejection, time to rejection, nephrotoxicity, neurotoxicity, and mean duration of hospitalisation were seen between the two groups. There was a statistically significant higher survival rate in the ECP cohort when compared to historical controls.

In a prospective randomised study, the biological response to ECP combined with conventional immunosuppressive therapy as a prophylactic treatment in ten kidney transplant patients was compared by Kusztal et al. to a control group of ten patients receiving only a calcineurin inhibitor, mycophenolate mofetil, and steroids.(220). A total of 12-16 ECP treatments were performed over 2.5 months. The ECP group showed a positive trend towards a higher estimated glomerular filtration rate at three months (53 ± 11 vs 47.1 ± 9; p=0.17) and reached the level of statistical significance at six months (67.5 ± 10 vs 53.6 ± 3; p=0.03, Wilcoxon test). An increased percentage of T-reg-cells (CD3+, CD4+, CD25+) among the total CD3 cell count (4.9 ± 1% to 9.4 ± 15%) and inducible T-reg-cells (CD3+, CD8+, CD28-) were observed among CD3 cells (3.3 ± 3% to 11.8 ± 8%, p=0.025) within three months of ECP treatment. A significant difference in the percentage of T-reg-cells was noted between the ECP group and the control group (9.4 ±15% vs 3 ± 1%; p=0.01) after three months.

Existing clinical guidelines

In 2006, the British Photodermatology Group (BPG) and the UK Cutaneous Lymphoma Group (UKCLG) noted that there was sufficient evidence to support the use of ECP for the treatment of acute and recurrent acute cardiac rejection,

prophylaxis of cardiac rejection, and chronic cardiac rejection.(83) At that time, there was weak evidence to support the use of ECP for the management of renal or lung allograft rejection.

In 2007, the American Society for Apheresis published guidelines on the use of therapeutic apheresis in clinical practice.(146) The guidelines suggested that ECP may be appropriate for the treatment of select individuals with persistent acute lung rejection and early BOS. For cardiac allograft rejection, ECP prophylaxis was rated category I, evidence 1A (strong recommendation, high-quality evidence) and ECP treatment of cardiac allograft rejection was rated category II, evidence 1B (strong recommendation, moderate-quality evidence).

Recommendations

Patient selection

After lung transplantation, ECP is currently indicated mainly for patients with chronic allograft dysfunction (BOS). As mentioned above, patients with early onset of BOS (within the first three years posttransplant) seem to respond better to the treatment than others. ECP should be started as soon as possible after the diagnosis of BOS is established. In other indications (as a form of induction therapy, as rescue therapy in cases of recurrent or ongoing acute cellular rejection), ECP has been used with promising results, but no recommendations are published or available, so far.

For patients undergoing cardiac transplantation, some studies support ECP as a valuable addition to immunosuppressive regimens, but the treatment protocols vary considerably in both the ECP and immunosuppressive regimens used. It remains unclear whether or not the routine use of ECP in cardiac transplantation would be beneficial to transplant patients. Thus, ECP cannot be thoroughly recommended until a prospective, randomised, multicentre trial has positively addressed this question. Nevertheless, ECP appears to be a promising strategy for patients presenting with either treatment-resistant or recurrent rejection episodes.

Treatment schedule

One ECP treatment cycle consists of one procedure performed on two consecutive days, each. A typical ECP regimen includes one cycle every two weeks for the first two months, followed by one cycle once per month for another two to four months. The optimal duration of ECP therapy remains to be explored. The number of treatment cycles ranges from six to twenty-four. If clinical stabilisation occurs with ECP, long-term continuation might be warranted to maintain the clinical response. Based on the ten-year, single-centre experience, twelve ECP cycles are considered the initial dose, and long-term continuation is recommended for responders.

Response assessment

Efficacy of ECP is routinely monitored using the pulmonary function test, with the FEV1 parameter being the main surrogate marker for the severity of BOS and the response to therapy. Successful treatment of BOS is usually defined as ‘stabilisation’ or ‘slowing’ of the FEV1 decline.

IX. CROHN’S DISEASE

Crohn’s disease is a chronic progressive inflammatory disorder of the gastrointestinal tract - it can affect any segment of the tract, but mostly involves the terminal ileum and colon. Stricturing and penetrating complications arise as sequelae of the inflammation, necessitating intestinal surgery in the majority of patients.(221) Evidence suggests that Crohn’s disease derives from perturbations at the interface between the intestinal microbiota and the innate immune system, based on genetic predisposition, which results in mucosal hyperimmunity and inflammation.(43) Thus, current treatment strategies almost exclusively harness immunosuppressive mechanisms of action and include steroids, thiopurines, methotrexate, and anti-TNF-α agents. Such treatment strategies are associated with an increased risk of infection, however, and recently advocated strategies combining thiopurines and anti-TNF-α agents may further increase this risk.(222)

Data on the use of ECP in Crohn's disease remain scarce and from uncontrolled studies. A small single-centre study evaluated the use of ECP in patients with prospectively evaluated steroid-dependent Crohn's disease.(42) ECP was administered as two treatments every two weeks for a total of twenty-four weeks. In four out of nine patients (44%), steroid therapy could be completely withdrawn during ECP without relapse of symptoms; in another four patients, the dose of steroids could be reduced by at least 50%; only one patient, with long disease duration and a high baseline steroid dose, experienced therapeutic failure. In a subsequent multicentre study (CD1 study), patients with steroid-dependent Crohn's disease received two treatments every other week, for a twenty-four-week steroid-tapering period, and underwent a forced steroid-tapering protocol.(223) Steroid-free remission was achieved in seven out of thirty-one patients (23%). In general, steroid-free remission is an endpoint that is difficult to achieve in patients with steroid-dependent Crohn's disease that is refractory to, or intolerant of, other therapies, including immunosuppressants or anti-TNF-α agents. From the literature, a steroid-free remission rate of a maximum of 25% is expected to be achieved by a switch to a second-line anti-TNF-α agent, whereas the placebo steroid-free remission rate is close to 0%.(224)

The CD2 study followed a different approach. Patients with moderate-to-severe active Crohn's disease refractory to immunomodulators and/or anti-TNF-α agents received ECP twice weekly for four weeks, tapering to twice every other week for another six weeks.(225) Among the twenty-eight patients included, there was a marked reduction in the Crohn's Disease Activity Index score during the twelve-week treatment period, with fourteen patients (50%) being classified as responders and seven patients (25%) achieving remission.

Existing data show some promise for the use of ECP in Crohn's disease. To date, two conditions have been investigated in open-label trials, namely steroid-dependent Crohn's disease and moderate-to-severe active Crohn's disease. Most patients included in these trials had shown no benefit following previous exposure to the available standard of care, including immunosuppressants and anti-TNF-α agents; data are lacking on a patient population less progressed in

disease and, therefore, possibly more sensitive to a tolerogenic response. Thus, a clear identification of patients most likely to benefit from ECP is currently impossible. We are still waiting for proof of the efficacy of ECP in Crohn's disease outside of clinical trials, and it should, therefore, be used primarily for patients with Crohn's disease not responding to or intolerant to the standard of care.

Existing clinical guidelines

None.

Recommendations

Based on the published literature, ECP is well tolerated in patients with Crohn's disease. ECP may help to control disease progression in select patients. However, at present, no treatment recommendations can be made.

X. USE OF EXTRACORPOREAL PHOTOPHERESIS IN PAEDIATRIC PRACTICE

While the absolute number of paediatric patients undergoing haematopoietic stem cell transplantation is much smaller than that of adults undergoing such treatment, paediatric patients constitute a substantial proportion of the overall transplant activity. Proportionately, more paediatric patients are treated with ECP for acute or chronic GvHD than for rejection after solid organ transplantation. The most recent activity report from the European Society for Blood and Marrow Transplantation (EBMT) noted that almost 20% of the overall haematopoietic stem cell transplants (3,338 transplants) in 2015 were paediatric allogeneic transplants.(226) There are plenty of data in the literature that support the use of ECP in paediatric patients (Table 6). However, to date, there are no randomised clinical trials available that demonstrate the superiority of ECP to other treatments in acute or chronic paediatric GvHD.(227, 228) Despite the invasive nature of the ECP procedure, numerous case reports and case series attest its beneficial effects and good tolerability with very few side

effects reported even in low body weight patients. In a recent survey of ECP procedures in paediatric patients performed in the UK, no serious adverse events related to ECP were found in 105 patients.(229)

Although the use of ECP is well established in paediatric patients, it remains a challenging task.(230) The placement of venous access by use of catheters large enough to facilitate adequate flow rates can be very problematic. The treatment of patients of less than 35 kg requires blood-priming of the apheresis equipment to prevent hypovolemic hypotension as blood is drawn from the patient.(231) A rare but potentially fatal complication in low body weight patients is mechanical haemolysis induced by the equipment.(232) For the UVAR XTS and CELLEX apparatuses commonly used, the haematocrit of paediatric patients needs to be higher than 27% for the collection of an effective buffy coat. Platelet counts higher than 20,000/mL in non-bleeding patients, or higher than 50,000/mL in bleeding patients should be achieved before the start of the procedure. The volume of blood necessary to process during ECP should be assessed on an individual patient basis. To avoid fluid overload in distinct cases, the surplus fluid should not routinely be returned to the patient at the termination of the ECP procedure. Reinfusion of the buffy coat should be taken into consideration according to the haemodynamic stability of the patient; in small bodyweight patients, the volume may need to be adjusted to prevent adverse reactions.(82) However, when taking these measures into account, low body weight patients can be treated successfully.(233) The management of paediatric haematopoietic stem cell transplant patients can be challenging, particularly in those patients who are presenting with severe GvHD. Best results are likely to be achieved if these patients are managed by paediatric transplant teams and apheresis staffs in specialised centres. The patients treated with ECP will probably benefit from its steroid-sparing effect.

XI. ATOPIC DERMATITIS

Atopic dermatitis (AD; atopic eczema) is a common inflammatory, chronically relapsing skin disease characterized by itchy eczematous skin lesions that can

affect the entire body surface in severe cases.(234-236) Histologically, AD lesions show epidermal changes, including spongiosis and epidermal hyperplasia with slight hyperkeratosis and parakeratosis (depending on the disease stage) and dermal infiltrates composed of T-lymphocytes, monocytes, and eosinophils. The details on the pathogenesis of AD remain unclear. A multifactorial trait involving numerous gene loci on different chromosomes has been proposed, and the highest correlations have been shown with mutations in the filaggrin gene associated with a disturbed epidermal barrier function.(237) Functional failure of T-reg-cells and an abnormal Th2/Th17-driven immune response to exogenous and/or endogenous antigens seem to be the main driving force leading to the typical skin changes in genetically predisposed AD patients.(238-241) Clinical studies have demonstrated a correlation between disease severity and levels of immunoglobulin (Ig)E and surrogate markers, such as eosinophil cationic protein, soluble IL-2 receptor (sIL-2R) and soluble E-selectin.(242, 243)

In adults, AD typically has a chronic relapsing course associated with a significant physical and psychological disability. The disease usually responds adequately to emollients, topical corticosteroids, calcineurin emollients, or phototherapies such as UVA-1, 311nm UVB, or PUVA.(234, 235, 237, 244, 245). However, standard therapy remains unsatisfactory in some patients. These patients often require immunosuppression with systemic cyclosporine, dupilumab, methotrexate, azathioprine corticosteroids to prevent severe disability. Third-line approaches, which include rituximab, omalizumab, mepolizumab or ustekinumab have been found to be effective in severe cases of AD.(246, 247) Treatment with the anti-IgE antibody omalizumab or the anti-IL-5 mepolizumab was useful in some cases of moderate-to-severe AD. Dupilumab, a human monoclonal antibody against the interleukin-4α receptor, which inhibits the signalling of interleukin-4 and interleukin-13 type 2 cytokines, has been launched as a breakthrough treatment for moderate to severe AD.(248) A randomised controlled phase 2 study has revealed that nemolizumab, a humanised monoclonal antibody targeting the interleukin-31 receptor A, was particularly effective in reducing pruritus that was inadequately controlled by topical treatments in patients with moderate to severe atopic

dermatitis.(249) Many other antibodies targeting IL-4Ra, IL-5, IL-12/23, IL-13, IL-17, and IL-22 are currently under investigation in clinical studies.(250) Also, small molecules inhibiting JAK and a variety of new topical agents targeting PDE4, arachidonic acid, or leukotrienes (among others) are in the research pipeline of AD.(251) ECP is safer with less risk of adverse effects than many systemic and topical therapies for CTCL.(252-260)

In 1994, Prinz et al. first described the successful administration of ECP in the treatment of three severe cases of AD.(252) Thereafter, several open clinical trials with mostly small numbers of patients have corroborated that ECP may be useful in severe cases of AD that are resistant to standard treatment.(253-261) In most studies, ECP was administered in biweekly cycles for at least twelve weeks and continued after that, depending on the patient's response. In the most extensive study reported so far, Radenhausen et al. administered 6-10 cycles of ECP to thirty-five patients with severe generalised AD.(257) ECP led to a significant decrease ($p<0.05$) in Scoring Atopic Dermatitis (SCORAD) from 74.4 to 36.8 after ECP therapy compared to baseline (after a mean of ten cycles). Approximately 70% of patients had a favourable response to ECP, requiring at least six cycles.

The results from all studies of ECP in AD are summarised in Table 8. The combined patient response rates of the pooled data of the ninety patients with AD from those studies were as follows: CR 10%, PR 44%, minor response 24%, no response 21%. The reported percentages on SCORAD reduction range from 16% to 99%. ECP seems to be particularly useful if an intensified treatment regimen in combination with other drugs is administered and maintained over extended periods of treatment cycles in patients with erythrodermic AD refractory to first-line-therapy.(261) ECP performed according to a twenty-week protocol led to a SCORAD reduction of more than 25% in only three of ten patients.(255) On average, the authors observed a small but significant decrease in SCORAD from 64.8 at baseline to 54.5 at week twenty (i.e., a decrease of 15.9%) if all patients were taken together. However, the change in the quality of life as measured by different scores such as SKINDEX, the thirty-six-item short-form health survey (SF-36) that is a set of generic, coherent and

easily administered quality-of-life measures, and the Functional Assessment of Cancer Therapy (FACT) did not reach the level of statistical significance.(255)

The effect of ECP (administered on two consecutive days a month) was compared to oral cyclosporine A (3 mg/kg/day) in a randomised crossover study including twenty patients with severe AD (SCORAD index 41-89) refractory to other therapies.(262) Patients were allocated to a four-month course of either of the two treatment modalities, and fifteen patients completed cross-over treatment. Both ECP and oral cyclosporine A significantly decreased the SCORAD (from sixty-nine to thirty-seven, i.e., an overall reduction of 46%; and sixty-seven to forty-four, i.e., a reduction of 34%) and the pruritus index (from 6.5 to 2.4 and 7.3. to 4.0, respectively) in the patients, though the differences between the treatments did not reach statistical significance. However, notably, in an overall global assessment on a scale from 5 to 0 (substantial improvement to progression), ECP, with a score of 3.5, was statistically superior to cyclosporine A treatment, with a score of 2.2. Intriguingly, none of the biomarkers (including serum levels of sIL-2Rα, E-selectin, and IgE, as well as basophilic and eosinophilic granulocyte values in the blood) significantly changed upon ECP or cyclosporine treatment. In other studies, ECP improved the laboratory correlates of active AD including elevated levels of IgE, eosinophilic cationic protein, sIL-2R and/or E-selectin.(255-258) Radenhausen et al. reported no significant correlation between a decrease in these levels and values of blood eosinophils.(257) However, in comparison with ECP responders, most non-responders were characterised by very high levels of total IgE before and during therapy.(257)

It is intriguing to note that ECP has also been shown to be effective in erythrodermas of another nonatopic origin, such as red man syndrome, erythrodermic pityriasis rubra pilaris, or photoaccentuated erythroderma associated with CD4+ T-lymphocytopenia.(263-266) Together, no serious side effects have been reported so far in AD and other diseases treated with ECP.(255, 262)

In summary, several open clinical trials with small numbers of patients and one randomised crossover study comparing ECP to cyclosporine have suggested

that ECP is safe and can be useful in severe cases of AD (including erythrodermic variants) that exhibit resistance to standard treatment. Though ECP is not a routine treatment of AD, based on the existing data and given the relative safety of ECP, it would be worthwhile investigating its usefulness as an immunomodulatory agent in the treatment of earlier phases of AD.(267)

Existing clinical guidelines

According to US guidelines, response rates to ECP differ among AD patients, ranging from complete remission to no response.(267, 268) Given the lack of consistent improvement, ECP is not recommended for the routine treatment of AD. However, though the level of evidence is not convincing, and given the safety profile of ECP, clinical studies should be further encouraged.(192, 235, 246, 247)

Recommendations

Patient selection

According to the inclusion criteria of a prospective, multicentre, investigator-initiated study, ECP therapy may be considered useful in patients with severe atopic dermatitis i) of at least twelve months' duration, ii) with a SCORAD >45; iii) with resistance to all first-line therapies, including topical steroids and topical calcineurin inhibitors, in the last twelve months, and iv) with resistance to one form of phototherapy (UVA, UVB, or PUVA), dupilumab, or either systemic steroids or cyclosporine as a second-line therapy.(255)

Treatment schedule

AD should be treated by one ECP cycle (i.e., one treatment on two consecutive days) every two weeks for twelve weeks — a treatment schedule that has been applied in most previous studies. Thereafter, ECP should be continued at intervals depending on the patient´s individual treatment response. ECP therapy should be tapered to one treatment cycle every six to twelve weeks when the maximum response has been observed, and ECP therapy will be stopped. Relapse can be treated by returning to the ECP interval and treatment schedule that has previously been effective.

Response assessment

Primary endpoints

The primary efficacy parameter and outcome should be determined according to SCORAD assessments.(255, 257, 258, 260, 261, 269) CR, PR, minor response, and no response are defined as ≥95%, ≥50%, ≥25%, and <25% reduction in SCORAD, respectively. SCORAD assessments should be performed at baseline, at two-week intervals during the treatment period for the first twelve weeks, and then at four-week intervals or longer depending on the individual ECP treatment schedule. Together with SCORAD, the quality of life of patients should be assessed by using scores such as the Dermatological Life Quality Index, SKINDEX, SF-36, or FACT.(255, 270-272)

Secondary endpoints

The quantification of the amount of topical steroids spared, the decrease in serum levels of IgE, and the decreases in eosinophilic cationic proteins and soluble IL-2-receptors (sIL-2R) from baseline may be considered as secondary endpoints of the response to ECP treatment.(242, 243, 255) The assessment of plasma levels and the function of circulating CD4+CD25+^{bright} T-reg-cells may be of additional help to predict, identify, and/or monitor AD patients who may respond to ECP.(40)

XII. TYPE 1 DIABETES

Type 1 diabetes is a common and serious disease with an increasing incidence worldwide. It is regarded as an autoimmune disease, mediated by self-reactive T-cells against pancreatic insulin-producing β-cells. Despite the use of intensive treatment with multiple daily injections of insulin and self-monitoring of blood glucose, type 1 diabetes is linked with substantial morbidity and mortality.(273-277) Residual insulin secretion facilitates metabolic control and reduces the risk of ketoacidosis, and even modest β-cell function has been reported to reduce long-term complications.(278, 279) Moreover, the drive to save β-cells and improve their function has become even more pertinent since some studies

have indicated that β-cells may regenerate.(280) If so, there is new hope for the prevention and treatment of this disease.

It is not known what exactly precipitates or stimulates the autoimmune process against β-cells.(281) Viral infections may be relevant (e.g. coxsackievirus, CMV, Epstein Barr virus, rotavirus), as may nutritional agents from cow's milk proteins or gluten. Another hypothesis suggests that increased demand for insulin for reasons such as increased weight, reduced physical exercise, or increased psychological stress combined with the consequent burden on β-cells leads to the presentation of autoantigens and possibly heat shock proteins that may precipitate an autoimmune reaction leading to insulitis in genetically predisposed individuals with an imbalanced immune system. Causes of an imbalanced immune system could include increased hygiene and/or abnormal gut flora. Autoreactive T-cells (CD4+ and CD8+ cells) are implicated as active players in β-cell destruction, while autoantibodies, often detected prior to the clinical disease, are considered as markers of an ongoing disease process in the pancreatic islets. The autoantibodies react against either the islet cells, specific autoantigens such as insulin autoantibodies, glutamic acid decarboxylase, tyrosine phosphatase, or zinc transport antigen.(282)

Several immune interventions have been tested, with the aim of preserving residual β-cell function, but to date, these measures have been insufficient or have been linked to unacceptable adverse effects.(283-291) There is a need for interventions that do not suppress but rather modulate and rebalance the immune system or that create tolerance to the autoantigens involved in the autoimmune process.

In the nonobese diabetic mouse model of type 1 diabetes, delivery of ECP-treated cells significantly delayed the development of type 1 diabetes. The combination of ECP-treated cells with β-cell antigens appeared to improve the efficacy of ECP therapy. ECP induced FoxP3+ T-reg-cells, suggesting that it may protect from type 1 diabetes through the promotion of immune regulation. ECP-treated spleen-cell therapy also induced suppression of the immune response to β-cell antigens. In contrast to ECP-treated cells alone, the combination of ECP-treated cells plus β-cell antigens appeared to improve the

protective effect, as shown by the marked reduction in insulitis in the islets. These results indicate that the protective effects of ECP against type 1 diabetes include the production of T-reg-cells and the suppression of the T-cell response to autoantigens. These data also suggest that combined therapy may be required to optimise ECP therapy in type 1 diabetes patients. For instance, the combination of ECP with β-cell antigens might provide a more potent protective effect.(292).

To date, there is only a single well-designed study available in the literature using ECP in newly diagnosed patients with type 1 diabetes.(44) This study used placebo pills and sham ECP in the control group. A total of forty-nine children aged 10-18 years at diagnosis of type 1 diabetes were included; forty patients completed the study, five double ECP/placebo treatments were given over three months, and patients were then followed up for three years (nineteen patients received active treatment with ECP, twenty-one patients received placebo treatment). The amount of C-peptide urinated by ECP-treated children was significantly higher than in the control group during follow-up. C-peptide values in serum showed similar differences between the two groups. The insulin dose/kg body weight required to reach HbA1c targets was always lower in the ECP group, although there was no difference in HbA1c values between the groups during follow-up. ECP was well tolerated.

In conclusion, clinical and experimental findings suggest that ECP might influence and delay the disease progress in type 1 diabetes by enhancing the production of T-reg-cells and having an immunosuppressive effect. The efficacy of autoantigen treatment may be increased by ECP, which might be regarded as a kind of vaccination of transformed autoreactive T-cells.

Existing clinical guidelines

None.

Recommendations

Experience is minimal and, thus, ECP should only be used in the treatment of type 1 diabetes in well-designed clinical trials — an opinion that is supported by previously published guidelines.(83)

XIII. PEMPHIGUS

Eleven patients with drug-resistant severe pemphigus (nine with pemphigus vulgaris [PV] and two with pemphigus foliaceus) who had cutaneous and mucous membrane involvement underwent ECP.(293-297) The OR rate was 91% (10/11 patients), with 73% (8/11) having CR, 18% (2/11) having PR, and 9% (1/11) having stable disease. A retrospective analysis of eight patients with PV treated with ECP on two consecutive days at four-week intervals reported CR in all but one patient after two to six (mean 4.5) cycles. Prednisolone doses were tapered in all patients.(298) In another study, three patients with recalcitrant foliaceus pemphigus received ECP: CR was seen in one patient, and PR was detected in two patients.(295, 297, 299)

ECP was performed every two to four weeks for a minimum of two cycles, allowing the doses of combined therapies (including corticosteroids and immunosuppressants) to be tapered. Decreased levels of circulating anti-intercellular substance autoantibodies have been reported.

Existing clinical guidelines

The British Association of Dermatologists' guidelines, published in 2003, concluded that ECP could be considered in refractory cases of PV for which conventional therapy has failed.(300) The strength of the recommendation was B (good evidence to support the use of the procedure) based on the quality of evidence III (opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees).

Recommendations

Patient selection

ECP can be considered for those patients with recalcitrant pemphigus vulgaris or foliaceus pemphigus in whom conventional therapy and second-line interventions (such as immunoadsorption, rituximab, and intravenous immunoglobulins) failed.

Treatment schedule

Initial treatment during weeks 0-12 should be one cycle of two procedures every two to four weeks, followed by one cycle of two procedures every four weeks for three to six months until complete remission. After six months, treatment should be tapered according to clinical response (e.g., prolonging the treatment intervals by one week every three months).

Response assessment

The clinical response should be monitored by two currently accepted clinical scores, namely the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) and the Pemphigus Disease Activity Index (PDAI).(301) Also, the determination of autoantibody titres should be performed, at least in pemphigus vulgaris.

XIV. EPIDERMOLYSIS BULLOSA ACQUISITA

No series of epidermolysis bullosa acquisita (EBA) patients treated with ECP has been reported. One report on the use of ECP in EBA patients studied eight subjects who were resistant to several systemic immunosuppressives or experienced severe adverse effects from immunomodulatory agents.(298, 302-304) The number of ECP cycles ranged from three to thirty-two, given at three to four-week intervals. The OR was 88% (7/8 patients), with 50% (4/8) of patients achieving CR. The time to CR was short: six to eight weeks of ECP. It is worth noting that two patients were able to stop ECP combined with drugs and did not relapse after ECP tapering, unlike the patients reported by Sanli et al.(298) After ECP, circulating anti-basement membrane zone autoantibodies were no longer

detected in the four patients with positive tests at the start of ECP. Major adverse events were observed in only one patient, who developed herpes zoster, pneumococcal sepsis, and idiopathic cardiomyopathy fourteen months after the last cycle. Reported follow-up lasted eleven to twenty-four months for five patients.

Existing clinical guidelines

None.

Recommendations

Patient selection

ECP is a therapeutic option for severe EBA refractory to conventional systemic therapy (according to local guidelines [e.g., cyclosporine, mycophenolate mofetil, immunoadsorption, rituximab and intravenous immunoglobulins]).

Treatment schedule

ECP treatment should be started three months after the initiation of conventional therapy; no washout period is required. Initial ECP treatment should consist of one cycle (two ECP procedures) every two weeks for twelve weeks, followed by one cycle every four weeks for weeks 12-24 until CR.

After twenty-four weeks, treatment should be tapered according to the clinical response (e.g., treatment intervals should be prolonged by one week every three months).

Response assessment

The clinical response should be monitored by the two currently accepted clinical scores, namely ABSIS and PDAI.(301).

XV. EROSIVE ORAL LICHEN PLANUS

The first series of seven patients with severe, multiresistant, histologically proven chronic erosive oral lichen planus (EOL) were treated successfully with

ECP in 1998.(305) Time to improvement was rapid: 1.5 months on average, with all patients having CR after a mean of twelve ECP sessions. No recurrence was observed after ECP discontinuation within the twenty-four-month follow-up period .

Other studies have tested the efficacy of ECP for EOL, including case reports and one open study of twelve patients, in a total of twenty-six patients.(306-310) In all these reports, ECP regimens differed widely from one cycle every week to one cycle every month. The overall response was 100%, with 77% CR and 23% PR. Healing of the genital lesions and cutaneous lesions occurred in nine and five patients, respectively.(308, 310) Clinical improvement was detected as early as 1.5 months, but up to one year of ECP therapy may be necessary to achieve CR. Although no relapse was mentioned in the original articles, the researchers later reported that ECP had exerted a palliative effect, as EOL recurred in twelve of thirteen patients either during ECP therapy or long-term follow-up (mean 8.3 months after ECP withdrawal).(308, 310) However, relapses were sensitive to ECP reintroduction. ECP was exceptionally well-tolerated, with lower lymphocyte counts observed only in a few patients.(308, 310)

Existing clinical guidelines

None.

Recommendations

Patient selection

ECP could represent an alternative therapy for recalcitrant EOL when classical treatments, including topical and/or systemic therapies, have failed to prove effective.

Treatment schedule

Initial treatment during weeks 0-12 should be one cycle of two procedures every two weeks, followed by one cycle of two procedures every four weeks for the weeks 12-24 until CR.

After twenty-four weeks, treatment should be tapered according to the clinical response (e.g. prolonging the treatment intervals by one week every three months).

Response assessment

Disappearance of oral lesions.

XVI. LUPUS ERYTHEMATOSUS

Nonspecific anti-inflammatory and immunosuppressive drugs such as nonsteroidal anti-inflammatory drugs, corticosteroids, thalidomide, antimalarial drugs, cytotoxic agents, and biologics are the standard treatments to control lupus erythematosus (LE).(109, 311, 312) However, some patients are nonresponsive or poorly responsive to these treatments, have contraindications, or develop toxic adverse events.(109, 312)

Although not yet included by international guidelines for the treatment of LE and guidelines for clinical use of ECP, preliminary results indicate that ECP could represent an innovative, effective, and safe therapeutic option for the treatment of LE.(109, 312)

To date, eighteen female patients with LE have been treated with ECP.(313-318) All patients had mild to moderate disease activity that was inadequately controlled with standard treatment options; they had all experienced a flare of disease activity upon attempted reduction and/or elimination of these drugs. A flare was considered a worsening of the patient's disease activity such that (in the investigator's opinion) it required treatment intensification going beyond the permitted supportive therapy. Eight patients were affected by systemic LE (SLE), six by subacute cutaneous LE (one was also affected by lupus tumidus), three by disseminated chronic cutaneous LE, and one patient had lupus tumidus, lupus panniculitis, and chilblain lupus. Ten patients reported photosensitivity. In all but one report, ECP cycles consisted of two ECP sessions on consecutive days at monthly or bi-monthly intervals for six months

or until remission.(313-318) Afterwards, the treatment was interrupted or performed at longer intervals to maintain remission, if any.

A marked or complete remission that was leading to the withdrawal (or a substantial decrease of dosage) of corticosteroids and cytotoxic drugs was observed in sixteen patients. In the case series reported by Knobler et al., only a few patients suffered from LE lesions such as arthritis, arthralgias, and myalgias; these, however, improved too.(313) Of note, ECP therapy did not induce exacerbation of other SLE symptoms, irrespective of the patient's photosensitivity status.(313-317) Remission was prolonged (up to four years) in many patients, even without maintenance ECP therapy.(314, 316) In one patient, an early relapse was detected, but LE lesions were amenable to another treatment cycle.(314) Marked changes in levels of specific routine laboratory parameters and autoantibodies were not seen.(313-318)

Hypovolaemic hypotension was documented in one patient during the ECP procedure, and three patients were found to develop nausea after ingestion of the 8-MOP capsules.(313) One patient died six months after initiation of the ECP programme, with death occurring ten days after the start of ECP. A connection to the ECP treatment was not entirely ruled out, although autopsy did not reveal any signs of pulmonary embolism or occluded arteries.(313) Serious side effects have not been observed during ECP therapy in the remaining patients. In general, ECP treatment was well tolerated.(314-318)

In summary, the use of ECP in LE is supported only by low-level evidence, i.e., results derived from individual case reports or small case series using different treatment protocols and short follow-up periods. Therefore, the employment of ECP in LE patients is exploratory. However, the preliminary clinical results are positive and randomised controlled clinical trials should be encouraged to assess therapeutic efficacy and cost-effectiveness in the future. The focus should also be placed on the optimal duration of an ECP treatment cycle, immunosuppressive drugs that can be combined with ECP, clinical manifestations considered highly responsive to ECP, and potential long-term side effects.

XVII. OTHER INDICATIONS

ECP has also been used in prospective studies investigating diseases such as psoriasis, rheumatoid arthritis, multiple sclerosis, nephrogenic fibrosing dermopathy, and scleromyxoedema, with inconclusive evidence.(319-331)

XVIII. SUMMARY/CONCLUSIONS

The first results from an international, prospective, multicentre clinical study on the use of ECP for the treatment of CTCL were published by Edelson et al. almost thirty-two years ago.(2) Based on these data, the US FDA approved ECP as the first cellular immunotherapy for cancer. This approval triggered many investigators to test ECP in the prevention and treatment of a variety of T-cell mediated diseases as outlined in the present guideline document. Over the last two decades, a large body of data has been derived from retrospective or prospective single and multicentre clinical trials with ECP that allow for the provision of recommendations on treatment schedules for different patient populations. These recommendations are summarised in Table 9.

ECP is a well-tolerated therapy with an excellent safety profile. No significant side effects have been reported in any of the conditions reviewed here except for the short-term effects of oral 8-MOP observed in the earlier studies. Unlike other immunosuppressive therapies, ECP has not been associated with an increased incidence of infections. New technical developments and advances have substantially shortened the cycle duration and qualified ECP for the use in children. Initially, ECP had only been used empirically in clinical settings. However, recent preclinical and clinical research activities are throwing more light on the complexities of its mechanisms of action. Also, promising data on the identification of potential surrogate markers that are considered predictive of clinical response to ECP therapy are emerging.

Recent technical advances and a large body of data on the usefulness, safety, and efficacy of ECP have established this method as a well-recognised and

accepted immunomodulatory second-line therapy in a variety of dermal and non-dermal diseases.

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I. Tables:

Table 1: ECP devices in current use in adults and children (adapted from Wong and Jacobsohn).(7)

• **Methodology**	• **Automated**	• **Weight limit**	• **Cell separator** • **Extracorporeal volumes**	**Cell separator technology**
One-step methods				
CELLEX (Therakos)*	Yes (double needle)	RBC prime needed if >115% ECV	Variable, dependent on Hct, blood volume processed, return bag threshold (lower than UVAR XTS)	IFC (continuous buffy coat collection with intermittent fluid return) (Latham Bowl)
	Yes (single needle)	RBC prime needed if >115% ECV	Variable, dependent on Hct, blood volume processed, return bag threshold (higher than double needle method)	CFC (Latham Bowl)

UVAR XTS (Therakos)	Yes (single needle)	>40 kg (need to satisfy ECV limits)	Variable, dependent on Hct, number of cycles, and bowl size (225 or 125 mL)	IFC (Latham Bowl)
Two-step methods **				
Spectra OPTIA (Terumo BCT) and UVA irradiator	Yes (only cell separation)	None	253 mL (Continuous mononuclear cell collection (CMNC), version 1.3); 147 mL (AutoPBSC procedure, Version 3.8)	CFC
Mini-buffy coat and UVA irradiator	No	Smaller children	None, but limited to 5-8 mL/kg whole blood draw	Standard manual buffy centrifugation technique
Three-step methods†				
Spectra OPTIA (Terumo BCT) & UVAR XTS (Therakos)	Yes (only cell separation)	None	See above for MNC and AutoPBSC procedure	CFC

Suitable for low body weight patients.

**Only cell separation is automated, while the UVA irradiator is operated manually. Other dedicated continuous or intermittenT-cell separators may also be used, such as Amicus (Fenwal, MNC kit) and AS104 (Fresenius Kabi) which have extracorporeal volumes of 163 and 175 mL respectively.

†Three-step methods involve standard mononuclear cell collection using dedicated continuous cell separators followed by red blood cell priming of the UVAR-XTS instrument and photoactivation treatment of the 8-methoxypsoralen treated mononuclear cells within the UVAR-XTS instrument after programming the instrument that the last ECP cycle has occurred. CFC, continuous flow centrifugation; ECV, extracorporeal cell volume; Hct, haematocrit; IFC, intermittent flow centrifugation; MNC, mononuclear cell; RBC, red blood cell; PBSC, peripheral blood stem cel

Table 2: European CE mark and FDA approval status of "one-step" closed photopheresis apparatuses and various cell separation and drug photoactivation devices used in "Multistep" photopheresis procedures.

	Company	**European CE mark**	**FDA approval**
Closed photopheresis apparatuses			
CELLEX*	Therakos	√For photopheresis	√For photopheresis
UVAR XTS	Therakos	√For photopheresis	√For photopheresis
Tubing set (XTS and CELLEX)	Therakos	√For photopheresis	√For photopheresis
Uvadex	Therakos	√For photopheresis	√For photopheresis
Cell separation system (standard apheresis device)			
Spectra Optia	Terumo BCT	√For therapeutic plasma exchange, RBC exchange, and WBC collection	√For therapeutic plasma exchange, leucocyte collection, and RBC exchange
Com. Tec	Fresenius Kabi	√For therapeutic plasma exchange and WBC collection	√For therapeutic plasma exchange and WBC collection

MCS plus	Haemonetics	√For therapeutic plasma exchange and leucocyte collection	√For therapeutic plasma exchange and leucocyte collection
AMICUS	Fenwal	√For therapeutic plasma exchange and leucocyte collection	√For therapeutic plasma exchange and leucocyte collection
Drug photoactivation system			
PUVA light system	Macopharma	CE marked (indicated to treat psoriasis, not dedicated to ECP)	No
MACOGENIC	Macopharma	UVA illumination machine CE 0459	No
MACOGENIC G2	Macopharma	UVA illumination machine CE 0459	No
XUV bag	Macopharma	UVA illumination machine CE 0459	No
8-MOP	Macopharma	AMM PTA 07.10.109 (indicated for nuclear cell photosensibilisation)	No
UVA PIT system	MedTech Solutions	Medical System for photoimmune therapy (body MDC 0483)	No
UVA PIT Kit	MedTech Solutions	Medical System for photoimmune therapy (body IMQ 0051)	No
PUVA Combi-Light UVA Illuminator	Cell.Max GMBH	CE marked medical device	No

*Suitable for low body weight patients. CE, Conformité Européenne; WBC, white blood cell; RBC, red blood cell.

Table 3: Summary of studies using extracorporeal photopheresis as monotherapy or in combination with other therapies for the treatment of cutaneous T-cell lymphoma (adapted from Scarisbrick et al., 2008).(55)

	Patients (n)	**OR (%)**	**CR (%)**	**PR (%)**	**MR (%)**
Edelson et al., 1987 (2)	37 (erythrodermic 29)	73 (27/37) 83 (24/29)	24 (9/37)	35 (13/37)	14 (5/37)
Heald et al., 1989 (64)	32 (erythrodermic 22)	NK 86 (19/22)	 23 (5/22)	 45 (10/22)	 18 (4/22)
Nagatani et al., 1990 (332)	7	43 (3/7)	NK	NK	
Zic et al., 1992 (333)	20	55 (11/20)	25 (5/20)	30 (6/20)	
Koh et al., 1994 (334)	34 (erythrodermic 31)	53 (18/34)	15 (5/34)	38 (13/34)	
Prinz et al., 1995 (335)	17 (erythrodermic 3)	71 (12/17)	0 (0/17)	41 (7/17)	29 (5/17)
Duvic et al., 1996 (336)	34 (erythrodermic 28)	50 (17/34)	18 (6/34)	32 (11/34)	
Gottlieb et al., 1996 (65)	28 (erythrodermic NK)	71 (20/28)	25 (7/28)	46 (13/28)	
Stevens et al., 2002 (337)	17 (erythrodermic)	53 (9/17)	29 (5/17)	24 (4/17)	
Zic et al., 1996 (66)	20 (erythrodermic 3)	50 (10/20)	25 (5/20)	25 (5/20)	
Konstantinow et al., 1997 (338)	12 (erythrodermic 6)	67 (8/12) 50 (3/6)	8 (1/12) 0 (0/6)	42 (5/12) 50 (3/6)	17 (2/12)
Miracco et al., 1997 (339)	7	86 (6/7)	14 (1/7)	71 (5/7)	

Russell-Jones et al., 1997 (340)	19 (erythrodermic)	53 (10/19)	16 (3/19)	37 (7/19)†	
Vonderheid et al., 1998 (341)	36 (erythrodermic 29)	33 (12/36) 31 (9/29)	14 (5/36) 10 (3/29)	19 (7/36) 21 (6/29)	
Zouboulis et al., 1998 (342)	20	65 (13/20)	NK	NK	
Jiang et al., 1999 (343)	25 (erythrodermic)	80 (20/25)	20 (5/25)	60 (15/25)	
Bisaccia et al., 2000 (69)	37	54 (20/37)	14 (5/37)	41 (15/37)	
Crovetti et al., 2000 (344)	30 (erythrodermic 9)	73 (22/30) 66 (6/9)	33 (10/30) 33 (3/9)	40 (12/30) 33 (3/9)	
Wollina et al., 2000 (345)	20	65 (13/20)	50 (10/20)	15 (3/20)	
Wollina et al., 2001 (346)	14	50 (7/14)	29 (4/14)	21 (3/14)	
Bouwhuis et al., 2002 (347)	55 SS	80 (44/55)	62 (34/55)	18 (10/55)	
Knobler et al., 2002 (348)	20 (erythrodermic 13)	50 (10/20) 85 (11/13)	15 (3/20) 15 (2/13)	 54 (7/13)	 15 (2/13)
Suchin et al., 2002 (67)	47	79 (37/47)	26 (12/47)	53 (25/47)	
Quaglino et al., 2004 (349)	19	63 (12/19)	NK	NK	
De Misa et al., 2005 (350)	10 (advanced SS)	60 (6/10)	10 (1/10)		
Rao et al., 2006 (351)	16	44 (7/16)	NK	NK	
Gasova et al., 2007 (352)	8 (2 with CTCL)	100 (2/2)	NK	NK	

Tsirigotis et al., 2007 (56)	5 (SS 2)	80 (4/5)	20 (1/5)	60 (3/5)	
Arulogun et al., 2008 (57)	13 (all SS; 12 erythrodermic)	62 (8/13)	15 (2/13)	46 (6/13)	
Booken et al., 2010 (58)	12 (all SS)	33 (4/12)	0 (0/12)	33 (4/12)	
McGirt et al., 2010 (59)	21 (18 erythrodermic)	57 (12/21)	14 (3/21)	19 (4/21)	24 (5/21)
Quaglino et al., 2013 (62)	48 (all erythrodermic;12 MF, 36 SS)	60 (29/48)	13 (6/48)	48 (23/48)	
Raphael et al., 2011(61)	98 (all erythrodermic)	74 (73/98)	30 (29/98)	45 (44/98)	
Talpur et al., 2011 (60)	19 (all early-stage MF)	63 (12/19)	11 (2/19)	53 (10/19)	

CR, complete response; MF, mycosis fungoides; MR, minor response (>25% improvement in skin scores); NK, not known; OR, overall response (CR + PR); PR, partial response (>50% improvement in skin scores); SS, Sézary syndrome; CTCL, cutaneous T-cell lymphoma.

[†]Combined PR and MR.

Table 4: Baseline predictors of response to photopheresis in the treatment of CTCL.

Low Tumour Load Of Malignant T Cells	**Parameter**	**Reference**
Skin	Erythroderma	(62), (192)
	Plaques < 10-15% total skin surface	(353), (192)
Blood	Lower percentage of elevated circulating Sézary cells	(354), (61), (59)
	Lower CD4/CD8 ratio < 10-15	(354), (355), (61), (62)
	Lower % CD4+CD7- < 30%	(337), (61)
	Lower % CD4+CD26- < 30%	(61)
	Normal LDH levels	(355), (62)
	B0 or B1 blood-stage	(62)
	Lymphocyte count < 20,000/µl	(353)
Lymph nodes	Lack of bulky adenopathy	(353)
Visceral organs	Lack of visceral organ involvement	(353)
Peripheral Blood Involvement		
	B1 blood stage > B2 blood stage	(62), (81), (353)
	Presence of a discrete number of Sézary cells (10-20% mononuclear cells)	(192)

Relatively Intact Immune System		
	Higher % monocytes > 9%	(61)
	Increased eosinophil count > 300/mm^3	(59)
	No previous intense chemotherapy	(356), (353)
	Short disease duration before ECP (<2 yrs from diagnosis)	(353), (62)
	↑ NK cell count at 6 months into ECP therapy	(335), (62)
	Near-normal NK cell activity	(192)
	Normal CD3+CD8+ cell count > 200/mm^3	(62)
	High levels of CD4+Foxp3+CD25- cells at baseline	(357)
Other Monitored Factors		
PBMC microRNA levels	↑ miR-191, ↑ miR-223, ↑ miR-342 at three months into ECP monotherapy	(358)
Soluble IL-2 receptor	↓sIL-2R at 6 months into ECP	(351)
Neopterin	↓ neopterin at six months into ECP	(351)
Beta^2-microglobulin	↓ beta^2-microglobulin at 6 months into ECP	(351)
Response at 5-6 months of ECP	Predicts durable response and long-term survival	(337), (66)

LDH lactate dehydrogenase, NK natural killer, ECP extracorporeal photopheresis, PBMC, peripheral blood mononuclear cell. Adapted from Zic JA. Extracorporeal photopheresis in the treatment of mycosis fungoides and Sézary syndrome.(78)

Table 5: Extract of studies using extracorporeal photopheresis in adult patients with chronic graft versus host disease.

	Patients (n)	**CR/PR Skin (%)**	**CR/PR Liver (%)**	**CR/PR Mouth (%)**	**OR (%)**
Greinix et al., 1998 (119)	15	80	70	100	NK
Apisarnthanarax et al., 2003 (359)	32	59	0	NK	56
Seaton et al., 2003 (360)	28	48	32	21	36
Foss et al., 2005 (361)	25	64	0	46	64
Rubegni et al., 2005 (362)	32	81	77	92	69
Couriel et al., 2006 (363)	71	57	71	78	61
Greinix et al., 2006 (364)	47	93	84	95	83
Flowers et al., 2008 (103)	48	40	29	53	
Dignan et al., 2012 (365)	82	92	NK	91	74
Greinix et al., 2011 (366)	29	31	50	70	NK

CR, complete response; NK, not known; OR, overall response; PR, partial response.

Table 6: Summary of studies using extracorporeal photopheresis in paediatric patients with chronic graft versus host disease.

	Patients (n)	**CR/PR skin (%)**	**CR/PR liver (%)**	**CR/PR mouth (%)**	**Comment**
Rossetti et al., 1995 (367)	7	33 (2/6)	100 (1/1)	-	50% (2/4) lung CR
Dall'Amico et al., 1997 (368)	4	67 (2/3)	-	-	67% (2/3) lung improved
Salvaneschi et al., 2001 (114)	14	83 (10/12)	67 (6/9)	67 (8/12)	79% OS
Halle et al., 2002 (369)	8	88 (7/8)	67 (4/6)	-	100% OS
Perseghin et al., 2002 (370)	9	88 (7/8)	100 (2/2)	67 (2/3)	-
Perutelli et al., 2002 (371)	7	-	-	-	43% (3/7) CR; 57% (4/7) improved
Messina et al., 2003 (115)	44	56 (20/36)	60 (12/20)	-	77% OS
Duzovali et al., 2007 (372)	7	-	-	-	43% (3/7) improved; 43% (3/7) died
Kanold et al., 2007 (116)	15	75 (9/12)	82 (9/11)	86 (6/7)	67% (10/15) alive
Perseghin et al., 2007 (373)	25	67 (4/6)	67 (4/6)	78 (7/9)	76% (19/25) alive
Gonzales-Vicent et al., 2008 (117)	3	100 (2/2)	100 (2/2)	-	100% (3/3) alive
Perotti et al., 2010 (118)	23	96 (22/23)	100 (4/4)	80 (4/5)	83% (19/23) alive at 5 years

CR, complete response; PR, partial response; OS, overall survival.

able 7: Summary of studies using extracorporeal photopheresis in the second-line treatment of acute graft versus host disease.

	Patients (n)	**CR skin (%)**	**CR liver (%)**	**CR gut (%)**	**OS (%)**
Salvaneschi et al., 2001 (114)	9	67 (6/9)	33 (1/3)	60 (3/5)	67
Dall'Amico et al., 2002 (122)	14	71 (10/14)	57 (4/7)	60 (6/10)	57
Messina et al., 2003 (115)	33	76 (25/33)	60 (9/15)	75 (15/20)	69 at 5 years
Garban et al., 2005 (127)	12	67 (8/12)	0 (0/2)	40 (2/5)	42
Greinix et al., 2006 (126)	59	82 (47/57)	61 (14/23)	60 (9/15)	47 at 5 years
Kanold et al., 2007 (116)	12	90 (9/10)	56 (5/9)	83 (5/6)	75 at 8.5 months
Calore et al., 2008 (130)	15	92 (12/13)	–	100 (14/14)	85 at 5 years
Gonzales-Vicent et al., 2008 (117)	8	100 (8/8)	100 (2/2)	57 (4/7)	38
Perfetti et al., 2008 (128)	23	65 (15/23)	27 (3/11)	40 (8/20)	48 at 37 months
Perotti et al., 2010 (118)	50	83 (39/47)†	67 (16/24)†	73 (8/11)†	64 at 1 year
Jagasia et al., 2013 (139)	57	67 (38/57) †	67 (38/57) †	67 (38/57) †	59 at 2 years
Calore et al., 2015 (133)	72	78 (50/64)	84 (10/12)	76 (42/55)	71 at 5 years

CR, complete response; OS, overall survival; PR, partial response.

†Combined CR and PR.

Table 8: Summary of studies using extracorporeal photopheresis as systemic monotherapy for the treatment of severe atopic dermatitis.

	Patients (n)	**Male/female**	**Age range (years)**	**Patient characteristics**	**ECP treatment cycle**	**Concomitant treatment**	**CR (%)**	**PR (%)**	**MR (%)**	**NR (%)**	**SCORAD (Means ± SD; or as described otherwise)**	
											Before ECP	**After ECP (% reduction)**
Prinz et al.,1994 (252)	3	2/1	32–52	Longstanding AD with erythrodermic eczema unresponsive to standard treatment	Every 4 weeks for 12 months, thereafter at 6-week intervals	Topical steroids	67 (2/3)	33 (1/3)			NK	NK
Richter et al., 1998 (259)	3	2/1	27–56	Longstanding AD with Costa score >45	Weeks 0, 2, 4, 6, 8	None		100 (3/3)			NK	NK
Mohla et al., 1999 (254)	1	1/0	49	Lifelong history of AD with severe skin manifestation	Weeks 0, 2, 4, 6, 8, 12, 16	Topical steroids	100 (1/1)				NK	NK

Prinz et al.,1999 (256)	14	9/5	29–77	Erythrodermic AD unresponsive to standard treatment	Weeks 0, 2, 4, 6, 8, 10, 12	Topical steroids	29 (4/14)	43 (6/14)		29 (4/14)	NK	NK.
Radenhausen et al., 2003 (258)	10	6/4	35–67	Severe AD with SCORAD >45	Weeks 0, 2, 4, 6, 8	Antihistamine and topical steroids	NK	NK	NK	NK	87.3±9.1	35.7±12.3 (59)
Radenhausen et al., 2004 (257)	35[&]	20/10 [&]	18–70	AD of at least 5 years, SCORAD >45, resistant to standard therapies[+]	Weeks 0, 2, 4, 6, 8 (10, 12, 14, 16, 18)[†]	Short-term topical steroids	3 (1/30) [&]	37 (11/30) [&]	40 (12/30) [&]	20 (6/30)[&]	74.4±15.5	36.8±16.8 (51)
Sand et al., 2007 (260)	7	4/3	NK (median age 47)	Severe, refractory AD of at least 1 year's duration[#]	Weeks 0, 2, 4, 6, 8, 10, 12 (14, 16, 18, 20)[†]	Antihistamine and topical steroids	NK	NK	NK	NK	77.7 ±8.5	55.6 ±10.3 (28)
Wolf et al., 2008 ((269))	5	0/5	30–67	First-line therapy refractory AD with severe and/or erythrodermic skin manifestation	Weeks 0, 2, 4, 6, 8, 10, 12; thereafter in 4-week intervals	Topical steroids	NK	NK	NK	NK	NK	39-99 reduction after long-term treatment in 3/5 patients

Hjuler et al., 2010 (253)	6	3/3	33–63	Long history of severe recalcitrant AD previously treated with various systemic therapeutics	Every 4 weeks for 12 months	Topical steroids, calcineurin inhibitors or coal tar	17 (1/6)	83 (5/6)			NK	NK
Wolf et al., 2013 (255)	10	6/4	29–61	Severe, refractory AD[$]	Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20				30 (3/10)	70 (7/10)	64.8±18.9	54.5±22.8 (16)
Rubegni et al., 2012 (261)	7	3/4	18–72	AD recalcitrant to standard therapies for >6 months	Every 2 weeks for 3 months, then modified according to clinical response (all patients received >24 cycles)	Cyclosporin A, 6-methyl-prednisolone or none	NK	NK	NK	NK	78-85	0–26 at 24 months (stabilisation at 12 months in 57 [4/7] of patients)

Chiricozzi et al., 2014 (374)	3	2/1	10-57	Recalcitrant and debilitating atopic dermatitis with SCORAD 41 to 58, previously received topical and systemic therapies with poor response	Variable schedule with a total of 4, 10 and 20 cycles within 2 to 20 weeks	NK	0/3 (0)	2/3 (67)	1/3 (33)	0/3 (0)	50.3±7.0	24±8.0 (52)
Koppelhus et al., 2014 (262)	20	15/5	20-45	Chronic severe atopic dermatitis with SCORAD 40-89, refractory to topical steroids, tar, and UVA, UVB, PUVA	Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16	Topical emollients	0/20 (0)	12/20 (60)	6/20 (30)	2/20 (10)	69±16	37±16 (46)
Summary of all studies (2018 Table)							10 (9/90) *	44 (40/90) *	24 (22/90) *	21 (19/90)*		

AD, atopic dermatitis; CR, complete response; ECP, extracorporeal photopheresis; MR, minor response (>25% improvement in skin lesions/scores); NK, not known; NR, no response; PUVA, psoralen plus UVA; PR, partial response (>50% improvement in skin lesions/scores); SCORAD, SCORing Atopic Dermatitis; SD, standard deviation; UV, ultraviolet.

[#]In the twelve months before ECP, patients were refractory to all three first-line therapies, i.e., topical steroids, topical calcineurin inhibitors and one form of phototherapy (UVA, UVB or PUVA).

[$]Inclusion criteria: severe, refractory AD; SCORAD >45; during last twelve months refractory to first-line therapies, including topical steroids, calcineurin inhibitors and phototherapy as well as refractory to one second-line therapy, including systemic steroids or cyclosporine.

+Standard therapies included photo(chemo)therapy, externally and internally administered corticosteroids and other immunosuppressive drugs (e.g. cyclosporine).[&]Five patients were not evaluated (due to short treatment course) and were not included in the further analysis, including the calculation of male/female ratio.

†Numbers in parentheses indicate treatment cycles that were given only to a portion of the patients.

*From a total of 34 patients of four studies (258, 260, 261, 269) a categorised response was not available, resulting in a total number of 67 patients as the base for the percentage calculation of the response rates.

Table 9: Synopsis of recommendations on the use of ECP in different diseases.

Condition	Patient selection	Treatment schedule	Maintenance treatment	Response assessment
Cutaneous T-cell lymphoma (mycosis fungoides, Sézary syndrome)	First-line treatment in erythrodermic stage IIIA or IIIB, or stage IVA1–IVA2	One cycle every 2 weeks initially, then every 3-4 weeks Continue treatment for 6-12 months for response evaluation	Treatment should not be stopped, prolonged for >2 years (treatment intervals up to 8 weeks)	To be performed every 3 months Wait for at least 6 months of treatment before concluding that ECP is not effective
Chronic graft versus host disease	Second-line therapy Individual clinical settings may justify first-line treatment	One cycle every 1-2 weeks for 12 weeks followed b interval prolongation in accordance with response	After 12 weeks, treatment intervals could be increased by 1 week every 3 months depending on response	The disease should be monitored according to the NIH guidelines
Acute graft versus host disease	Second-line therapy in pts refractory to corticosteroids (2 mg/kg/day)	Weekly basis, 2–3 treatments per week	Discontinue ECP in patients with CR No evidence that maintenance is beneficial	Every 7 days with staging according to published criteria
Solid-organ transplantation (lung)	Salvage therapy for lung transplant rejection when conventional	One cycle every 2 weeks for the first 2 months, then	If clinical stabilisation occurs with ECP, long-term continuation might be	Pulmonary function test (FEV1 value)

	therapies do not produce an adequate response	once monthly for 2 months (total of 6)	warranted to maintain the clinical response	Successful treatment defined as FEV1 stabilisation or slowing decline
Scleroderma	Second-line or adjuvant therapy in mono- or combination therapy ECP should be considered to treat skin but not organ involvement	One cycle every 4 weeks for 12 months	Increase the intervals by 1 week every 3 months based on clinical course	Clinically and photographically using validated scoring systems
Atopic dermatitis	Second-line and if >18 months' duration; SCORAD >45; refractory in the last year to all first-line therapies (topical steroids, calcineurin inhibitors, dupilumab and phototherapy) or to one second-line therapy (systemic steroids, cyclosporine)	One cycle every 2 weeks for 12 weeks	Intervals depending on the individual response of a patient, e.g., every 4 weeks for another 3 months; at maximal response, treatment should be tapered to one treatment cycle every 6–12 weeks	SCORAD assessment every 2 weeks for the first 12 weeks, and thereafter every 4 weeks or at longer intervals
Crohn's disease	Moderate to severe steroid-dependent disease, refractory or intolerant to immunosuppressive and anti-TNF agents	One cycle every 2 weeks for 12–24 weeks	No data available	Crohn's Disease Activity Index Score
Miscellaneous dermatological diseases (pemphigus, epidermolysis bullosa acquisita,	Recalcitrant to conventional systemic therapies	One cycle every 2-4 weeks for 12 weeks then one cycle every 4 weeks	Treatment tapering by increasing intervals by 1 week every 3 months	Clinically and photographically using validated scoring systems and autoantibody titre, at least in the case of pemphigus vulgaris.

erosive oral lichen planus)				

CR, complete response; ECP, extracorporeal photopheresis; FEV1, forced expiratory volume in 1 second; NIH, National Institutes of Health; SCORAD, SCORing Atopic Dermatitis; TNF, tumour necrosis factor.

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Conflicts of interest disclosures

Dr. Arenberger has nothing to disclose.

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