DOI: 10.1111/jdv.16889 JEADV

GUIDELINES

European dermatology forum: Updated guidelines on the use of extracorporeal photopheresis 2020 – Part 2

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Abstract

Background Following the first investigational study on the use of extracorporeal photopheresis for the treatment of cutaneous T-cell lymphoma published in 1983, this technology has received continued use and further recognition for additional earlier as well as refractory forms. After the publication of the first guidelines for this technology in the JEADV in 2014, this technology has maintained additional promise in the treatment of other severe and refractory conditions in a multidisciplinary setting. It has confirmed recognition in well-known documented conditions such as graft-vs.-host disease after allogeneic bone marrow transplantation, systemic sclerosis, solid organ transplant rejection including lung, heart and liver and to a lesser extent inflammatory bowel disease.

Materials and methods In order to further provide recognized expert practical guidelines for the use of this technology for all indications, the European Dermatology Forum (EDF) again proceeded to address these questions in the hands of the recognized experts within and outside the field of dermatology. This was done using the recognized and approved

guidelines of EDF for this task. All authors had the opportunity to review each contribution as it was added.

Results and conclusion These updated 2020 guidelines provide at present the most comprehensive available expert recommendations for the use of extracorporeal photopheresis based on the available published literature and expert consensus opinion. The guidelines were divided into two parts: PART I covers Cutaneous T-cell lymphoma, chronic graft-vs.-host disease and acute graft-vs.-host disease, while PART II will cover scleroderma, solid organ transplantation, Crohn's disease, use of ECP in paediatric patients, atopic dermatitis, type 1 diabetes, pemphigus, epidermolysis bullosa acquisita and erosive oral lichen planus.

Received: 26 June 2020; Accepted: 6 August 2020

Conflict of interest

Dr. Arenberger has nothing to disclose. Dr. Arun reports research from Mallinckrodt Ltd, personal fees from Mallinckrodt Ltd, outside the submitted work. Dr. Assaf has nothing to disclose. Dr. BAGOT reports personal fees from Kyowa Kirin, personal fees from Takeda, personal fees from Helsinn, personal fees from Innate Pharma, outside the submitted work; in addition, Dr. BAGOT has a patent Anti-KIR3DL2 antibody licensed. Dr. Berlin has nothing to disclose. Dr. Bohbot reports other from Therakos during the conduct of the study. Dr. Calzavara-Pinton has nothing to disclose. Dr. Child has nothing to disclose. Dr. Cho has nothing to disclose. Dr. French has nothing to disclose. Dr. Gennery reports grants from Mallinkrodt, during the conduct of the study. Dr. Gniadecki reports personal fees from Mallinckrodt, during the conduct of the study, personal fees from Lilly, personal fees and other from AbbVie, grants and personal fees from Sanofi, personal fees from Sun Pharma, personal fees from Janssen, outside the submitted work. Dr. Prof.Dr. Gollnick has nothing to disclose. Dr. Greinix reports personal fees from Mallinckrodt, personal fees from Novartis, personal fees from Roche, personal fees from Amgen, personal fees from Celgene, during the conduct of the study. Dr. Guenova reports personal fees from Mallinckrodt, outside the submitted work. Dr Peter Jaksch has nothing to disclose. Dr. Jantschitsch has nothing to disclose. Dr. Klemke has nothing to disclose. Dr. Knobler reports speaker fees from Mallinckrodt-Therakos. Dr. Ludvigsson has nothing to disclose. Dr. Papadavid has nothing to disclose. Dr. Scarisbrick has nothing to disclose. Dr. Schwarz has nothing to disclose. Dr. Stadler has nothing to disclose. Dr. Wolf reports grants and other from AbbVie, other from Almirall, other from Amgen, other from Celgene, other from Eli Lilly, other from Janssen-Cilag, other from Kwizda, other from Leo Pharma, other from Merck Sharp & Dohme, other from Novartis, other from Sanofi-Aventis, grants and other from Pfizer, personal fees from Therakos, during the conduct of the study. Dr. Zic has nothing to disclose. Dr. Zouboulis reports personal fees from AccureAcne, Allergan, Almirall, Bayer Healthcare, General Topics, GSK/Stiefel, Idorsia, Incyte, Jafra Cosmetics, Janssen, Jenapharm, L'OREAL, Regeneron, Sobi; personal fees and honoraria to his employer for his participation to clinical studies from AbbVie, Galderma, Novartis, InflaRx, NAOS-BIODERMA, Pierre Fabre, PPM and UCB; and honoraria to his employer for his participation to clinical studies from AOTI and Astra Zeneca. Dr. Zuckermann reports personal fees from Therakos-Mallinckrodt, outside the submitted work.

Funding sources

None declared.

Introduction

This manuscript is Part II of the *European Dermatology Forum Updated Guidelines on the Use of Extracorporeal Photopheresis 2020* and contains the following indication for extracorporeal photopheresis: scleroderma, solid organ transplantation, Crohn's disease, use of ECP in paediatric patients, atopic dermatitis, type 1 diabetes, pemphigus, epidermolysis bullosa acquisita and erosive oral lichen planus.

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.[1,2] 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%.[3] 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.[3-6]

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 DR-specific human leucocyte antigen alleles such as DR-5) and/or viruses (retroviruses, cytomegalovirus [CMV]) may be associated with the development of SSc.[7]

Interestingly, it has been shown that foetal $CD3^+$ T cells from prior pregnancies are detectable in blood and lesional skin of females with SSc.[8] This observation suggests that in distinct cases, T-cell microchimerism may be directly involved in the pathogenesis of SSc by initiating a graft-vs.-host-like response. Furthermore, clonal T-cell populations have been identified in the blood and skin of patients with SSc.[9-11]

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 randomized, controlled trials.[2] 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 randomized clinical trials, seven open trials, prospective or retrospective series, and several case reports. In the first multicentre trial, 79 patients with SSc of recent onset (mean symptom duration 1.83 years) and progressive skin involvement entered into a randomized, 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.[12] At both the 6- and 10-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 6 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 10 months.

In a crossover trial reported by Enomoto in 1999, nineteen patients with progressive SSc of less than 5 years' duration were randomly assigned to one of two groups: Group A (n = 10) received ECP according to the standard protocol for 1 year, and group B (n = 9) received no treatment.[13] The main outcome parameter was the skin score after 1 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 randomized, double-blind, placebo-controlled, multicentre clinical trial reported by Knobler *et al.* in 2006, a total of 64 patients with SSc received monthly either active (n = 27) or sham (n = 37) ECP therapy on two consecutive days for 12 months, and the severity of both skin and joint involvement was assessed.[14] A statistically significant improvement in skin scores compared with baseline was observed at 6 ($P = 0.0024$) and 12 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 6 ($P = 0.002$) and 12 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 16–57 months revealed an overall improvement and/or stabilization of skin changes and physical performance in 5 of the 11 patients (45%).[15] Extracutaneous manifestations deteriorated in 10 of the 11 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 6 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.[16] 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.[17] 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 correlates with amelioration of skin symptoms in the nineteen SSc patients included in the study.[18]

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.[19] 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].[20,21] However, ECP therapy did not affect the risk of lung cancer in patients with SSc.[19]

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 randomized, 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 4 weeks for 12 months.[14]

Maintenance should only consist of one treatment cycle per month for skin symptoms of SSc. Before stopping ECP, treatment intervals can be prolonged by 1–2 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.

Solid organ transplantation

Lung transplantation

Based on the recent ISHLT registry data, more than 4000 lung transplantations were performed in 2015.[22] 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.[23] 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 characterized 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%.[24] 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.

Bronchiolitis obliterans syndrome is a significant factor limiting long-term survival after lung transplantation, which is approximately 50% at 5 years. The most precipitous decline of airflow typically occurs in the first 6 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).[25] 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 are 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 'stabilization' or 'slowing' of the decline of FEV1 rather than the real improvement or normalization 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.[26]

ECP is utilized as salvage therapy for the treatment of lung transplant rejection when conventional therapies result in an inadequate clinical response.[27] Importantly, ECP is not associated with an increased risk of infection, which, however, frequently occurs with immunosuppressive drugs.[28] 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 3 weeks and histologically after 4 weeks of ECP therapy.[29] 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 stabilized the decline of pulmonary function.[30] ECP was performed at monthly intervals without the detection of significant complications. Then, ECP was implemented in the therapy of refractory BOS. ECP stabilized pulmonary function and improved survival after monthly treatment cycles, each performed on two consecutive days.[31,32] Villanueva *et al.* reported on their experiences with ECP in fourteen lung transplant patients – all were diagnosed with BOS and received 3–13 (median 6) ECP treatments.[32] 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 retransplanted).[32]

O'Hagan *et al.* described five patients with severe BOS refractory to augmented immunosuppression, such as methotrexate, ATG and OKT3. Temporary stabilization 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.[31] 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 36 months, four patients remained in stable clinical condition without the occurrence of any ECP-related complication.[33]

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.[34] In transplant recipients with BOS, the decline in FEV1 was 112 mL/month before ECP was started, but only 12 mL/month after 12 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 stabilization.

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.[35] 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 51 patients with BOS treated with ECP between 2001 and 2011.[36] A total of thirty-one (61%) patients responded to the ECP therapy and showed continued stabilization of lung function (FEV1 range −5% to +5% compared with baseline at the start of ECP) over 6 months. Responders to ECP showed significantly better survival probabilities and less need for retransplantation 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.[37] Out of a total of sixty-five patients treated with ECP, 64 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 categorized 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 stabilized, 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.[38]

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.[39] 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.[40] 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 proinflammatory and anti-inflammatory cytokines. ECP also reduced circulating levels of proinflammatory 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 1 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 United States.[41] This registry study plans to enrol 160 patients from multiple centres across the United States 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 stabilization of lung function.[30,31,34,38,42] 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[43] 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 post-TX 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 post-TX 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 re-evaluated. In cases of further decrease in 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 5000 cardiac transplantation procedures were performed in 2015.[44] 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.[44] 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.[45] After the first year, CAV is the second most common cause of death (the first is malignancy). Its pathogenesis, although not fully understood, is characterized by a fibroproliferative process that affects all cardiac arteries and results in concentric narrowing, obliteration and ultimately allograft failure.[45] CAV is detectable by angiography in 8% of survivors within the first year and in more than 30% within the first 5 years.[44] 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.[45]

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 2–4 ECP treatments. In 1998, the first multicentre randomized clinical trial of cardiac transplant recipients receiving ECP was published.[46] In this study, sixty patients were randomized post-transplant to receive either standard triple immunosuppressive therapy or standard triple immunosuppressive therapy plus ECP started within 30 hours after transplant surgery. After 6 months of follow-up, the addition of ECP (10 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 ($P = 0.036$).[46]

In 2000, a prospective randomized 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.[47] 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 6–8 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 12 and 24 months was detected in the ECP group.[47]

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.[44] However, some patients still experience severe organ rejection and steroid-resistant and/or recurrent rejection episodes.

Dall'Amico investigated 11 patients with recurrent acute cardiac rejection who received ECP therapy for 3 months. In general, patients responded well and showed a significant reduction in acute rejection episodes and the severity of rejection grades.[48] However, six patients suffered from chronic organ rejections in the first 5 years after the start of treatment. In another study, Lehrer published a report on four patients presenting with severe organ rejections (ISHLT R3).[49] 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.[50] In this retrospective analysis, 36 patients receiving ECP therapy for at least 3 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 the use of multivariate hazard function analyses. After 3 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.[50]

In 2014, Dieterlen *et al.* published the first report on immunological parameters in cardiac transplant patients undergoing ECP.[51] 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.[52] 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 6 months. Overall survival rates were 84% in the first year after ECP and 53% after three years. The authors suggested that non-adherence to medication in 55% of patients is associated with worse outcome (adherent: 3-year survival rate is 53%; non-adherent: 3-year survival rate is 18%, $P = 0.06$).[52]

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.[53]

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 randomized multicentre trial is essential to clarify the role of ECP in cardiac transplantation in the future.[54]

Existing clinical guidelines

The UK Photopheresis Society noted the following[55]:

- 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 are 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.[56] 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 randomized trials or meta-analysis of such studies) for the treatment of recurrent or resistant acute cellular rejection.[57]

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 randomized 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 titre 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.[58-71] In 2007, Urbani *et al*. published a prospective study in 36 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.[72] ECP was administered at day two and day six post-transplant, 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 hospitalization 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 randomized 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.[73] 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 6 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 ($4.9 \pm 1\%$ to $9.4 \pm 15\%$) and inducible T-reg cells ($CD3^+$, $CD8^+$, $CD28^-$) were observed among CD3 cells ($3.3 \pm 3\%$ to $11.8 \pm 8\%$, $P = 0.025$) 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 ($9.4 \pm 15\%$ vs. $3 \pm 1\%$; $P = 0.01$) after 3 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.[74] 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.[75] 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 3 years post-transplant) 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, randomized, 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 2 weeks for the first 2 months, followed by one cycle once per month for another 2–4 months. The optimal duration of ECP therapy remains to be explored. The number of treatment cycles ranges from 6 to 24. If clinical stabilization 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 'stabilization' or 'slowing' of the FEV1 decline.

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.[76] 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.[77] 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.[78]

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.[79] ECP was administered as two treatments every two weeks for a total of 24 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 24-week steroid-tapering period, and underwent a forced steroid-tapering protocol.[80] Steroid-free remission was achieved in 7 out of 31 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%.[81]

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 4 weeks, tapering to twice every other week for another 6 weeks.[82] Among the 28 patients included, there was a marked reduction in the Crohn's Disease Activity Index score during the 12-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.

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 (3338 transplants) in 2015 were paediatric allogeneic transplants.[83] There are plenty of data in the literature that support the use of ECP in paediatric patients (Table 1). However, to date, there are no randomized clinical trials available that demonstrate the superiority of ECP to other treatments in acute or chronic paediatric GvHD.[84,85] 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.[86]

Although the use of ECP is well established in paediatric patients, it remains a challenging task.[87] The placement of venous access by the 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.[88] A rare but potentially fatal complication in low body weight patients is mechanical haemolysis induced by the equipment.[89] 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 body weight patients, the volume may need to be adjusted to prevent adverse reactions.[55] However, when taking these measures into account, low body weight patients can be treated successfully.[90] 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 specialized centres. The patients treated with ECP will probably benefit from its steroid-sparing effect.

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.[91–93] 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.[94] 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.[95–98] 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.[99,100]

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, 311 nm UVB or PUVA.[91,92,94,101,102]. 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

Table 1 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[109]	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[116]	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[111]	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[113]	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[115]	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[114]	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[117]	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[126]	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[110]	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[112]	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)

Table 1 *Continued*

	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)
Rubegni *et al.*, 2012[118]	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-methylprednisolone or none	NK	NK	NK	NK	78-85	0–26 at 24 months (stabilization at 12 months in 57 [4/7] of patients)
Chiricozzi *et al.*, 2014[192]	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 2–20 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[119]	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 12 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[115,117,118,126], a categorized response was not available, resulting in a total number of 67 patients as the base for the percentage calculation of the response rates.

include rituximab, omalizumab, mepolizumab or ustekinumab, have been found to be effective in severe cases of AD.[103,104] 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.[105] A randomized controlled phase 2 study has revealed that nemolizumab, a humanized 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.[106] 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.[107] 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.[108] ECP is safer with less risk of adverse effects than many systemic and topical therapies for CTCL.[109–117]

In 1994, Prinz *et al.* first described the successful administration of ECP in the treatment of three severe cases of AD.[109] 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.[110–118] In most studies, ECP was administered in biweekly cycles for at least 12 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 generalized AD.[114] 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 summarized in Table 2. 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% and 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.[118] ECP performed according to a 20-week protocol led to a SCORAD reduction of more than 25% in only 3 of 10 patients.[112] 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.[112]

The effect of ECP (administered on two consecutive days a month) was compared to oral cyclosporine A (3 mg/kg/day) in a randomized crossover study including twenty patients with severe AD (SCORAD index 41–89) refractory to other therapies.[119] Patients were allocated to a 4-month course of either of the two treatment modalities, and fifteen patients completed crossover treatment. Both ECP and oral cyclosporine A significantly decreased the SCORAD (from 69 to 37, i.e. an overall reduction of 46%; and 67–44, i.e. a reduction of 34%) and the pruritus index (from 6.5 to 2.4 and 7.3–4.0, 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.[112–115] Radenhausen *et al.* reported no significant correlation between a decrease in these levels and values of blood eosinophils.[114] However, in comparison with ECP responders, most non-responders were characterized by very high levels of total IgE before and during therapy.[114]

It is intriguing to note that ECP has also been shown to be effective in erythrodermas of another non-atopic origin, such as red man syndrome, erythrodermic pityriasis rubra pilaris or photoaccentuated erythroderma associated with $CD4^+$ T-lymphocytopenia.[120–123] Together, no serious side effects have been reported so far in AD and other diseases treated with ECP.[112,119]

In summary, several open clinical trials with small numbers of patients and one randomized 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.[124]

Existing clinical guidelines

According to US guidelines, response rates to ECP differ among AD patients, ranging from complete remission to no response.[124,125] 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.[43,92,103,104]

Table 2 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-vs.-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-vs.-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 therapies do not produce an adequate response	One cycle every 2 weeks for the first 2 months, then once monthly for 2 months (total of 6)	If clinical stabilization occurs with ECP, long-term continuation might be warranted to maintain the clinical response	Pulmonary function test (FEV1 value) Successful treatment defined as FEV1 stabilization 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, erosive oral lichen planus)	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.

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.

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 12 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 12 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.[112]

Treatment schedule Atopic dermatitis 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 6–12 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.[112,114,115,117,118,126] 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 2-week intervals during the treatment period for the first 12 weeks, and then at 4-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.[112,127-129]

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.[99,100,112] 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.[130]

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.[131–135] 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.[136,137] 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.[138] 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.[139] 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.[140]

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.[141–149] 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 non-obese 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 optimize ECP therapy in type 1 diabetes patients. For instance, the combination of ECP with β-cell antigens might provide a more potent protective effect.[150]

To date, there is only a single well-designed study available in the literature using ECP in newly diagnosed patients with type 1 diabetes.[151] 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; 40 patients completed the study, five double ECP/placebo treatments were given over 6 months, and patients were then followed up for 6 years (19 patients received active treatment with ECP, 21 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.[74]

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.[152–156] 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.[157] In another study, three patients with recalcitrant foliaceus pemphigus received ECP: CR was seen in one patient, and PR was detected in two patients.[154,156,158]

ECP was performed every two to 4 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.[159] 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 4 weeks for 3–6 months until complete remission. After 6 months, treatment should be tapered according to clinical response (e.g. prolonging the treatment intervals by 1 week every 3 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).[160] Also, the determination of autoantibody titres should be performed, at least in pemphigus vulgaris.

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.[157,161–163] The number of ECP cycles ranged from three to 32, given at 3–4-week intervals. The OR was 88% (7/8 patients), with 50% (4/8) of patients achieving CR. The time to CR was short: 6–8 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*.[157] After ECP, circulating antibasement membrane zone autoantibodies was 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 11–24 months for 5 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 3 months after the initiation of conventional therapy; no washout period is required. Initial ECP treatment should consist of one cycle (two ECP procedures) every 2 weeks for 12 weeks, followed by one cycle every 4 weeks for weeks 12–24 until CR.

After 24 weeks, treatment should be tapered according to the clinical response (e.g. treatment intervals should be prolonged by 1 week every 3 months).

Response assessment The clinical response should be monitored by the two currently accepted clinical scores, namely ABSIS and PDAI.[160].

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.[164] 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 24-month follow-up period.

Other studies have tested the efficacy of ECP for EOL, including case reports and one open study of 12 patients, in a total of 26 patients.[165-169] 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.[167,169] 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 12 of 13 patients either during ECP therapy or long-term follow-up (mean 8.3 months after ECP withdrawal).[167,169] However, relapses were sensitive to ECP reintroduction. ECP was exceptionally well-tolerated, with lower lymphocyte counts observed only in a few patients.[167,169]

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 2 weeks, followed by one cycle of two procedures every 4 weeks for the weeks 12–24 until CR.

After 24 weeks, treatment should be tapered according to the clinical response (e.g. prolonging the treatment intervals by 1 week every 3 months).

Response assessment Disappearance of oral lesions.

Lupus erythematosus

Non-specific anti-inflammatory and immunosuppressive drugs such as non-steroidal anti-inflammatory drugs, corticosteroids, thalidomide, antimalarial drugs, cytotoxic agents and biologics are the standard treatments to control lupus erythematosus (LE).[56,170,171] However, some patients are non-responsive or poorly responsive to these treatments, have contraindications or develop toxic adverse events.[56,171]

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.[56,171]

To date, eighteen female patients with LE have been treated with ECP.[172–177] 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 bimonthly intervals for 6 months or until remission.[172–177] 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.[172] Of note, ECP therapy did not induce exacerbation of other SLE symptoms, irrespective of the patient's photosensitivity status.[172–176] Remission was prolonged (up to 4 years) in many patients, even without maintenance ECP therapy.[173,175] In one patient, an early relapse was detected, but LE lesions were amenable to another treatment cycle.[173] Marked changes in levels of specific routine laboratory parameters and autoantibodies were not seen.[172–177]

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.[172] One patient died six months after initiation of the ECP programme, with death occurring 10 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.[172] Serious side effects have not been observed during ECP therapy in the remaining patients. In general, ECP treatment was well tolerated.[173–177]

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 randomized 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.

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.[178–190]

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 32 years ago.[191] 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.

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

Acknowledgements

The authors thank Christian Joukhadar, Christian Kunte, Pablo Luis Ortiz-Romero, Meinhard Schiller, Ulrike Just, Harald Maier and Constanze Jonak for their excellent assistance in the development of these guidelines.

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