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Therapeutic implications of extracorporeal photopheresis for rheumatic diseases

Implikacje terapeutyczne fotoferezy zewnątrzustrojowej w chorobach reumatycznych

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Summary

Extracorporeal photopheresis (ECP) procedure is based on mononuclear cells (MNC) apheresis and their extracorporeal UVA exposure. It has been applied mainly in hematology and transplantation. Over thirty years of experience confirmed its effectiveness, outstanding safety profile and good tolerance. These observations encourage the implementation of ECP in the treatment of autoimmune connective tissue diseases. The procedure might be considered in refractory cases, when the first line treatment strategies do not control disease activity or immunosuppressants are contraindicated and in the group of patients with high risk of infections. Current literature about using ECP in rheumatology is scarce and most data come from case reports and small observational studies. Systemic sclerosis is the most studied rheumatic disease in the field of ECP use. The disease appeared on the list of clinical applications of ECP therapy according to American Society for Apheresis. However, no European or American guidelines, or recommendations for the treatment in rheumatology suggest ECP as the treatment option. There are no standards in performing ECP in rheumatic diseases concerning indications, length of therapy, concomitant immunosuppressive treatment, follow up or patients characteristic. In this review, we have searched literature concerning ECP use in rheumatic diseases.

Keywords: **ECP, extracorporeal photopheresis, rheumatic diseases, systemic sclerosis**

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Abbreviations: **ACR** – American College of Rheumatology, **aGvHD** – acute graft versus host disease, **APCs** – antigen presenting cells, **AS** – ankylosing spondylitis, **ASFA** – American Society for Apheresis, **cGvHD** – chronic graft versus host disease, **CR** – complete response, **DCs** – dentritic antigen-presenting

cells, **ECP** – extracorporeal photopheresis, **EF** – eosinophilic fasciitis, **EULAR** – European League Against Rheumatism, **GvHD** – graft versus host disease, **LE** – lupus erythematosus, **MNC** – mononuclear cells, **8-MOP** – 8-methoxypsoralen, **PUVA** – psoralen and ultraviolet A, **SLE** – systemic lupus erythematosus, **T regs** – regulatory T cells.

INTRODUCTION

Extracorporeal photopheresis (ECP) is a method of white blood cells ex vivo manipulation to decrease T cells activity after they are reinfused to the patients. The modality has been successfully used in cytotoxic T cells-mediated injuries for over thirty years. The first successful employment of ECP took place in cutaneous T cell lymphoma [10]. Based on some observations regarding the cytotoxic mechanism of some diseases, ECP has been further applied in graft versus host disease (GvHD) following hematopoietic stem cells transplantation [31], in graft rejection following solid organ transplantations [3, 8, 47, 49] and recently in some autoimmune diseases [1, 23, 41], which is the main interest of this review.

The mechanism of ECP remains still ambiguous. Recent data support the idea of ECP immunomodulatory effect based on dendritic antigen-presenting cells (DCs) activation. The process of monocytes to DCs maturation is initiated by extracorporeal surfaces of ECP device. DCs as antigen presenting cells get loaded with patient specific lymphoid antigens. As a result lymphoid cells undergo apoptosis and phagocytosis. ECP is a sophisticated method modifying two main tasks of the immune system: tolerance for self cells and recognizing foreign antigens (pathogens and damaged/cancer cells) [6]. For that reason ECP is a clinically useful therapy method in many areas of medicine: oncology, hematology, transplantology, rheumatology and etc. [34].

Current therapy of rheumatic disease is based on immunosuppressants and in recent years many new drugs with different mechanism of action were developed. Simultaneously, concerns about side effects are being raised in the context of infections or malignancies during a long-term immunosuppressive therapy.

ECP with an excellent safety profile and relatively high response rate in cell-mediated autoimmunity remains a very good therapeutic option, especially when the first line treatment strategy is not effective or immunosuppressants are contraindicated.

ECP PROCEDURE

ECP procedure is based on mononuclear cells (MNC) apheresis and their extracorporeal UVA exposure. There are two main modalities of ECP procedure currently available: so-called "on-line system" based on integrated apheresis and phototherapy device (Therakos®) and another one, so called "off-line system " (Macopharma®, PIT Medical Systems®), which needs an independent cells apheresis system and its product is irradiated in a dedicated UVA device. Regardless of the system used, the ECP idea remains the same. MNC (mainly lymphocytes) are harvested from peripheral blood of patients in centrifugal apheresis procedure of blood without any prior stimulation (red cells and plasma are returned to the patient). When collected, cells are mixed with 8-methoxypsoralen (8-MOP) added into a collection bag and after all the apheresis product is illuminated with UVA and immediately reinjected to the patient. It is essential to keep low hematocrit of the product not to let RBC interfere with WBC UVA access. The photoactivated 8-MOP binds to pyrimidine bases of DNA resulting in cross-linking of the two DNA strands and further induces the treated cells to apoptosis along with activating antigen presenting cells (APCs) [4, 29]. Up to 5–15% of treated mononuclear cells undergo apoptosis on reinfusion and mainly localize in the spleen or liver where they are phagocytized by APCs. The number of MNC undergoing apoptosis is relatively low, so the procedure must be repeated to sustain the immunomodulating effect.

ECP POTENTIAL MECHANISM OF ACTION IN AUTOIMMUNE DISEASES

APCs have been proved to play an essential role in "programming" immune system into tolerance or active response. APCs recognize T-cell apoptotic markers and induce down regulation of cellular response. ECP may enhance this effect by forcing T cells into apoptotic pathway. During ECP, photoactivated 8-MOP causes crosslinking of DNA within the nuclei of lymphocytes, leading to apoptosis of these cells. After reinfusion of the illuminated apheresis product, APCs recognize T cells surface apoptotic markers and communicate with spleen cells of the same antigen specificity which results in the production of some specificity regulatory T cells (T regs) [50]. It means ECP pushes the immunological balance towards the clonal specific T regs predominance with immunological tolerance in effect. There have been some experiments partly explaining the above observations.

Morelli et al. reported reduced levels of proinflammatory cytokines (IL-1, IL-6, TNF-a) after incubation of APCs with apoptotic cells [32]. Lamioni et al. concluded that ECP increases the number of T regs in peripheral blood [26]. On the other hand, Maeda et al. showed that ECP increases the level of anti-inflammatory IL-10 in serum what is another example of ECP "pro tolerance" action [27]. Very interesting results have come from Gatza et al. They were able to reverse experimental graft versus host disease by transferring T regs from ECP-treated donors [15]. In summary, ECP by increasing the number of T regs and changing cytokine balance towards anti-inflammatory direction is a unique method of multivariate modulation of immune system response toward tolerance.

ECP ADVANTAGES AND SIDE EFFECTS

ECP has been widely tested and implemented in acute graft versus host disease (aGvHD), a life-threatening complication after allogeneic stem cells transplantation [5, 16, 36]. Despite a high response rate, the procedure proved to be more effective and safer than conventional immunosuppression with anticytokine therapy included [14, 21]. Jagasia et al. compared the results of treatment in steroid refractory aGvHD patients treated with ECP vs etanercept. The complete response (CR) rate was significantly higher for ECP. In the same work, a non-relapse mortality (including infectious complications and GvHD progression) in a multivariate analysis was significantly lower for ECP [21]. Another paper by Greinix et al. presents very interesting results. The authors estimated the results of ECP in steroid dependent aGvHD and the possibility of steroid dose reduction. In the whole 56 patients group, the median steroid dose at the start of ECP was 2.1 mg/kg b.w./day and after 4 and 8 weeks of ECP it was 0.9 and 0.3 mg/kg b.w./day, respectively. In all patients, steroids were discontinued in a median time of 55 days with a satisfactory response [19]. The other condition with ECP implemented in a wide range of studies was chronic graft versus host disease (cGvHD) [17, 20, 36], a severe complication of allogeneic stem cells transplantation with a multi-organ involvement and variety of symptoms coming from sclerodermic features frequently. A very large study of Flowers et al. comparing conventional treatment (with cyclosporin A, mycophenolate mofetil and tacrolimus) vs conventional treatment combined with ECP in steroid dependent cGvHD cases revealed a comparable advantage of combined treatment. Both groups of patients were heavily steroid pretreated, but the median time of pre-study steroid treatment was similar (ECP and non-ECP group – 55 and 50 weeks, respectively). The most significant result of the study (the endpoint designed as >50% reduction of steroid dose with a final steroid dose <10 mg-kg b.w./day) was achieved by 21% of patients in the ECP group vs 6% of patients in a non-ECP group. The cumulative probability of response was 46% vs 11%, respectively (significant results). The authors did not find any specific or more increased complications for the ECP group [13].

There are very few disadvantages of ECP procedure, and they do not differ from other therapeutic apheresis complications. ECP is a very well tolerated procedure and the incidence of any adverse events is less than 0.003% [37]. The most common side effects, such as nausea or headache, are mild and occasionally observed [18, 37]. During cell collection, the transient hypotension may occur, but it can be easily managed with a proper fluid flow. Other adverse events include central catheter related complications, which are widely known. There are no data on increasing infection or malignancy rate by ECP [37]. ECP does not interfere with the concurrent immunosuppressive treatment, helping to reduce steroid dose with no additional complications. The above mentioned data support the idea of using ECP as an option for steroid dependent or refractory patients and/or with infectious complications patients with autoimmune diseases.

ECP IN RHEUMATIC DISEASES

ECP seems to be useful in diseases with T-cell activity abnormalities. The hypothesis is that ECP influences the immune system by physicochemically altered lymphocytes. According to literature data, among rheumatic diseases those treated with ECP are the following: systemic sclerosis, systemic lupus erythematosus (SLE), rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis. In most cases, ECP was used as a second-line therapy, in severe, refractory disease course, after the failure of a standard treatment regimen.

Current literature about using ECP in rheumatology is scarce. Systemic sclerosis is the most studied rheumatic disease in the field of ECP use. No European (European League Against Rheumatism, EULAR) or American (American College of Rheumatology, ACR) guidelines, or recommendations for the treatment in rheumatology suggest ECP as the treatment option. There are no standards in performing ECP in rheumatic diseases concerning indications, length of therapy, concomitant immunosuppressive treatment, follow up or patients characteristic. It is a result of the lack of controlled and randomized clinical trials in this particular area. Most data come from case reports, small observational studies, or case-control studies. However, available data from clinical observations bring encouraging results. The ECP method may allow for the reduction of steroids and immunosuppressant drugs, leading to the reduction of side effects, mainly due to steroids use. Safety and good tolerance of ECP make this method promising and worth analyzing.

Current guidelines of the American Society for Apheresis (ASFA) on the use of therapeutic apheresis in clinical practice summarize up-to-date literature data (Eight Special Issue) on using a wide range of procedures, including ECP, in different disease manifestations [34]. Among them, one rheumatic disease is mentioned in which ECP may be considered as a therapeutic option. Classification to the third category and low grade of recommendation is a result of limited data and quality of literature evidence. In previous ASFA recommendations (2016), dermatomyositis/polymyositis was mentioned with IV category and 2C grade of recommendations meaning very weak references (other alternatives may be equally reasonable) [34, 42]. In 2019 due to the lack of new evidence published, a committee of experts decided to retire the dermatomyositis/polymyositis fact sheets from these guidelines. The summary of the modifications of guidelines on the use of therapeutic apheresis in rheumatic diseases is presented in Table 1.

SYSTEMIC SCLEROSIS

Systemic sclerosis is a chronic disease which leads to permanent organ impairment and is connected with high

Table 1. Category and grade of recommendations for the use of ECP in rheumatic diseases and psoriasis (based on Therapeutic Apheresis Guidelines (ASFA) from 2007 to 2019 (current edition)

ASFA guidelines, year	Disease	Category	Grade
ASFA 2007 [45, 46]	Scleroderma (systemic sclerosis)	IV	–
ASFA 2010 [47]	Scleroderma (systemic sclerosis)	IV	1A
ASFA 2013 [44]	Scleroderma (systemic sclerosis)	III III	2B 2B
ASFA 2016 [43]	Dermatomyositis/polymyositis Scleroderma (systemic sclerosis) Psoriasis	IV III III	2C 2A 2B
ASFA 2019 [35]	Scleroderma (systemic sclerosis) Psoriasis (disseminated pustular)	III III	2A 2B

Definitions: category III – optimum role of apheresis therapy is not established, decision making should be individualized; category IV – disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful; grade 1A – high-quality evidence, strong recommendation, can apply to most patients in most circumstances; grade 2A – high quality evidence, weak recommendation, best action may differ depending on circumstances or patients' or societal values; grade 2B – moderate-quality evidence, weak recommendation, best action may differ depending on circumstances or patients' or societal values; grade 2C – low-quality or very low-quality evidence, very weak recommendations; other alternatives may be equally

risk of mortality. In the pathomechanism of systemic sclerosis, a very important role in the early phase play immunological reaction and vasculopathy, which precede fibrosis process. Systemic sclerosis mainly diffuse form has the worst prognosis among systemic connective tissue disease. The available treatment ameliorates consequences and reduces the progression of the disease. There is a special need to develop a new beneficial therapeutic option. Patients with systemic sclerosis are the largest group of rheumatic patients treated with ECP and reported in the literature on the subject [52].

Systemic sclerosis is on the list of clinical applications of ECP therapy according to the American Society for Apheresis categorized with the number III (role not established) [34]. The most recent observation about the usefulness of ECP in systemic sclerosis was published in 2012 as a case study [35]. The results of three randomized studies and few other case studies are ambiguous. Knobler et al. carried out a double blind randomized placebo controlled study involving 64 patients with systemic sclerosis of less than two years duration [23]. ECP procedure active or shame was performed on two consecutive days, monthly for 12 months at 16 investigational sites in the United States, Canada, and Europe. The patients did not use any other treatment specific for systemic sclerosis. The thickening of the skin (in 22 areas of the body surface) and joint involvement were included in the clinical assessment. After this therapy in the active group (27 patients), improvement in skin and joint changes was noticed after 6 and 12 months in relation to baseline. However, there was no statistically significant difference between the results in the study (active ECP) and the control groups (shame ECP).

The highest number of participants was involved in the study of Rook at al. [41]. In this single-blinded randomized study, in 31 patients with early systemic sclerosis and progressive thickening of the skin ECP was performed also on two consecutive days every month. Significant improvement of skin involvement (severity and area in percentage), oral aperture and hand closure measurements were observed in comparison to baseline after six and ten months of treatment and to the control group with treatment involving D-penicyllamine.

Enomoto et al. described a cross-over design randomized trial with 18 patients [11]. In the first year, the first nine patients received ECP treatment for 12 months and in the second year the group was changed. In this study, there were no statistically significant changes after the treatment in cutaneous involvement, immunologic parameters, or quality of life.

Further publications concerning ECP in systemic sclerosis are case-series studies. The study groups were heterogeneous in type of disease, organs involvement and disease duration. It is also worth noticing that they usually used additional immunosuppressive treatment for systemic sclerosis. ECP treatment was given on two consecutive days at 2-6 weeks intervals. The photosensitive agent, 8-methoxypsoralen (8-MOP) was added ex vivo to the blood cell concentrate but in some cases it was used orally [7, 12, 51]. The duration of the treatment varied from a few to 453 procedures [25]. In most of the studies, the improvement in clinical status of patients was noticed primarily in cutaneous involvement (statistically significant changes), but the treatment was not effective in all of the patients [38]. In the prospective study published by Muellegger et al. in the 11 treated patients skin changes stabilized or improved only in 5; some of them noticed hand function enhancement, but what is really important in 10/11 the organ impairment progressed [33]. What is even more noteworthy in different studies is the fact that the methods of assessment of organ involvement and especially skin involvement were individually designed, which may have influenced the study results.

In all carried out experiments, the procedure of ECP was well tolerated and there were no serious adverse events including infections or malignancies.

The currently available data support the thesis that there is some evidence for the effectiveness of ECP in treatment of skin involvement in systemic sclerosis above all, at an early stage of the disease. Probably, ECP may not be useful in other organs' involvement.

Due to the limited number of available therapies with established efficacy in systemic sclerosis, ECP seems to be a safe method worth considering in some patients, possible at an early stage, combined with other immunosuppressive drugs, with a domination of cutaneous involvement, resistant to other methods of treatment with a special careful monitoring of internal organs function.

SYSTEMIC LUPUS ERYTHEMATOSUS

ECP may represent a promising option in SLE treatment. This method was used in both systemic lupus erythematosus and different manifestations of cutaneous lupus. Knobler et al. studied the effectiveness of ECP in an open clinical trial. Eight out of ten patients with an SLE diagnosis (mild to moderate activity) completed the study [24]. Of the remaining two patients who did not complete the study, one discontinued because of personal reasons and one died 10 days after the last ECP cycle (six months after the initiation of the treatment). Because of close time relationship with the procedure, the influence of ECP cannot be excluded. In the remaining eight patients, improvement in median clinical activity score was observed (decrease from 7 to 1). The study protocol established photopheresis cycles following orally taken 8-methoxypsoralen (according to the scheme: 6 ECP monthly, 3 ECP bimonthly). Improvement in arthritis and skin manifestations (discoid rush, alopecia, but not photosensitivity) was observed. The response to the treatment was noted after 4–6 months and almost all patients (7/8) were able to reduce the dose of steroids and immunosuppressants. No flares occurred during the follow-up lasting 18–30 months. Interestingly, no significant changes in laboratory measurements (including serology tests) were found. The ECP procedure was well tolerated and no serious adverse events (except one presented above) occurred during the treatment and follow-up period.

The literature review also reports on successful ECP treatment of refractory cutaneous lupus erythematosus (LE) – subacute cutaneous LE, chronic discoid LE, disseminated discoid LE and lupus tumidus [22, 39, 51]. The ECP treatment of over a dozen patients with cutaneous LE resulted in most cases in marked regression or complete remission of skin changes. Prolonged remission was observed even after discontinuation of ECP cycles.

There is not enough clinical data supporting ECP treatment in daily practice. However, available results from case reports and small observational studies make ECP a promising therapeutic option. More data from well-designed clinical trials are needed to evaluate the role and safety concerns of ECP in SLE treatment.

DERMATOMYOSITIS

Available data concerning the usefulness and effectiveness of ECP in dermatomyositis is scarce. There is a case report about using ECP in a patient with a diagnosis of juvenile dermatomyositis who did not respond to standard treatment regimen with methotrexate [9]. The alternative management consists of a combination of ECP and methotrexate. The treatment resulted in clinical improvement in muscle strength and decrease in muscle enzymes. Another case report deals with treatment of refractory dermatomyositis with modified ECP using autologous cryopreserved mononuclear cells. Cryo-ECP technology significantly reduced the number of apheresis cycles by freezing biologic sample for later application [30]. Taking into consideration the above, the use of ECP in overlap syndromes, primarily, systemic sclerosis and dermatomyositis needs further evaluation.

EOSINOPHILIC FASCIITIS

A case report of three patients with a diagnosis of eosinophilic fasciitis (EF) reveals a successful treatment with ECP in refractory cases or contraindications to conventional treatment strategies. According to the treatment protocol after a standard apheresis procedure, 8-methoxypsoralen was added to the lymphocyte solution (not orally) [40]. ECP procedure included cycles given every two weeks for three months and every four weeks thereafter depending on the clinical response. Both clinical assessment and skin elastometry measurements confirmed good response in two patients. However, in one case the improvement was less pronounced, ECP enabled the reduction in immunosuppressive treatment and improvement in quality of life.

PSORIATIC ARTHRITIS

There are only a few reports about using ECP in psoriatic arthritis. Vahlquist et al. reported a series of eight patients treated with ECP (with 8-methoxypsoralen taken orally) for twelve weeks followed by another twelve weeks of combined ECP and PUVA [48]. Four out of eight patients showed significant improvement in both skin manifestation and arthritis. Interestingly, a decrease in Ritchie articular index was seen within the first twelve weeks when ECP was given alone and improvement in skin lesions was mainly observed after subsequent PUVA treatment. Clinical response concerning joints was sustained for over twelve months post therapy. Only mild adverse effects were observed mostly related to PUVA procedure and psoralen intake.

RHEUMATOID ARTHRITIS

The great improvement in biologic treatment enabled most of patients to achieve the predefined goal of therapy. The paucity of clinical data and inconsistence of results questions the role of ECP in rheumatoid arthritis. Though the ECP in rheumatoid arthritis management has a rather limited or no application, it is worth mentioning. The pilot

study of Malawista et al. reports that ECP may be effective, but deterioration in a relatively short time period is possible [28]. The researchers emphasize good tolerance and low toxicity of the method. The study population consisted of 7 patients with active disease despite the treatment of methotrexate. Prednisone in a maximum dose of 10 mg daily was allowed, higher doses and other disease modifying antirheumatic drugs needed to be stopped with appropriate time of wash out. The protocol defined 6 months of ECP with ingestion of methoxsalen before the procedure. As a result 4 out of 7 patients responded to the treatment (about 71% of reduction in affected joint count in 3 patients, in one patient moderate improvement was observed with reduction of 33%). In most cases improvement was seen after 12 to 16 weeks. During the follow up period 2 of 4 patients who primarily responded to the therapy experienced the exacerbation of the disease (2–3 months after discontinuation of ECP). No concomitant medication was taken in such cases.

ANKYLOSING SPONDYLITIS

In 2011 a case report of ECP treatment given to the patient with coexistence of cutaneous T-cell lymphoma and ankylosing spondylitis was published. The primary reason for ECP introduction was mycosis fungoides refractory to psoralen-UVA [2]. The interferon alpha was also administered but it had to be stopped because of exacerbation of axial symptoms and peripheral arthritis due to ankylosing spondylitis. To treat cutaneous lymphoma the patient underwent three cycles of ECP added to PUVA therapy. One month after ECP, introduction inflammatory makers dropped down significantly. After three months, major improvement was noted and after 12 months of follow up complete remission of peripheral arthritis and inflammatory back pain was observed. To our knowledge, the publication mentioned above is the only one describing successful ECP use in this indication. More studies are needed to assess the effectiveness of ECP in ankylosing spondylitis or other inflammatory spondyloarthropathies.

CONCLUSIONS

The mode of action and therapeutic effect of ECP leading to changes in immune system allowed us to recommend this method mainly in hematology and transplantation. Over thirty years of experience with ECP confirmed its outstanding safety profile and good tolerance. No clinically significant adverse events have been observed so far. These observations encourage the implementation of ECP in the treatment of autoimmune connective tissue diseases. ECP may be considered in refractory cases, when the first line treatment strategies do not control disease activity or immunosuppressants are contraindicated and in the group of patients with high risk of infections. It also seems reasonable to consider the procedure as a corticosteroid sparing agent. More studies on large cohorts of patients are needed to verify current and new clinical indications for ECP use in rheumatology.

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