

Extracorporeal photoimmune therapy: A therapeutic alternative treatment of cutaneous T-cell lymphoma and immunological diseases

Review Article

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Abbreviations: 8-methoxypsoralen, (8-MOP); acid citrate dextrose, (ACD); cutaneous T-cell lymphoma, (CTCL); disease-free survival, (DFS); Extracorporeal photoimmune therapy, (ECP); Food and Drug Administration, (FDA); graft-versus-host-disease, (GVHD); interferon, (IFN); partial remission, (PR); systemic lupus erythematosus, (SLE); total skin electron beam therapy, (TSEBT); Ultraviolet A therapy, (PUVA); ultraviolet light, (UVA)

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Summary

Extracorporeal phototherapy (ECP) is an immunotherapeutic modality that has demonstrated clinical efficacy in cutaneous T cell lymphoma/Sezary syndrome (CTCL), scleroderma, in patients with refractory acute and chronic gvhd after bone marrow transplantation and other autoimmune disorders. ECP involves extracorporeal exposure of peripheral blood mononuclear cells to photoactivated 8-methoxypsoralen (8-MOP), followed by reinfusion of the treated cells. 8-MOP is a naturally occurring furocoumarin that is biologically inert, unless exposed to ultraviolet A light, whereupon it becomes photoactivated and covalently binds and crosslinks DNA, leading to initiation of apoptosis. During a single treatment cycle of ECP, approximately 240 cc of buffy coat and 300 ml of plasma are collected into a buffy coat bag from six collection cycles. The cells are exposed to UVA at 2 Jcm²/cell beginning immediately after the first cells are collected. Examination of the cells after UVA exposure and prior to reinfusion demonstrates that about 2–5% of the total circulating peripheral blood mononuclear cells undergo apoptosis. An intravenous formulation of 8-MOP, UVADEX, allows direct instillation of the photosensitising agent into the collected plasma and buffy coat *ex vivo* prior to UVA exposure. The implications of these immunomodulatory effects of ECP on pathogenesis and clinical outcome remain a fertile area for future research.

I. Introduction

Extracorporeal photoimmune therapy (ECP) is an immunological treatment, which is defined as the extracorporeal exposure of pathogenic leucocytes to irradiation by ultraviolet light (UVA) in the presence of a photosensitising drug known as 8-methoxypsoralen (8-MOP). ECP was introduced for the first time by Edelson et al, (1987) for the treatment of Sezary's syndrome and was approved in 1988 by the United States Food and Drug Administration (FDA) for the treatment of advanced forms of cutaneous T-cell lymphoma (CTCL); subsequently ECP

has been used in the treatment of systemic sclerosis and other autoimmune diseases and for complications involving transplants of organs (rejection) or allogeneic bone marrow (*graft-versus-host-disease*, GVHD).

The immunomodulating mechanism of action was described for the first time in mice exposed to UVA in the presence of 8-MOP. Immunosuppression was accompanied by a reduction in the number and function of the epidermoidal Langerhans cells and by a change in the production of cytokines by the keratinocytes (Vogelsang et al, 1987). Subsequently numerous experiments showed that administering spleen and bone marrow cells, treated

with ECP, to mice which had undergone allogenic bone-marrow transplants, significantly reduced the occurrence of GVHD, providing evidence of a UVA effect on the cells responsible for alloreactivity (Ullrich, 1991).

II. The "Photopheresis" system

Taking samples of lymphocytes from the patient using a process of leucapheresis, and then activating them with 8-MOP and UVA carried out ECP in an extracorporeal circulation. The drug is activated by the presence of UVA radiation, and so only the cells exposed to this light are modified. The half-life of photoactivated 8-MOP is extremely short; therefore the cells can be re-infused immediately once treatment has been completed with very few side effects for the patient. Completion of each individual procedure normally requires between 3 and 5 hours; good patient venous access from a peripheral vein or, alternatively, from a central venous catheter, is essential.

There are two ECP systems:

1) The Therakos system, which uses UVAR XTS™ apparatus, following a protocol of two procedures in 2 consecutive days for each treatment cycle (125 ml bowl, 6-9 fractionation cycles; 225ml bowl, 3-4 fractionated cycles); the machine, using a single needle, allows whole blood to be taken from the patient and centrifuged in order to produce a blood fraction enriched with leucocytes. 8-MOP in liquid form is mixed with the *buffy coat* fractionated in this way, then this fraction is exposed to the prescribed quantity of UVA rays in order to photoactivate the drug. The red corpuscles and the remaining portion of plasma are re-infused into the patient, without being subjected to the ultraviolet light treatment. The advantage of this system is that the circuit is continuous, and therefore allows blood to be taken, separated, irradiated and then returned to the patient in a sterile and closed circuit;

2) The Bio-Genic system, developed by Vilber Lourmat, in which the mononucleate cells are collected using various cell separation systems, and then processed, irradiated and finally infused in two separate and distinct phases ("open" system). The main disadvantage of this system is the risk of bacterial contamination correlated with the blood manipulation before the reinfusion in the patient.

Various treatment protocols are proposed. The basic CTCL protocol requires two treatments, carried out on 2 successive days, every 4 weeks; more aggressive protocols are normally applied when dealing with rejection after organ transplant. The total duration of treatment is established by evaluating the condition and treatment response of the individual patient. The side effect, which occurs most frequently during the procedure, is photophobia, consequently it is a good rule to give the patient the protection of dark goggles for the hours immediately following treatment. In some patients a temporary rise in temperature has been noted with an increase of the erythema, which can accompany the pyrexial reaction. In addition it is essential to carefully monitor blood pressure throughout the procedure, because

when using discontinuous flow apparatus in an extracorporeal circulation, there is a high risk of hypotension.

III. Cutaneous T-cell lymphoma

The photopheresis procedure was developed initially by Edelson et al, (1987) as a therapy for treating CTCL and Sezary's syndrome. In the initial study responses in excess of 60% were noted in the patients treated, with an average response time of 4-6 months when treatment was carried out once a month for 2 consecutive days (Rook and Wolfe, 1994; Wolfe et al, 1994; Lim and Edelson, 1995). In a retrospective analysis of 450 patients treated in the United States and in Europe, the response percentage was 56 and 66%, respectively. Immunological studies have shown that the subset characterised by the CD4+/CD7- pattern and by a normal CD4/CD8 ratio had a higher likelihood of clinical response (Rook et al, 1999). The anti-tumoral effect was correlated with the appearance of CD8+ cytotoxic T-cells in the peripheral blood and cutaneous tumoral infiltration. The number of Sézary cells dropped in the majority of patients treated with ECP, while there were no significant variations in the population of normal CD4+ lymphocytes.

Edelson et al, (1987) subsequently showed, in the same group of patients, an increase in average survival of 60 months *versus* 33 months in the historical control group not treated with ECP. Further trials confirmed the good results, but they all presented the scientific limitation of not being randomised studies (Fraser-Andrew et al, 1998; Russel-Jones, 2000).

Gottlieb et al (1996) published the results of a retrospective study involving an appreciable number of patients, evaluated over 10 years, in which ECP was used on its own or combined with interferon (IFN) (12 patients) and other topical or systemic drugs. In this cohort of patients, 31 underwent 6 or more cycles of ECP while 28 patients received ECP as monotherapy. 71% of patients responded to the treatment; a further 7 patients (25%) obtained partial remission. In this study it was very significant to observe that the presence of Sézary cells in the peripheral blood was associated with a favourable clinical response, as has been confirmed in other experiments (Rook et al, 1999). Gottlieb et al, (1996) showed that treatment with ECP is associated with an improved survival rate. In this study, average survival was 77 months from the start of treatment and 100 months from diagnosis.

In a similar retrospective reevaluation Duvic et al, (1996) reported an overall response of 50% in a group of 34 patients; 6 patients (18%) achieved complete remission (CR) and 11 (32%) partial remission (PR). It must be emphasised that 28 of the 34 patients had an erythrodermic form of CTCL and that the best response was obtained with a treatment schedule involving two monthly procedures. Duvic's experiment involved a treatment which had been modified in comparison with the one described by Edelson, increasing cell separation cycles from 6 to 9 and using ACD (acid citrate dextrose) as anti-coagulant instead of heparin; he also intensified treatment

for non-responding patients to intervals of 2 weeks. The modifications made did not result in any advantage for the patients. One interesting fact was an increase in type G immunoglobulin, suggesting that ECP could be associated with an improvement of the immune function.

No clear advantages of ECP in terms of the survival of patients suffering from CTCL emerged from one single trial (Russel-Jones et al, 1997).

Numerous publications have also shown that combining ECP with biological response modifiers such as IFN can work in non-responding patients (Rook et al, 1991; Gottlieb et al, 1996; Jumbou et al, 1999; Fimiani et al, 1999).

Rook et al, (1991) had already published a work showing that combining ECP with low doses of IFN can achieve CR with the T-cells disappearing from the peripheral blood. Recent studies evaluated the combination of immunomodulator drugs such as interleukin-2 (Fritz et al, 1999), interleukin-12, or GM-CSF (Rook et al, 1997; Wood et al, 1999) with ECP.

The most important data published in literature, concerning the therapeutic synergism of treatment schemes used in order to improve long-term results, mainly concerned the combination of total skin electron beam therapy (TSEBT) and ECP (Wilson et al, 1995, 2000). In an initial work Wilson et al, (1995) assessed 163 patients who had been treated with TSEBT with a total dose of 36 Gy at 1 Gy/day for 9 weeks. All patients obtained CR or good PR with TSEBT, and then they were randomised in order to be treated with polichemotherapy schemes (anthracyclin + cyclophosphamide) or with ECP. In patients treated with chemotherapy survival after 3 years was 75% while in those treated with ECP it was 100%. In the analysis of the overall survival curves, only the group treated with ECP achieved a statistically significant difference ($p < 0.06$).

The same group subsequently recorded its own experience of using ECP in combination with TSEBT in mycosis fungoides, in its erythrodermic variant (Wilson et al, 2000). In this retrospective, non-randomised study, 44 patients were evaluated, 73% of who achieved CR and overall *disease-free survival* (DFS) was 63%. After stratifying the patients, the DFS was 49% for those treated with TSBET alone and 81% in patients treated in combination with ECP.

From the cumulative results from numerous groups, we conclude that conventional ECP is efficacious in a high percentage of those CTCL patients who have circulating malignant T cells in the context of a still-near-normal immunocompetence. However, it is equally clear that a sizeable population of patients with extensive CTCL do not fit the profile of good responders to conventional ECP. Given the increased understanding of the mechanism underlying the efficacy of ECP and the improvements that have recently been made in the treatment modality, we favor the initiation of randomized trials of the improved ECP method, rather than the presumably antiquated conventional method.

A. Immunomodulation of ECP in T lymphoma

The direct anti-idiotypic antibody response against the clonal T-cell population, which occurs during ECP, is probably induced by UVA-mediated cell damage. During the procedure 8-MOP remains biologically inert until it is activated by the specific waves of UVA energy. The T lymphocytes seem to be the cell population which is most sensitive to this effect, as demonstrated by Yoo et al, (1996), who pointed out that only the normal T population and the T pattern of the Sézary syndrome showed signs of a process of apoptosis within 24 hours of carrying out ECP, with the appearance of typical markers such as annexin (Bladon and Taylor, 1999). ECP determines a selective variation of the subpopulations of T-cells, with normalisation of the CD4/CD8 ratio (Zouboulis et al, 1998) and maturation of the CD4+ line towards the inflammatory line (Th1), in comparison with the adjuvant one (Th2). In pathology such as CTCL, the increase in Th1 production in turn determines a higher production of IL-2 by the monocytes, with a negative feedback effect towards the Th2, which are probably the cytokines responsible for the clinical symptoms of the lymphoma (Di Renzo et al, 1997). While the lymphocytes seem to be resistant to the apoptotic effects of photopheresis, the induction of TNF- secretion by the photoactivated monocytes facilitates apoptosis of the lymphocytes (Vowels et al, 1992). In addition, the photoactivation of the monocytes seems to stimulate their differentiation into dendritic CD 83+ and CD 36+ cells, capable of phagocytizing the apoptotic T-cells (Berger et al, 2001). In the presence of coadjuvant molecules, these dendritic cells are capable of determining an initial immune-cellular response (Edelson, 1991). These mechanisms are not, however, sufficient to justify the induced immunogenicity because the percentage of lymphocytes treated during ECP constitutes 10-15% of the total lymphocyte population. Consequently the problem of the mechanism of action of photopheresis still leaves a wide margin for future studies.

IV. ECP and graft-versus host-disease (GVHD)

GVHD remains a major cause of morbidity and mortality after allogeneic stem cell transplantation. While improvements in immunosuppressive regimens have reduced the frequency and severity of acute GVHD, the incidence of chronic GVHD remains unchanged at 27–50% after sibling matched related donor transplants and 42–72% after unrelated donor bone marrow or peripheral blood stem cell transplanted (Lazarus and Rowe, 1995; Urbano-Ispizua et al, 1997; Remberger et al, 2001). Factors associated with cGVHD have been well described and include increased donor and recipient age, HLA-disparate and unrelated donor transplants, prior acute GVHD, and use of alloimmune female donors (Ratanatharathorn et al, 2001). The onset of cGVHD has arbitrarily been defined as occurring 100 days after allogeneic stem cell infusion, and its clinical features are distinguished from acute GVHD in that they more closely resemble autoimmune diseases. Histopathologic changes

which include sclerodermatous skin changes resulting from collagen deposition, pulmonary fibrosis, esophageal dysfunction, dry mouth or mucocutaneous ulcerations, cholestasis and myositis or fasciitis are thought to be initiated, in part, by autoantibodies to cell surface and intracellular proteins (Shulman et al, 1978).

This pathology is responsible for the significant post-transplant morbidity and mortality, due to both direct organ dysfunction and the significant increase in predisposition towards serious infections. The factors mostly responsible for this phenomenon are the donor's T-lymphocytes, although other types of cells are implicated, with the consequent amplification of this process by various cytokines.

Conventional therapeutic approaches for cGVHD, including corticosteroids and immunosuppressive agents have demonstrated limited efficacy in patients with extensive disease. Ultraviolet A therapy (PUVA), while effective in alleviating the symptoms of chronic skin GVHD, has had no impact on visceral involvement. Novel strategies, including humanized anti-CD25 antibody (dacluzimab) and anti-TNF-antibody (infliximab), have shown promise in limited pilot studies (Przepiorka et al, 2000; Simpson, 2000; Basara et al, 2001).

A. ECP and acute GVHD

The work with the highest number of patient recruits suffering from GVHD who received treatment was published by Greinix et al, (2000). In this trial 21 patients with a median age of 38 years who developed steroid-refractory acute GVHD grades II to IV after stem cell grafting from sibling or unrelated donors and were referred to ECP. Three months after initiation of ECP 60% of patients achieved a complete resolution of GVHD manifestations. Complete responses were obtained in 100% of patients with grade II, 67% of patients with grade III, and 12% of patients with grade IV acute GVHD. Three months after start of ECP complete responses were achieved in 60% of patients with cutaneous, 67% with liver, and none with gut involvement. Adverse events observed during ECP included a decrease in peripheral blood cell counts in the early phase after stem cell transplantation (SCT). At the time of trial, 57% of patients were alive at a median observation time of 25 months after SCT. Probability of survival at 4 years after SCT was 91% in patients with complete response to ECP compared to 11% in patients not responding completely. Their findings suggested that ECP was an effective adjunct therapy for acute steroid-refractory GVHD with cutaneous and liver involvement, but, in patients with acute GVHD grade IV or gut involvement other therapeutic options are warranted.

Our comment is that the experience of ECP treatment of patients with acute GVHD is still limited. Furthermore, there are differences in patient selection, entry criteria, additive immunosuppressive treatment and tapering down during ECP treatment and frequency of treatment among different centers. All these aspects stress the importance of randomized prospective multicenter studies.

B. ECP and chronic GVHD

Owsianowski et al, (1994) published the first work that evaluated the association between ECP and chronic GVHD. The author reported the experience of one individual case that showed improvement of lichenoid lesions on the skin, muscle thickening and sicca syndrome, and normalisation of the CD4/CD8 ratio and increase of NK cells from 8 to 20%.

Subsequently, in 1996, Rosetti et al published a trial on 9 paediatric patients showing improvement of cutaneous, hepatic and pulmonary GVHD. ECP was carried out for 2 consecutive days every 3 weeks for 6 months, and then monthly. The patients who responded showed normalisation of the CD4/CD8 ratio and a reduction in the number of CD56+ and HLA-DR+ cells after 9 months of treatment (Rosetti et al, 1996). A further study was published by Abhivankar et al, (1998) with a very small number of patients, who had a response in the case of scleroderma-type skin symptoms, but not in the case of visceral involvement.

Two recent studies reported the results of treatment in 11 and 15 patients, respectively (Greinix et al, 1998; Child et al, 1999). None of the patients had responded to 1st and 2nd line treatment with corticosteroids and cyclosporin. In one study ECP had been started at a late point after the onset of GVHD (average of 510 days), while in the other study it had been started at an early stage (average 178 days). In the group receiving early treatment the clinical responses were 12/15 in the case of cutaneous pathology; 11/11 in the case of muco-cutaneous involvement; 7/10 for hepatic GVHD and 5/6 in the case of ocular disease. In the group receiving late treatment the response on the skin was also good (10/10) but not for the other locations, confirming that the best responses are obtained if treatment is started within 10 months of the transplant. Intensification of treatment (twice per month for the first 4-6 months) had an impact on the response percentage. The clinical improvement allowed the immunosuppressive therapy to be reduced. The average time for suspending cortisone was 80 days, the average duration of response after suspension of ECP 12 months, with 14% of patients relapsing after suspending treatment.

A more systemic immunomodulatory effect, however, has been achieved with ECP, where direct exposure of peripheral blood mononuclear cells to UVA-activated 8-methoxypsoralen by apheresis is administered. Complete responses of cutaneous chronic GvHD have been reported in up to 80% of steroid-refractory patients, with improvement even in sclerodermatous skin (Messina et al, 2003; Seaton et al, 2003; Di Venuti et al, 2002) (**Table 1**). Improvement in visceral chronic GvHD has been less consistent. Reports of high complete response rates in hepatic and gut GvHD (Messina et al, 2003) have not been consistently observed (Seaton et al., 2003). No clinical factor predicting response to ECP has been observed.

Ilhan et al (2004) treated eight patients with a median age 42 (range, 17-43) with ECP (UVAR XTS) on 2 consecutive days every 2-4 weeks until resolution of GVHD over a period of 6-15 months concomitantly with immunosuppressive agents. Beyond extensive steroid

Table 1. ECP treatment of refractory chronic GVHD

| Authors | Study design | No. | CR | PR | Comment |
|------------------------|---------------|-----|----|-----|--|
| Greinix <i>et al</i> | Retrospective | 15 | 0 | NA* | CR in 12 of 15 patients with cutaneous GVHD, and in 7 of 10 with liver GVHD |
| Messina <i>et al</i> | Phase II | 44 | 15 | 10 | Ages 0.3-25 years. Highest responses in liver (60%) and gut (58%) chronic GVHD. Response significantly associated with improved survival (96 vs 58% 5-year survival, p=0.04) |
| Seaton <i>et al</i> | Phase II | 28 | NA | NA | Responses described by site only. Skin chronic GVHD (1/21 CR and 9/21 PR), Liver GVHD (8/25 PR), Oral (3/6/ PR) |
| Di Venuti <i>et al</i> | Phase II | 23 | 0 | 14 | Highest responses seen in skin GVHD (67%), responses also seen in gut (2/3) and oral mucosa (4/13) |

*Criteria for PR often not well defined. NA = not available

refractory cutaneous cGVHD, three patients had also bronchiolitis obliterans (BO). Skin scores were assessed by an experienced dermatologist. Clinical, laboratory and radiological findings after 4 months of ECP were accepted as response criteria. The patients received in this almost fully automated system mean 261.4 ml buffy-coat was processed within 193 min using UVADEX sterile solution. After a median of 12 cycles of treatment, 6 patients showed a favorable response. ECP was tolerated well only one patient developed thrombocytopenia and another patient had a massive GIS bleeding due to an esophageal tear. Reduction in cholestatic parameters was observed in patients with liver cGVHD, improvement in respiratory functions and CT evaluations in two, and reduction in immunosuppressive requirement in all patients. The most impressive result was the reduced need for hospitalization of these patients and improvement of skin lesions. All but one of the skin biopsy scores was also better after ECP.

At the Reggio Calabria Transplant Centre, the Therakos system is being used in a study conducted on patients suffering from acute and chronic GVHD following allogeneic bone-marrow transplant, with recycling of ECP at intervals of 7 days. To date 15 patients have been treated with good overall response (unpublished data). However there are still no definitive responses with regard to whether or not such an intensive treatment, compared with one spread out over a longer period, could have significant clinical advantages, without causing the patient side effects.

The rising incidence of cGVHD and poor response of many patients to conventional immunosuppressive treatments have led to the increasing use of ECP as a treatment for refractory disease. This series illustrates that ECP can produce clinical improvements in patients with advanced disease and features that are associated with an adverse prognosis. Nevertheless, ECP is a time-consuming and relatively expensive treatment that requires specialized equipment and staff expertise. Improved criteria for patient selection would be useful to improve direction of this treatment resource. Several analysis of pretreatment patient characteristics and laboratory parameters did not identify any variables that were predictive of a favourable response to treatment. However, comparison of international data with previous smaller

series suggests that the initiation of ECP at an earlier stage is associated with more favorable response to treatment.

Seaton *et al.* (2003) led a study of patients with advanced cGVHD, ECP was initiated approximately 3 years after allogeneic transplantation and 2 years after onset of cGVHD. These data provide new evidence that ECP can be effective in extensive, long-standing cGVHD when treatment is initiated at an advanced stage after conventional immunosuppressive and corticosteroid therapy has failed. ECP should be considered most beneficial for patients with predominantly mucocutaneous cGVHD. However, in the absence of baseline criteria that accurately predict response, selection of these patients must continue to be made on clinical grounds.

C. Mechanism of action of ECP in GVHD

There is little data in the literature analysing the immunomodulation of ECP in chronic GVHD. Although acute GVHD is unanimously recognised as a pathology correlated to alloreactivity, the etiology of chronic type GVHD is disputed and it is believed that it may be a development of the acute form or the result of a change in post-transplant reconstitution of immunology with the development of auto-antibodies and clonal T-cells auto-reactive against their own organism. Acute GVHD is probably correlated with a change in function of the Th1 cells and certainly the inflammatory cytokines, such as IL-2, IL-1, IFN and TNF, contribute to tissue damage (Abhyankar *et al*, 1993; Tanaka *et al*, 1997).

Recently Alcindor *et al.* (2001) published a study evaluating the function of lymphocytes and dendritic cells in patients suffering from chronic GVHD who underwent ECP for 2 consecutive days every 2 weeks. The average time following the transplant was 667 days; 7 out of 10 patients treated had a clinical response, particularly in the skin (improvement of ocular symptoms in 5/7 patients: in lesions of the oral mucous membrane in 5/8; in the liver in 2/3). Immunosuppressive treatment was reduced or suspended in 7 out of the 10 patients. The results contrasted with those reported by other authors (Simpson, 2000), who emphasised the non-effectiveness of ECP if started a long time after the onset of GVHD. In all the patients who responded there was a reduction of over 50% of the population of the CD 80+ and CD123 + dendritic

population, without significant changes in the expression of CD28 on the surface of the lymphocytes, suggesting that ECP did not act on the type I major histocompatibility complex, responsible for the functional control of the T cells. The reduction of the cells presenting the antigen, together with a reduction of CD8+ cells, revealed an overall suppression of alloreactivity.

V. ECP and organ transplants

In order to evaluate the incidence of post-heart transplant rejection, Barr et al, (1998) randomised 60 patients into groups receiving standard immunosuppressive treatment (with cyclosporin, azathiaprine and prednisone) on its own or in combination with ECP. This study demonstrated a statistically significant reduction in the number of acute rejection episodes in recipients of cardiac transplants who received photopheresis therapy in addition to standard triple-drug immunosuppression. Longer follow-up will be required to assess the effects of a reduction in the risk of acute rejection on long-term graft function, the long-term survival of graft recipients, and the the development of graft vasculopathy.

O'Hagan et al, (1999) published a case history of 4 patients who underwent lung transplants complicated by obliterating bronchiolitis, not responding to immunosuppressive treatment. ECP was used for 2 consecutive days twice per month until the pulmonary condition stabilised, then as maintenance therapy every 4-6 weeks; the results obtained resulted in temporary stabilization of the condition and slight improvement of respiratory parameters.

These studies present a preliminary look at the potential clinic value of photopheresis as an additional to standard immunosuppression in organ transplants. Future trials will need to include an analysis of the cost-benefit ratio of photopheresis, and additional clinical studies and long-term follow-up will be required to assess the value of photopheresis in recipients of solid-organ transplants and the ultimate effect of this treatment on graft and patient survival.

VI. ECP and autoimmune disease

The autoimmune pathologies that might potentially benefit from ECP are summarised in **Table 2**. An initial study using ECP to treat autoimmune disease produced favorable results in patients with pemphigus vulgaris (Rook et al, 1990).

Table 2 Potential fields of application of extracorporeal photochemotherapy

| |
|--|
| Oncology |
| Sézary syndrome (T-cell cutaneous lymphoma) |
| Chronic lymphocytic leukaemia |
| Dermatology |
| Psoriasis |
| Autoimmune disease |
| Scleroderma |
| Multiple sclerosis (anecdotal data) |
| Rheumatoid arthritis |
| Pemphigus vulgaris |
| Crohn's disease (anecdotal data) |
| Organ transplant |
| Rejection of heart transplant |
| Rejection of lung transplant |
| Rejection of kidney transplant |
| Bone-marrow transplant and haemopoietic stem cells |
| <i>Graft-versus-host-disease</i> (GVHD) |
| Infectious diseases |
| Hepatitis C (anecdotal data) |
| AIDS (anecdotal data) |
| Metabolic diseases |
| Type 1 diabetes mellitus |

Four patients with uncontrolled disease, despite prolonged courses of treatment with high dose of prednisone in combination with cyclophosphamide or azathiopirine, responded to ECP. All patients initially had improvement in the extent of their skin disease that allowed for significant tapering of all treatment. Significant reduction in serum levels of antiepidermal cell immunoglobulin occurred in conjunction with clinical improvement. Three patients achieved CR and halted immunosuppressive treatment; 3 suffered a relapse but CR was easily obtained with new photopheresis treatment. It's a common experience that once clinical improvement occurs, gradual tapering of corticosteroids and immunosuppressive medications can proceed; however, simultaneous abrupt tapering of ECP along with the tapering of other medications may result in the early reoccurrence of skin lesions. ECP produced no serious adverse effects in any of the four patients during several years of follow-up.

In 1992 a multi-center randomized study was published (Rook et al, 1992) which evaluated the results of a study on 72 patients suffering from systemic sclerosis of recent onset with progressive involvement of the skin, comparing ECP with treatment with D-penicillamine. Substantial skepticism has arisen regarding the use of ECP for systemic sclerosis because it manifests primarily as a fibrosing disease with increased deposition of collagen within the skin and involved visceral organs. Despite its status as a fibrosing disease, recent observation have implicated the immune system as a prime factor in the genesis of the increased collagen production. In this study, after 6 months of treatment, an improvement was registered in the skin in 68% of the patients treated with ECP, as opposed to 32% of those treated in the other arm of the study. Thus, in the early phases of treatment, a significantly higher response rate was obtained with ECP ($p=0.02$). At both the 6 and 10 mo evaluation point, the mean skin severity score, mean percentage involvement, and mean oral aperture measurements were significantly improved from baseline among those who received ECP. Mean right- and left-hand closure measurements had also improved significantly by 10 mo of therapy. Skin biopsy studies demonstrated an association between clinical improvement and decreases thickness of the dermal layer. It is noteworthy that adverse effects of ECP were minimal during this trial and did not require discontinuation of treatment by any patients. In contrast, 25% of patients who received D-penicillamine were required to permanently discontinue this drug due to side-effects when used for aggressive cases of recent onset systemic sclerosis.

In 1992 a trial was published (Knobler et al, 1992) conducted on patients suffering from systemic lupus erythematosus (SLE) which showed that in 5 patients treated with ECP, in combination with conventional cures, CR was obtained and was persisting after 30 months of follow-up, even though there was no change in the laboratory parameters characterising the disease.

In addition to these studies, the results of pilot trials have suggested the potential efficacy of ECP for rheumatoid arthritis (Malawista et al, 1991), epidermolysis bullosa acquisita (Miller et al, 1995; Gordon et al, 1997), atopic dermatitis (Prinz et al, 1994). Other clinical

indications that have been studied where efficacy has not been demonstrated include multiple sclerosis, chronic hepatitis C, and AIDS-related complex.

VII. Conclusions

The future prospects of ECP concern defining the mechanism of action, its use in other pathologies and the combination of ECP-pharmacological treatment and/or radiotherapy. Photopheresis is a relatively safe and promising treatment. This review clearly shows that the fields of application of the procedure could be vast, and could include metabolic diseases, such as recently demonstrated by Ludvigsson et al, (2001) who presented a randomised study in 49 children suffering from type 1 diabetes mellitus, demonstrating possible control of the disease using phototherapy. It could also include pathologies of an infectious nature (hepatitis C) (O'Brien et al, 1999) and even diseases such as Crohn's disease (Reinisch et al, 2001).

It is clear that all the published works present case histories involving small numbers and, in addition, that there are few randomised studies. Starting from these premises, national and international studies, aimed not only at developing the clinical possibilities of the treatment, but also at evaluating its biological aspects, are desirable, given the potential of the treatment, which, for the time being, has many unknown aspects.

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