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CONTROVERSIES IN DERMATOLOGY

Extracorporeal Photopheresis in Dermatology

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Resumen. Extracorporeal photochemotherapy or photopheresis is an immunomodulatory therapy that combines leukapheresis with phototherapy. Blood from the patient is processed to give a leukocyte-rich plasma, which is then treated ex vivo with a photosensitizer and ultraviolet A radiation before reinfusion back into the patient. The exact mechanism of action of photopheresis has not been fully elucidated although it is thought that induction of leukocyte apoptosis and formation of dendritic cells is essential for the development of an immune response to pathogenic cells. Extracorporeal photopheresis was initially used for treating cutaneous T-cell lymphoma. Since then, in view of its efficacy and safety, it has been used in a number of cutaneous and non cutaneous diseases with uneven results, which can in part be explained by the different patient selection criteria, therapy regimens, and follow-up protocols used in different hospitals.

Key words: photopheresis, photochemotherapy, extracorporeal, treatment.

FOTOFÉRESIS EXTRACORPÓREA EN DERMATOLOGÍA

Resumen. La fotoquimioterapia extracorpórea o fotoféresis es una terapia inmunomoduladora que combina la leucoféresis con la fototerapia. Después de la separación de un plasma rico en leucocitos, se administra ex vivo un fotosensibilizante junto con radiación ultravioleta A y posteriormente se reinfunde en el paciente. El mecanismo de acción exacto de la fotoféresis no se conoce completamente, aunque se piensa que la inducción de apoptosis de linfocitos y la formación de células dendríticas desempeña un papel fundamental en el desarrollo de una respuesta inmunológica contra las células patógenas. Esta terapia se utilizó inicialmente para el tratamiento del linfoma cutáneo de células T. Desde entonces, basándose en su eficacia y seguridad, se ha empleado en múltiples patologías tanto cutáneas como no cutáneas, con resultados variables. Los distintos centros han utilizado diferentes criterios de selección de pacientes, pautas de tratamiento y protocolos de monitorización, lo que podría contribuir a la diferencia de resultados.

Palabras clave: fotoféresis, fotoquimioterapia, extracorpórea, tratamiento.

Introduction

Extracorporeal photochemotherapy or photopheresis is a type of therapy used to treat autoreactive or neoplastic disorders caused by aberrant clones of T lymphocytes. It combines aspects of leukapheresis and traditional phototherapy. In 1987, Edelson et al published the first study showing the efficacy of this technique in the treatment of cutaneous T-cell lymphoma (CTCL).[1] Given its efficacy and safety profile, extracorporeal photopheresis has since been used in several disorders (Table 1), with varying results. The variability of these results, both between different disorders and within the same condition, has generated some controversy among research groups as to the effectiveness of the technique. In the present work, we review the use of this therapy to treat skin conditions and show where it has proved effective and where the results are contradictory.

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Procedure

Extracorporeal photopheresis is an immunomodulatory treatment that involves exposure of peripheral blood mononuclear cells to photoactivated 8-methoxypsoralen

Table 1. Diseases in Which Extracorporeal Photopheresis Has Been Used

Cutaneous Diseases
Cutaneous T-cell lymphoma
Graft-versus-host disease
Pemphigus
Pemphigoid
Epidermolysis bullosa acquisita
Psoriasis
Atopic eczema
Systemic sclerosis
Systemic lupus erythematosus
Discoid lupus erythematosus
Subacute lupus erythematosus
Lichen planus
Scleromyxedema
Scleredema
Dermatomyositis
Eosinophilic fasciitis
Pityriasis rubra pilaris
Solar urticaria
Nephrogenic fibrosing dermopathy
Noncutaneous Diseases
Lyme arthritis
Chronic hepatitis C virus infection
Chronic lymphocytic leukemia
Inflammatory bowel disease
Solid organ transplant rejection
Type 1 diabetes mellitus
Multiple sclerosis
Rheumatoid arthritis
Psoriatic arthritis

(8-MOP) followed by reinfusion of the treated cells. This process is performed in 3 stages: leukapheresis, photoactivation with 8-MOP/ultraviolet (UV) A, and reinfusion. It takes approximately 3 to 4 hours. The only commercially available closed system for therapy with extracorporeal photopheresis is UVAR XTS (Therakos). During leukapheresis, the patient's blood is extracted and centrifuged to obtain the leukocyte concentrate, which is the fraction drawn off by the device for treatment. Photoactivation initially involved the use of 8-MOP administered orally; however, this led to gastrointestinal side effects and erratic absorption. Therefore, it was replaced by a solution of 8-MOP (Uvadex, Therakos) that is administered directly into the bag containing the leukocyte concentrate, thus avoiding the undesirable effects of systemic administration and providing stable and predictable concentrations. The 8-MOP molecule enters the cell and its nucleus quickly. When exposed to UV-A radiation (1-2 J/cm^2), it is activated by being transformed into a highly reactive molecule that is capable of forming covalent bonds with the pyrimidine bases of DNA, intercalating into the molecule, and causing DNA strand breakage.[2,3]

Mechanism of Action of Extracorporeal Photopheresis

The mechanism of action of extracorporeal photopheresis is not clearly established. Two explanations have been proposed:

T-Cell Apoptosis

Tumor and autoreactive lymphocytes are more sensitive to the effect of UV-A–activated psoralen, which interacts with the nuclear DNA chain, membrane DNA, proteins, and lipids, thus leading to death by apoptosis. These apoptotic cells are reinfused back into the patient, where they are phagocytosed by antigen-presenting cells that activate cytotoxic T cells to produce an anticlonotypic response.[3-7]

Dendritic Cells

Dendritic cells (derived from blood monocytes) are the most efficient antigen-presenting cells, and play a central role in the initiation and control of the immune response. After treatment with extracorporeal photopheresis, blood monocytes become resistant to the apoptotic stimulus[8] and, due to the temporary adhesion of these cells to the plastic surface of the device,[9] they differentiate into immature dendritic cells.[10] In the presence of pathogenic stimuli (or Sézary cells), the dendritic cells mature. These mature cells present the tumor antigens to cytotoxic CD8 T lymphocytes, thus initiating an antitumor response.[11]

Patients with CTCL have a reduced ratio of type 1 helper T cells (T_H) to T_H2 cells with an increased T_H2 response.[12,13] Extracorporeal photopheresis seems to stimulate the T_H1 response in these patients, thus favoring a return to normal values for the T_H1/T_H2 ratio and initiation of the cytotoxic response. Recently, a modified form of extracorporeal photopheresis—transimmunization—has been developed for the treatment of CTCL. In this form, the mononuclear cells are incubated overnight (thus leading to greater maturation of the dendritic cells) before being reinfused the following day.[14] This technique could prove effective in patients in whom the standard extracorporeal photopheresis regimen has failed.[15]

The T_H1 response predominates in patients with graft-versus-host disease (GVHD) and autoimmune diseases. In these patients, the absence of costimulatory molecules would maintain dendritic cells in an immature state.[10] These immature dendritic cells produce a large quantity of interleukin 10, which has an anti-inflammatory and immunosuppressive effect. They are also highly efficient at phagocytosing apoptotic lymphocytes without stimulating cytotoxic T lymphocytes, thus producing $CD4^+CD25^+$ T regulatory cells, which selectively inhibit the development of GVHD.[16] A change in the cytokine profile comes about in favor of the T_H2 response, and the T_H1/T_H2 ratio is reestablished.[17]

In summary, the action of extracorporeal photopheresis on different diseases seems to depend on the formation of dendritic cells and their state of maturation, which in turn depends on the presence or absence of maturation signals.

Adverse Effects

Most studies highlight the safety profile of extracorporeal photopheresis. The most common adverse effects are sporadic and usually involve headache, nausea (normally secondary to oral psoralen, much less common since Uvadex has been available), fever, and muscle pain. Other adverse effects include hypotension, exacerbation of skin lesions after treatment, vasovagal syncope, septicemia, and injection site infection. However, this is not an immunosuppressive therapy, and no increased incidence of opportunistic infections or cancer has been observed.[18-21] Our patients tolerated extracorporeal photopheresis well, with a low incidence of adverse effects. The most frequent were headache, nausea (with oral psoralen), and hypotensive episodes. Two patients with GVHD developed septicemia secondary to central catheter infection. There were no increases in the number of infections, tumors, or laboratory abnormalities.[3,18]

Skin Disorders Treated With Extracorporeal Photopheresis

CTCL

CTCL encompasses a group of lymphoproliferative disorders characterized by clonal expansion of T cells that mainly invade the skin. Over time, they can invade the lymph nodes, peripheral blood, and viscera. Several treatments have been used to manage the different stages of the disease, and results have varied.[22]

Based on the efficacy of phototherapy in CTCL, in 1987 Edelson et al[1] developed extracorporeal photopheresis, which they used to treat patients in the erythrodermic stage. They achieved a 73% response rate. Since then, several authors have highlighted the efficacy of this treatment in CTCL. Scarisbrick et al[21] recently presented a review of published studies on CTCL treated with extracorporeal photopheresis. They analyzed 30 studies covering 689 patients, with a 63% mean response rate and 20% complete response rate. The best results were in patients with erythrodermal-stage CTCL.[21] In most cases, the treatment regimen was consistent with that of Edelson et al,[1] that is, treatment on 2 consecutive days with monthly intervals between administrations. Zic et al[23] claimed that the early response within 6 to 8 months of treatment had 100% sensitivity and 90% specificity as a predictor of a favorable long-term response. Thus, patients who do not respond to extracorporeal photopheresis after 6 months will probably not have a long-lasting response to treatment.[23] Certain factors have repeatedly been shown to be predictors of a good response to extracorporeal photopheresis (Table 2),[24-27] and some authors suggest that this treatment could increase survival, with means of between 60 and 100 months[23,28,29] compared to between 30 and 60 months for historic controls, although there

Table 2. Predictors of a Favorable Response in Patients With Cutaneous T-Cell Lymphoma Treated With Photopheresis

Erythroderma
Less than 2 years since diagnosis
Leukocyte count lower than 20 000/μL
Presence of 10% to 20% circulating Sézary cells
Absence of palpable lymph nodes
Absence of visceral involvement
Absence of previous intensive chemotherapy
High peripheral blood CD8 lymphocyte count

are no randomized studies to support this observation. Wollina et al[30] obtained a somewhat lower survival value (26 months) in a group of patients with stage IIA and IIB CTCL. One comparative, nonrandomized retrospective study revealed greater survival in patients with Sézary syndrome treated with extracorporeal photopheresis than in patients who were not treated, although the results were not statistically significant.[31]

Several authors[28,30,32,33] have used combination treatment with other agents to improve the response to extracorporeal photopheresis. In a retrospective study, Suchin et al[32] obtained greater mean survival and response rates in a group of patients receiving extracorporeal photopheresis combined with interferon α, systemic retinoids, or sargramostim than in another group receiving extracorporeal photopheresis as monotherapy. However, the results were not statistically significant and the study was heterogeneous, since combinations of 1 or more drugs were used for varying times.[32] Duvic et al[33] also found slightly higher responses in a similar study. However, Zic et al[34] reviewed 19 series of patients published from 1987 to 2001 and found very similar response rates among patients treated with monotherapy (overall response, 55.5%) and patients treated with combination therapy (overall response, 55.8%).

Most studies have evaluated the response in patients with late-stage CTCL, and very few have examined the efficacy of treatment in early-stage disease. Miller et al[35] recently reviewed 16 studies in which extracorporeal photopheresis was administered to 124 patients with early-stage CTCL. The authors observed a response rate of 33% to 88% in patients receiving monotherapy, similar to the results in patients receiving combination therapy (50%-60%). However, in a randomized cross-over study, Child et al[36] observed that treatment with psoralen UV-A for 3 months was significantly more effective at producing complete responses than a 6-month course of extracorporeal photopheresis.

At our center, we administered a minimum of 6 treatment cycles to 14 patients with CTCL (Table 3). Treatment was administered in cycles on 2 consecutive days once per month. We used the scoring system of Edelson et al[19] to evaluate cutaneous involvement. Responders were considered to be those patients whose skin involvement improved by more than 25%. A complete response was defined as no CTCL-induced involvement of the skin, lymph nodes, or blood. Variables were compared using the Fisher exact test and the *t* test. A response was obtained during the first 6 treatment cycles in 7 patients (50%) (the response was complete in only 1 patient);

Table 3. Patients With Cutaneous T-Cell Lymphoma Treated With Extracorporeal Photopheresis at Our Center

		Stage	*Time Since Diagnosis*	*Cycles*	*Response*	*Associated Therapy*
1	Woman 30 y	SS	15 mo	78	PR	IFN, Bex
2	Man 40 y	SS	3 y	37	PR	Chlor, Pred
3	Woman 79 y	SS	2 y	25	PR	Pred
4	Woman 48 y	SS	4 y	35	Exacerbation	Pred, IFN, Bex, Mtx
5	Man 70 y	SS	4 y	8	No improvement	–
6	Woman 64 y	SS	3 y	18	PR	Pred, IFN, Mtx
7	Man 67 y	SS	2 y	24	Exacerbation	Acitr, Met, Chlor
8	Man 67 y	SS	1 y	6	PR	–
9	Man 36 y	SS	8 y	73	CR	–
10	Woman 57 y	SS	6 y	15	Exacerbation	–
11	Man 67 y	IA	30 mo	10	No improvement	–
12	Woman 50 y	IB	7 y	10	No improvement	–
13	Woman 37 y	IIB	6 y	38	Exacerbation	Pred, IFN, Bex, Mtx
14	Man 73 y	IB	14 mo	18	PR until cycle 10. Progression to SS	–

Abbreviations: Acitr, acitretin; Bex, bexarotene; Chlor, chlorambucil; CR, complete remission; IFN, interferon; Mtx, methotrexate; PR, partial remission; Pred, prednisolone; SS, Sézary syndrome.

the disease remained stable or progressed in the other 7 patients (50%). A greater number of responses (60% vs 25%) were achieved in patients in the erythrodermic stage (all of them had Sézary syndrome). Four of the responders (57%) obtained a long-term response for more than 24 cycles. There were no differences between responders and nonresponders with regard to laboratory variables, age, sex, or interval between diagnosis and initiation of extracorporeal photopheresis. We treated 10 patients with Sézary syndrome, defined as erythroderma with histopathology findings of CTCL in a skin biopsy, enlarged peripheral lymph nodes, and more than 5% circulating Sézary cells. Sixty percent of these patients achieved a response, which was complete in 1 patient. Histopathologic involvement of bone marrow was more frequent in nonresponders with Sézary syndrome (100%) than in responders (33%), and was associated with a lower survival rate.[37] Mean survival of patients with Sézary syndrome in our series was 47 months; this was greater in responders (80 months) than in nonresponders (30 months) (P<.05).[37] Three patients (11, 12, and 14) were treated in the initial phases; only 1 obtained a response, although this was not sustained, and progressed to a more advanced phase of the disease after 10 cycles. As for the overall response, our results are similar to those of other authors: we obtained slightly greater responses in patients in the erythrodermic stage (Table 4).

Our data and those of the literature allow us to state that extracorporeal photopheresis is effective in the treatment of CTCL, with varying response rates, which, nevertheless, appear to be greater in erythrodermic forms.

The different response rates observed between studies could be due to differences in patient selection, disease stage, previous therapy, the extracorporeal photopheresis protocol, duration of extracorporeal photopheresis, and the response criteria. Extracorporeal photopheresis seems to increase survival, and this is consistent with our results. Nevertheless, the effect of extracorporeal photopheresis on the survival of patients with CTCL has not been clearly established, since there are no prospective or comparative studies to evaluate this claim. In the initial phases of CTCL, our results were not very satisfactory. We believe that, in most cases, it would be advisable to use other approaches, given the lack of controlled studies, the high cost of the procedure, and the existence of other effective treatments.

GVHD

GVHD is a clinical syndrome that is generally observed as a sequela of allogeneic bone marrow transplant. It is classified as acute GVDH (onset during the first 100 days after transplantation) and chronic (onset after day 100). Little is known about the pathophysiology of GVHD. There is evidence to suggest that chronic GVHD is an autoimmune-like syndrome that is modulated by B cells, as well as by T cells.[37] Current treatment of GVHD is based on immunosuppressive therapy with corticosteroids and other agents, although toxicity limits their use.[3] Extracorporeal photopheresis is a second-line immunomodulatory approach that could be considered for patients; it has good tolerability and minimum toxicity.

Table 4. Main Studies on the Treatment of Cutaneous T-Cell Lymphoma With Extracorporeal Photopheresis

Study	Patients	*Overall Response*	*Complete Response*	*Partial Response*
Edelson, 19871	37 (29 erythrodermic)	73% 83%	24%	49%
Duvic, 199688	34 (28 erythrodermic)	50 %	18 %	32 %
Vonderheid, 199824	36 (29 erythrodermic)	33% 31%	14% 10%	19% 21%
Fritz, 199989	17	70%	0%	70%
Bisaccia, 200090	37	54%	13%	41%
Crovetti, 200091	30 (9 erythrodermal stage)	73% 66%	33% 33%	40% 33%
Suchin, 200232	47	79%	26%	53%
Our experinence	14 (10 erythrodermic)	50% 60%	7% 10%	43% 50%

Chronic GVHD

There are few laboratory parameters to evaluate the activity of chronic GVHD, and there are no criteria to define when there is a clinical response. In most studies, the response is not defined, and others consider a response to be a greater than 25% reduction in baseline involvement. This makes it difficult to draw comparisons between studies. Nevertheless, studies using extracorporeal photopheresis consistently report better responses in the skin, mucosa, and liver. Experience in other manifestations, such as lung involvement, neuromuscular effects, and thrombocytopenia is limited, although positive effects have been reported.[38-43] Reduced concomitant immunosuppression has also been proposed by some authors as a factor that enables the response to treatment to be evaluated.[40,42,43]

Scarisbrick et al[21] reviewed studies on the effectiveness of extracorporeal photopheresis in the treatment of chronic GVHD. They analyzed 23 studies covering 521 patients. The mean response rate for the skin was 68%, for the liver 63%, the mucosa 63%, the lung 46%, and for the gastrointestinal tract 29%. Karnold et al[43] carried out a review of published cases of pediatric patients with chronic GVHD treated with extracorporeal photopheresis (10 studies covering 54 cases). A clinical improvement was observed in the skin in 75% of cases, in the liver in 81%, and in the lung in 0.6%. The authors recommended using extracorporeal photopheresis early and as second-line therapy in pediatric patients.

The ideal treatment regimen has not been established. Treatment is usually administered on 2 consecutive days every 2 to 3 weeks. This is reduced to monthly intervals when there is a response. It seems that 2 cycles per week is no more effective than 2 cycles every 2 weeks.[44] The optimal duration of therapy is not clear either; most authors recommend a minimum of 6 months.[42]

Several studies have shown an increase in survival in patients who responded to extracorporeal photopheresis compared with nonresponders,[40,42] although the studies were retrospective and nonrandomized, and provide insufficient evidence to confirm such an improvement.

There have been no reports of other clinical, historical, or laboratory parameters that can predict which patients might be expected to respond to extracorporeal photopheresis.[44] Researchers have suggested that the best responses occur when extracorporeal photopheresis is initiated as soon as possible during the course of the disease, before there is severe tissue damage, and in patients who have received few immunosuppressive agents.[39] Most recommend extracorporeal photopheresis early after failure of the first line of immunosuppressive therapy.

Our experience is based on treating 10 cases of chronic GVHD for a minimum of 6 cycles (Table 5). The patients had already received immunosuppressive treatment, with a poor response. We scored the degree of skin or mucosal involvement as mild (0% to 33% of the mucosa or skin surface), moderate (34% to 66%), or severe (67% to 100%). As for the degree of induration of the skin, 15 areas of the skin surface were evaluated according to the following scale: 0, absence; 1, mild; 2, moderate; 3, severe. A score of between 0 and 45 was obtained (mild, 0-15; moderate,

Table 5. Patients With Chronic Graft-Versus-Host Disease Treated With Extracorporeal Photopheresis at Our Center

	Involvement, Time Since Diagnosis	*Regimen*	*Cycles*	*Response*	*Reduction in Combination Therapy*
1	Cutaneous S, 6 mo	Fortnightly	15	Moderate PR[a]	No
2	Cutaneous S, 5 mo	Fortnightly	34	Moderate PR	Yes
3	Mucosal, cutaneous L, pulmonary, 10 mo	Monthly	29	Mucosal CR Skin, stable. Lung, stable.	No
4	Cutaneous S, 3 mo	Monthly	19	Moderate PR	Yes (suspension, cycle 5)
5	Cutaneous S, pulmonary; 36 mo	Monthly	9	Skin: stable. Lung: stable.	Yes (suspension, cycle 6)
6	Cutaneous S, 12 mo	Monthly	6	Mild PR[a]	No
7	Cutaneous S, 36 mo	Monthly	7	Stable.	Yes
8	Cutaneous S, 36 mo	Monthly	16	Moderate PR	Yes
9	Mucosal, cutaneous L, hepatic, 14 mo	Monthly	8	Mucosa: moderate PR. Skin: moderate PR. Liver: mild PR	No combination therapy
10	Cutaneous S, 20 mo	Monthly	10	Mild PR	Yes

Abbreviations: L, lichenoid; PR, partial response; S, sclerodermiform.
[a] Moderate, improvement of 51% to 75%; mild, improvement of 25% to 50%.

16-30; severe, 31-45). An improvement of at least 25% over baseline was considered a partial response. As far as the skin was concerned, 7 patients (70%) had a partial clinical improvement, 2 (20%) remained stable, and 1 (10%) worsened during treatment. Involvement of the oral mucosa improved in 2 of the affected patients, one of whom had a partial response and the other a complete response. The only case of liver involvement showed an improvement of 50%[3] and there was no response in cases of lung involvement. In 5 of the responders (71%), it was possible to reduce immunosuppressive treatment to the extent that it was discontinued in 3 patients, one of whom remained stable without treatment 1 year after finishing extracorporeal photopheresis.[45]

We consider that the response rate achieved by our patients was similar to that found in the main studies (Table 6), with a 70% partial improvement, although complete remission was not achieved. The improvement in mucosal involvement was similar to that described above, with a response (1 of which was complete) in all patients. As for visceral involvement, the response seems to be somewhat less favorable than in previous studies. We chose monthly treatment in 8 patients and fortnightly treatment in the other 2. The 2 patients on fortnightly treatment obtained moderate partial improvements; only 2 of the 8 patients who received monthly treatment had a similar response. Therefore, we feel that shorter intervals could improve the response, although the number of patients is too low to be able to draw conclusions. Comparative studies must be performed in order to clarify this point.

At present, there seems to be sufficient clinical evidence for the usefulness of extracorporeal photopheresis in the treatment of GVHD. However, the differences in study results could be due to the lack of consensus on clinical response, associated treatments, and extracorporeal photopheresis regimen and duration. To conclude, clinical response is better in cases of mucocutaneous involvement and when treatment is started early. In addition, this allows immunosuppressive therapy to be reduced in a high percentage of patients (50% in our case).

Acute GVHD

The traditional approach to acute GVHD is based on systemic corticosteroids. However, there is no standardized treatment for patients with acute GVHD that is resistant to these agents.[46] There are few reports of patients with acute GVHD treated with extracorporeal photopheresis. Most studies have reported high response rates in skin symptoms, with somewhat lower rates in liver and gastrointestinal involvement.[42,47-49] In 2005, McKenna et al[24] reviewed all published cases of acute GVHD treated with extracorporeal photopheresis and found response rates of 58% for skin involvement and 40% for liver involvement. Greinix et al[48] treated 59 patients with acute GVHD and obtained an 82% response rate for the skin, 61% for the liver, and 61% for the gastrointestinal tract.[48] Complete resolution using extracorporeal photopheresis is favored by a low grade of GVHD at the beginning of therapy, no gastrointestinal involvement, and starting corticosteroids late after transplant. These authors insist on the importance of intensified treatment, with better response rates when a weekly regimen was used than when a fortnightly regimen was chosen.[48]

Therefore, extracorporeal photopheresis proved to be an effective approach in acute GVHD, especially with respect to cutaneous involvement in patients with a low grade of GVHD and few organs affected.[21,48]

Table 6. Main Studies on the Treatment of Chronic Graft-Versus-Host Disease With Extracorporeal Photopheresis

Study	*No.*	*Regimen*	*Skin*	*Mucosa*	*Lung*	*Liver*
Roseti et al 1996[92]	83	Every 3 wk	43% PR, 29% stable	20%	40%	33%
Salvaneschi 2001[93]	23	Unknown	70%	–	–	–
Apisarnthanarax 2003[94]	32	Mean of 6 sessions per mo	22 CR, 34% PR, 64% saving in CS	–	CR, 14% PR	–
Messina 2003[42]	44	Variable	55% PR, 29% stable	–	CR 30%, PR 14%	CR 33%, PR 14%
Foss 2005[44]	25	Fortnightly	80%	24%	–	–
Perseghin 2007[95]	25	19 treatments	80%	–	–	–
Authors' experience	10	Fortnightly or monthly	70% PR, 20% stable	50% PR, 50%	0%	100% PR

Abbreviations: CR, complete response; CS, corticosteroids; PR, partial response.

Systemic Sclerosis and Morphea

Systemic sclerosis is perhaps the most controversial condition with regard to the effectiveness of extracorporeal photopheresis. Rook et al[50] were the first group to use extracorporeal photopheresis to treat this condition. They carried out a 10-month study comparing patients treated with extracorporeal photopheresis with other patients treated with D-penicillamine and obtained a significantly greater number of patients in the extracorporeal photopheresis group (69% compared with 50%) who experienced an improvement greater than or equal to 15% with respect to baseline values for skin.[51] This study was criticized by Trentham et al,[52] who indicate that several aspects could affect the results. Zachariae et al[53,54] studied 8 patients who had had the condition for less than 3 years. They concluded that extracorporeal photopheresis in severe progressive forms of systemic sclerosis may not be sufficient as monotherapy and that it should be combined with immunosuppressive agents. Other authors too were unable to find favorable results in the treatment of systemic sclerosis.[55-57]

However, several studies and isolated case reports did detect an improvement in systemic sclerosis treated with extracorporeal photopheresis.[58-60] Di Spaltro et al[58] treated 9 patients with a history of progressive systemic sclerosis of less than 4 years. They observed a significant reduction in the degree of induration of the skin, number of skin ulcers, severity of Raynaud phenomenon, presence of arthralgia, and presence of dyspnea or dysphagia. Nevertheless, there were no relevant changes in mouth opening, renal function, or circulating antibody titers.[58] Knobler et al[60] carried out a randomized, double-blind, placebo-controlled study of 64 patients with a history of systemic sclerosis of less than 2 years. They found a significant improvement for joints and skin compared with baseline in the group that received extracorporeal photopheresis for 12 months, and no difference in the group that did not receive treatment.

Table 7. Clinical Evaluation of Patients With Systemic Sclerosis

Grade of cutaneous induration	Palpation and pinching of 10 areas: 0: Normal skin 1: Mild induration 2: Moderate induration 3: Severe induration
Mouth opening:	Interincisor distance in mm
Flexion index	Distance in mm between the palmar fat pad of the third finger and the palm
Number of skin ulcers cutáneas	0: no ulcers 1: 1-3 ulcers 2: 3-5 ulcers 3: More than 5 ulcers
Severity of Raynaud phenomenon	0: Absent 1: Mild 2: Moderate 3: Severe
Osteomuscular symptoms osteomuscular (arthralgia)	0: Absent 1: Mild 2: Moderate 3: Severe
Functional indexes: evaluation of several daily activities	0: No difficulty 1: Mild limitation 2: Severe limitation 3: Unable to perform

We used a minimum of 6 cycles of monthly extracorporeal photopheresis in 6 patients with systemic sclerosis. Clinical evaluation was based on the parameters shown in Table 7. A reduction of 35% or more over baseline was considered a significant improvement. All the patients showed a clinical improvement in the parameters for cutaneous induration, functional index, number of ulcers, presence of osteomuscular symptoms, and quality of life. No results were obtained for visceral involvement (this even progressed in 3 patients), episodes of Raynaud phenomenon, or cutaneous biopsy specimens.[3,18] Our results, which are similar to those of Di Spaltro et al,[58] and those published to date seem to indicate that treatment is more effective mainly with regard to a decreased cutaneous induration in cases of systemic sclerosis with a shorter history,[58,59] with no effect on visceral involvement, at least in the short term[56,58] We believe that patient selection should be very rigorous. Thus, patients with progressive clinical forms of recent onset (less than 2 years) and no visceral involvement, and those whose peripheral blood has a clonal T-cell population[61] would be ideal candidates.

There are few published cases of localized scleroderma. Zacharie et al[53] used extracorporeal photopheresis alone to treat a patient with limited severe morphea, achieving a partial remission of symptoms. Criber et al[55] used extracorporeal photopheresis alone to treat severe morphea in 2 patients, one of whom improved while the other remained stable.

The 2 patients with localized scleroderma that we included for treatment with extracorporeal photopheresis in our study had histories of 5 and 8 years, respectively. Symptoms stabilized with no progression in 1 patient after 12 treatment cycles.[3] The other patient had a mild partial clinical response of the cutaneous induration after 10 cycles of treatment, although the subjective improvement in quality of life was significant. The poor response achieved in our patients could be due to the fact that they had a long history of symptoms before starting

treatment (a poor prognostic factor). According to published data and the results obtained in our patients, we feel that there is insufficient evidence to recommend extracorporeal photopheresis in patients with localized scleroderma.

Atopic Dermatitis

Prinz et al[62] were the first group to use extracorporeal photopheresis to treat severe, erythrodermic, treatment-refractory atopic dermatitis. After satisfactorily treating 3 patients, they carried out an open-label clinical trial with 14 patients,[62] and observed a clinical improvement in 71.4% and a lack of response in 28.6%.[63] Radenhausen et al[64] treated 35 patients, with a favorable response in 70%. These results are consistent with those of previous studies, in some of which immunoglobulin (Ig) E levels fell among responders.[65,66]

Our experience is based on a patient with a 22-year history of severe atopic dermatitis that had not responded to numerous topical and systemic treatments. The patient underwent 12 monthly treatment cycles, although there was no improvement and no reduction in IgE levels.[3] Therefore, our results contrast with those of most published studies, which show that extracorporeal photopheresis is an effective treatment for refractory atopic dermatitis.

Chronic Erosive Lichen Planus

The first study of extracorporeal photopheresis used to treat chronic erosive lichen planus was carried out by Bécherel et al,[67] who used extracorporeal photopheresis alone in 7 patients with chronic erosive lichen planus that had proven refractory to several treatments. After a mean of 13 sessions, all 7 patients achieved complete remission. Guyot et al[68] treated 12 patients with chronic erosive lichen planus using a similar regimen to that of Bécherel et al. Nine patients achieved complete remission and the remaining 3 patients achieved partial remission. When treatment was stopped, 11 of the patients experienced relapses of their lesions; these disappeared again, or partial remission was observed when extracorporeal photopheresis was reintroduced.

At our center, we treated a 46-year-old woman with a 4-year history of severe chronic erosive lichen planus that responded well to corticosteroids but recurred when the dose was reduced. The patient presented with severe symptoms, but this improved to mild disease after 19 monthly treatment cycles, and the corticosteroid dose was reduced to a minimum that had never before been achieved without exacerbation.[3] Therefore, extracorporeal photopheresis seems to be an effective and safe option for the treatment of refractory chronic erosive lichen planus.

Pemphigus

Since extracorporeal photopheresis was first used to treat pemphigus in 1989, several cases have been published. Most of them involved pemphigus vulgaris, and the results have been favorable.[69-74] Rook et al[69] used extracorporeal photopheresis every 3 weeks to treat 4 patients with severe pemphigus vulgaris that had not responded to corticosteroids or azathioprine. Clinical remission was achieved in 3 patients, with the withdrawal of combination therapy in 2, and the circulating antibody titers decreased. Other authors have reported equally favorable responses, with very significant or complete remission, in isolated cases or small case series of pemphigus vulgaris treated with extracorporeal photopheresis. Antibody titers fell in some patients during treatment, but not in others.[70-72]

As for pemphigus foliaceus, few cases have been reported in the literature. Licht-Mbalyohere et al[73] treated 1 patient with pemphigus foliaceus using fortnightly extracorporeal photopheresis combined with systemic corticosteroids. Symptoms improved partially, and the corticosteroid dose was reduced; however, the patient remained positive for circulating autoantibodies. Wollina et al[72] found a similar response with partial remission in the patient with pemphigus foliaceus they treated with extracorporeal photopheresis, although combination therapy could not be reduced.

We used extracorporeal photopheresis to treat 6 patients—5 with pemphigus vulgaris and 1 with pemphigus foliaceus—who had not responded to systemic corticosteroids, whether combined or not with immunosuppressive agents. In order to evaluate the extent of cutaneous involvement, a value of 100% was assigned to that presented by patients at the beginning of the study, and any changes induced were expressed as a percentage. Treatment was administered every 2 to 4 weeks. A complete response was defined as the disappearance of all the lesions, and a partial response was defined as a greater than 25% reduction in baseline lesions. The response was very good, with complete remission in 4 patients (66%), one of whom had pemphigus foliaceus, and partial remission in the other 2 (33%). It was then possible to reduce the dose of combination treatment and even discontinue it in 3 cases (50%), with no exacerbations. The results obtained for pemphigus vulgaris are similar to those of published cases, and for pemphigus foliaceus they are better. In most cases, the response correlated with a reduction in antibody titers or clearance of antibodies. In published cases of

pemphigus foliaceus, the response was partial, unlike our case, in whom the response was complete, thus enabling us to withdraw combination therapy.[3,18,74]

Without larger controlled studies, our results (and those published elsewhere) suggest that extracorporeal photopheresis could be a useful, albeit expensive, adjuvant therapy in cases of severe treatment-resistant pemphigus. Controlled clinical trials evaluating the efficacy of extracorporeal photopheresis alone are necessary, since in those published to date it has always been used in combination with immunosuppressive therapy.

Other Skin Conditions Treated With Extracorporeal Photopheresis

The literature provides us with several examples of skin conditions that have been treated using extracorporeal photopheresis, in addition to those mentioned above (Table 1). The results are difficult to interpret, since most have involved the treatment of isolated cases, generally in combination with immunosuppressive agents. This leads to partial responses[75-87]; therefore, no conclusions can be drawn about the effectiveness of extracorporeal photopheresis in these entities.

Conclusions

Extracorporeal photopheresis has been used to treat several skin conditions since it first appeared 20 years ago. It is safe, with few side effects, although it is expensive and available at few centers. Therefore, its use is limited and it is necessary to obtain clinical and laboratory data to enable us to select those patients who stand to benefit most from this technique. Extracorporeal photopheresis has proven effective, both in the literature and in our study, for the treatment of CTCL and GVHD; however, we feel that larger multicenter studies are necessary to be able to define the best regimen and to establish the role of adjuvant therapy. We also need more studies to verify the real effectiveness of this approach in the treatment of systemic sclerosis, since the literature offers contradictory results. Our data support the effectiveness of extracorporeal photopheresis for the treatment of this condition, although we believe that the greatest benefit would be obtained mainly in the skin in a selected group of patients. This technique also seems effective in pemphigus vulgaris, chronic erosive lichen planus, and atopic dermatitis, although there are few reports. This therapy should be reserved for cases that do not respond to other approaches. Extracorporeal photopheresis is, therefore, a safe second-line option that could be used as an alternative in various conditions in which standard therapy is either ineffective or contraindicated.

Conflicts of Interest
The authors declare no conflicts of interest.

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