Use of Extracorporeal Photopheresis in Scleroderma: A Review

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Keywords

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Abstract

Background: Scleroderma is a heterogeneous group of diseases that can be localized or systemic. Localized scleroderma is a fibrosis of the skin characterized by inflammation and thickening due to excessive collagen deposition, and systemic sclerosis (SSc) is characterized by vasculopathy, immune dysregulation and skin fibrosis. In general, the prognosis of scleroderma highly depends on the degree of visceral involvement and relates to the degree of skin fibrosis. Despite the numerous therapies used for patients with scleroderma, the disease-related morbidity and mortality are high. Studies have explored the effects of extracorporeal photopheresis (ECP) in scleroderma treatment. Originally used in the treatment of cutaneous T-cell lymphoma, ECP is an immunomodulatory procedure in which a patient's white blood cells are treated with 8-methoxypsoralen and exposed to UVA radiation to inhibit cell proliferation and induce immunosuppression. **Summary:** Multiple lines of evidence suggest that ECP may be a safe and possibly effective

therapy for patients with scleroderma, specifically demonstrating improvement in patients with cutaneous manifestations of the disease. However, future studies assessing its role in managing visceral involvement are needed. Our review aims to examine and consolidate the results of clinical studies and propose a possible role for ECP in the management of scleroderma. **Key Points:** ECP may be an effective and safe procedure for the treatment of SSc.

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Introduction

Scleroderma is a heterogeneous group of diseases that can be localized or systemic. Localized scleroderma (morphea) is a fibrosis of the skin characterized by inflammation and thickening due to excessive collagen deposition [1]. It can be limited where linear and/or plaque-like lesions may develop, or diffuse morphea. In contrast, systemic sclerosis (SSc) is characterized by vasculopathy, immune dysregulation and skin fibrosis. It is classified into two subgroups: limited or diffuse disease. Limited cutaneous SSc can have associated scleroderma restricted to the hands, face, forearms and feet with potential delayed

pulmonary arterial hypertension, whereas diffuse cutaneous SSc is characterized by early-onset systemic and/or visceral fibrosis with skin sclerosis proximal to the elbow and knees. Both forms are associated with the development of vascular complications such as Raynaud's phenomenon and digital ulcers, which are often antecedent to the development of visceral fibrosis [2]. Histologically, lesions from patients with SSc resemble those found in graft-versus-host disease [3].

In general, the prognosis of SSc highly depends on the degree of visceral involvement and relates to the degree of skin fibrosis [4, 5]. Despite the numerous therapies used for patients with SSc, their disease-related morbidity and mortality are high. Many of these therapies have employed the use of immunosuppressive regimens (e.g., methotrexate, cyclosporine, cyclophosphamide, abatacept, prednisone, mycophenolate mofetil, rituximab) to reduce skin fibrosis, and with modest efficacies. The efficacy of these therapies has been reviewed elsewhere and is beyond the scope of this article. A number of studies and trials have explored the role of extracorporeal photopheresis (ECP) in the treatment of scleroderma, although its use as a first-line agent remains controversial. In this review, we aim to examine and consolidate the results of these studies and will propose a possible role for ECP in the management of SSc.

ECP and Rationale in Scleroderma

Originally used in the treatment of cutaneous T-cell lymphoma, ECP is an immunomodulatory procedure in which a patient's white blood cells (WBCs) are treated with 8-methoxypsoralen and exposed to ultraviolet (UV) A radiation to inhibit cell proliferation and induce immunosuppression [6]. Simply put, the procedure includes collection of the patient's blood, separation of the buffy coat, which includes the WBCs, from remaining blood components, immediate re-infusion of non-buffy-coat blood components back into the patient, photoactivation of the WBCs with UVA in the presence of 8-methoxypsoralen and re-infusion of irradiated WBCs back into the patient. ECP potentially mimics the natural process of peripheral tolerance by generating immature dendritic cells and apoptotic leukocytes, which work to suppress the action of self-reactive T and B cells [7]. A graphical depiction of the potential mechanism of action of ECP is shown in Figure 1.

It has been shown to be effective in a variety of immune diseases such as cutaneous T-cell lymphoma, graft-

versus-host disease and Sézary syndrome. Due to its efficacy and low side effect profile in treating these conditions, investigators have expanded the use of ECP to other immune disorders, such as scleroderma, as well [8].

Clinical Responses to ECP in Scleroderma

Published data on the use of ECP in scleroderma are limited and are summarized in Table 1. There has been a total of 3 randomized controlled trials, several prospective studies, 1 retrospective study and a small number of case reports. The general consensus of these studies was a positive clinical response to treatment with minor to no adverse effects. The treatment protocols for these studies were normally scheduled for 2 consecutive days every 2–6 weeks, and treatment occurred for approximately 1 year in the randomized trials [9–11] and ranged from 6 months to 2 years in the prospective studies and case reports [12–20]. Assessment of results in the controlled trials involved using various forms of a modified Rodnan skin score (mRSS), a clinical skin score based on rating skin thickness on a scale from 0 to 3 (0 = normal skin; 1 = mild thickness; 2 = moderate thickness; 3 = severe thickness with inability to pinch the skin into a fold) in multiple predefined areas of the body to generate a sum defined as the total skin score [21]. It should be noted, however, that mRSS has been shown to improve over time in all patients, regardless of treatment, thus posing a challenge when designing studies that utilize mRSS as an outcome measure. Additional parameters of oral aperture size and joint mobility were also assessed in the trials. Assessment of results in the prospective and retrospective studies and case reports varied greatly between studies but all included an mRSS or clinical skin evaluation in addition to other methods.

Each of the randomized trials took a unique approach in study design but all demonstrated some improvement in skin manifestations. The earliest conducted trial ($n = 79$) was a randomized, single-blinded parallel-group clinical trial comparing the effects of systemic sclerosis treated using ECP with those using D-penicillamine. Assessment of disease progression was conducted at baseline and monthly thereafter using a clinical skin score. Analysis showed statistically significant improvement in skin score in the ECP group when compared to the D-penicillamine group. The mean clinical skin scores for the 31 patients who received ECP for 6 months decreased from a baseline of 21.37 ± 9.09 to 17.24 ± 8.95 ($p < 0.001$), with a median change of -5.00 . The mean scores for the 25 patients who received D-penicillamine for 6 months de-

Fig. 1. Proposed mechanism of action of extracorporeal photopheresis. **A** Buffy coat, containing monocytes, polymorphonuclear monocytes (PMN), B cells and T cells, is extracted from the patient. **B** Buffy coat is photoactivated with 8-methoxypsoralen (8-MOP) and treated with ultraviolet A (UVA) light. **C** Treatment results in the generation of apoptotic cells from lymphocytes. Nonapoptotic cells generate immature dendritic cells, which interact with apo-

ptotic cells via TAM (Tyro3, Axl, Mer) receptors. **D** Treated buffy coat is re-infused into the patient. **E** This ligand-receptor interaction promotes the generation of anti-inflammatory cytokines and suppresses pro-inflammatory cytokines via the generation of tolerogenic dendritic cells (DC; low CD80 CD86, MHC II and high PDL1 or IDO).

creased from a baseline of 21.70 ± 9.34 to 20.16 ± 10.24 ($p = 0.488$), with a median change of 0.00 [9]. A subsequent crossover trial ($n = 19$) randomized patients to either receive ECP treatment during the first year and no treatment during the second year, or no treatment during the first year and photopheresis treatment during the second year. A skin score was obtained every 3 months in both patient groups. There was not a statistically significant difference between ECP treatment and no treatment but mild improvement in skin score was still noted on observation. In the group that received ECP in the first year, the average skin score improved by 5.4% after 12 treatments (standard error [SE], 20.8%). During the same year, the skin score in the control group worsened by 4.5% (SE, 13.8%) ($p = 0.71$) [10]. Oral aperture size and joint/hand mobility were also followed in the above studies; however, significant improvement in these parameters was only noted in the first trial [9, 10]. The most re-

cent trial ($n = 64$) was a randomized, double-blind, placebo-controlled trial conducted at 16 sites across the USA, Canada and Europe. Patients were randomized to receive either active or sham ECP, and assessment of disease progression was again performed by conducting an mRSS each month. A statistically significant improvement in skin scores was noted in the active ECP group compared to baseline, with a mean decrease of 5.6 points ($p = 0.008$), but not to the sham ECP group due to the small sample size of study arms. Joint involvement also significantly improved in terms of decreasing the appearance of new joint contractures and increasing the frequency of improvement of affected joints when compared to baseline ($p = 0.001$) [11]. No adverse effects were reported in these controlled trials; however, follow-up data are lacking to assess for disease recurrence after completion of treatment. Moreover, the trials did not follow visceral organ involvement closely, likely because the

Table 1. Summary of literature on extracorporeal photopheresis in scleroderma

Authors	Journal	Year	Study design	Population, <i>n</i>	Schedule of treatment	Method of clinical assessment	Clinical response
Knobler et al. [11]	Journal of the American Academy of Dermatology	2006	Randomized controlled trial	64	2 consecutive days every 4 weeks for 12 months	Clinical skin score (mRSS), joint involvement	Statistically significant improvement in skin score and joint involvement with active ECP vs. baseline, but not sham ECP
Enomoto et al. [10]	Journal of the American Academy of Dermatology	1999	Randomized controlled trial	19	2 consecutive days every 4 weeks for 12 months	Clinical skin score (mRSS), oral aperture, immunological parameters, quality of life	Minor improvement in skin score without statistical significance; no statistically significant changes observed in oral aperture size, hand mobility, immunological parameters and quality of life with ECP treatment vs. controls
Rook et al. [9]	Archives of Dermatology	1992	Randomized controlled trial	79	2 consecutive days every 4 weeks for 10 months	Clinical skin score (mRSS), percent surface area involvement, oral aperture, hand mobility, skin biopsy, PFT, serological studies	Statistically significant improvement in skin score, percent surface area involvement, oral aperture size and hand mobility with ECP treatment vs. baseline and D-penicillamine treatment; no statistically significant changes in PFT and serology; reduced skin thickness with ECP treatment
Papp et al. [12]	Clinical Immunology	2012	Prospective study	16	2 consecutive days every 6 weeks for 12 months	Clinical skin score (mRSS), oral aperture, joint mobility, dermal thickness	Statistically significant improvement in skin score, oral aperture size, joint mobility and dermal thickness vs. baseline
Muellegger et al. [13]	Photodermatology, Photoimmunology and Photomedicine	2000	Prospective study	11	2 consecutive days every 4 weeks for 16–57 months	Clinical skin score (mRSS), percent skin involvement, grip strength, oral aperture, hand mobility, histology, internal imaging, quality of life	5/11 with improvement and/or stabilization of skin changes and physical performance; 10/11 with deterioration of extracutaneous manifestations; 2/11 with improvement in oral aperture size, 4/11 in grip strength, 3/11 in hand mobility; no change in histology
Krasagakis et al. [14]	Dermatology	1998	Prospective study (observational)	16	2 consecutive days every 4 weeks for 6–45 months	Clinical skin score (mRSS), joint/hand mobility, number of ulcers	6/16 with marked improvement; 2/16 with mixed response; 3/16 with stable disease; 5/16 with progressive disease with ECP treatment
Fimiani et al. [15]	Archives of Dermatological Research	1997	Prospective study	3	2 consecutive days every 4 weeks for 12–24 months	Oral aperture, hand mobility, computerized skin elastometry, Raynaud's phenomenon, skin ulcers, dysphagia, fatigue, arthralgia, pulmonary function test	3/3 with marked improvement in skin, elasticity, oral aperture size, Raynaud's phenomenon, skin ulcers, dyspnea, dysphagia, fatigue and arthralgia; 3/3 with stabilized pulmonary function; 1/3 with improved hand mobility
Cribier et al. [16]	Dermatology	1995	Prospective study	9	2 consecutive days every 2–4 weeks for 6 months	Clinical skin score (mRSS), esophageal status, PFT, arthralgia, Raynaud's phenomenon, oral aperture	No improvement in skin score, esophageal status, Raynaud's phenomenon, oral aperture size; minor improvement in PFT in 1 patient
Di Spaltro et al. [17]	International Journal of Dermatology	1993	Prospective study	9	2 consecutive days every 4 weeks for 6–21 months	Skin evaluation, functional index, Raynaud's phenomenon, dyspnea, fatigue, dysphagia, arthralgia, skin ulcers, PFT, oral aperture, joint mobility	9/9 with skin improvement; 6/6 with improved joint mobility; 3/9 with oral aperture improvement; 7/8 with improvement of Raynaud's symptoms, ulcers, dyspnea, dysphagia, fatigue, arthralgia; 6/8 with improved functional index; 6/7 with pulmonary stabilization
Reich et al. [18]	Journal of the American Academy of Dermatology	2007	Retrospective study	20	Treatment for 12 months	Response or nonresponse to ECP treatment, pulmonary involvement	11/20 responded (30% with partial remission, 25% with stable disease) and 9/20 did not respond (45% with progression) to ECP treatment
Pileri et al. [19]	Dermatology Online Journal	2014	Case report	1	2 consecutive days every 2–8 weeks for 16 months	Clinical observation of skin changes	Clinical improvement after 4 months and complete remission by 16 months of ECP treatment
Neustadter et al. [20]	Archives of Dermatology	2009	Case report	1	2 consecutive days every 2–8 weeks	Clinical observation of skin changes	Clinical improvement of symptoms after 1–2 months; softening of sclerotic skin, increased range of motion in joints, resolution of abdominal and lower extremity plaques
Schlaak et al. [22]	Journal of the European Academy of Dermatology and Venereology	2008	Case report	1	2 consecutive days every 2 weeks for 6 months, tapering to longer intervals	Clinical observation of skin changes	Clinical improvement in pain after 4 weeks, resolution of most skin ulcers after 10 weeks and complete resolution of skin ulcers after 6 months of ECP treatment

mRSS, modified Rodnan skin score; ECP, extracorporeal photopheresis; PFT, pulmonary function test.

composite classification system for SSc [2] was not yet validated at the time.

A total of 6 prospective studies and 1 retrospective chart review were also completed. Among these 7 studies, the results of 5 showed a considerable amount of skin im-

provement [12, 14, 15, 17, 18]. However, fewer of these studies showed significant improvement in the noncutaneous manifestations of systemic sclerosis [15, 17]. Overall, the median positive response rate from patients was around 40% or greater after approximately 1 year of con-

tinuous ECP treatment with no significant adverse effects noted. In the studies that documented it, ECP treatment was started anywhere between 6 months to 4 years after the patient had been diagnosed with scleroderma [13, 14, 16, 17]. As previously mentioned, the assessment criteria varied between studies, but included skin ultrasound [12, 13], computerized skin elastometry [15] and body diagram comparisons [17] in addition to a clinical skin score or mRSS comparison. Some promising skin findings across the 7 studies included decreased frequency of episodes of Raynaud's phenomenon, decreased number of digital ulcers and increased amount of cutaneous elasticity and softening. Changes in oral aperture size were followed in 5 studies [12, 13, 15–17], with 3 of them demonstrating marked improvement [12, 15, 17]. In terms of extracutaneous changes, among the 4 studies that assessed joint mobility [12, 14, 15, 17], all showed that approximately one third of their patients improved. Three studies assessed dysphagia and arthralgias [15–17], with 2 showing improvement in symptoms [15, 17]. Most patients assessed for lung involvement showed pulmonary improvement or stabilization on pulmonary function testing [15, 17]. One study did not show any cutaneous or extracutaneous improvement in their patients; however, their patients were only under treatment for 6 months [16].

Data from 3 case reports fall in line with results from the aforementioned trials and studies, demonstrating clinical improvement of skin manifestations [19, 20, 22].

According to the 2014 European Dermatology Forum guidelines, ECP should be used as second-line or adjuvant therapy to treat skin, but not organ, manifestations of scleroderma. It should be initiated in early progressive disease, ideally within the first 2 years of diagnosis [8].

Immunomodulatory Effects of ECP in Scleroderma

Although there may be an improvement of skin disease in SSc, the immunomodulatory effects of ECP in SSc have not been extensively studied. In 1 study, the frequency of Th17 cells decreased and the numbers of regulatory Tr1 and CD4⁺ CD25⁺ regulatory T cells increased [12]. Additionally, a shift from pro- to anti-inflammatory and antifibrotic cytokines was observed, with decreased blood levels of CCL2 and TGF- β , and increased blood levels of IL-1Ra, IL-10 and hepatocyte growth factor. The authors also found a reduction in IL-17 levels in association with attenuated skin thickness measured by ultrasonography. Further, a direct negative correlation between the mRSS and Tr1 cell ratios was also elucidated [12].

Future Research Directions

While the majority of currently available data explores the effects of ECP on cutaneous manifestations of scleroderma, studies have shown that it is more so the extracutaneous complications of the disease, such as pulmonary fibrosis, that lead to greatest patient mortality. A registry-based study demonstrated that the 9-year cumulative survival rate of all patients with severe organ involvement was 38%, compared to 72% in patients without such involvement ($p < 0.0001$) [23]. As such, further research is urgently needed to assess the role of ECP in the management of visceral manifestations of scleroderma.

Moreover, in 2013, the American College of Rheumatology and the European League against Rheumatism published a new set of 7 classification criteria for SSc. Each item is given a weighted score, and a composite score of more than 9 is diagnostic of SSc [2]. While it should be noted that these criteria were developed primarily for clinical research and cannot be applied to patients with skin thickening sparing the fingers or to patients having a SSc-like disorder better explaining their manifestations (e.g., graft-versus-host disease, generalized morphea), incorporation of these validated criteria into outcome measures of future studies would be beneficial.

Conclusion

In summary, our review suggests that ECP may be a safe and possibly effective therapy for patients with diffuse cutaneous SSc. Future studies assessing its role in managing visceral involvement are needed. With the availability of novel effective therapies (e.g., autologous bone marrow transplantation), future studies are required to gain a better understanding of what role ECP plays in scleroderma management. From our review of the data, regimens implementing ECP should be used early in the course of the disease (within 2 years from the onset of non-Raynaud's phenomenon manifestations) and for 2 consecutive days every 2–6 weeks with clinical assessments conducted at regular intervals (e.g., every 1–3 months) for at least 1 year. The progression of disease in patients who benefitted from ECP demonstrated gradual but continuous improvement and suggests that the skin responds better to this therapy than extracutaneous involvement. Future clinical studies should also be complemented with laboratory studies assessing the immunomodulatory effects of ECP in SSc.

Key Message

Extracorporeal photopheresis may be a safe and possibly effective therapy for patients with diffuse cutaneous systemic sclerosis.

Statement of Ethics

As our study was a review of published literature, we did not require ethics approval by a Research Ethics Board to conduct our research.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.X.D. was responsible for acquisition and interpretation of data and drafting the manuscript for this work. M.A.O. and R.G. critically revised the work for important intellectual content and flow of ideas. All authors provided final approval of the version to be published and agree to be accountable for all aspects of the work.

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