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Evidence-based practice of photopheresis 1987–2001: a report of a workshop of the British Photodermatology Group and the U.K. Skin Lymphoma Group

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Summary

Photopheresis or extracorporeal photochemotherapy (ECP) is a novel immunomodulatory therapy which involves separation of the patient's leucocyte-rich plasma, followed by *ex vivo* administration of a photosensitizer and ultraviolet A radiation, before reinfusion. ECP has been used successfully for the treatment of cutaneous T-cell lymphoma (CTCL: Sézary syndrome), graft-versus-host disease (GVHD) and cardiac transplant rejection. ECP has a dose-sparing effect on concurrent immunosuppressive therapy. The procedure induces apoptosis of the irradiated lymphocytes, but the exact mechanism by which ECP exerts its therapeutic effect in these different conditions is uncertain. The treatment has very few adverse effects and in particular is not associated with an increased incidence of opportunistic infections. The evidence for the efficacy of ECP has been appraised by a combined British Photodermatology Group and U.K. Skin Lymphoma Group workshop on the basis of evidence published up to the end of 2001 and on the consensus of best practice. There is fair evidence for the use of ECP in erythrodermic CTCL and steroid-refractory GVHD, but randomized controlled studies are needed. There is good evidence supporting the use of ECP in preventing cardiac rejection following transplantation. Randomized controlled trials have also shown a therapeutic benefit in type 1 diabetes mellitus, but the inconvenience associated with the procedure outweighed the clinical benefit. There is fair evidence not to use ECP for the treatment of systemic sclerosis and multiple sclerosis, and good evidence not to use ECP for other forms of CTCL.

Photopheresis or extracorporeal photochemotherapy (ECP) was first reported by Edelson *et al.* in 1987[1] and was approved by the U.S. Food and Drug Administration for the treatment of advanced cutaneous T-cell lymphoma (CTCL) in 1988. Since then its application has been reported in the treatment of a variety of other T-cell-mediated disorders including graft-versus-host disease (GVHD),[2] cardiac transplant rejection[3] and type I diabetes mellitus.[4] Other conditions where ECP has been used include other types of solid organ transplant rejection,[5] scleroderma,[6] multiple sclerosis (MS),[7] bullous disorders,[8] rheumatoid arthritis (RA),[9] psoriasis,[10] psoriatic arthritis,[11] atopic eczema,[12] systemic lupus erythematosus,[13] discoid lupus erythematosus,[14] lichen planus,[15] AIDS-related complex,[16] scleromyxoedema,[17] scleredema,[18] dermatomyositis,[19] Lyme arthritis,[20] chronic hepatitis C infection[21] and chronic lymphocytic leukaemia.[22] ECP is now used in 160 centres worldwide (Therakos, personal communication); however, the treatment is moderately expensive and time consuming, and approved indications are restricted. In addition, the mechanism(s) of action of ECP are still not fully understood and the optimum parameters for administration of this therapy and specific indications for its use require clarification. A joint British Photodermatology Group and U.K. Skin Lymphoma Group workshop was held in December 2001 to address these issues. The use of ECP for a variety of indications was appraised using criteria previously applied in guideline reports on the basis of evidence published in the English language[23,24] (Appendix 1 and 2).

Mechanism of action of extracorporeal photochemotherapy

In ECP, separated leucocyte-enriched plasma is exposed to ultraviolet (UV) A radiation in the presence of extracorporeally administered 8-methoxypsoralen (8-MOP), resulting in covalent cross-linking of DNA and proliferative arrest.[25] The treated lymphocytes are then reinfused to the patient and undergo apoptosis over a period of 48–72 h.[25–27] However, lymphocyte depletion alone cannot account for the beneficial effect of ECP as only 2–5% of the total lymphocyte population is exposed to psoralen and UVA during ECP treatment.[28] Various other mechanisms have been suggested, including the generation of clone-specific suppressor T cells,[29] the release of cytokines by the reinfused white blood cells (WBC),[30,31] and shifting of T-cell phenotype.[32–34] Recent research indicates that the monocyte/macrophage plays a central role in the mechanism of action of ECP.[35–39] Monocytes do not undergo apoptosis following ECP but show an increased avidity for the phagocytosis of apoptotic lymphocytes.[37] These cells and cells derived from monocytes/macrophages (dendritic cells) acquire antigen from apoptotic lymphocytes and induce expression of adhesion molecules, class I major histocompatibility complex antigens and tumour antigens on their cell surface.[35,38,40] The latter antigens may induce a cytotoxic CD8+ T-lymphocyte-mediated host immune response.

Extracorporeal photochemotherapy procedure and procedural complications

The Therakos (a Johnson & Johnson company; Exton, PA, U.S.A.) UVAR model was replaced by the UVAR XTS system in 1999. This is the only closed system available commercially (separate components are used in some centres in France). As the latter system is most commonly used and the open systems may have variable components, a comparison of these two treatment modalities has not been made.

The photopheresis procedure takes place in three stages: leukapheresis, photoactivation and reinfusion.[41–43] In the Therakos UVAR XTS system whole blood is removed from the patient, typically from a peripheral or central vein. During the leukapheresis process the blood is centrifuged to separate the red blood cells (RBC) and plasma from the WBC. Typically 225 mL of blood is processed through three cycles or 125 mL through six cycles (lower haematocrit or smaller patient). The collected WBC (along with some plasma and RBC) form the buffy coat. The total buffy coat volume is approximately 240 mL. The buffy coat is then mixed with saline and 8-MOP (UVADEX; Therakos) is added at 0·017 mL mL^{-1} buffy coat. The buffy coat is then passed through a 1-mm plastic film between two banks of fluorescent UVA lamps to allow photoactivation. The RBC and plasma are returned at the end of each cycle and the buffy coat is returned at the end of the last cycle.

Alternatively, 8-MOP can be administered orally;[44] however, plasma levels can be erratic,[45–47] and there are side-effects of nausea, vomiting, diarrhoea and a risk of burning. To avoid these problems direct injection of psoralen into the treatment bag before collection of first buffy coat was introduced.[48] Adverse events associated with the latter ECP procedure are uncommon.[41–43] The major limiting factor of treatment is that of venous access. Reported side-effects include transient hypotension (5%), low-grade pyrexia (10%) and increase in erythema of the skin (13%).[1] Anaemia can also occur with long-term ECP due to inadequate complete reinfusion and rarely because of haemolysis. Contraindications include clinical situations where the extracorporeal volume loss cannot be tolerated, such as severe cardiac, renal or hepatic impairment, hypersensitivity to psoralen compounds and coagulation disorders.

Ultraviolet A dosimetry

The dose of UVA delivered to the lymphocytes during ECP is 1–2 J cm^{-2}, which is sufficient to produce lethal damage of these cells.[49,50] The Therakos UVAR XTS machine automatically calculates and sets irradiation time depending on detection of: (i) buffy coat volume; (ii) haematocrit (important as retained RBC act as 'light shields'); and (iii) irradiance of UVA lamps. The exposure time is based on measured irradiance initially (during manufacture), with a correction applied to account for lamp output decline. It would be desirable to be able to check the lamp output for consistency and to detect individual failed lamps. An alarm system is fitted to the Therakos machine which signals if a lamp fails; however, if this occurs all lamps have to be changed.

Treatment protocols

Treatment regimens are based on the original paper published by Edelson *et al.*[1] in 1987. The outcome of ECP for responsive diseases can potentially vary according to the ECP system used, treatment regimen/protocol followed and patient selection. Patients with advanced CTCL (stage III/IV) typically receive ECP on two consecutive days once per month. If patients respond to treatment this can be continued until maximum response is obtained. The frequency of treatment can be increased in poor responders. Treatment is generally continued for 6 months before declaring treatment failure. Treatment can be tapered in those who have responded to treatment, or maintenance treatment can be used. Maintenance treatment schedules include treatment every 6–8 weeks or discontinuation of therapy after three cycles at 8-week intervals if no active disease is present.

Patient assessment includes skin scoring, assessment of lymph node involvement, examination of blood for Sézary cell count, CD4+ cell count, CD4/CD8 ratio, T-cell receptor gene analysis and skin biopsy for histology. Skin scoring is usually based on the system used by Edelson *et al.*,[1] which is the sum of the products of severity score (0, normal; 1, barely detectable erythema and scaling; 2, readily detectable erythema, oedema and scaling; 3, marked erythema and exfoliation; 4,

fissuring, maximal erythema, induration and tumours) and surface area percentage for defined body regions. The highest possible score is 400 (4 × 100%). Primary efficacy parameters include a complete response (CR) or partial response (PR), i.e. > 50% reduction in skin score, > 50% reduction in CD4/Sézary cell count or loss of clonal disease from peripheral blood. Most authorities advocate assessment after 6 months of therapy. In poor responders treatment can be increased to fortnightly, or ECP can be combined with other therapeutic modalities such as interferon (IFN)-α.

For the management of chronic GVHD (cGVHD) an accelerated regimen has been used to gain rapid control of the disease with treatment administered initially weekly with two or three consecutive treatments every 2–3 weeks.[2] The rationale for an accelerated regimen is empirically based on the potential for increased immunological stimulus; however, studies have not been carried out comparing such regimens with other treatment regimens. Typically after 4 months of therapy, treatment is maintained, reduced to monthly or stopped, depending on response. Patient assessment includes skin scoring, skin biopsy for histology, liver function tests, chest X-ray and pulmonary function tests (PFTs). Assessment is carried out at baseline and usually at 3-monthly intervals. Cutaneous manifestations of GVHD can be scored with various scoring systems.[51–54] An example of such a scoring system is: (i) erythematous and lichenoid eruptions (according to surface area affected and grading of erythema: 0, no lesions; 1, erythema or lichenoid lesions; 2, both erythema and lichenoid lesions); (ii) scleroderma-tous lesions (0, normal skin thickness; 1, thickened; 2, thickened and fixed; 3, hidebound, unable to pinch); and (iii) mucosal involvement (0, absent; 1, present).[51]

Extracorporeal photochemotherapy for cutaneous T-cell lymphoma

ECP is licensed for the treatment of CTCL, and has been used to treat mainly erythrodermic disease, including patients with Sézary syndrome (SS) who present with erythroderma and have circulating atypical mononuclear cells (Sézary cells). Reported overall response rates vary between 31% and 86% (see Table 1).[1,55–69] CR rates, however, are much lower, ranging from 0 to 33%. Different response rates may relate to differences in entry criteria such as the presence of a peripheral blood T-cell clone, prior or adjuvant therapy, interval between diagnosis and treatment, ECP protocol, duration of ECP and definition of treatment response. Factors which have been reported to provide a favourable response to ECP include patients treated within 2 years of diagnosis and those with near normal CD8+ cell counts,[56] immunocompetence,[31] the presence of Sézary cells and a higher baseline Sézary cell count,[59,70] and a high initial CD8+ cell count.[71] Other studies, however, have found that the baseline CD8+ cell count is not a predictor of response in erythrodermic CTCL.[70] These differences may relate to entry criteria such as the presence of a peripheral blood T-cell clone.[55,72]

Similar considerations apply to studies reporting survival in patients with erythrodermic CTCL treated with ECP.[73] The median survival of these patients varies depending upon the presence of lymphadenopathy and the degree of haematological involvement. However, most series reporting survival in erythrodermic CTCL following therapy with ECP do not provide adequate data on the clinical factors which are known to affect prognosis. Variable median survival data have been

Table 1 Summary of studies using extracorporeal photochemotherapy (ECP) for the treatment of cutaneous T-cell lymphoma (CTCL)

	Patients	Overall response	CR	PR	MR
Edelson *et al.* (1987)[1]	Total 37	73% (27/37)	24% (9/37)	35% (13/37)	14% (5/37)
	(erythrodermic 29)	83% (24/29)			
Heald *et al.* (1989)[56]	Total 32	NK			
	(erythrodermic 22)	86% (19/22)	23% (5/22)	45% (10/22)	18% (4/22)
Stevens *et al.* (1996)[57a]	Total 17 (erythrodermic)	53% (9/17)	29% (5/17)	24% (4/17)	
Koh *et al.* (1994)[58a]	Total 34 (erythrodermic 31)	53% (18/34)	15% (5/34)	38% (13/34)	
Gottlieb *et al.* (1996)[59]	Total 28 (erythrodermic NK)	71% (20/28)	25% (7/28)	46% (13/28)	
Prinz *et al.* (1995)[60]	Total 17 (erythrodermic 3)	70% (12/17)	0% (0/17)	41% (7/17)	29% (5/17)
Duvic *et al.* (1996)[61]	Total 34 (erythrodermic 28)	50% (17/34)	18% (6/34)	32% (11/34)	
Zic *et al.* (1996)[62]	Total 20 (erythrodermic 3)	50% (10/20)	25% (5/20)	25% (5/20)	
Russell-Jones *et al.* (1997)[63a]	Total 19 (erythrodermic)	53% (10/19)	16% (3/19)	37% (7/19)[b]	
Konstantinow and Balda (1997)[64]	Total 12	67% (8/12)	8% (1/12)	42% (5/12)	17% (2/12)
	(erythrodermic 6)	50% (3/6)	0% (0/6)	50% (3/6)	
Vonderheid *et al.* (1998)[65]	Total 36	33% (12/36)	14% (5/36)	19% (7/36)	
	(erythrodermic 29)	31% (9/29)	10% (3/29)	21% (6/29)	
Jiang *et al.* (1999)[66]	Total 25 (erythrodermic)	80% (20/25)	20% (5/25)	60% (15/25)	
Crovetti *et al.* (2000)[67]	Total 30	73% (22/30)	33% (10/30)	40% (12/30)	
	(erythrodermic 9)	66% (6/9)	33% (3/9)	33% (3/9)	

CR, complete response; PR, partial response (> 50% improvement in skin scores); MR, minor response (> 25% improvement in skin scores); NK, not known. [a]Abstract/letter; [b]combined PR and MR.

reported for SS including 30 months[74] and 60 months.[71] Others have reported much longer median survival for CTCL treated by ECP but not all patients had erythrodermic disease or they had also received other therapies in combination.[59,62] Fraser-Andrews *et al.* reported no significant difference in median survival in 29 patients with SS receiving ECP (39 months) compared with those who did not (22 months), or in historical controls treated before ECP was available (26·5 months).[75]

Evidence for the utility of ECP for the treatment of nonerythrodermic mycosis fungoides (MF) is poor. In the original study by Edelson *et al.*,[1] 38% of patients with plaques or tumours obtained clinical benefit. However, in a cohort of 20 patients with mainly nonerythrodermic, generalized patch/plaque-stage MF (five IB, eight IIA), an overall response rate of 50% has subsequently been reported.[76] Case reports or small series of patients with generalized patch/plaque-stage MF (stage T2/IB) have also reported benefit with ECP.[77,78] A randomized cross-over study to compare standard photochemotherapy (PUVA) and ECP in the treatment of plaque-stage (T2/IB) MF with molecular evidence of peripheral blood T-cell clones was reported by Child *et al.*[79] At 3 months of treatment PUVA was significantly more effective than 6 months' ECP at producing a clinical CR.

In summary, there is good evidence to support the rejection of the use of ECP for the treatment of nonerythrodermic MF and fair evidence to support the use of ECP for erythrodermic MF/SS. [*CTCL, nonerythrodermic (stage IA–IIB): Strength of Recommendation E, Quality of Evidence I; CTCL, erythrodermic (stage III/IVA/B1/0): Strength of Recommendation B, Quality of Evidence II-i.*]

Extracorporeal photochemotherapy and combination therapy for cutaneous T-cell lymphoma

Extracorporeal photochemotherapy and interferon

Several studies of ECP plus IFN-α have been published.[59,80–82] None of these studies was a randomized controlled trial and it is difficult to assess how much of the clinical benefit was due to IFN-α and how much to ECP. Dippel *et al.*[80] reported 19 patients with stage IVA disease in an uncontrolled open study. Three patients were erythrodermic and six had tumours. Six of nine patients who received ECP plus IFN-α responded, compared with one of 10 treated with ECP alone. Gottlieb *et al.*[59] carried out a retrospective study on 41 patients with CTCL stage III–IV. Twenty-eight patients received ECP alone. Nine of these patients went on to receive combination therapy with IFN-α (maximum 5 MU). Although five of nine patients had an enhanced clinical response, some patients received other therapies as well, such as topical nitrogen mustard and etretinate. Bisaccia *et al.*[81] reported a retrospective cohort study of 69 T2–T4-stage patients. Thirty-seven patients were treated with ECP alone, and an overall response rate of 54% (14% CR and 41% PR) was reported. Thirteen patients with recalcitrant disease were subsequently treated with adjuvant therapy (five with IFN-α). The response rate increased from 31% (four of 13) to 69% (nine of 13). Again, as other adjuvant therapies were used it is very difficult to assess the efficacy of IFN-α alone. Wollina *et al.*[82] reported 14 stage IIA/IIB patients in a prospective but nonrandomized study. Patients received ECP twice per month and IFN-α three times per week (maximum 18 MU). Overall response rate was 50%. Among patients with stage IIA disease the response rate was 60% in contrast to only 25% for those in stage IIB. A few case reports have also reported clinical and molecular remission of advanced CTCL with ECP combined with IFN-α.[83,84]

In summary, there is fair evidence to support the rejection of the use of IFN-α with ECP for nonerythrodermic disease. There is poor evidence to support the use of the latter for erythrodermic disease. Randomized studies are needed. (*CTCL, nonerythrodermic: Strength of Recommendation D, Quality of Evidence II-ii; CTCL, erythrodermic: Strength of Recommendation C, Quality of Evidence II-ii.*)

Extracorporeal photochemotherapy and total skin electron beam therapy

Wilson *et al.*[85] carried out a retrospective study of 44 patients with erythrodermic MF/SS treated with total skin electron beam therapy (TSEB), 21 of whom also received concurrent or adjuvant ECP. TSEB consisted of 32–40 Gy with 4–6 MeV over 3–9 weeks. The overall CR was 73% with a 3-year disease-free survival (DFS) of 63%. For those receiving TSEB alone the 3-year DFS was 49% and for those receiving combined TSEB/ECP this was 81%.

In summary, on the basis of the latter study there is fair evidence to support the use of TSEB with ECP for erythrodermic MF/SS. (*Strength of Recommendation B, Quality of Evidence II-ii.*)

It is important that there are further randomized studies of ECP combination therapies in erythrodermic CTCL stratified for lymph node stage. These studies should compare ECP vs. ECP + IFN-α and TSEB vs. ECP + TSEB. The role of the retinoid X receptor-selective retinoid, bexarotene[86] in combination with ECP remains to be evaluated. It is recommended that if patients with erythrodermic MF/SS fail to respond to ECP after 6 months, combined ECP and IFN-α (low to maximal tolerated dose) could be considered. Those patients with erythrodermic MF/SS who respond to TSEB could be offered adjuvant or neoadjuvant ECP therapy.

Extracorporeal photochemotherapy for graft-versus-host disease

GVHD complicating allogeneic bone marrow transplantation can target various organs including the skin, gastrointestinal tract and liver and is subdivided into acute (aGVHD) and chronic (cGVHD) stages. ECP has been used in the treatment of steroid/immunosuppressive-refractory GVHD for the past 10 years. However, most published reports are limited by small numbers of patients and the lack of randomized controlled studies.

Owsianowski *et al.*[87] first reported clinical benefit of ECP on skin and joint mobility in a patient with cGVHD in 1994. Since then there have been several reports on the benefit of ECP for cGVHD.[2,51–54,88–90] See Table 2 for response rates for the latter publications. It has been suggested that ECP may be more beneficial if started earlier in the course of cGVHD.[53] A review of eight peer-reviewed papers[2,52–54,88–91] and 10 abstracts[92–101] indicates available evidence for efficacy of ECP for cGVHD. These patients were all refractory to steroids and other immunosuppressive agents and these medications were frequently continued concomitantly with ECP (see Table 2). Criteria for assessment of organ improvement in GVHD are variable, but PR was typically defined as > 50% improvement from baseline parameters and CR as complete resolution of organ involvement.[2,54,90] Overall 184 cases of cGVHD have been reported, and sites of involvement (response rates: CR + PR) are as follows: skin, 158 (75%); liver, 67 (66%); lung, 31 (25%); gut, 22 (18%); and mucous membranes, 72 (68%). In the largest studies of patients with cGVHD treated with ECP the response of associated hepatic disease was inconsistent.[2,51,90] The majority of reports suggested that concurrent immunosuppression could be reduced during ECP therapy, and no increase in opportunistic infections was reported. Of the 21 deaths reported 18 were infection related and three were due to progressive liver GVHD; however, follow-up was variable and incomplete.

Table 2 Summary of papers using extracorporeal photochemotherapy (ECP) for the treatment of chronic graft-versus-host disease

Reference	No. patients	Treatment regimen	Organ site (% improvement)					Immunosuppression	
			Skin	Mucosa	Lung	Liver	GI	Prior to ECP	During ECP
Rossetti *et al.* (1996)[88]	8	Two treatments/ 3 weeks for 6 months then taper	3/7 (43%) clear/ improve++ 2/7 (29%) stable	1/5 (20%)	2/5 (40%)	1/3 (33%)	0/3 (0%)	PSE (5), CSA (5), Az (3), Th (3), MTX (2), Ab (1), NK (2)	PSE (3), CSA (3), NK (4)
Schooneman and Claise (1996)[52]	3	2 treatments/ 2 weeks	2/3 (66%) CR/ improve++ 1/3 (33%) stable	–	–	1/2 (50%)	1/1 (100%)	NK	NK
Dall'Amico *et al.* (1997)[53]	4	2 treatments/ 3 weeks	2/3 (66%) improvement of SkS > 70%	0/2 (0%)	2/3 (66%)	1/1 (100%)	0/1 (0%)	PSE (4), CSA (4), Az (1), Th (1), MTX (1), PUVA (1), Ab (1)	PSE (3), CSA (2), NK (1)
Besnier *et al.* (1997)[89]	5	3 treatments/ week for 3 weeks then taper	2/2 (100%) improved/ partially clear	–	2/2 (100%)	1/1 (100%)	–	PSE (2), MP (1), CSA (1), Az (1), Th (1), None (2)	PSE/MP (3), CSA (1), Az (1), Th (1)
Smith *et al.* (1998)[2]	18	2–3 treatments/ week to 2 treatments/ 3 weeks	4/11 (36%) ulcers healed CR/PR	NK	0/3 (0%)	3/10 (30%)	NK	PSE (18), CSA (18), Th (8), PUVA (5)	PSE + CSA (all)
Greinix *et al.* (1998)[90]	15	2 treatments/ 2 weeks for 3 months then 2 treatments/ 4 weeks	12/15 (80%) CR	11/11 (100%)	–	7/10 (70%)	–	MP (13), CSA (11), Az (1), Th (2), PUVA (2)	MP (8), CSA (8), Th (1), None (2)
Child *et al.* (1999)[51]	11	2 treatments/ 2 weeks for 4 months then taper	9/10 (90%), % reduction of SkS 16.5–95%	3/4 (75%)	2/5 (40%)	1/5 (20%)	–	PSE (9), CSA (7), Az (6), Th (3), PUVA (3)	PSE (7), CSA (5), Az (4)
Dippel *et al.* (1999)[54]	4	2 treatments/ 2 weeks	4/4 (100%), % reduction of SkS 58–100%	1/1 (100%)	–	–	–	PSE/MP (3), CSA (1), Az (2)	PSE/MP (3), CSA (1), Az (1), None (2)

GI, gastrointestinal; CR, complete response; PR, partial response; improve++, marked/significant improvement; SkS, skin score; NK, not known; PSE, prednisolone; MP, methylprednisolone; CSA, ciclosporin; Az, azathioprine; Th, thalidomide; PUVA, psoralen + ultraviolet A, MTX, methotrexate; Ab, OKT3 monoclonal antibody.

In summary, there is fair evidence to support the use of ECP in cGVHD with cutaneous or mucosal involvement, but the evidence in hepatic disease is poor. There is fair evidence to support the rejection of the use of ECP for gastrointestinal or pulmonary cGVHD. (*cGVHD cutaneous/mucous membranes: Strength of Recommendation B, Quality of Evidence II-ii; cGVHD hepatic: Strength of Recommendation C, Quality of Evidence II-iii; cGVHD gastrointestinal/pulmonary: Strength of Recommendation D, Quality of Evidence II-ii.*)

The number of reports of the use of ECP therapy for aGVHD is less than for cGVHD.[2,88,89,102–105] The reported cases total 32 with involvement of the following sites (response rates: CR + PR): skin 24 (58%) and liver 20 (40%), but insufficient cases for other site involvement have been reported. The data in aGVHD are primarily from a single centre[105] (21 cases) suggesting benefit in cutaneous and liver disease. However, in a different centre failure of ECP in six of six cases of hepatic aGVHD was reported.[2] The difference in results obtained for liver involvement in aGVHD in the latter two centres could relate to their using differing treatment protocols, treatment frequency and adjuvant therapy.

In summary, there is poor evidence to support the use of ECP for cutaneous or hepatic aGVHD. (*aGVHD cutaneous/hepatic: Strength of Recommendation C, Quality of Evidence II-iii.*)

Extracorporeal photochemotherapy for cardiac transplantation rejection

ECP has been used as an alternative to immunosuppressive drug therapy in the management of various forms of cardiac transplant rejection including acute rejection, recurrent acute rejection, prevention of rejection and chronic rejection.

Acute cardiac rejection

Sixteen patients with rejection grades II, IIA, IIIB determined by endomyocardial biopsy (EMB)[106] were randomized: nine to receive ECP, and seven to receive steroids.[107] Rejection was reversed in eight of nine patients treated with ECP (five required one procedure and four required two) and in seven of seven patients treated with steroids. The median time from treatment to rejection reversal was 25 days (ECP) and 17 days (steroid group). It was suggested that ECP could be used as an alternative to corticosteroid pulses.

Recurrent acute cardiac rejection

Recurrent acute rejection is defined as equal to or greater than three consecutive episodes of moderate/severe acute rejection.[108] Dall'Amico *et al.*[109] reported eight patients with recurrent rejection who received ECP for 6 months with EMB monthly. Seven patients had reduced number and severity of rejections. The fraction with EMB negative for rejection changed from 13% to 41%. Grade IIIA/IIIB changed from 41% to 21% and there was also decreased requirement for immunosuppressive drugs (prednisolone reduced by 44%, azathioprine by 29% and ciclosporin by 21%). In a larger cohort of 22 patients with multiple episodes of rejection a more aggressive treatment protocol with weekly treatments for the first 1 month and then every 2 weeks for the next 2 months brought about a more rapid histological reversal of rejection.[110]

Prophylaxis of cardiac rejection

ECP was first reported by Rose *et al.*[111] as a prophylactic therapy against cardiac rejection in four high-risk cardiac recipients maintained on standard triple immunosuppression (prednisolone, azathioprine, ciclosporin). These patients experienced fewer rejection episodes and decreased level of panel reactive antibodies (PRA) over a 1-year treatment period. Meiser *et al.*[112] subsequently reported that rejection was less in those cardiac transplant patients who receive more frequent ECP. Barr *et al.*[3] reported 60 cardiac transplant patients treated with ECP to prevent rejection across 12 centres in the U.S.A. and Europe, randomized to standard triple therapy or standard triple therapy plus ECP (initial weekly treatment for first month, then every 2 weeks for 2–3 months, then monthly) after cardiac transplantation. At 6 months a significant reduction in mean number of episodes of acute rejection was observed: 1·44 ± 1 with standard therapy compared with 0·9 ± 1 with standard therapy plus ECP.

Chronic cardiac rejection

Chronic rejection is manifested by accelerated graft atherosclerosis and/or increased coronary artery intimal thickening, and is associated with the production of PRA. Barr *et al.*[113] reported a randomized controlled trial of 23 heart transplant patients. Ten were randomized to adjuvant ECP (two consecutive days every 4 weeks for the first year then treatment tapered) and 13 to standard triple therapy. Patients were treated and followed up over a 2-year period. Patients were assessed by EMB and intracoronary artery ultrasound. There was no difference in infection or acute rejection incidence in these two groups. However, there was a significant decrease in PRA in those receiving ECP. There was also a significant reduction in coronary artery intimal thickening compared with the standard therapy group.

In summary, there is good evidence to support the use of ECP for the treatment of acute rejection, recurrent acute rejection, prophylaxis of rejection and chronic cardiac rejection. (*Strength of Recommendation A, Quality of Evidence I.*)

Extracorporeal photochemotherapy for renal allograft rejection

ECP has also been reported to be helpful in the management of renal allograft rejection but the number of patients reported is small. Horina *et al.*[5] reported three patients, two with chronic rejection and one with recurrent acute rejection, treated with monthly ECP for 3 months. All patients failed to respond to the therapy and required continual maintenance dialysis.

Sunder-Plassman *et al.*[114] reported three patients, one with chronic rejection, one with recurrent acute rejection and one with acute rejection. These patients received more frequent (every 2 weeks) and longer term ECP (4–9 months). Improvement in graft function occurred in two patients and stabilized in the other. Dall'Amico *et al.*[115] reported ECP (weekly for first 1 month then tapered) combined with prednisolone for 6 months in four patients with recurrent renal transplant rejection and showed improvement of renal biopsy findings in all patients, improved creatinine clearance and a progressive reduction of oral steroids in three patients. Single case reports have also reported benefit of ECP for renal transplant rejection.[116,117] No randomized trials are reported.

In summary, there is poor evidence to support the use of ECP for the management of renal allograft rejection. (*Strength of Recommendation C, Quality of Evidence II-iii.*)

Extracorporeal photochemotherapy for lung transplant rejection

Lung transplantation can be complicated by acute rejection and the development of bronchiolitis obliterans syndrome (BOS) which can be graded in severity histopathologically.[118] ECP has been reported to be of benefit in the management of lung transplant rejection but the number of reports is small.

Slovis *et al.*[119] reported three patients with BOS and chronic rejection 9–14 months following lung transplant refractory to intensive immunosuppression whose PFTs stabilized over a 6–23-month period following the initiation of monthly ECP. Salerno *et al.*[120] reported eight patients with progressively decreased lung graft function: seven were in BOS grade II before the initiation of ECP. The condition of five of eight patients objectively improved after a median of six ECP treatments, with stabilization of PFTs, and in two patients there was histological reversal of rejection. Villanueva *et al.*[121] retrospectively reviewed 14 patients treated with ECP for 4 months (treatment every 2 weeks for 2 months, then monthly) for BOS following lung transplantation who also received concurrent standard immunosuppression treatment. This group concluded that ECP was a promising therapy for early BOS but was not beneficial for BOS II or III. It was also suggested that it may have a role in the treatment of acute lung allograft rejection. Benefit of ECP for lung transplant rejection has also been reported in single case reports or in abstracts.[122–124]

In summary, there is poor evidence to support the use of ECP for the management of lung allograft rejection. (*Strength of Recommendation C, Quality of Evidence II-iii.*)

Other indications for extracorporeal photochemotherapy

Scleroderma

Rook *et al.*[6] reported results of a multicentre study comparing ECP (two consecutive days per month) with D-penicillamine (DP) for the treatment of early progressive systemic sclerosis (PSS). The study was randomized, parallel group, prospective and single blind. At 6 months there was significant improvement in skin severity in 21 of 31 patients (68%) receiving ECP compared with eight of 25 (32%) receiving DP. This change was not statistically significant at 10 months follow-up. However, three of 18 (16%) patients receiving DP had worsened by the 10th month evaluation compared with three of 29 (10%) worsening on ECP therapy and a significant number of patients in the DP arm of the study (seven of 25) had discontinued treatment between 6 and 10 months of therapy. Since this study several groups have reported either a beneficial effect[125,126] or no significant benefit/worsening of scleroderma following ECP.[127–129] Enomoto *et al.*[130] studied 19 patients with PSS of less than 5 years' duration treated with ECP in a randomized crossover study. One group received ECP (two consecutive treatments every 4 weeks) and the other group no treatment, then treatments were reversed at 1 year. No significant change of skin scores and other clinical parameters was observed and no effects on immunological parameters or quality of life were noted.

In summary, there have been only two randomized trials assessing ECP for scleroderma, one showing benefit at 6 months which was not sustained statistically at 10 months[6] and a study which showed no benefit.[130] A significant proportion of patients from the DP arm of the study reported by Rook *et al.*[6] had dropped out by 10 months due to toxicity or disease progression, reducing the statistical power of this study. A multicentre study with sham ECP, with careful patient selection, i.e. those with active, progressive disease, and assessment of adequate end-points, including quality of life, is required to decide whether there is any role for ECP in the management of scleroderma. (*Strength of Recommendation D, Quality of Evidence I.*)

Multiple sclerosis

Based on animal experimental evidence on allergic encephalitis[131] and the response of two patients with MS to ECP,[132] a randomized, double-blind, placebo-controlled trial was carried out to confirm the efficacy of ECP in MS.[7] In this trial 16 patients with MS were treated monthly for 1 year with either ECP or sham treatment and were followed up for 6–12 months. No clinical benefit was observed and there were no differences in progression of magnetic resonance imaging plaque burden or evoked potential latencies.

In summary, there is fair evidence to support the rejection of the use of ECP for the treatment of MS. (*Strength of Recommendation D, Quality of Evidence I.*)

Type I diabetes mellitus

Ludvigsson *et al.*[4] reported a double-blind, randomized, placebo-controlled trial of the use of ECP (five double treatments in a 3-month period) in 40 children (19 active

treatment, 21 placebo) aged 10–16 years with recent onset of type I diabetes who were followed up for 3 years. Increased C peptide secretion and lowered insulin requirement to maintain haemoglobin A_{1c} was observed in the treated group. This effect was significant but too small to be of major clinical benefit. No further studies have been reported.

In summary, the effect of ECP on the disease process at the onset of type I diabetes is weak and further studies are required before it can be considered as a routine treatment modality for newly diagnosed type I diabetes. (*Strength of Recommendation C, Quality of Evidence I.*)

Rheumatoid arthritis, psoriasis and psoriatic arthropathy

In seven patients with RA treated with ECP monthly for 6 months, three significantly improved, one modestly improved but required alternative therapy, and in the remaining three ECP had no effect.[9] In a further study of seven patients with RA all improved with ECP (eight treatments over 3 weeks) and an early and prolonged effect was observed in two patients.[133] Vonderheid *et al.*[10,134] reported improvement in four patients with severe psoriasis treated with alternate-week ECP; however, two of these patients also required methotrexate therapy. Wilfert *et al.*[11] reported slight to moderate clinical improvement in four of five patients with long-standing psoriatic arthritis treated by monthly ECP for between 20 and 60 weeks (patients continued to take nonsteroidal anti-inflammatory medication); however, none showed improvement in their skin lesions of psoriasis. De Misa *et al.*[135] reported three patients with psoriasis and psoriatic arthritis which both improved with monthly ECP for 1 year but they were also receiving other topical and systemic treatments including methotrexate, prednisolone and etretinate. Vahlquist *et al.*[136] reported eight patients with psoriasis and seronegative arthritis who received ECP (initially every 2 weeks, then monthly) for 12 weeks, then ECP and PUVA for a further 12 weeks. Four patients experienced a marked improvement of joint symptoms that lasted at least 12 months post-therapy.

In summary, there is poor evidence to support the use of ECP for RA, psoriasis or psoriatic arthritis. (*Strength of Recommendation C, Quality of Evidence II-iii.*)

Miscellaneous conditions

ECP has been reported to be of benefit in small numbers of patients with a variety of other disorders including blistering diseases: epidermolysis bullosa acquisita,[137–140] pemphigus/bullous pemphigoid,[8,141,142] atopic eczema,[12,143,144] systemic lupus erythematosus,[13] discoid lupus erythematosus,[14] lichen planus[15] and AIDS-related complex.[16,145,146] There have been single case reports of the benefit of ECP for scleromyxoedema,[17,147,148] scleredema,[18] dermatomyositis[19] and Lyme arthritis.[20] (*Strength of Recommendation C, Quality of Evidence III.*)

No benefit of ECP alone was observed in 15 patients with chronic hepatitis C infection.[21] However, 30% responded to ECP when combined with IFN-α. Three patients with B-cell chronic lymphocytic leukaemia failed to show any benefit with ECP.[22] (*Strength of Recommendation D, Quality of Evidence III.*)

Establishing a photopheresis service

Factors which should be taken into account on setting up such a service include the current availability of the service, where it should be located, resources required and cost/benefit analysis. Currently there are five centres in the U.K. which offer ECP: Belfast, Glasgow, London, Manchester and Rotherham. Factors which are important regarding service location include whether the proposed base hospital is a regional cancer centre, if there is an already established apheresis unit in the haematology department, and the availability of an inpatient dermatology service or other relevant specialty service. Resources required include machine purchase/maintenance, procedural costs (see Appendix 3), nursing staff, staff training, hospital accommodation, investigations and secretarial support. Cost benefits include reduced travelling and accommodation costs. It is important that more than one nurse is trained, and peer contact should be established with alignment of the service with an associated centre. Two-day training with a Therakos representative and nurse trainer is included in the cost of machine purchase. Additional training is also required in the use of skin scoring assessment of conditions such as CTCL or GVHD. Patient information should be made available.[149] In the U.K. all photopheresis centres are managed either by a dermatologist or a haematologist. However, provided that the nurses/technicians are appropriately trained, then the photopheresis service can be managed by other specialists, depending on the condition being treated. Of greater importance is that the clinical service is audited, and that good liaison is maintained with the referring clinician.

Extracorporeal photochemotherapy: conclusions

ECP is a novel immunomodulating therapy which is of good or fair clinical benefit in erythrodermic CTCL, GVHD, cardiac transplant rejection and type I diabetes mellitus. The treatment has few side-effects and does not result in an increased incidence of opportunistic infections. Although the procedure may remain limited to relatively few centres, owing to complexity and cost issues, the results of this workshop suggest that there are clinical indications for expansion of service provision. Currently, some of the strongest evidence for the use of ECP is in the field of cardiac transplant rejection. However, surprisingly, this treatment has not been used in the U.K. for this indication (U.K. Cardiac Transplant Centres, personal communications). Randomized controlled prospective trials are needed to define and clarify the use of ECP

in some of the above clinical indications and in RA, Crohn disease and other T-cell-mediated disorders. These studies will require collaboration between multiple centres to produce worthwhile data.

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Appendix 1: Strength of recommendations and quality of evidence

Strength of recommendations

A There is good evidence to support the use of the procedure.
B There is fair evidence to support the use of the procedure.
C There is poor evidence to support the use of the procedure.
D There is fair evidence to support the rejection of the use of the procedure.
E There is good evidence to support the rejection of the use of the procedure.

Quality of evidence

I Evidence obtained from at least one properly designed, randomized controlled trial.
II-i Evidence obtained from well-designed controlled trials without randomization.
II-ii Evidence obtained from well-designed cohort or case–control analytical studies, preferably from more than one centre or research group.
II-iii Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the result of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.
IV Evidence inadequate owing to problems of methodology (e.g. sample size, length of comprehensiveness of follow-up or conflicts in evidence).

Appendix 2: Strength of recommendations and quality of evidence assessment of extracorporeal photochemotherapy (ECP) for various conditions

	Strength of recommendation	Quality of evidence
Cutaneous T-cell lymphoma		
Nonerythrodermic (stage IA–IIB)	E	I
Erythrodermic (stage III/IVA/B1/0)	B	II-i
Cutaneous T-cell lymphoma (ECP and combination therapy)		
ECP + interferon-α		
Nonerythrodermic (stage IA–IIB)	D	II-ii
Erythrodermic (stage III/IVA/B)	C	II-ii
ECP+ total skin electron beam therapy	B	II-ii
Graft-versus-host disease		
Chronic graft-versus-host disease		
Cutaneous/mucous membrane	B	II-ii
Hepatic	C	II-iii
Gastrointestinal/pulmonary	D	II-ii
Acute graft-versus-host disease		
Cutaneous	C	II-iii
Hepatic	C	II-iii
Transplantation rejection		
Cardiac	A	I
Renal	C	II-iii
Lung	C	II-iii
Other		
Systemic sclerosis	D	I
Multiple sclerosis	D	I
Type I diabetes mellitus	C	I
Rheumatoid arthritis	C	II-iii
Psoriasis	C	II-iii
Psoriatic arthritis	C	II-iii
Atopic eczema	C	III
Blistering disease[a]	C	III
Systemic lupus erythematosus	C	III
Lichen planus	C	III
AIDS-related complex	C	III
Chronic hepatitis C infection	D	III
B-cell chronic lymphocytic leukaemia	D	III

[a]Epidermolysis bullosa acquisita, pemphigus vulgaris, bullous pemphigoid, pemphigus foliaceus.

Appendix 3: Cost of photopheresis

1 Cost of system:
- Cost of Therakos UVAR XTS system £ 41 082.
- Most commonly purchased under a lease arrangement which can vary in terms and length depending on the requirements of the customer.

2 Maintenance and servicing:
- There is a 1-year free warranty following purchase. A 1-year extended warranty is £4345. The warranty extends throughout the leasing period.
- XT20 lamp assembly replacement (every 150 h) £1051.

3 Procedural costs (per cycle: two treatments):
- Procedure kit £1062.
- Price based on lowest quantity of cases (four kits per case) ordered.
- UVADEX (10 mL vial) £81·50.
- Nursing staff (Grade E) £104·76.

4 Additional costs:
- Investigations, secretarial support and accommodation if required.