

Treatment of Autoimmune Disease with Extracorporeal Photochemotherapy: Pemphigus Vulgaris— Preliminary Report

ALAIN H. ROOK, M.D., PETER W. HEALD, M.D.,
GEORGE T. NAHASS, M.D., WILLIAM MACEY, R.N.,
WILLIAM K. WITMER, M.D., GERALD S. LAZARUS, M.D.,
AND BRIAN V. JEGASOTHY, M.D.

*General Clinical Research Center, Hospital of the University of Pennsylvania,
Philadelphia, Pennsylvania, and Departments of Dermatology, Hospital of the
University of Pennsylvania, Philadelphia, and Yale University School of Medicine,
New Haven, Connecticut*

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Extracorporeal photochemotherapy is a new form of immunotherapy which involves the extracorporeal photoinactivation of peripheral blood cells by 8-methoxypsoralen in the presence of ultraviolet A irradiation, followed by readministration of the cells. To explore the efficacy of this therapy in the treatment of autoimmune disease, four patients with a lengthy history of corticosteroid and immunosuppressive drug-resistant pemphigus vulgaris were initiated on extracorporeal photochemotherapy. Three patients experienced a complete remission in cutaneous disease expression, permitting discontinuation of medications in two and a substantial decrease in the third. Significant reductions in serum antiepidermal cell antibody titers occurred in all four patients. The treatments were well tolerated without the occurrence of adverse events. These results in a small number of patients suggest that extracorporeal photochemotherapy may prove to be a useful tool in the treatment of aggressive autoimmune disease.

Pemphigus vulgaris is an autoimmune blistering disease that involves the mucosal [1] and cutaneous surfaces. It is characterized by the presence of serum immunoglobulin G antibodies against a 130 kilodalton protein within the epidermis [2]. During the early course of the disease, many patients experience the formation of intraoral ulcers. This condition is usually followed by the occurrence of flaccid cutaneous blisters, which easily rupture to leave superficial erosions [1]. Prior to the era of corticosteroid use, more than 80 percent of patients with pemphigus vulgaris died as a result of complications of their disease [3]. Although the current use of steroids and immunosuppressive drugs simplifies the management of patients with pemphigus vulgaris, disease control often requires excessive doses of these medications, with the inevitable occurrence of drug-related complications, including life-threatening infections, osteoporosis, diabetes mellitus, and hypertension. Moreover, frequent disease relapses often necessitate the chronic use of these medications.

Extracorporeal photochemotherapy is a new form of immunotherapy, which permits the extracorporeal exposure of pathogenic peripheral blood leukocytes to the natural

Abbreviation: 8-MOP: 8-methoxypsoralen

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Address reprint requests to: Alain H. Rook, M.D., Dept. of Dermatology, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104

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TABLE 1
Clinical Course Antibody Titers and Drug Therapy in Pemphigus Patients

Patient (Disease Duration and Extent)	Month of Therapy (Photochemotherapy plus Prednisone and Azathioprine or Prednisone Alone)										
	Baseline	6	12	18	24	25	26	30	36	42	48
Patient 1 (4 years; mouth, face, trunk, extremities)											
Activity ^a	++++	+	++	+	++	++	++++	+	0	0	
Antibody titer	1/320	1/160	1/640	1/80	1/80	1/2,560	1/2,560	1/320	0	0	
Drug therapy	100/150	15/50	20/50	10/50	10/50	50/150 ^b	80/150 ^b	50	20	20	
Patient 2 (3 years; mouth, face, trunk)											
Activity	++++	0	+	+	++			++	++	+	0
Antibody titer	1/1,280	Not done	1/80	0	1/160			1/320	1/80	1/160	0
Drug therapy	100/100	0	40 ^c	5 ^c	30 ^c			20 ^c	10 ^c	15 ^c	0
Patient 3 (6 years; mouth, face, vagina)											
Activity	++++	+	++++	+	+			+	0	0	
Antibody titer	1/320	1/80	1/640	1/160	1/40			1/40	1/40	Not done	
Drug therapy	120	10 ^c	50	15	7.5 ^c			5 ^c	0	0	
Patient 4 (1 year; face, trunk)											
Activity	++++	++	+	++	++++						
Antibody titer	1/640	1/640	1/80	1/160	1/160						
Drug therapy	80/100	80/100	40/100	40/100	100/100						

^aRepresents percentage of initial disease activity at initiation of extracorporeal photochemotherapy, with ++++ equivalent to 100 percent.

^bPatient 1 at months 25 to 30 received prednisone and cyclophosphamide; otherwise, drug treatment consisted of prednisone and azathioprine or prednisone alone in all patients.

^cAdministration of prednisone at this time was every other day.

compound 8-methoxypsoralen (8-MOP) and ultraviolet A radiation. This therapy has recently been demonstrated to provide substantial clinical benefit for certain advanced forms of cutaneous T-cell lymphoma [4]. At our institutions, we have observed an unprecedented number of sustained complete remissions of the Sezary form of cutaneous T-cell lymphoma in patients who were treated with extracorporeal photochemotherapy. In this report, we describe our satisfactory experience with the use of extracorporeal photochemotherapy in the treatment of four patients with chronic pemphigus vulgaris who had previously required large doses of immunosuppressive drugs to control the disabling effects of their disease.

PATIENTS

Four patients with a biopsy-confirmed diagnosis of pemphigus vulgaris (two from Yale University School of Medicine and two from the Hospital of the University of Pennsylvania) were treated with extracorporeal photochemotherapy under protocols approved by the respective institutional review boards. Patient characteristics, including disease duration, extent of clinical involvement, and drug treatment at the time of initiation of extracorporeal photochemotherapy, are listed in Table 1. Prior to starting extracorporeal photochemotherapy, cutaneous lesions from all patients were evaluated by hematoxylin and eosin staining for the presence of suprabasilar epidermolysis and by direct immunofluorescence for the presence of immunoglobulin in the intercellular spaces of the epidermis. At baseline and at three-month intervals, assessment of serum levels of antiepidermal cell antibodies was performed by indirect immunofluorescence.

TREATMENT PROCEDURE

The treatment of the patients was accomplished using the UVAR photopheresis system (Therakos, West Chester, PA) in a manner similar to that which has been previously described for cutaneous T-cell lymphoma [4]. Briefly, two hours following the ingestion of 0.6 mg of 8-MOP per kilogram of body weight, patients underwent a discontinuous leukapheresis procedure with subsequent exposure of removed leukocytes to ultraviolet A radiation. During the procedure, approximately 240 ml of leukocyte-enriched blood was mixed with 300 ml of the patient's plasma and 200 ml of sterile normal saline. The final buffy coat preparation contained an estimated 25–50 percent of the total peripheral blood leukocyte compartment and had a hematocrit ranging from 2.5 to 8 percent. The buffy coat then passed as a 1 mm film through a sterile cassette, permitting a 270-minute exposure to ultraviolet A, yielding an average exposure per lymphocyte of 2 J/cm². Following exposure of the cells to ultraviolet A, the buffy coat is returned to the patient. During the initial phases of therapy, patients received the treatment on each of two successive days at four-week intervals. If, after three treatments, improvement was not observed, therapy was increased to two treatments on successive days at two- to three-week intervals.

CASE HISTORIES

Patient 1

Patient 1 was a 61-year-old male with a four-year history of pemphigus vulgaris. At the time of referral for extracorporeal photochemotherapy, he had on his face, scalp, neck, and trunk extensive blisters and erosions, which had been resistant to many months of therapy with doses of prednisone and azathioprine as high as 100 mg and

150 mg, respectively. His serum antiepidermal cell antibody titer had ranged from 1:80 to 1:640. Extracorporeal photochemotherapy was initiated with treatments on two consecutive days every three weeks. By the third cycle of treatment, new blister formation had ceased, and by the fourth cycle prednisone and azathioprine had been tapered to 20 mg and 50 mg, respectively. At the seventh cycle, treatment frequency was reduced to every five weeks. Two months subsequently, numerous new skin lesions appeared, coincident with a fourfold rise in serum antiepidermal cell antibody titer. Extracorporeal photochemotherapy treatments were administered every two weeks, with suppression of new lesion formation and clearing of erosions. The antibody titer dropped from 1:1,280 to 1:40 over a three-month period. During the next seven months, while treatments were maintained every two to three weeks, one to three new blisters occurred between treatments. The time between treatment cycles was again extended to four weeks, and prednisone was decreased to 10 mg daily, while azathioprine remained at 50 mg daily. Within two months, numerous new lesions were noted, and the patient elected to discontinue extracorporeal photochemotherapy (month 24, Table 1).

Prednisone was increased from 10 mg daily to 80 mg daily during the next month, and cyclophosphamide at a dose of 2 mg/kg daily was added. Despite continuing this therapy for six months, more than 50 percent of the body surface area became involved with numerous large erosions (Fig. 1A). The antiepidermal cell antibody titer rose to 1:2,560. Cyclophosphamide was discontinued, and extracorporeal photochemotherapy treatments were reinstated, with four treatments administered over eight days, followed by treatment cycles every three weeks. By the second three-week cycle, no new lesions had appeared, and by the third three-week cycle, all skin erosions had healed (Fig. 1B), and the antibody titer had dropped to 1:80.

Patient 2

Patient 2 was a 78-year-old female with a three-year history of pemphigus vulgaris, manifesting as recurrent blisters and erosions on her face, trunk, and oral mucosa. From 1979 to 1982, prednisone in doses ranging from 60–100 mg daily was necessary to prevent new lesion formation. During the use of prednisone, hypertension and diabetes mellitus occurred, and bilateral cataract formation was observed. The serum antiepidermal cell antibody titer fluctuated between 1:80 and 1:640. In November 1982, extracorporeal photochemotherapy treatments were initiated, with two consecutive daily treatments administered every two to four weeks (Fig. 1C). At this time, repetitive examination of peripheral blood lymphocyte phenotypes revealed an absence of suppressor (CD8+) T cells with 100 percent of cells staining with CD4 (helper T cells). By February 1983, new lesions had ceased appearing and progressive healing was noted. By August 1983, the skin had cleared completely, while the serum antiepidermal cell antibody titer had dropped from 1:1,280 to an undetectable level. Levels of CD8+ T cells were noted to increase to 34 percent of the peripheral blood lymphocyte compartment. By September 1983, prednisone had been discontinued completely. Extracorporeal photochemotherapy treatments were provided every four to five weeks until June 1984, when treatments were discontinued in the absence of clinical disease and an undetectable serum antiepidermal cell antibody titer. In September 1984, a mild disease flare occurred in association with a fall in CD8+ cells to 10 percent. She again responded to resumption of extracorporeal photochemotherapy treatments every two to three weeks with a rise in CD8+ cells to 24 percent. The

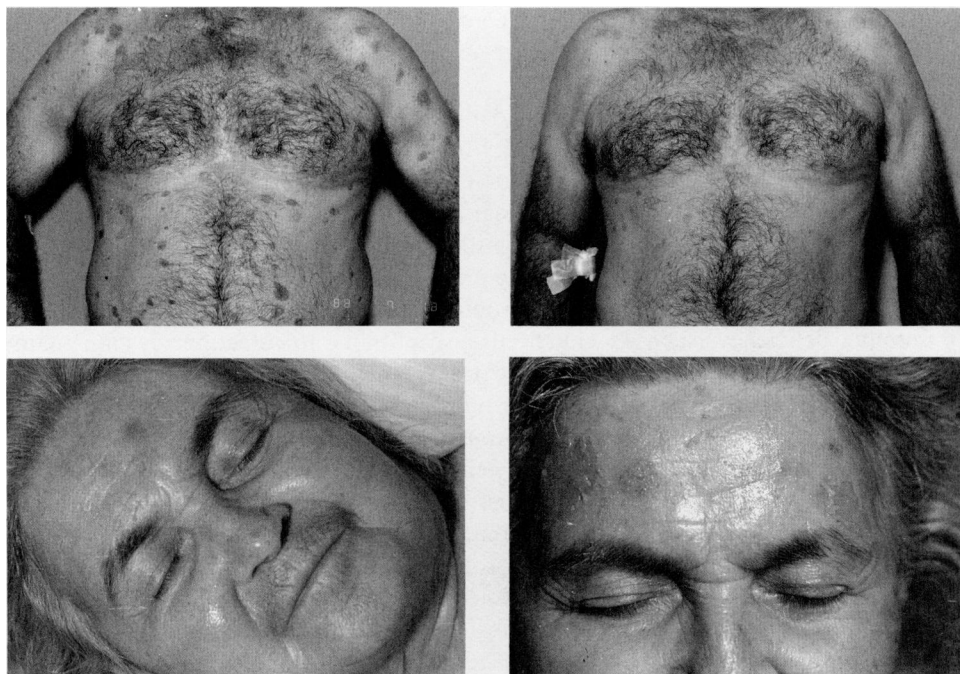


FIG. 1. A. Patient 1 at month 26 (off extracorporeal photochemotherapy). B. Patient 1 at month 30, following aggressive resumption of extracorporeal photochemotherapy. C. Patient 2, prior to initiation of extracorporeal photochemotherapy. D. Patient 2, demonstrating a complete response to treatment.

patient has been off all therapy since 1986 without evidence of skin lesions and with undetectable serum antiepidermal antibodies (Fig. 1D).

DISCUSSION

As demonstrated by the case reports and the clinical data in Table 1, all four patients with chronic drug-resistant pemphigus vulgaris treated in this pilot study experienced clinical improvement during the initial phases of the protocol employing extracorporeal photochemotherapy. In parallel, all four experienced significant decreases in their serum antiepidermal cell antibody titers. Three patients had prolonged remissions, which permitted reductions in glucocorticoid and immunosuppressive medications to trivial amounts. Moreover, patients 2 and 3 have been able to terminate all therapy during a four-year and a one-year period, respectively, during which they have been in complete remission.

The time course for the induction of a beneficial therapeutic response to extracorporeal photochemotherapy was variable. In the case of patient 1, an aggressive regimen, consisting of four treatments over an eight-day period, appears to have been responsible for the rapid reinduction of a clinical remission over just a three-week period, which had not been previously possible with high doses of cyclophosphamide and prednisone. In our experience, weekly or biweekly treatments will suppress disease activity in those patients exhibiting accelerated progression of clinical symptoms, while maintenance therapy provided every three to four weeks is generally satisfactory for sustaining an improved clinical response. In this regard, it is noteworthy that patient 4, who initially improved when treated with extracorporeal photochemotherapy, but who

now continues to develop new vesicles, has not received an aggressive course of therapy comparable to that of patient 1. We are expecting to undertake such a course of therapy in the future.

At present, the use of corticosteroids and immunosuppressive drugs is responsible for inducing clinical remissions in the majority of patients with pemphigus vulgaris. The mortality remains at 5–15 percent of cases, however, largely due to the complications of these potent immune-suppressing medications. It should be emphasized that the use of extracorporeal photochemotherapy permitted reductions in drug dosage in all of our patients. Although the precise therapeutic mechanism of extracorporeal photochemotherapy is currently unknown, the observation that none of our patients exhibited signs of immune deficiency, such as enhanced susceptibility to infection, despite many months of therapy, strongly suggests that extracorporeal photochemotherapy mediates its beneficial effect by means other than blunting of the immune response. In fact, recent evidence from an experimental murine system suggests that 8-MOP and ultraviolet A treatment of autoreactive T cells followed by the reintroduction of these cells can lead to a clone-specific immune response which may down-regulate the activity of the pathogenic T cells [5]. Moreover, our data on patient 2 indicate that an immunoregulatory imbalance in suppressor T cells may be favorably altered by extracorporeal photochemotherapy treatments. A correction of this imbalance in response to treatment may be relevant to the decrease in production of antibodies observed in all of our patients.

Thus, we have demonstrated that extracorporeal photochemotherapy appears to be a well-tolerated alternative form of therapy for patients with aggressive cases of pemphigus vulgaris that fail to respond to high doses of immunosuppressive medications. This treatment has produced a remarkable corticosteroid-sparing effect while inducing clinical remissions in three of four patients. We anticipate that future clinical trials may reveal the usefulness of this new form of therapy for other autoimmune diseases.

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