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Psoralen and Ultraviolet A Irradiation (PUVA) as Therapy for Steroid-Resistant Cutaneous Acute Graft-versus-Host Disease

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ABSTRACT

Psoralen plus ultraviolet A irradiation (PUVA) has immunomodulatory effects and is used to treat a variety of immune-mediated dermatologic diseases. We administered PUVA to 103 patients for treatment of steroid-resistant acute graft-versus-host disease (GVHD) of the skin. Twenty-nine patients had related donors (12 HLA-mismatched) and 74 had unrelated donors (23 HLA-mismatched). The median onset of GVHD was day 13 after transplantation, and the median onset of PUVA treatment was day 46. PUVA was administered as secondary therapy for 86 patients and tertiary therapy or greater for 17 patients. The median number of treatments was 16, and the mean cumulative exposure was 41 J/cm^2. PUVA was generally well tolerated with 8 patients discontinuing therapy because of toxicity. At the start of PUVA treatment, 48 patients had rash affecting >50% of their body surface area (BSA), and 91 had rash involving >25% BSA. Of 65 patients who were evaluated after 6 weeks of PUVA treatment, 11 still had rash involving >50% BSA, 24 had rash involving >25% BSA, and 24 had no rash. The mean daily dose of prednisone at the start of PUVA therapy was 1.6 mg/kg compared to 0.7 mg/kg after 6 weeks of therapy. Fifty-nine patients (57%) did not require additional therapy for skin GVHD after starting PUVA. Ninety-two percent of patients developed chronic GVHD. Fifty-three patients (51%) remain alive at 129-1883 days after transplantation. These results suggest that PUVA can be an effective therapy for steroid-resistant acute GVHD of the skin.

KEY WORDS

Acute graft-versus-host disease • PUVA • Hematopoietic stem cell transplantation

INTRODUCTION

Acute graft-versus-host disease (GVHD) is a major complication after hematopoietic stem cell transplantation, particularly in recipients of unrelated and HLA-mismatched grafts [1,2]. Cutaneous involvement is the most frequent manifestation of acute GVHD, with severity ranging from mild pruritic morbilliform erythema to exfoliative erythroderma. Less than half of patients with acute GVHD achieve durable sustained responses after treatment with high-dose corticosteroids [3]. Response rates of 11% to 40% have been reported after secondary therapy, but mortality for nonresponders exceeds 75% [4,5]. Antithymocyte globulin (ATG), a standard treatment for steroid-resistant acute GVHD, has induced responses in up to 30% of patients, but mortality rates have been reported as high as 95% [6,7]. A variety of new immunosuppressive agents have been explored in phase I/II studies [8-12], and clearly, new treatment modalities are needed to reduce the morbidity and mortality associated with both GVHD and its therapy.

Through a variety of mechanisms, including alterations in cell surface antigens and interference in transmembrane signaling and intracellular activation, UV irradiation has profound immunogenetic effects that can prevent or inhibit allorecognition between donor and host cells and tissues [13]. Photochemotherapy with the use of psoralen plus ultraviolet A light (PUVA) has been used for many years to treat a variety of dermatologic diseases, including vitiligo, psoriasis, lichen planus, atopic dermatitis, eczema, and cutaneous T-cell lymphoma [14]. The beneficial effects seen with PUVA in

these immune-mediated disorders led to preliminary testing in patients with acute [15,16] or chronic GVHD [17-19]. This report describes our experience with the use of PUVA to treat steroid-resistant acute GVHD of the skin. The objectives of this study were (1) to assess the clinical response to PUVA as a treatment for acute GVHD of the skin, and (2) to determine whether the addition of PUVA would lessen the requirement for other immunosuppressive GVHD treatments, particularly corticosteroids.

MATERIALS AND METHODS

Selection of Patients

A retrospective analysis was conducted of treatment results in 103 consecutive cases of patients in hematologic remission who received PUVA treatment for steroid-resistant acute GVHD of the skin within 100 days of allogeneic marrow or peripheral blood stem cell transplantation at the Fred Hutchinson Cancer Research Center between July 1994 and May 2000. Thirty-six patients were treated as part of an institutional review board–approved phase II clinical study, and 67 patients subsequently received PUVA as standard therapy. The treatment plans were identical for both groups. All patients had either cutaneous GVHD that was partially responsive to corticosteroids after 10 to 14 days of therapy or cutaneous GVHD that had recurred after initiating a steroid taper. Patients with concurrent intestinal or hepatic acute GVHD were treated with PUVA if involvement of those organs was mild and appeared to be resolving.

Prophylaxis, Diagnosis, and Treatment of GVHD

Most patients received methotrexate plus cyclosporine (CSP) for GVHD prophylaxis [20,21]. Cutaneous GVHD was diagnosed based on the presence of a characteristic rash, with or without a confirmatory biopsy. For most patients, a 14-day course of corticosteroids (2 mg/kg per day) was the initial treatment for acute GVHD. Secondary therapy, other than PUVA, included ATG, thymoglobulin, mycophenolate mofetil (MMF), rapamycin, or investigational antibodies. Continuation of concurrent immunosuppression, initiation of additional therapy, and tapering of steroids after the start of PUVA therapy was based on clinical response and was at the discretion of the attending physician.

PUVA Therapy

PUVA was administered in a full body supine unit (SonnenBräune Wolff System 624; SonnenBräune, Ringgold, GA) equipped with 24 fluorescent bulbs (Nuvalarium N2-10-100W; Voltarc Technologies, Waterbury, CT). Methoxsalen (Oxsoralen-Ultra) or 8-methoxypsoralen (8-MOP) was taken orally at doses of 0.4-0.9 mg/kg, 1.5 to 2 hours before exposure to UVA. Patients were instructed to use appropriate eye protection for 24 hours after ingesting methoxsalen. UVA-blocking goggles were worn by all patients during the treatment, and zinc oxide was applied to the lips. Male patients had the genital area shielded during therapy. The starting dose of UVA was 0.25 to 1.0 J/cm^2 and, in the absence of toxicity, exposure was increased in increments of 0.25 J/cm^2 per treatment. Patients were initially treated 3 times per week (M/W/F). The frequency of treatment was later decreased to twice a week if patients showed responses. Depending on response and patient tolerance, PUVA therapy was continued for the duration of glucocorticoid treatment or until patients were discharged from our care.

Measurements of Responses to PUVA Therapy

Responses to PUVA therapy were measured in 3 ways: (1) the change in skin morbidity defined as the total body surface area involved with rash, (2) the change in the dose of steroids during PUVA therapy, and (3) the requirement for additional therapy for GVHD, including additional steroids. Skin morbidity was staged as the percentage of body surface area involved with rash or erythema or the presence of bullae: stage 1, ≤25% of skin surface area involved; stage 2, 26% to 50%; stage 3, >50%; stage 4, bullae formation. Skin morbidity was staged without consideration for other concomitant factors that might contribute to changes in the skin, including phototoxicity from PUVA [22]. Steroid doses were calculated as the total daily dose of oral prednisone based on body weight (mg/kg per day). Where applicable, a factor of 1.25 was used to convert intravenous methylprednisolone to the equivalent of prednisone.

Skin morbidity staging and steroid doses were determined at the start of PUVA therapy and at weekly intervals for 6 weeks after the start of therapy or until PUVA was discontinued, whichever occurred first. Responses to PUVA therapy were also evaluated according to the reason for discontinuing PUVA and the requirement for additional immunosuppression to treat GVHD after initiating PUVA therapy. Patient charts were reviewed to determine the need for additional immunosuppressive therapy for GVHD through 100 days after transplantation, until recurrence of malignancy or death, or until discharge to home, whichever occurred first. In most cases, patients returned home between 80 and 100 days after transplantation.

PUVA Toxicity

Phototoxicity was assessed by physical exam at each treatment and was defined as the presence of erythema, erythroderma, or tenderness in the skin not caused by GVHD, as assessed by characteristic sparing of the axillae and other less exposed surfaces. Toxicity from psoralen was defined as an elevation in liver function test results or the presence of nausea/vomiting presumed to be caused by psoralen.

Statistical Analysis

Descriptive statistics were used to summarize changes in steroid doses during PUVA therapy and the requirement for additional GVHD therapy after the start of PUVA. Average daily prednisone doses were calculated for each patient by week and summarized over time with mean values and standard errors. Differences between skin morbidity scores before PUVA therapy and after 6 weeks of treatment, or at the end of PUVA therapy if treatment was discontinued earlier, were summarized and compared using the Wilcoxon matched pairs signed rank test.

RESULTS

Patient and GVHD Characteristics

Patient and GVHD characteristics are summarized in Tables 1 and 2. Twenty-nine patients received marrow or

Table 1. *Patient Characteristics (n = 103)*

Age, y, median (range)	**28 (1-56)**
Sex, n	
Male	**68**
Female	**35**
Disease risk, n*	
Low	**49**
High	**54**
GVHD prophylaxis, n	
Methotrexate/cyclosporine	**82**
Methotrexate/tacrolimus	**4**
Other regimens	**17**
HLA match, n	
Related donor	
HLA matched	**17**
HLA mismatched	**12**
Unrelated donor	
HLA matched	**51**
HLA mismatched	**23**

*Low-risk diseases included CML in chronic phase; acute leukemia in first remission; refractory anemia without excess blasts; and lymphoma in first remission, first untreated relapse or second remission. All other diseases were included in the high-risk category.

peripheral blood stem cells from related donors (17 HLA-matched, 12 HLA-mismatched), and 74 received transplants from unrelated donors (51 HLA-matched, 23 HLA-mismatched). The median onset of acute GVHD was 13 days after transplantation. Eighty percent of the patients had histological confirmation of skin GVHD at some time before starting therapy or within 5 days after starting PUVA; 15% did not have a biopsy performed before starting PUVA therapy, and 5% had an equivocal or negative biopsy for GVHD before starting PUVA therapy. In this latter group, with one exception, the biopsy was performed early after transplantation, at the onset of hyperacute GVHD, when it is very difficult to distinguish GVHD from chemoradiation damage. Initial treatment for acute GVHD consisted of corticosteroids alone in 88 patients (85%). Fifteen patients received other immunosuppressive therapies for initial treatment, including oral beclomethasone, CSP, tresperimus (a deoxyspergualin-like compound), or an anti-CD3 antibody. Before starting PUVA therapy, 11 patients (11%) had received secondary immunosuppressive therapy for GVHD, and 6 patients (6%) had received tertiary therapy. At the start of PUVA therapy, 67 patients (65%) had recurrent GVHD during the first attempt to taper steroid therapy, and 5 patients (5%) had recurrent GVHD during each of 2 successive attempts to taper steroid therapy. Thirty-one patients (30%) had active skin GVHD after initial therapy and had not yet commenced a steroid taper before starting PUVA therapy. In evaluating response to PUVA and tolerance to therapy (phototoxicity), there appeared to be no difference between those patients who had previously failed a steroid taper and those who had not yet commenced a taper.

PUVA Therapy and Skin Response

The median time of initiation of PUVA therapy was 46 days after transplantation. The median number of treatments administered was 16 (range, 1-78), with a mean cumulative UVA exposure of 41 J/cm^2. The median maximum UVA exposure was 2.5 J/cm^2 per treatment. The Figure shows the change in skin morbidity staging during 6 weeks of therapy. At the start of PUVA therapy (week 0), 12 patients had stage 1 skin morbidity, 43 patients had stage 2, and 48 had stage 3. No patients had stage 4 skin morbidity at the start of therapy. Thirty-eight patients (37%) discontinued PUVA therapy before week 6. Thirteen patients (13%) had PUVA discontinued because of GVHD, 10 because of progressive skin disease, and 3 because of new-onset intestinal GVHD requiring additional systemic therapy (Table 3). Of 65 patients who were evaluated after 6 weeks of PUVA treatment, 24 patients had no rash, 17 had stage 1 skin morbidity, 13 had stage 2, and 11 had stage 3.

Skin morbidity scores decreased significantly for all patients as seen by scores before the start of PUVA therapy compared to those after 6 weeks of therapy or, for those patients in whom treatment was discontinued earlier, at the end of PUVA therapy ($P < .001$). Results were also analyzed based on the duration of therapy. Morbidity scores decreased significantly for patients who completed 6 weeks of therapy and also for those who discontinued PUVA before 6 weeks, although the magnitude of the changes for the latter group was smaller (Table 4).

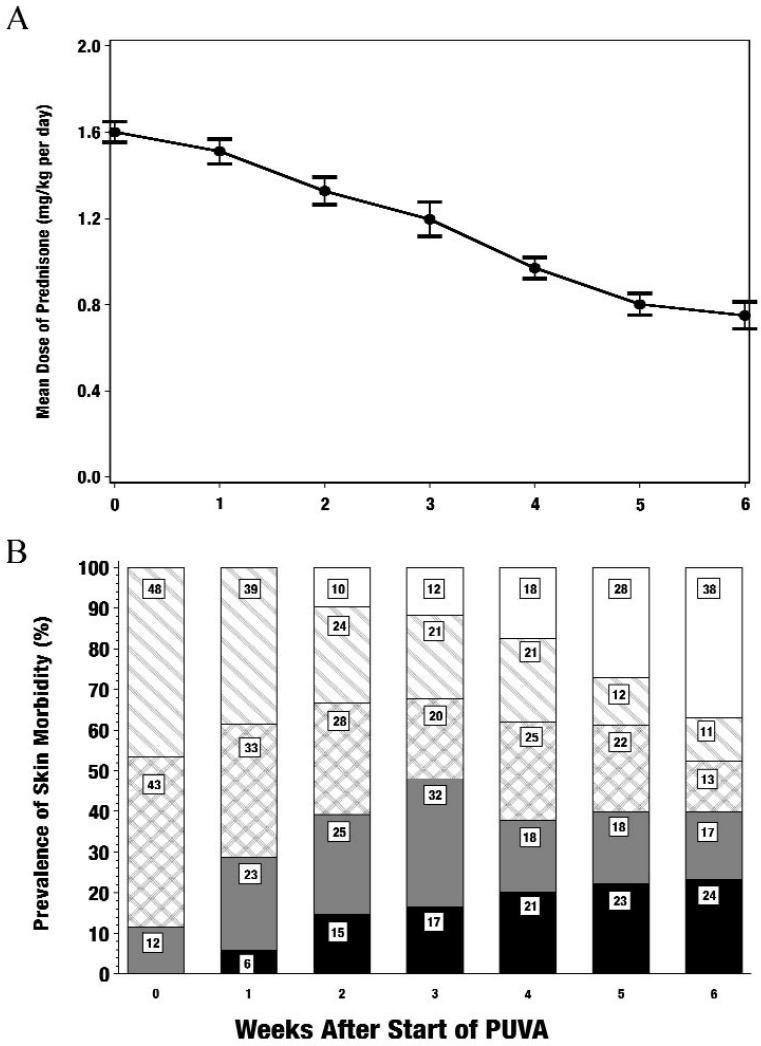
Requirement of Additional GVHD Therapy

Fifty-one patients (50%) required additional GVHD therapy after starting PUVA therapy, including increased doses of steroids (Table 5). Other modalities used to treat GVHD included tacrolimus, MMF, ATG, thalidomide, azithioprine, oral beclomethasone, and sirolimus. Forty-four patients (43%) required additional therapy for GVHD involving the skin alone or the skin plus other organs, and 7 (7%) required therapy for GVHD limited to the gut (Table 5). The median time for starting additional immunosuppressive therapy was 68 days after transplantation. In total, 59 patients (57%) did not require additional therapy for GVHD of the skin after starting PUVA therapy.

Nine patients received 4 or fewer PUVA treatments before discontinuing therapy. Six of the 9 had progressive skin GVHD requiring additional systemic therapy. One patient developed chronic GVHD, 1 patient was discharged to home in hematologic relapse, and 1 patient refused additional PUVA therapy because of the risk of phototoxicity.

Table 2. *Characteristics of Acute GVHD (n = 103)*

Days between transplantation and onset of GVHD, median (range)	**13 (4-50)**
Days between onset of GVHD and treatment with PUVA, median (range)	**30 (11-79)**
GVHD treatment regimens before PUVA, n (%)	
1	**86 (83%)**
2	**11 (11%)**
≥3	**6 (6%)**
Skin morbidity grade at the start of PUVA, n (%)	
Stage 1	**12 (12%)**
Stage 2	**43 (42%)**
Stage 3	**48 (46%)**



Skin morbidity staging and steroid dosing after start of PUVA. Evaluation of skin morbidity and determination of steroid dose began with the start of PUVA (week 0) and continued at weekly intervals through 6 weeks of therapy or until PUVA was discontinued, whichever occurred first (A). Each week, dosing was captured as the average daily dose of oral prednisone per subject. Mean values ± one standard error are presented. B, Skin morbidity was categorized as stage 0: ■, 1: ▩, 2: ▨, or 3: ▧, based on criteria described in methods. The number noted in each grid indicated the number of patients with designated skin score at the specified time point. At study weeks 1, 2, and 3, 1 patient had a skin morbidity stage of 4. The empty bar (□) indicates the number of patients withdrawn from PUVA therapy. At study week 1, 1 patient had withdrawn from therapy.

Steroid Dosing

PUVA therapy appeared to have a steroid-sparing effect. The mean dosage of prednisone at the start of PUVA therapy was 1.6 mg/kg per day. At week 6 of PUVA therapy, the mean prednisone dosage was 0.7 mg/kg per day (Figure).

Toxicity, Chronic GVHD, and Outcome

Phototoxicity, manifested as mild erythema or tenderness in the skin and thought to be related to UVA, developed in 45 patients (44%). Thirty-five patients (34%) had treatment temporarily withheld or required a decrease in UVA exposure time, and 5 patients (5%) had PUVA therapy discontinued after 10 to 32 treatments because of phototoxicity. Ten patients (10%) developed nausea and vomiting attributed to psoralen, and therapy had to be discontinued in 1 patient. One patient had increasing liver function abnormalities after starting psoralen, and PUVA therapy was discontinued. One patient with a history of squamous cell carcinoma had recurrence of the malignancy after 10 PUVA treatments, and therapy was discontinued.

Eighty-seven (92%) of 95 evaluable patients developed extensive chronic GVHD. Fifty-three patients (51%) remain alive 129 to 1883 days after transplantation. The Kaplan-Meier estimate of survival at 5 years after the start of PUVA therapy was 43% (data not shown).

DISCUSSION

Our review of PUVA therapy for steroid-resistant acute skin GVHD suggests that this treatment can be safe and effective. Analysis of responses to PUVA over 6 weeks of treatment showed a decline in skin morbidity scores, thereby allowing a decrease in steroid treatment. Fifty-seven percent of patients required no additional therapy for skin

Table 3. *Details of PUVA Therapy*

Days between transplantation and treatment with PUVA, median (range)	46 (21-95)
Number of treatments, median (range)	16 (1-78)
Cumulative UVA exposure, J/cm^2, mean (range)	41 (0.25-696)
Patients discontinuing PUVA before 6 wk, n (%)	38 (37%)
Reasons for discontinuing PUVA	
Discharge home	9 (24%)
Progressive skin GVHD	10 (26%)
Other GVHD (not skin)	3 (8%)
Recurrent malignancy	3 (8%)
Toxicity	4 (10%)
Patient refusal	3 (8%)
Other*	6 (16%)

*Treatment for chronic GVHD (n = 2), too ill to continue therapy (n = 2), resolution of rash (n = 1), prednisone dose increased for treatment of idiopathic pneumonitis syndrome (n = 1).

GVHD after starting PUVA. The lack of a control group and the selection of patients with cutaneous GVHD as their major problem at the start of therapy limited our ability to compare results with those of other GVHD treatments. In some studies of initial or secondary treatment, acute GVHD of the skin was more responsive than GVHD of the liver or gastrointestinal tract [4,6,10], but not all studies have supported this conclusion [5,11]. Also, longitudinal analysis of skin morbidity scores is biased toward responding patients who are able to continue therapy. In our study, only 63% of patients continued to receive PUVA therapy for 6 weeks. That said, our analysis showed that there was a significant decrease in skin morbidity from the start of PUVA therapy to the end of treatment, regardless of duration of therapy.

The photobiological effect of PUVA and the mechanisms involved in the generation of immunosuppression to treat GVHD are not fully understood. In vitro and in vivo, UVA and UVB irradiation have been shown to deplete cell surface markers and reduce the number of dendritic epidermal cells, specifically Langerhans cells (LCs), and interfere with their antigen-presenting capacity [23-26]. Both contact and delayed hypersensitivity reactions are suppressed following photochemotherapy [27,28]. In controlled studies with psoriatic patients, the total numbers of $CD3^+$ and $CD4^+$ peripheral T-cells, as well as the percentage of $CD3^+$ lymphocytes producing interferon-γ (IFN-γ) and interleukin-2 (IL-2), were significantly reduced following PUVA therapy [29-31]. Ultraviolet irradiation also modifies proinflammatory and inhibitory cytokine production in the epidermis and peripheral mononuclear cells. UV-induced IL-10 secretion from keratinocytes contributes to systemic impairment of splenic and LC antigen–presenting function.

Table 4. *Change in Skin Morbidity Score during PUVA Therapy*

Duration of PUVA Therapy	No. of Patients	Change in Score, Mean (SD)	*P**
6 wk	65	–1.15 (1.18)	<.001
<6 wk	38	–0.42 (0.95)	.02

**P* value from Wilcoxon signed rank test comparing pre-PUVA to final score.

Also, the activity of T-helper 1 cells is suppressed by IL-10, and the production of IL-2 and INF-γ is decreased [32,33]. Studies in healthy individuals and in patients with psoriasis have demonstrated that PUVA, both in vivo and in vitro, reduced levels of proinflammatory cytokines IL-1, IL-6, IL-8, and tumor necrosis factor α [34]. The therapeutic benefit derived from PUVA to treat GVHD is likely because of a combination of these effects.

The previously reported experience with the use of PUVA for treatment of acute GVHD consists of case studies or small series of patients. PUVA therapy has been used primarily to treat patients with cutaneous GVHD. Our initial experience in 18 patients using PUVA after failure of primary or secondary therapy for acute GVHD showed a response rate of 72% for skin manifestations. Five patients also showed some improvement of hepatic and enteric GVHD. Eight of 9 patients with complete response tolerated a taper of corticosteroids. Wiesmann et al. reported an overall response rate of 75% in 20 patients receiving PUVA as secondary treatment for acute GVHD. In patients with GVHD limited to the skin, the response rate was 92%, but only 2 of 6 patients with extracutaneous involvement had improvement after treatment with PUVA. Fifty-five percent of patients were alive at the time of the report [16].

Our experience with PUVA for treatment of acute GVHD cannot be easily compared to results reported by other investigators. First, interpretations are limited by differences in GVHD risk factors and organ involvement. Second, most studies have used traditional grading measures to assess response in skin GVHD [35]. Application of this grading system is particularly difficult for studies of PUVA because the treatment can cause cutaneous changes that are nearly indistinguishable from GVHD. Erythema or burns secondary to PUVA therapy can occur in 10% to 20% of patients [36,37]. In our series, 44% of patients developed phototoxicity, with erythema, hyperpigmentation, or tenderness attributed in part to PUVA. Although a longitudinal assessment of morbidity involving the skin does not strictly measure changes in skin GVHD, this approach may provide a more objective and comprehensive

Table 5. *Outcome after PUVA Treatment (n = 103)*

Patients requiring additional therapy for GVHD after starting PUVA treatment, n (%)	51 (50%)
Treatment modalities, n	
Increased corticosteroids	41
Mycophenoalte mofetil	16
Tacrolimus	7
Antithymocyte globulin	6
Other	16
Affected organs requiring additional treatment for GVHD, n	
Skin alone	23
Skin plus other organ(s)	21
Other organ (excluding skin)	7
Extensive chronic GVHD, n (%)	
Yes	87 (92%)
No	8 (8%)
Not evaluable	8

assessment of outcome for the skin. Third, we have evaluated results with respect to concomitant steroid treatment and the need for additional immunosuppressive therapy, outcomes that are sometimes not included in published reports. In our study the use of PUVA appeared to have a steroid-sparing effect. To further assess the benefits of PUVA, a prospective randomized controlled study is needed. Consideration should be given to testing this therapy in combination with steroids versus steroids alone as primary treatment for acute GVHD of the skin.

PUVA therapy appeared to be well tolerated. Although 44% of patients experienced some degree of phototoxicity, only 5% had therapy discontinued because of phototoxicity. To date, only 1 patient in this series has developed a cutaneous malignancy, and this patient had a history of squamous cell carcinoma before transplantation. Continued surveillance of patients, however, will be needed to determine the long-term risk of skin cancers after the use of PUVA for treatment of GVHD.

Our results suggest that PUVA can serve as a safe and effective treatment for acute GVHD involving the skin. Although it is difficult to compare the efficacy of this approach to other GVHD treatments, PUVA appears to have a steroid-sparing effect and may alleviate the need to use the other systemic immunosuppression that may have increased toxicity.

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