# Prospects for ultraviolet A1 phototherapy as a treatment for chronic cutaneous graft-versus-host disease

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*Background and Objectives*. Standard or investigative immunosuppressive therapies for cutaneous chronic graft-versus-host disease (GVHD) may prove not only ineffective but also cause serious adverse effects. Repeated exposure of the skin to ultraviolet radiation in the wavelength range 340-400 nm (so-called ultraviolet A1) was recently reported to have a strong local (intracutaneous) immunomodulatory activity. This study was undertaken to evaluate efficacy and safety of this phototherapy.

*Design and Methods*. Nine patients with cutaneous (4 lichenoid and 5 sclerodermoid) GVHD and mild or no other organ involvement were enrolled. All patients had developed serious drug toxicity and/or opportunistic infections. Phototherapy was administered three times a week.

*Results*. Complete remission was seen in 5 (2 lichenoid and 3 sclerodermoid) cases and a partial improvement in 4 (2 lichenoid and 2 sclerodermoid) after having received 15.8±3.8 (lichenoid GVHD) or 21.6±8.0 (sclerodermoid GVHD) sessions of phototherapy. Adverse effects were not registered. At follow-up (range: 6-25 months), two patients with sclerodermoid lesions relapsed after 5 months but responded to another treatment cycle. Patients with lichenoid GVHD showed relapses within one month and prolonged maintenance phototherapy was needed. Problems of drug toxicity and opportunistic infections improved as phototherapy allowed the reduction or interruption of systemic drug therapies.

*Interpretation and Conclusions*. Ultraviolet A1 phototherapy may be considered as an appropriate therapeutic approach for sclerodermoid GVHD with no or mild involvement of internal organs. Patients with lichenoid GVHD should be treated only if they develop serious adverse effects to immunosuppressive therapies and opportunistic infections because of the carcinogenic hazard of high cumulative doses of ultraviolet A1 radiation.

Key words: phototherapy, ultraviolet radiation, graft-versus-host disease, scleroderma.

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Despite improvements in post-transplant immunosuppression, up to 60% of patients who receive an allogeneic bone marrow transplant develop chronic graft-versus-host disease (GVHD) that contributes substantially to morbidity and mortality. Several organs are targets of chronic GVHD but the most frequently affected organ is the skin.[1] Cutaneous involvement is characterized by lichen-planus-like papules and/ or sclerodermatous changes.[1] Standard first-line treatments of chronic GVHD are corticosteroids and cyclosporine A.[2] If these fail to induce noticeable improvement, investigational strategies, e.g. etretinate,[3] thalidomide,[4] azathioprine,[5] tacrolimus,[6] mycophenolate mofetil,[7] antithymocyte globulin,[2] phototherapy with ultraviolet B (280-320 nm) radiation,[8] psoralen photochemotherapy[4,9] and extracorporeal photopheresis[10] are utilized with variable success. Recently, selective ultraviolet phototherapy with wavelengths strictly limited to the 340-400 nm spectrum (so-called ultraviolet A1 radiation) was found effective and well tolerated in the treatment of one and six patients, respectively, affected by cutaneous sclerodermoid chronic GVHD.[11,12] However these studies did not report a prolonged follow-up and the role of ultraviolet A1 radiation, a potential carcinogen, in the treatment of these immunosuppressed patients remains unclear. In addition, the therapeutic response of lichenoid chronic GVHD lesions has not so far been reported. We report the clinical and laboratory findings of 9 patients to whom we administered ultraviolet A1 phototherapy for lichenoid or sclerodermoid chronic GVHD. The follow-up period ranged between 6 to 25 months.

## Design and Methods

### Patients

We enrolled 9 patients who had received allogeneic bone marrow transplant and developed cutaneous chronic GVHD, as established by clinical and pathohistological criteria (Table 1). Donors were HLA-identical siblings in 7 cases and unrelated in 2 cases (patients 7 and 9). All patients had a platelet count >100,000/μL. Four patients had generalized lichenoid chronic GVHD skin lesions. Five patients had sclerodermoid skin involvement, which was localized in four of them and generalized in one. Additional findings related to chronic GVHD were mild biopsy-proven liver damage (3 cases), xerophthalmia (1 case), oral ulcers (2 cases), polyserositis (2 cases) and diffuse cortical atrophy of the

**Table 1. Clinical characteristics of patients undergoing UVA1 phototherapy.**

| *Patient#* | *1* | *2* | *3* | *4* | *5* | *6* | *7* | *8* | *9* |
|---|---|---|---|---|---|---|---|---|---|
| Age (yrs)/ Sex | 36/ M | 35/ M | 52/ M | 6/M | 27/ F | 40/ F | 8/ M | 12/ M | 4/M |
| Diagnosis | AML | AML | CLL | AML | RAEB-t | AML | WA | ALL | MH |
| Conditioning regimen | FLU | CY, TH, FTBI | CY, MM, FLU, FTBI | BU, CY | CY, ATG, FTBI | CY, ATG, FTBI | CY, TH, BU, ATG | CY, VIN, BU, TH, ATG, FTBI | CY, ATG, BU |
| Prophylaxis | CSA; MP; A | CSA; MP; A; | CSA; MP | CSA | CSA; MP; ME | CSA; MP; MTX | CSA; MP; MTX | CSA; MP; | CSA |
| Acute GVHD onset | 15 days | NA | 19 days | NA | 21 days | NA | NA | 11 days | 10 days |
| Stage/Grade | 2/ I | NA | 3/ II | NA | 2/ II | NA | NA | 2/ II | 2/ II |
| Chronic GVHD onset | 100 days | 160 days | 120 days | 70 days | 90 days | 560 days | 330 days | 60 days | 105 days |
| Type | P | DN | P | DN | Q | DN | DN | P | P |
| Skin lesions | generalized | generalized | generalized | generalized | localized | localized | localized | generalized | localized |
| Histology | L | L | L | L | S | S | S | S | S |
| Other chronic GVHD involvement | mouth, liver | eye, liver | mouth | serosa | | | | liver, CNS, serosa | CNS |
| Therapy before UVA1 | CSA (200 mg/d); MP (20 mg/d); A (100 mg/d) | MP(40 mg/d); ECP (1 treat. cycle/m); ME (50 mg/d); CY (1100 mg/m) | CSA (300 mg/d); MP (20 mg/d) | MP(5 mg/d); MM (400 mg/d) | MP (20 mg/d); ME (50 mg/d) | CSA (100 mg/d); MP (10 mg/d); MM (500 mg/d) | CSA (100 mg/d); MP (5 mg/d) | CSA(150 mg/d); MP (5 mg/d); ECP (1 treat. cycle/m); MM (1000 mg/d) | CSA (50 mg/d); MP (2.5 mg/d) |
| Therapy adverse effects | CRF, bone necrosis | CRF, bone necrosis | CMV gastritis, hypertension | Mycotic hepatitis, CRF, CMV gastritis | worsening of viral hepatitis | | recurrent meningitis | diabetes, CRF, hypertension | CRF |

*A: azathioprine; GVHD: graft-versus-host disease; AML: acute myelogenous leukemia; ALL: acute lymphoblastic leukemia; ATG: anti-thymocyte globulin; BU: busulphan; CLL: chronic lymphocytic leukemia; CMV: cytomegalovirus; CRF: chronic renal failure; CSA: cyclosporine A; CY: cyclophosphamide; d: day ; DN: de novo; ECP: extracorporeal photopheresis; FLU: fludarabine; FTBI: fractionated total body irradiation; L: lichenoid; m: month; ME: mercaptopurine; MH: malignant histiocytosis; MM: mycophenolate mofetil; MP: methylprednisolone; MTX: methotrexate; NA: not applicable; P: progressive; Q: quiescent; RAEB-t: refractory anemia with excess of blasts in transformation; S: sclerodermoid; TH: thiotepa; VIN: vincristine; WA; Wiskott-Aldrich disease.*



brain (2 cases). All patients had failed to respond to standard as well as investigational immunosuppressive therapies. In addition, 8 patients had developed severe adverse reactions to systemic immunosuppressive agents (chronic renal failure in 5 patients, hypertension in 2, bilateral aseptic necrosis of whirlbones in 1 and heads of humeri in 2 and diabetes in 1). Furthermore, one patient's $HbsAg^+$ chronic hepatitis worsened, one patient suffered from mycotic hepatitis, two patients from chronic CMV gastritis and recurrent bacterial meningitis was diagnosed in another patient. All patients underwent skin biopsy before and after ultraviolet A1 phototherapy.

### Radiation source

Ultraviolet A1 radiation was emitted by a Dermalight UltrA1-24KW irradiation unit (Hönle GmbH, Martinsried, Germany). Irradiance was measured with a SR 9910 spectroradiometer (Macam Photometrics Ltd, Livingston, UK) and found to be 80 mW/cm$^2$ at skin level.

### Irradiation protocol

Fixed, medium doses (50 J/cm$^2$) of ultraviolet A1 radiation were delivered 3 times weekly. This protocol was selected on the basis of results of previous studies on the treatment of sclerodermic chronic GVHD as well as scleroderma.[11,12] High dosages (100-120 J/cm$^2$) did not appear to be more effective and raised the risk of adverse effects, while low dosages (10-20 J/cm$^2$) may be uneffective.[12] Treatment was continued until complete clearance of the lesions was obtained (i.e. resolution of clinical evidence of induration of sclerodermoid changes with re-epithelization of erosions and disappearance of hyperkeratosis and palpable infiltration of lichenoid lesions) or until partial

response or no response (respectively, greater or lees than 50% decrease of skin changes compared to the examination before ultraviolet A1 phototherapy) was reached, with no further improvement despite 3 additional treatments. Patients were followed up with clinical examinations at intervals of 15-30 days. If a relapse occurred (after a disease-free interval of less than 1 month), patients received maintenance treatment of 2 weekly irradiations. If the relapse occurred later, patients were re-enrolled in the same treatment protocol.

### Controls

Six patients had skin lesions in areas that were inaccessible to ultraviolet A1 radiation. These were located in the perineo-crural area of 4 patients, in the internatal cleft of 4 patients and in the armpits of 6 patients. These lesions were chosen to serve as unirradiated controls.

### Immuno-cytological studies

Peripheral blood mononuclear cells of all patients were used for flow cytometric analysis of lymphocyte subsets using fluorescence-labeled monoclonal antibodies against the antigens CD3, CD4, CD7, CD8, CD45RO and CD95. These studies were performed before starting the therapy, and after its termination.

### Statistical analysis

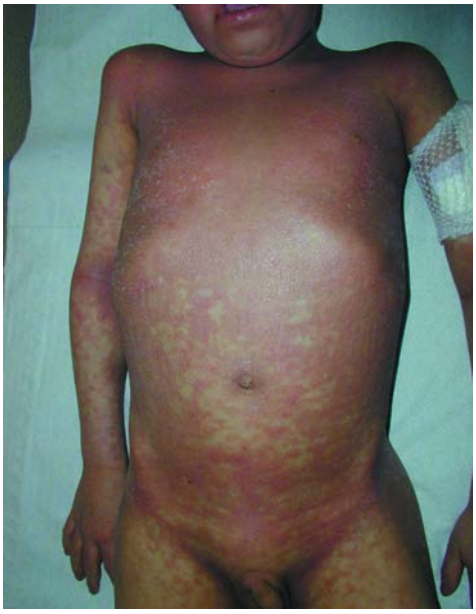
Data were analyzed using the paired sample Student's t test. Significance was defined as $p<0.05$.

## Results

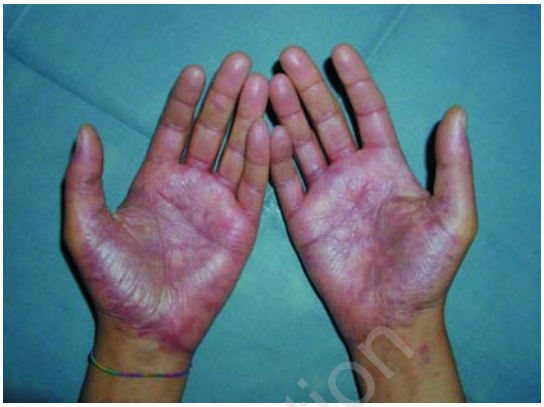
Two of the 4 patients with generalized lichenoid chronic GVHD skin disease (Figures 1a and 2a) had a complete remission (Figures 1b and 2b) and the other two a partial remission (Table 2). Three of the 4 patients with localized sclerodermoid chronic GVHD showed a complete response and the remaining one had a partial response. The patient with severe generalized sclerodermoid involvement had a partial improvement with consistent softening of the skin of the trunk and face, whereas lesions of the limbs did not respond to the treatment and there was only slight subjective improvement of joint mobility (Table 3). Patients with sclerodermoid or lichenoid chronic GVHD discontinued ultraviolet A1 phototherapy after 21.6±8.0 or 15.8±3.8 sessions of exposure, respectively. The control lesions that were located in body areas inaccessible to ultraviolet A1 radiation were not improved by treatment. The subjective and objective clinical remissions were accompanied by improvement of histopathological findings. Before treatment, lichenoid lesions showed an intense inflammatory infiltrate and many apoptotic basal keratinocytes. After treatment, these inflammatory findings were markedly reduced (Figures 3a and 3b). Sclerodermoid lesions were characterized by severe sclerotic changes with mild inflammatory, mainly perivascular, infiltrates. The clinical response was accompanied by a reduction of sclerosis and inflammatory changes. An additional positive feature of this treatment was that the use of systemic immunosuppressive drugs in all patients could be ceased or reduced. At this time appropriate drug treatments led to a complete eradication of mycotic hepatitis in one patient, chronic CMV gastritis in two patients and recurrent bacterial meningitis in another patient. Serologic markers of hepatic necrosis (aspartate and alanine transaminases) improved in the patient with chronic $HbsAg^+$ hepatitis. Overall improvement of toxic drug damage was seen in almost all patients. Blood and urinary parameters of renal damage improved in all patients with chronic renal failure. One patient had a reduced need of drugs for high blood pressure whereas another did not. Steroid-related diabetes improved in another patient and the diabetes could be controlled by dietary measures alone. Bone necrosis in 2 patients stopped progressing and the patients felt less pain although X-ray findings were substantially unchanged. Extracutaneous chronic GVHD manifestations remained unchanged. At follow-up (mean±SD: 18.2±6.4 months), patients with lichenoid chronic GVHD showed early relapses within one month of discontinuing therapy, and were entered into a prolonged maintenance regimen, which is currently being continued with sustained remissions. In contrast, 3 patients with localized sclerodermoid lesions showed persistent remissions that allowed the ultraviolet A1 phototherapy to be discontinued without adverse effects on the overall disease course. Two patients, one with generalized and one with localized sclerodermoid chronic GVHD lesions had a relapse after 5 months. These relapses responded to another treatment cycle. Results of the flow cytometric evaluation of the total number of lymphocytes and circulating lymphocyte subpopulations ($CD3^+$, $CD3^+/CD4^+$, $CD3^+/CD8^+$, $CD4^+/CD45RO^+$ and $CD4^+/CD95^+$ cells) were within normal limits and ultraviolet A1 phototherapy did not lead to significant changes.

## Discussion

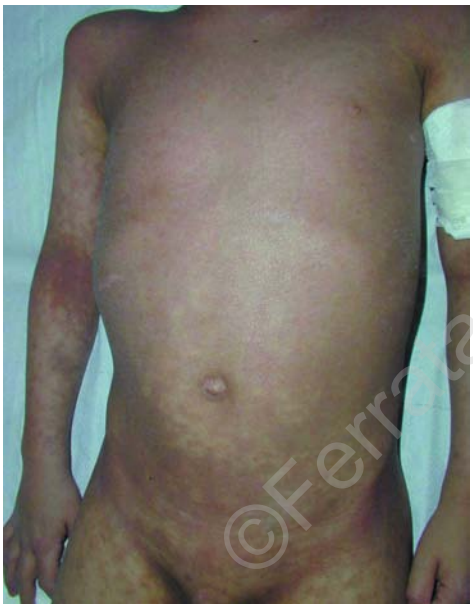
The present study demonstrates that ultraviolet A1 phototherapy is a well tolerated and effective therapy for cases of cutaneous chronic GVHD which do not respond to standard or investigational treatments. The A1 phototherapy induced complete remissions in 5 patients and a partial improvement in 4. The treatment effect was measured by subjective and objective improvements of cutaneous lesions, and the reversal or reduction of histopathological findings. The positive effect of ultraviolet A1



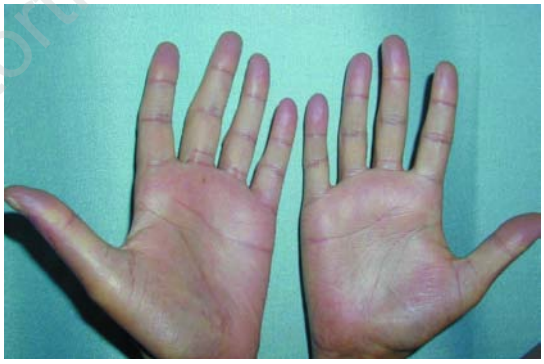
1A



2A



1B



2B



**Figure 1. Lichenoid lesions of the trunk before (A) and after (B) UVA1 therapy and figure 2: palmar lesions before (A) and after (B) UVA1 therapy.**

phototherapy allowed for reduction or discontinuation of systemic immunosuppressive therapy in all patients. Therefore toxic, drug-related lesions and immunosuppression-related side effects such as opportunistic infections improved remarkably. The beneficial effect of ultraviolet A1 phototherapy seems strictly limited to the irradiated skin and offers no improvement of unirradiated cutaneous control areas or changes of circulating lymphocyte subsets. In addition, extracutaneous chronic GVHD disease, which was mild in all patients, was not modified by ultraviolet A1 phototherapy but was also not negatively affected by changes in systemic immunosuppressive therapies. Patients with sclerodermoid chronic GVHD lesions showed stable remissions and, if a relapse occurred, it responded to another treatment cycle. However, patients with lichenoid chronic GVHD lesions showed relapses soon after therapy discontinuation and needed prolonged maintenance therapy leading to a high cumulative dosage of irra-

**Table 2. Treatment results of generalized lichenoid chronic graft-versus-host disease.**

| *Patient #* | *1* | *2* | *3* | *4* |
|---|---|---|---|---|
| Treatment cycle | | | | |
| N. of UVA1 exposures | 15 | 12 | 21 | 15 |
| Total UVA1 dose (J/cm2) | 750 | 600 | 1050 | 750 |
| Response | | | | |
| irradiated skin | complete | partial | partial | complete |
| control sites | no change | no change | no change | no change |
| Follow-up (months) | 25 | 21 | 18 | 6 |
| Remission (months) | <1 | <1 | <1 | <1 |
| Maintenance therapy | | | | |
| N. of UVA1 exposures | 196 | 160 | 138 | 48 |
| Cumulative UVA1 doses (J/cm$^2$) | 9800 | 8000 | 6900 | 2400 |
| Therapy before UVA1 | CSA (200 mg/d); MP (20 mg/d); A (100 mg/d) | MP(40 mg/d); ECP (1 treatment cycle/m); ME (50 mg/d); CY (1100 mg/m) | CSA (300 mg/d); MP (20 mg/d) | MP(5 mg/d); MM (400 mg/d) |
| Therapy adverse effects | CRF, bone necrosis | CRF; bone necrosis; | CMV gastritis, hypertension | Mycotic hepatitis, CRF, CMV gastritis |
| Current therapy | A (100 mg/d); UVA1 | CY (1100 mg/m); UVA1 | CSA (100 mg/d); MP (5 mg/d), UVA1 | MP (2 mg/d), UVA1 |

*A: azathioprine; CMV: cytomegalovirus; CRF: chronic renal failure; CSA: cyclosporine A; CY: cyclophosphamide; d: day ; ECP: extracorporeal photopheresis; ME: mercaptopurine; m: month; MM: mycophenolate mofetil; MP: methylprednisolone.*

**Table 3. Treatment results of sclerodermoid chronic graft-versus-host disease.**

| *Patient #* | *5* | *6* | *7* | *8* | *9* |
|---|---|---|---|---|---|
| Skin lesions | localized | localized | localized | generalized | localized |
| Treatment cycles | | | | | |
| N. of UVA1 exposures | 15 | 18 | 15 | 33 | 27 |
| Total UVA1 dose (J/cm$^2$) | 750 | 900 | 750 | 1650 | 1350 |
| Response | | | | | |
| Irradiated skin | complete | complete | complete | partial | partial |
| Control sites | NA | NA | NA | no change | no change |
| Follow-up (months) | 20 | 14 | 24 | 24 | 12 |
| Remission (months) | 20 | 14 | 24 | 5 | 5 |
| Treatment cycles at follow-up | | | | 1 | 1 |
| N. of UVA1 exposures | | | | 33 | 24 |
| Cumulative UVA1 doses (J/cm2) | | | | 1650 | 1200 |
| Response | | | | | |
| Irradiated skin | | | | partial | partial |
| Control side | | | | no change | no change |
| Therapy before UVA1 | MP (20 mg/d); ME (50 mg/d) | CSA (100 mg/d); MP (10 mg/d); MM (500 mg/d) | CSA (100 mg/d); MP (5 mg/d) | CSA(150 mg/d); MP (5 mg/d); ECP (1 treatment cycle/m); MM (1000 mg/d) | CSA (50 mg/d); MP (2.5 mg/d) |
| Therapy adverse effects | worsening of viral hepatitis | | recurrent meningitis hypertension | diabetes, CRF, | CRF |
| Current therapy | | | | CSA (100 mg/d); UVA1 | MP(2.5 mg/d); UVA1 |

*CRF: chronic renal failure; CSA: cyclosporine A; CY: cyclophosphamide; d: day ; ECP: extracorporeal photopheresis; ME: mercaptopurine; m: month; MM: mycophenolate mofetil; MP: methylprednisolone.*

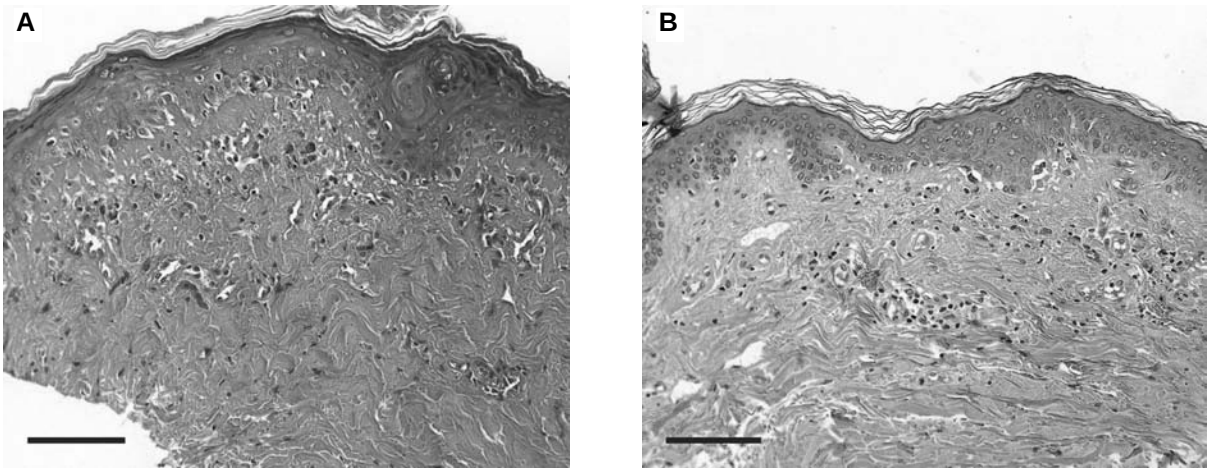



**Figure 3. Histology of lichenoid lesions before (A) and after (B) UVA1 therapy.**

diation. The quick relapse of the aggressive lichenoid inflammatory infiltrate may be caused by the lack of modulation of systemic reactivity offered by ultraviolet A1 radiation. The reduction or suspension of systemic immunosuppression may play an additional role. However we had had to reduce or discontinue immunosuppressive drugs in our series because these patients had previously developed severe systemic toxicity and/or recalcitrant opportunistic infections. The mechanisms of action of ultraviolet A1-induced modulation of immune elements in the skin are not well understood at present. However, ultraviolet A1 radiation affects the immunological functions of several cell lines, e.g. keratinocytes, epidermal and dermal dendritic cells, dermal mast cells, and normal and neoplastic T cells.[13] At a molecular level, ultraviolet A1 radiation affects not only the production of soluble mediators with anti-inflammatory activity (e.g. IL-10, $\alpha$-MSH and $PGE_2$) but also the expression of cell-surface associated molecules (e.g. ICAM-1 and ELAM-1) and the induction of apoptosis in pathogenetically relevant cells.[13,14] In addition, ultraviolet A1 radiation may affect the synthesis and degradation of collagen by matrix metalloproteinases of dermal fibroblasts[15] thus counteracting the abnormalities of collagen metabolism that have been found in sclerodermoid chronic GVHD skin.[16] The absence of systemic effects could represent a therapeutic advantage because ultraviolet A1 radiation should not interfere with the graft-versus-tumor effect that is recognized in patients who develop chronic GVHD[17] and is associated with a reduced incidence of tumor relapse. In the present investigation, ultraviolet A1 phototherapy was well tolerated though mild and transitory skin dryness occurred. Long-term adverse effects of ultraviolet A1 phototherapy are unknown but the potential hazard of carcinogenesis must be taken into account,[18] particularly if patients require prolonged maintenance therapy.[19] Other types of phototherapy, e.g. psoralen photochemotherapy[4,9] and phototherapy with ultraviolet B radiation,[8] were previously found to be effective in the treatment of chronic GVHD skin lesions. However, they often create short-term problems, such as excessive phototoxic reactions and episodes of gastro-intestinal intolerance to 8-MOP, and long-term problems, including carcinogenesis and photoaging. Ultraviolet A1 phototherapy is much cheaper and also better than extracorporeal photopheresis, although this latter strategy remains preferable if significant extracutaneous chronic GVHD disease is present.

In conclusion, ultraviolet A1 phototherapy may be considered a valuable treatment option for selected patients with cutaneous sclerodermoid chronic GVHD with little or no involvement of internal organs. Patients achieve a quick and durable remission and the administration of immunosuppressive drugs can be reduced or discontinued. Patients with lichenoid chronic GVHD show a good response but often quickly relapse and prolonged maintenance therapy is needed. Therefore, ultraviolet A1 phototherapy should be considered only for patients without systemic involvement who are resistant to standard and other investigational immunosuppressive therapies and/or who have developed serious adverse effects to those therapies. However, these patients should be carefully evaluated with a long-term follow-up because of the carcinogenic potential of ultraviolet phototherapy. Patients with severe systemic involvement, regardless of the cutaneous involvement, should not be treated because their systemic immunosuppression must be maintained and this enhances the carcinogenetic potential of ultraviolet A1 radiation.

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### Pre-publication Report & Outcomes of Peer Review

*Contributions*

PCP, FP, TI, MV, RC, CZ, FF, LDN: wrote and revised critically the paper. All the authors gave their final approval to the final manuscript..

*Disclosures*

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

*Manuscript processing*

This manuscript was peer-reviewed by two external referees and by Professor Mario Cazzola, Editor-in-Chief. The final decision to accept this paper for publication was taken jointly by Professor Cazzola and the Editors. Manuscript received August 19, 2003; accepted September 8, 2003.

In the following paragraphs, Professor Cazzola summarizes the peer-review process and its outcomes.

*What is already known on this topic*

The majority of patients who receive an allogeneic bone marrow transplant develop chronic graft-versus-host disease (GVHD), which contributes substantially to morbidity and mortality. Although several organs are targets of chronic GVHD, skin is most frequently affected. Standard immunosuppressive therapy is effective in only some of these patients.

*What this study adds*

This study shows that ultraviolet A1 phototherapy may be considered as an appropriate therapeutic approach for sclerodermoid GVHD with no or mild involvement of internal organs.