UV-A1 Phototherapy vs Clobetasol Propionate, 0.05%, in the Treatment of Vulvar Lichen Sclerosus
A Randomized Clinical Trial

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**IMPORTANCE**  Topical corticosteroids are the current first-line therapy for vulvar lichen sclerosus (VLS). UV-A1 phototherapy may be a promising alternative treatment option, but controlled studies are lacking.

**OBJECTIVE**  To compare the efficacy of high-potent topical corticosteroids with UV-A1 phototherapy in the treatment of VLS.

**DESIGN, SETTING, AND PARTICIPANTS**  A 2-arm randomized clinical trial was conducted at a university hospital dermatology department according to the intention-to-treat principle with last observation carried forward. The study population comprised 30 female patients with VLS.

**INTERVENTIONS**  Treatment of VLS with clobetasol propionate, 0.05%, ointment applied once daily for 3 months or medium-dose UV-A1 (50 J/cm²) home-based phototherapy, performed 4 times weekly for 3 months.

**MAIN OUTCOMES AND MEASURES**  Mean relative reduction of the total clinician's score (TCS) was considered the primary outcome measure. Secondary outcome measures included the reduction of pruritus and burning and/or pain according to a visual analog scale (VAS), a health-related quality of life score (Skindex-29), 20-MHz ultrasonography, and histopathological analysis before and after 3 months of therapy.

**RESULTS**  Fifteen patients were randomized in each treatment arm, and 2 patients dropped out in both treatment arms. After therapy, both therapies resulted in a significant decrease in mean TCS (51.4% [95% CI, 39.7% to 63.0%] for clobetasol ointment [P < .001] and 35.6% [95% CI, 18.2% to 53.1%] for UV-A1 phototherapy [P = .006]). No significant difference was found between both treatments (P > .05). The Skindex-29 (mean difference [MD], 29.6 [95% CI, 7.9 to 51.2] [P = .009]) and the VAS score for pruritus (MD, 4.6 [95% CI, 1.5 to 7.7] [P = .005]) and burning and/or pain (MD, 4.2 [95% CI, 1.9 to 6.6] [P = .001]) significantly decreased after clobetasol treatment. After UV-A1 phototherapy, the VAS score for burning and/or pain (MD, 3.2 [95% CI, 0.7 to 5.7] [P = .01]) was also significantly reduced; however, there was no significant reduction in pruritus (MD, 2.1 [95% CI, 0.5 to 3.7] [P = .16]) and in the Skindex-29 score (MD, 4.9 [95% CI, −12.6 to 22.4] [P > .99]). A significant reduction of the corium thickness and a significant increase in dermal density in 20-MHz ultrasonography as well as significant histopathological reduction of the inflammatory infiltrate was observed after clobetasol treatment but not after UV-A1 phototherapy.

**CONCLUSIONS AND RELEVANCE**  Although resulting in a significant clinical improvement, UV-A1 phototherapy was inferior to the current gold standard treatment with topical high-potent corticosteroids with respect to practicability, relief of itch, and improvement in quality of life. UV-A1 phototherapy may be considered a potential second-line treatment for VLS.

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Lichen sclerosus (LS) is a connective tissue disease that predominantly affects the anogenital area. An autoimmune background is likely, given the high association with other autoimmune diseases and the presence of highly specific antibodies targeting extracellular matrix protein-1.1,2 Although vulvar lichen sclerosus (VLS) is relatively common and may have substantial psychological and emotional consequences, to date, only a few therapies have been evaluated in controlled studies. The “gold standard” of treatment for VLS consists of high-potent topical corticosteroids, such as clobetasol dipropionate applied once daily for 12 weeks.3 Other therapeutic options include topical calcineurin inhibitors or, in severe and recalcitrant disease, surgery or cryotherapy.3,5 UV-A1 phototherapy has been reported to be effective in the treatment of several sclerotic skin diseases including localized scleroderma and extragenital LS.6-11 UV-A1 irradiation increases collagenase activity and suppresses collagen synthesis, resulting in a softening of former sclerotic skin lesions.7 Moreover, UV-A irradiation has strong melanogenic properties, inducing a repigmentation of the hypopigmented lesions in LS.7,9 Currently, only few data are available on UV-A1 phototherapy in VLS. The present controlled study was therefore initiated to compare the efficacy of UV-A1 phototherapy with topical high-potent corticosteroids, the current gold standard for VLS.

Methods
Study Design, Setting, and Participants
The study protocol was approved by the ethics review board of Ruhr University Bochum (No. 3435-09) and registered at ClinicalTrials.gov (NCT01400022). All patients gave their written informed consent to participate in the study. This is an open 2-arm randomized clinical trial performed at a university hospital in Germany investigating UV-A1 phototherapy vs standard treatment (clobetasol propionate, 0.05%, ointment) in patients with VLS. From August 1, 2010, to January 31, 2012, 30 female patients older than 18 years were recruited from the outpatient clinic for connective tissue diseases of the Department of Dermatology, Venereology, and Allergology at Ruhr University Bochum. Inclusion criteria were (1) active, histopathologically confirmed LS causing symptoms such as itch, burning, or pain present for less than 2 years and (2) age 18 years or older at study inclusion. If patients were treated with topical corticosteroids before initiation of the study, a washout period of 4 weeks was required. Exclusion criteria were (1) age younger than 18 years at study inclusion; (2) history of photoallergic reactions; (3) known genodermatoses with sensitivity to UV light; (4) history of skin cancer; or (6) phototherapy in the last 4 weeks before study inclusion or planned phototherapy in the next 9 months.

Randomization and Allocation to Treatment
The randomization was performed using a random allocation software as described previously.15 A total of 51 patients with genital lichen sclerosus were assessed for eligibility in this study. Among those, 21 patients were excluded because they did not meet the inclusion criteria or refused to participate. Thirty patients were randomized, 15 to each of the 2 treatment arms (UV-A1 phototherapy or topical high-potent corticosteroid). Of these 30 patients, 26 were included in the final analysis (Figure 1).

Primary Outcome Measures
Clinical examinations during the treatment and follow-up period were performed at day 0 (T0 or baseline), after 1 month (T1), after 2 months (T2), after 3 months (T3, end of therapy), and at follow-up 3 months after the end of therapy. Photographic documentation was performed at each visit. Lesional skin biopsies were performed at baseline and after 3 months of therapy. Because there is currently no validated clinical score available for VLS, clinical assessment of efficacy was performed using our own score, the total clinician’s score (TCS). In this score, hypopigmentation, sclerosis, atrophy, hyperkeratosis, erosions, edema, and erythema are each assigned a value from 0 to 3, with 0 indicating “absent”; 1, “slight”; 2, “moderate”; and 3, “severe.” The total of these values was considered the TCS, with a maximum score of 21. The primary outcome measure was the mean reduction in TCS at T3 (after 3 months of treatment). The observer determining the TCS could not be blinded because of lesional tanning after UV-A1 phototherapy.

Secondary Outcome Measures
Secondary outcome measures were patients’ scores evaluating pruritus and burning and/or pain and the Skindex-29 score at T3. Pruritus and burning and/or pain were evaluated at each clinical visit by means of a visual analog scale (VAS) score on a 0 to 10-point scale, with 0 indicating “no sensation” and 10, “maximum intensity of sensation.” The Skindex-29 is a validated...
questionnaire in the German language to measure the health-related quality of life. Additional secondary outcome measures included the increase of dermal density and reduction of dermal thickness (corium thickness in micrometers), as measured by 20-MHz sonography (DUB 20; taberna pro medicum), as well as the reduction of lesional lymphocytic infiltrates in hematoxylin-eosin-stained samples as measured semiquantitatively (0, no lymphocytes; 1, slight lymphocytic infiltrate; 2, moderate lymphocytic infiltrate; and 3, strong lymphocytic infiltrate) before and after treatment. The examination of the ultrasonographic images and histological specimens was performed by a blinded observer (M.S.).

Interventions
UV-A1 phototherapy was performed with a specially designed Sellas irradiation unit (System Dr Sellmeier) emitting wavelengths mainly from 340 to 400 nm. All patients received a portable irradiation unit to take home and performed the radiation therapy in a comfortable environment at a suitable time for the patients. An example of this UV-A1 irradiation device (the so-called vulva lamp) is shown in Figure 2. Irradiation intensity at body distance was 24 mW/cm². The distance between the irradiation unit and the irradiated genital area was approximately 25 cm. The UV-A1 doses were intensified during the first 5 treatment sessions. In the first session, a dose of 10 J/cm² was used, resulting in an irradiation time of approximately 5 minutes. In the following 4 sessions, the radiation energy was successively increased to 20 J/cm² (irradiation time approximately 10 minutes), 30 J/cm² (irradiation time approximately 16 minutes), 40 J/cm² (irradiation time approximately 22 minutes), and 50 J/cm² (irradiation time approximately 27 minutes), respectively. From the fifth session until the end of the treatment period, 50-J/cm² UV-A1 was applied, resulting in a medium-dose UV-A1 phototherapy. UV-A1 phototherapy was administered 4 times per week for a total of 12 weeks, resulting in 48 irradiations in total. Additional therapy was restricted to the use of emollients. Emollients were not applied shortly (within 60 minutes) before phototherapy. The comparative intervention was the use of topical high-potent corticosteroids. Clobetasol propionate, 0.05%, in white vaseline was applied once daily, preferably before bedtime, for 12 weeks.

Sample Size Calculation
The null hypothesis was based on the assumption that there is no significant difference of efficacy between UV-A1 phototherapy and clobetasol propionate, 0.05%, ointment in the treatment of VLS. On the basis of an expected mean difference (MD) of 6.1 points in TCS (difference of mean relative TCS reduction of 33%) and a statistical power of 80% at the 5% α level, at least 26 patients were needed in this study, excluding a dropout rate of approximately 20%.

Statistical Analysis
Data analysis was performed using the statistical package MedCalc Software. The primary outcome was analyzed on an intention-to-treat basis using baseline TCSs and last available TCSs of all randomized patients. Analysis of data distribution was assessed by the D’Agostino-Pearson test. Means, standard errors, and 95% confidence intervals were calculated. Repeated measures analysis of variance including Bonferroni correction was used to detect significant differences of parameters assessed at baseline, at T3, and at follow-up. Primary and secondary outcome measures evaluated at T3 were analyzed using the F test, followed by the independent 2-sided t test (assuming equal variances) or Welch test (assuming unequal variances). Statistical significance was set at the 5% α level (2-sided).

Results
A total of 30 patients were enrolled in the study, 15 in each of the 2 study arms. The median age was 60.3 years (range, 20-81 years). A flow diagram of patient treatment, including reasons for discontinuation, is shown in Figure 1. Of the 30 patients, 1 patient was excluded because the clinical diagnosis of VLS could not be histopathologically confirmed. One patient was excluded from the study because during the treatment phase, a systemic immunosuppressive therapy was initiated to treat another autoimmune disease. One patient dropped out of the study because of an acute bacterial skin infection in the genital area before initiation of the UV-A1 irradiation sessions. One patient was lost to follow-up. At baseline, both groups did not show any differences in any of the primary and secondary outcome measures (P > .50).

Primary Outcome
A summary of the results is detailed in the Table. After 3 months of treatment, both therapies resulted in a significant decrease in mean TCS (51.4% [95% CI, 39.7% to 63.0%] for clobetasol ointment [P < .001] and 35.6% [95% CI, 18.2% to 53.1%] for UV-A1 phototherapy [P = .006]) (Figure 3). No significant difference in the relative reduction of the TCS was found be-
between both treatments (P > .05; MD, −15.7% [95% CI, −35.2% to 37%]). Representative clinical pictures before and after both therapies are depicted in Figure 4.

Secondary Outcome
After treatment with clobetasol ointment, the VAS score significantly decreased for pruritus (MD, 4.6 [95% CI, 1.5 to 7.7] [P = .005]) and burning and/or pain (MD, 4.2 [95% CI, 1.9 to 6.6] [P = .001]), and also the Skindex-29 score significantly decreased (MD, 29.6 [95% CI, 7.9 to 51.2] [P = .009]). After UV-A1 phototherapy, the VAS score for burning and/or pain (MD, 3.2 [95% CI, 0.7 to 5.7] [P = .01]) reduced significantly; however, there was no significant reduction in pruritus (MD, 2.1 [95% CI, 0.5 to 3.7] [P = .16]) and Skindex-29 score (MD, 4.9 [95% CI, −12.6 to 22.4] [P = .99]; Figure 3). Three months after the end of the therapy, all primary and secondary outcome points returned to the baseline level, before initiation of the treatment.

The clinical improvement seen at T3 was confirmed by 20-MHz ultrasonography. Corium thickness was relatively high before therapy and significantly decreased into normal ranges after topical clobetasol therapy (MD, −786 [95% CI, −235 to 338] [P = .003]). There was also a statistically significant increase of dermal density after clobetasol treatment (MD, 15.0 [95% CI, 8.0 to 22.0] [P < .001], correlating with a reduction of the edema. After treatment with UV-A1 phototherapy, a reduction of corium thickness and increase in dermal density could also be observed; however, it did not reach statistical significance (MD, −282 [95% CI, −1036 to 473] [P = .41], and MD, −0.1 [95% CI, −6.9 to 6.7] [P = .97], respectively).

In the histopathological evaluation of the lesional skin biopsy specimens before and after therapy, a significant reduction of lymphocytic infiltrates after topical corticosteroid therapy was observed (MD, 0.9 [95% CI, 0.2 to 1.7] [P = .02]), whereas after UV-A1 phototherapy, no significant reduction of lymphocytic infiltrates was seen (MD, 0.2 [−0.4 to 0.7] [P = .51]).

Tolerability
The predominantly reported short-term adverse effects of UV-A1 phototherapy include erythema, pruritus, xerosis cutis, and tanning. Patients treated with UV-A1 phototherapy in this study initially reported an increase of pruritus. We advised our patients to apply white vaseline directly (within 30 minutes) after the radiation session to prevent dehydration of the skin, which led to a marked subjective improvement. In total, there was only a slight, nonsignificant reduction of pruritus (P = .16) after 3 months of treatment with UV-A1 phototherapy. After UV-A1 treatment, a marked hyperpigmentation in the anogenital area was seen in all cases. However, this was not considered as a disturbing adverse effect by the patients. No erythema or sunburn following UV-A1 phototherapy was reported.

Discussion
According to the British Association of Dermatologists’ guidelines for the management of LS, the first-line treatment for VLS is the use of topical high-potent corticosteroids. In this context, clobetasol propionate, 0.05%, cream is currently considered the gold standard, leading to a substantial decrease of inflammation and clinical symptoms. After therapy with high-potent corticosteroids, approximately 60% of patients experience a complete remission of their symptoms, resulting in a resolution of ecchymoses, fissures, erosions, and hyperkeratoses. Thus, the use of clobetasol propionate is safe and effective in VLS, and there is yet no evidence of notable steroid-related damage following its appropriate use. However, skin atrophy, scarring, and hypopigmentation are irreversible in VLS.

UV-A1 phototherapy was previously shown to be effective in a variety of sclerotic skin diseases including localized scleroderma, systemic sclerosis, eosinophilic fasciitis, necro-
biosis lipoidica, chronic sclerodermic graft-vs-host disease, and scleroderma adultorum. UV-A1 phototherapy is generally divided into the following 3 dosages: low-dose UV-A1 (10-20 J/cm²), medium-dose UV-A1 (20-70 J/cm²), and high-dose UV-A1 (70-130 J/cm²). The treatment of extragenital LS with low-dose UV-A1 was first reported by our study group in 2001. In a small prospective uncontrolled trial, we later treated 10 patients with extragenital LS using low-dose UV-A1 phototherapy (20 J/cm²; cumulative dose of 800 J/cm²). Low-dose UV-A1 phototherapy resulted in a marked reduction of the clinical score and a statistically significant decrease of ultrasonographically measured skin thickness as well as a statistically significant increase of dermal density. Most patients reported a remarkable softening and repigmentation of the affected skin. Rombold et al later confirmed the good response of extragenital LS lesions using medium-dose UV-A1 phototherapy.

The exact mechanism of action of UV-A1 phototherapy in sclerotic skin diseases is not fully understood. In general, UV-A1 phototherapy influences both lesional fibroblasts and inflammatory cells. UV-A1 irradiation leads to an increased collagenase production in fibroblasts with up-regulation of metalloproteinases, partly due to the increased production of hydrogen peroxide, as well as an up-regulation of α-melanocyte-stimulating hormone. UV-A1 phototherapy induces a down-regulation of interleukins 6 and 8, both cytokines that play a pivotal role in collagen metabolism. Moreover, UV-A1 phototherapy influences the expression of SMAD-7, a major inhibitory regulator of the key-fibrogenic cytokine tissue growth factor-β, and increases the expression of interferon-γ, an antifibrotic cytokine.

To our knowledge, UV-A1 phototherapy in VLS has only been reported once in a small case series of patients. In this study, 7 women with severe and progressive VLS not responding to ultrapotent topical corticosteroids were included. UV-A1 therapy led to a moderate improvement in 3 and to a minimal improvement in 2 of the 7 patients.

The present study was the first randomized clinical trial to assess the effectiveness and safety of UV-A1 phototherapy in the treatment of VLS. Moreover, it is one of the few controlled studies that have so far been conducted in LS. In general, we could confirm the high efficacy of clobetasol propionate...
nate, 0.05%, in VLS. On the basis of our results and those of others, topical corticosteroids should be considered the first-line approach for VLS. However, we also demonstrated that UV-A1 phototherapy is an effective and well-tolerated treatment for VLS as well. Although in this study UV-A1 phototherapy was not as effective as the gold standard therapy with high-potent corticosteroids, it resulted in a significant clinical improvement and reduction of hyperkeratoses and erosions. The clinical pictures are representative of the outcome of the study, showing a significant improvement following therapy with clobetasol ointment (A and B) and UV-A1 phototherapy (C and D).

During follow-up, the primary and secondary end points in both therapies returned to the level before initiation of the therapy. This means that both treatments only transiently suppress the activity of disease. It also underlines the necessity to develop a long-term concept for treatment of VLS. Recently, it was published that once VLS has been stabilized with clobetasol ointment (0.05%, in VLS), it resulted in a significant clinical improvement and reduction of hyperkeratoses and erosions. The clinical pictures are representative of the outcome of the study, showing a significant improvement following therapy with clobetasol ointment (A and B) and UV-A1 phototherapy (C and D).

Conclusions

Both topical high-potent corticosteroids and UV-A1 phototherapy significantly improved VLS. However, UV-A1 was inferior with respect to practicability, relief of itch, and improvement in quality of life. Therefore, high-potent corticosteroids remain the first-line treatment for VLS. Nevertheless, UV-A1 phototherapy may be considered an alternative second-line treatment option.

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Original Investigation Research

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