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Research Article

Ultraviolet A Combined with Narrow-Band Ultraviolet B is an Effective Treatment Modality for Early Folliculotropic Mycosis Fungoides and Early Mycosis Fungoides Refractory to Narrow-Band Ultraviolet B: A Retrospective Cohort Study

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Background. Psoralen plus ultraviolet A (PUVA) is the preferred phototherapeutic modality for early-stage folliculotropic mycosis fungoides (FMF), and for early-stage non-FMF refractory to narrow-band ultraviolet B (NBUVB). However, PUVA has a problematic safety profile. Literature on the treatment with the combination of UVA and NBUVB for MF is sparse. *Objective*. To evaluate the effectiveness of UVA combined with NBUVB for early-stage MF, specifically for FMF and NBUVB-refractory non-FMF, in adult and pediatric patients. *Methods*. A retrospective analysis was conducted for patients treated with UVA combined with NBUVB at our center, during 1/2008–8/2022. *Results*. The cohort included 51 patients: 35 adults and 16 pediatric patients. The overall response rate (ORR) of 39 patients with early-FMF (25 adults and 14 children) was 95%, and the complete response (CR) was 62%. No significant differences in ORR/CR rates were noted between adult and pediatric patients. Of 12 patients with non-FMF (10 adults and 2 children), the ORR was 83% and the CR was 50%. In 17 patients (8 FMF and 9 non-FMF), prior NBUVB therapy resulted in partial response/stable disease; yet, UVA + NBUVB led to CR in 9 patients (4 FMF and 5 non-FMF). Side effects were minimal. *Conclusion*. Combined UVA and NBUVB is a good alternative to PUVA for adult or pediatric patients with early-stage MF , with FMF or non-FMF refractory to NBUVB.

1. Introduction

Ultraviolet light (UVL) based therapy has been a mainstay of treatment of mycosis fungoides (MF) for decades [1]. According to a large real-life study, phototherapy was selected for limited plaque disease (T1b) or for extended skin involvement (T2), with narrow-band ultraviolet B (NBUVB) being mainly given for patch/flat plaque MF, whereas psoralen plus ultraviolet A light (PUVA) photochemotherapy was given when the dominant disease component was thick plaques [2]. This reflects European and US guidelines, which indicate NBUVB for patients with patch/flat plaque, while PUVA for thick plaques or for folliculotropic mycosis fungoides (FMF), given the UVA potential to penetrate deeper into the dermis than UVB, and according to some of the guidelines, PUVA is also recommended for patients with dark skin [1, 3–6].

Yet, systemic PUVA is notorious for its short-term and long-term side effects [1, 7–12]. An alternative for oral PUVA

may be PUVA-bath. However, availability is limited to certain centers, as it is a treatment with higher cost, and is unsuitable for patients with facial involvement, and with physical disabilities preventing them from soaking in a bath [13–15]. Data regarding the use of other UVA-based treatments such as broadband UVA is sparse [16], while UVA1, although being an effective treatment according to several cohort studies and a few case reports, is a relatively expensive technology and is not widely available worldwide [17–24].

The treatment of UVA combined with NBUVB has been reported for inflammatory cutaneous diseases, mainly for atopic dermatitis (AD) [25–30].

We have previously published our encouraging experience with this combination in a few adult and pediatric early-stage MF patients [31–33].

The aim of the present study was to evaluate the effectiveness of UVA combined with NBUVB in the treatment of early-stage MF as an alternative to PUVA, specifically for FMF and for NBUVB-refractory non-FMF in both pediatric and adult patients. We report our experience with this simple-to-use inexpensive treatment modality.

2. Methods

2.1. Setting and Patients. The study group included patients diagnosed with MF who were treated concomitantly with UVA and NBUVB and followed at the outpatient Cutaneous Lymphoma Clinic of the Division of Dermatology of Rabin Medical Center.

An institutional database search was conducted, using internal or ICD-9 codes, for "cutaneous lymphoma" or "mycosis fungoides" combined with UVA and NBUVB treatment during 1/2008–8/2022. This search yielded 164 patients. We then reviewed each file separately, retrospectively. The diagnosis of MF was based on the criteria of the World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) classification [34]. Staging was determined by using the tumor node metastasis and blood system (TNMB) [35]. Specifically, early- and advanced-FMF were defined according to the clinicopathological criteria described in a previous report by us [36] and further validated by the Dutch group [37]. Early-stage FMF was defined as the presence of follicle-based patch/flat plaques, keratosis pilaris-like lesions, and/or acneiform lesions, and histologically by intrafollicular and sparse or lichenoid perifollicular infiltrates of atypical lymphocytes that were confined to the adventitial perifollicular dermis [36]. Exclusion criteria included patients treated with this combination of phototherapy for less than 1 month, and cases with insufficient data in their files on diagnostic or treatment parameters.

UVA and NBUVB radiations were delivered in a Waldmann UV 1000-k, with 7002 cabins, respectively (Herbert Waldmann GmbH & Co KG, Villingen-Schwenningen, Germany), and were given consecutively, one after the other, on the same day, starting with UVA. For UVA, treatment dose at initiation and increments were given in accordance with the protocol used in our department; the starting dose was 1 J/cm^2, increased at fixed increments of 0.5-1 J/cm^2 every session, up to a maximal dose of 15 J/cm^2, according to the tolerability and response. The starting dose for NBUVB was 0.1–0.3 J/cm^2, according to the Fitzpatrick skin type classification and the dosage was increased at fixed increments of 0.05–0.1 J/cm^2 every session, up to a maximal dose of 2.5 J/cm^2, according to the tolerability and response. Sessions were conducted 2-3 times/week during the induction period.

Maintenance treatment was given to a fraction of patients who achieved a complete response (CR), with the same last treated dose of UVA and NBUVB, but with a gradual decrease in the frequency of administration until once every 7–14 days. Face and genitalia were shielded, except for 11 patients with facial involvement, treated also for the face. Genital lesions were treated with mild to moderate topical steroids. Patients were monitored every 4–6 weeks for disease control and side effects.

The medical records of each patient were reviewed for demographic data; clinical characteristics; type and stage of MF; treatment/s given for MF and response before the combination treatment of UVA and NBUVB; and parameters on the combined treatment of UVA and NBUVB, including maximal response, dosages, number of treatments, time to CR/maximal response, time of follow-up post induction phase, and the status of the disease at the last follow-up.

The response to treatment was assessed clinically as the best/maximal response and was categorized as CR: 100%, partial response (PR): 50%–99%, stable disease (SD): <25% increase or <50% clearance in skin disease from baseline, and progressive disease: ≥25% increase in skin disease from baseline or new tumors in patients with patch/plaque or erythrodermic disease, according to the criteria and clinical endpoints recommended by the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the EORTC [38]. When postinflammatory changes could not be distinguished from a residual disease, a biopsy was performed.

The study was approved by the institutional ethical Helsinki Committee.

2.2. Statistical Analysis. Continuous variables were summarized using the sample median and range. Categorical variables were summarized with the number and percentage of patients. Comparisons between 2 groups were conducted using the Fisher exact test and the *t*-test.

3. Results

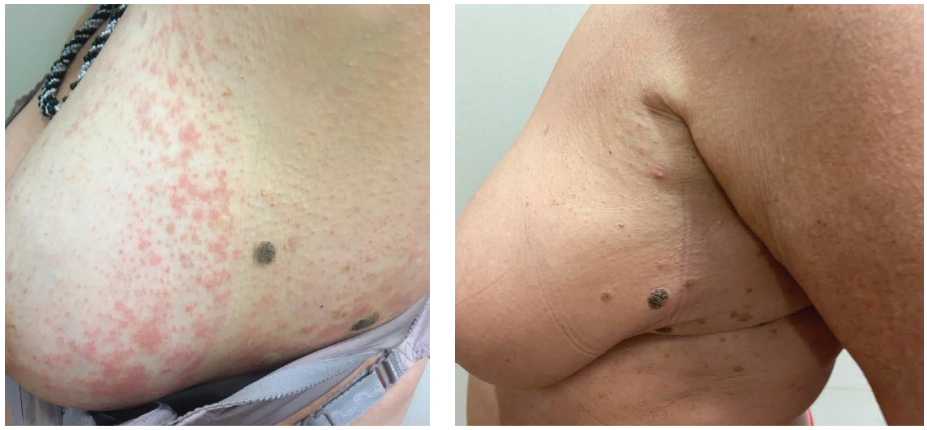
3.1. Patients' Characteristics. Overall, 51 patients were treated with UVA and NBUVB as monotherapy: 7 were reported by our group in earlier publications [31–33]. Table 1 delineates these patients' characteristics.

Thirty-nine patients had early-FMF, as the sole manifestation or combined with classic or other variants, (Figure 1(a) (median age was 44 years at the initiation of

Table 1: Characteristics of patients with early-stage mycosis fungoides treated with UVA combined with NBUVB.

Type of MF	Gender/age[#], median (range)	Stage of disease	Treatments prior to UVA + NBUVB and response
FMF: 39 patients	M-24, F-15/ 44 y (4–82)	IA-17 IB-22	Topical application: TCS: all; mechlorethamine gel: 2 SD Phototherapy: NBUVB: 8 (6 PR, 2 SD); systemic PUVA: 1 CR Other treatments: acitretin, IFN α[*]: 1 SD; MTX: 2 SD; LEB[*]: 1 CR
Non-FMF: 12 patients	M-9, F-3/ 50 y (7–83)	IA-2 IB-9 IIA-1	Topical application: TCS: all; mechlorethamine gel: 3 (2 SD, 1 stopped[&]) Phototherapy: NBUVB: 9 (6 PR, 3 SD); systemic PUVA: 1 CR Other treatments: MTX: 1 SD

CR, complete response; F, female; FMF, folliculotropic mycosis fungoides; IFN α, interferon α; LEB, localized electron beam; M, male; MTX, methotrexate; MF, mycosis fungoides; NBUVB, narrow-band ultraviolet B; PR, partial response; PUVA, psoralen plus ultraviolet A; SD, stable disease; TCS, topical corticosteroids; UVA, ultraviolet A; y, years. [#]Age at initiation of UVA and NBUVB. [*]One patient had relatively thick plaques. [&]Stopped treatment due to contact dermatitis.



(a) (b)

Figure 1: (a) A patient with early-stage classic mycosis fungoides combined with early folliculotropic mycosis fungoides, presenting with erythematous patches on the breast and in addition, follicular papules some with keratosis pilaris-like lesions extending to involve the adjacent axillary line, before treatment. (b) After 70 treatment sessions of UVA combined with NBUVB.

UVA and NBUVB, range 4–82 years), of whom 25 were adults and 14 were pediatric patients. Of all 39 patients, 21 had light skin complexion, 10 had pigmented skin, (all Fitzpatrick skin type 4), and in the other 8 patients, Fitzpatrick skin type was not reported. All early-FMF patients had skin color/slightly hypopigmented or erythematous patches or flat plaques, except for 1 patient with relatively thick plaques, with spiky erythematous follicular papules, and/or alopecia.

Twelve patients had non-FMF early-stage MF (median age was 50 years at the initiation of UVA and NBUVB, range 7–83 years), of whom 10 were adults and 2 were pediatric patients. Of all 12 patients, 8 had a light skin complexion, and 4 had pigmented skin (3 Fitzpatrick skin type 4 and 1 patient type 5). Clinical presentations included classic MF in 8 patients, and hyperpigmented/poikilodermatous MF in 4, and all had patches or flat plaques. Of these 12 patients, 9 were previously treated with NBUVB, achieving either PR or SD, and thus were placed on UVA combined with NBUVB. The other 3 patients were treated with this combination either because of a dark skin complexion and/or their refusal to use psoralen.

The most common prior treatments were skin-directed modalities: topical corticosteroids (all patients), NBUVB (as monotherapy in 17 patients), mechlorethamine (5 patients), systemic PUVA (2 patients), and localized electron beam (1 patient). Few patients received systemic treatments (Table 1).

3.2. Treatment with UVA Combined with NBUVB for Early-Stage MF and Response. Table 2 delineates the treatment parameters and response for adult and pediatric early-stage FMF and non-FMF groups.

The overall response rate (ORR) of all 39 patients with early-FMF was 95%, 24 patients (62%) achieved CR and 13 (33%) PR (Figures 1(a) and 1(b)). No significant differences in ORR/CR rates were noted between adult and pediatric patients ($p = 1.000$).

The median number of combined UVA and NBUVB treatments leading to CR in the entire group with FMF was overall 43: no significant differences in the number of treatments were noted between adults and pediatric patients ($p = 0.545$).

Of the 12 patients with non-FMF (Table 2), 10 patients responded (ORR: 83%), with 6 patients (50%) achieving CR, and 4 (33%) PR. The median number of combined UVA and NBUVB treatments leading to CR in this entire group was 53. Due to the small number of patients in each group, no statistical comparison was conducted between adults and children.

In overall 17 of all 51 patients (8 FMF and 9 non-FMF), prior NBUVB-therapy resulted in PR/SD, yet a course of UVA combined with NBUVB led to CR in 9 patients (53%) (4 FMF and 5 non-FMF).

Side effects were minimal, including pruritus in 10 patients, especially in the first few weeks of the treatment, with no treatment-limited side effects.

Maintenance treatment after achieving CR was given to 13 of the 24 early-FMF patients, and to 5 of the 6 non-FMF patients, for a median period of 4 months (range 2–8), with gradual tapering down to a treatment once per week in all except for 1 patient in whom the lowest frequency was once every 2 weeks.

3.3. Follow-Up. The median time of follow-up of all 51 patients, after achieving CR/best response, was 1.5 years (range 0.5–5 years). No stage progression was noted in any of the patients during the study period, and in the 30 patients who achieved CR, no evidence of the disease at the last follow-up was noted in 19 of the 24 early-FMF, and in 4 of the 6 non-FMF patients.

4. Discussion

The present study demonstrates the effectiveness of the combination of UVA and NBUVB for the treatment of early-stage FMF and early-stage NBUVB-refractory MF in both adult and pediatric patients.

Table 2: Adult and pediatric patients with early-stage FMF and non-FMF treated with UVA combined with NBUVB: treatment-related parameters and outcomes.

Response to treatment, FMF patients $N = 39$												
Adult patients $N = 25$					Patients ≤18 years $N = 14$					All patients $N = 39$		
ORR[#] (%)	CR[#] (%)	PR (%)	Number of treatments to CR[*], median/mean (range)	Final dose of UVA and NBUVB in the CR group, median (range) J/cm^2	ORR[#] (%)	CR[#] (%)	PR (%)	Number of treatments to CR[*], median/mean (range)	Final dose of UVA and NBUVB in the CR group, median (range) J/cm^2	ORR (%)	CR (%)	PR (%)
24 (96)	15 (60)	9 (36)	42/46 (20–75)	UVA: 9 (5–12); NBUVB: 2.4 (1.5–2.5)	13 (93)	9(64)	4(29)	57/50 (20–80)	UVA: 11 (10–15); NBUVB: 2 (0.8–2.4)	37 (95)	24 (62)	13 (33)
Response to treatment, non-FMF patients $N = 12$												
Adult patients $N = 10$					Patients ≤18 years $N = 2$					All patients $N = 12$		
ORR (%)	CR (%)	PR (%)	Number of treatments to CR, median/mean (range)	Final dose of UVA and NBUVB in the CR group, median (range) J/cm^2	ORR (%)	CR (%)	PR (%)	Number of treatments to CR	Final dose of UVA and NBUVB in the CR group, J/cm^2	ORR (%)	CR (%)	PR (%)
8 (80)	4 (40)	4 (40)	55/57 (40–72)	UVA: 9 (6–15); NBUVB: 2.3 (1.4–2.5)	2 (100)	2 (100)	0	46 and 50 treatments	UVA: 9 in both; NBUVB: 1 and 1.4	10 (83)	6 (50)	4 (33)

CR, complete response; FMF, folliculotropic mycosis fungoides; NBUVB, narrow-band ultraviolet B; ORR, overall response rate; PR, partial response; UVA, ultraviolet A. [#]No significant differences in the ORR and the CR rate were noted between the adult and the pediatric groups of patients ($p = 1.000$). [*]No significant difference in the median number of combined UVA and NBUVB treatments, leading to CR, was noted between the adult and the pediatric groups of patients ($p = 0.545$).

The effect of UVL on MF is multifactorial and is different for UVB and UVA. Because of its shorter wavelength, UVB is primarily absorbed in the epidermis and the papillary dermis with a less ability to penetrate beyond it compared to UVA, and therefore, the primary direct effects of UVB are on the epidermal keratinocytes, Langerhans cells, the superficial follicular infundibulum, and any cells in the upper dermis, including lymphocytes. Conversely, UVA is able to penetrate the entire dermis and possibly the subcutaneous tissue; therefore, in addition to those structures affected by UVB, UVA is able to directly affect lymphocytes also in the deep dermis as well as fibroblasts, dermal dendritic cells, mast cells, endothelial cells, macrophages, and deeper parts of the follicular apparatus [1, 39, 40].

UVA combined with UVB/NBUVB phototherapy has been used for AD and for other inflammatory skin disease since the early reports published in 1985 [25–30]. The combination of UVA and UVB was found to be superior to conventional broadband-UVB in AD, according to some studies [26, 27]. Nevertheless, other studies revealed no differences in pruritus score, disease activity, and quality of life [29, 30].

Our notion for the addition of UVA to NBUVB in the treatment of early-stage MF, as a possible alternative to systemic PUVA, is a likely additive or a possible synergistic effect of this combination on the cells in the epidermis and the dermis, including hair follicles.

PUVA-bath, a possible alternative to systemic PUVA, is associated with much lower serum psoralen levels, thereby reducing the risk of systemic side effects and the restrictions on sun exposure. Furthermore, unlike systemic PUVA, bath PUVA has not been linked to nonmelanoma skin cancer (NMSC) although the still few studies available preclude any definite conclusion. We used to give this modality especially to pediatric MF patients in whom we preferred to abstain from these restrictions required under systemic PUVA (especially ocular). However, the main disadvantages of this modality compared to the combination of UVA and NBUVB are the preclusion of the head and neck from the treatment field, higher cost, and the need for special bathing units [13–15]. As for UVA by itself, according to one published study in MF, the use of UVA with a higher dosage than in the present study, is comparable or even superior to PUVA, regarding efficacy for the treatment of early-stage MF [16]. More studies are needed for further evaluation of this treatment. UVA1, although reported in a few cohort studies as an effective treatment [17–24], is a relatively expensive and time-consuming technology.

Our early-stage FMF group (39 patients) had a CR rate of 62% under UVA and NBUVB, lower than the 70% CR rate achieved in our previous series of patients with early-FMF ($n = 27$) treated with systemic PUVA [33].

The non-FMF group (12 patients, mostly NBUVB-refractory) had a CR rate of 50%. There are no comparable data for systemic PUVA, but our previous collaborative study found that 50% of the other 12 patients with NBUVB-refractory non-FMF had CR under PUVA-bath [13].

When comparing the number of treatments to CR in the present study under UVA and NBUVB, with PUVA-bath or systemic PUVA, for early-stage FMF, in the present study, the median number of treatments to CR was 43, compared to other studies in which a time of 41 weeks was observed under PUVA-bath administered 3 times weekly [13], and a mean of 50–71 treatments under systemic PUVA [33]. For the cases of early-stage non-FMF patients, the median number of treatments to CR was 53, compared to other studies in which a time of 31 weeks was observed under PUVA-bath, administered 3 times weekly [13], and 30–38 treatments under systemic PUVA, given to patients treated at our clinic during the years 1995–2016 [33]. It is conceivable that all the above mentioned differences are not only due to the different treatment modalities, but also due to the different methodological parameters in the different studies. For example, during the last years our practice has been to treat with PUVA only patients with infiltrated plaques (usually combined with systemic retinoid or interferon alpha), while UVA combined with NBUVB has been given to patients with patch/flat plaque MF refractory to NBUVB or with early-stageFMF. Therefore, a direct comparison of the results of these 2 phototherapeutic modalities given at our clinic during the same time frame would be problematic. Prospective studies with comparable groups are needed to further evaluate the effectiveness of UVA combined with NBUVB versus systemic PUVA or PUVA-bath.

In previous research on pediatric FMF conducted by our group, UVA-based phototherapy as monotherapy was the most used modality in FMF patients (being the second most common variant of MF, affecting 42% of the patients), either as systemic PUVA, PUVA-bath, or UVA + NBUVB. Our present study consisting of 16 pediatric FMF patients, expands our previous experience with UVA combined with NBUVB as a simple modality reinforcing its effectiveness.

The overall side effects during treatment were minimal, and in no case were they a reason for discontinuation of treatment. When addressing the safety profile of PUVA versus UVA combined with NBUVB, the possible psoralen-related side effects should be considered, including gastrointestinal, rare hepatotoxicity, and ocular changes which mandate wearing UVA-absorptive eye protection during exposure to sunlight after psoralen ingestion. Both PUVA and UVA combined with NBUVB may cause erythema, pruritus, and xerosis, as well as later side effects, including photoaging and rarely hypertrichosis. Nail changes (subungual hemorrhage, photo-onycholysis, and melanonychia) were reported under PUVA.

As for secondary cutaneous malignancy, high cumulative exposure to oral PUVA is associated with a dose-related increase in the risk of NMSC. Whether exposure to PUVA increases the risk of developing melanoma is an area of controversy [1, 41, 42].

Unlike oral PUVA, based on the available literature, neither NBUVB, and recently also the combination of UVA and NBUVB given to patients with AD, has been linked to NMSC or to melanoma [41, 43].

Nevertheless, in view of the still-sparse data available, patient surveillance for side effects should be continued for a long term under this combination of phototherapy.

Our study is limited mainly by the retrospective design, and the fact that no comparative UVA group was studied, and therefore we have no data on the efficacy of UVA alone compared to UVA combined with NBUVB.

In summary, this study shows that the combination of UVA and NBUVB is an effective and well-tolerated treatment option for early-stage MF, including early-FMF and NBUVB-refractory early-stage MF. This combination should be considered in patients who have an indication for UVA-based therapy, especially if there are relative contraindications or technical considerations prohibiting PUVA. This alternative to PUVA may be beneficial especially for children and young adults, because of their difficulty in adhering to the restrictions of PUVA and the risk of long-term side effects. Larger studies with long-term follow-up are needed on this modality of phototherapy.

Abbreviations

UVL:	Ultraviolet light
MF:	Mycosis fungoides
NBUVB:	Narrow-band ultraviolet B
PUVA:	Psoralen plus ultraviolet A light
FMF:	Folliculotropic mycosis fungoides
AD:	Atopic dermatitis
WHO-EORTC classification:	World Health Organization-European Organization for Research and Treatment of Cancer classification
CR:	Complete response
PR:	Partial response
SD:	Stable disease
ORR:	Overall response rate
NMSC:	Nonmelanoma skin cancer.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request. The data are not publicly available due to information that could compromise the privacy of research participants.

Ethical Approval

This study was approved by the local IRB ethics committee (approval no. 0270-14 RMC).

Consent

The patient in this manuscript, of whom the clinical images belong, has given written informed consent to publish the case details.

Disclosure

The study was presented at the EORTC CLG Meeting, 2022, Madrid, Spain.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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