Actas Dermosifiliogr. 2007;98:259-64

ORIGINAL ARTICLE

Narrow Band UVB Therapy in Early Stage Mycosis Fungoides. A Study of 23 Patients

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Abstract. *Introduction.* Phototherapy is effective for mycosis fungoides. Narrow band UVB (UVB[1]) therapy is being used as an alternative to PUVA therapy for its efficacy and less adverse events. The objective of the study was to determine the efficacy of narrow band UVB therapy in early stage mycosis fungoides.

Methods. It is a retrospective study of 23 patients with stage IB mycosis fungoides that have received UVB[1] therapy following the phototherapy protocol of the Spanish Photobiology Group.

Results. Thirteen patients (57%) had a complete response, eight patients (35%) had a partial response and two patients (8%) did not respond. Half of the patients with complete response (n = 6) relapsed after one year of follow-up.

Conclusions. We consider that UVB[1] therapy is a good alternative for treatment of early stage mycosis fungoides, although the disease-free period is short.

Key words: mycosis fungoides, phototherapy, narrow band UVB.

TRATAMIENTO CON UVB DE BANDA ESTRECHA DE LOS ESTADIOS INICIALES DE LA MICOSIS FUNGOIDE. ESTUDIO DE 23 PACIENTES

Resumen. *Introducción.* La fototerapia ha demostrado ser de utilidad en la micosis fungoide. La radiación UVB de banda estrecha (UVB_1) está siendo utilizada como alternativa a la radiación UVA por su eficacia y menores efectos secundarios. El objetivo del estudio fue determinar la eficacia del tratamiento de la fototerapia con UVB_1 en los estadios iniciales de la micosis fungoide.

Métodos. Estudio retrospectivo sobre 23 pacientes con micosis fungoide en estadio IB que habían recibido fototerapia con UVB, según el protocolo de fototerapia del Grupo Español de Fotobiología.

Resultados. Se obtuvo respuesta completa en 13 pacientes (57%), respuesta parcial en 8 (35%) y no respondieron 2 (8%). La mitad de los pacientes con respuesta completa que finalizaron el año de seguimiento (n = 6) presentaron recidivas.

Conclusiones. Consideramos que la fototerapia con UVB_1 es una buena opción en el tratamiento de las fases iniciales de la micosis fungoide, aunque el intervalo libre de enfermedad no es prolongado.

Palabras clave: micosis fungoide, fototerapia, UVB banda estrecha.

Introduction

Mycosis fungoides is the most common form of cutaneous T-cell lymphoma. It usually responds well if diagnosed and treated in the initial stages, although recurrences are frequent.

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Manuscript accepted for publication January 15, 2007.

Given the slow and indolent course of the disease and good response of patients in the initial stages of the lymphoma, the approach should not be aggressive.[1] Current first-line treatments include topical corticosteroids, topical nitrogen mustards and carmustine, radiotherapy, and phototherapy. Response and long-term survival are similar for all these treatments, although the duration of the disease-free period and side effects may vary.

Phototherapy has been used for many years in the field of dermatology to treat diseases such as psoriasis, vitiligo, atopic dermatitis, and photodermatosis.[2] The appearance of mycosis fungoides lesions in unexposed areas of the body and the clinical improvement obtained on exposure to

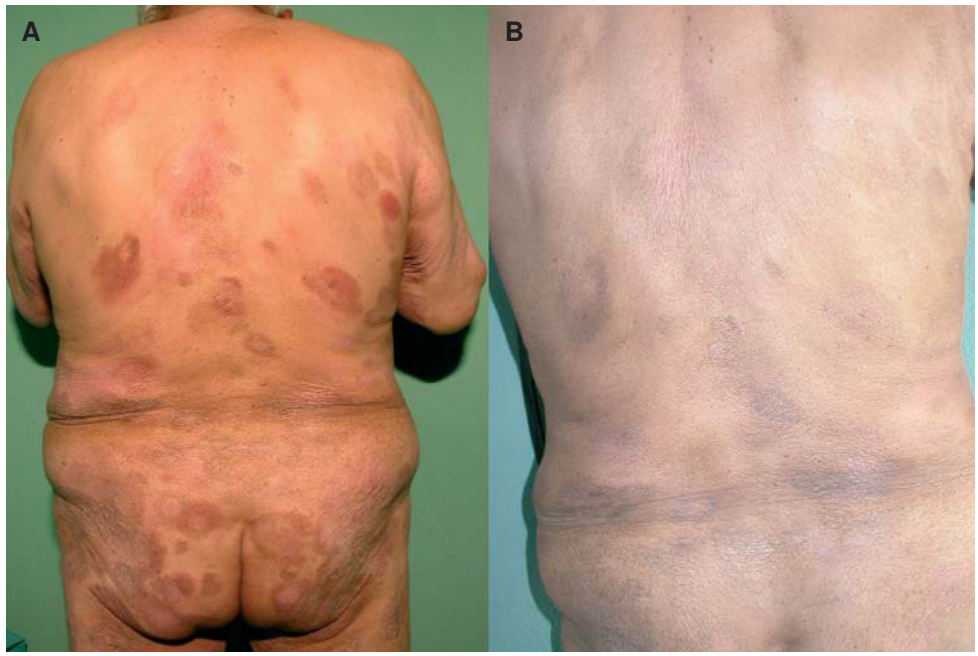

Figure 1. Patient with stage IB mycosis fungoides before treatment with narrowband UVB phototherapy (A) and after treatment (B).

sunlight suggest that phototherapy may be beneficial in these types of lymphomas.

Several phototherapy modalities are currently available to treat mycosis fungoides[3]: UVA (320-400 nm), long-wave UVA (UVA_1: 340-400 nm), broadband UVB (290-320 nm), and narrowband UVB (UVB_1: 311-313 nm), all of which can be potentiated when combined with psoralens. Choice of treatment depends on several factors, such as disease stage, and patient adherence and tolerance.

Phototherapy using UVA in conjunction with psoralen (PUVA) or UVA alone has been widely used to treat mycosis fungoides and has proven effective in the patch or plaque stages and even in incipient tumors. Long-term remission is achievable, but maintenance therapy is usually needed. The side effects of UVA phototherapy include increased risk of skin cancer, hyperpigmentation, paradoxical loss of pigmentation, more painful and longer-lasting burns than with UVB phototherapy, cataracts, and photosensitivity. Psoralens can cause nausea, vomiting, headaches, hepatotoxicity, and photosensitivity.

UVB radiation damages DNA and appears to stop the uncontrolled proliferation of T lymphocytes in mycosis fungoides. Its efficacy has been demonstrated in the patch stage, with complete response in 71%-75% of cases after an average of 5 months treatment[4,5]; however, it appears to be of little use in the plaque phase, perhaps due to its low capacity to penetrate plaque. The side effects of UVB therapy include phototoxic reactions, which are more frequent than with UVA, given that UVB radiation is more erythemogenic, and can trigger pruritus, immunosuppression, carcinogenesis, and light-induced dermatitis.

Narrowband UVB phototherapy (311 nm), also known as UVB_1, has proven to be as effective as PUVA therapy in the treatment of psoriasis and obtains better results than broadband UVB therapy. When compared to PUVA therapy, its advantages include less frequent side effects and the fact that psoralens are not required. The difference between UVB_1 therapy and broadband UVB therapy is that the former has greater penetrative power, given that lower doses are required to obtain the minimal erythema dose (MED).

Material and Methods

This was a retrospective study of patients with stage IB mycosis fungoides who had undergone UVB_1 phototherapy (Figure).

The study included 23 patients with a mean age of 62 years, with skin phototypes II to IV (2 patients classified as skin phototype II, 17 as skin phototype III, and 4 as skin phototype IV). All had stage IB mycosis fungoides (T2N0M0) with a follow-up time ranging from 6 months to 30 years (Table 1).

Before initiating treatment, the patients completed the dermatology unit protocol for treating cutaneous T-cell lymphoma (Table 2). Subsequently, the patients completed the phototherapy protocol of the Spanish Photobiology Group,[6] in which treatment starts with narrowband

Table 1. Demographic Characteristics of the Study Patients

Patient	*Age (Years)*	*Sex*	*Skin Phototype*	*Stage*	*Disease Duration*
1	73	Male	IV	IB	3 years
2	78	Male	IV	IB	1 year
3	48	Female	III	IB	10 years
4	78	Male	III	IB	5 months
5	46	Female	III	IB	17 years
6	62	Male	III	IB	6 years
7	53	Female	III	IB	8 years
8	67	Female	III	IB	2 years
9	59	Male	III	IB	10 years
10	75	Female	IV	IB	7 years
11	71	Male	II	IB	1 year
12	64	Male	III	IB	12 years
13	66	Male	III	IB	5 years
14	56	Male	III	IB	3 years
15	55	Male	III	IB	30 years
16	63	Female	III	IB	6 months
17	41	Male	III	IB	6 years
18	59	Female	III	IB	39 years
19	78	Male	IV	IB	3 years
20	54	Male	III	IB	14 years
21	39	Male	III	IB	5 years
22	47	Male	II	IB	30 years
23	83	Male	III	IB	20 years

Table 2. Protocol for Cutaneous T Lymphoma

Medical history
General physical examination
Dermatological exploration
Laboratory analysis Complete blood count Biochemical analysis LDH β_2 Microglobulin Peripheral blood smear Flow cytometry
Chest X-ray
Biopsy with immunohistochemical staining

Abbreviation: LDH, lactate dehydrogenase.

Table 3. Phototherapy Protocol of the Spanish Photobiology Group

Informed consent of the patient
Phototoxic drugs administered
Antinuclear antibody test
Photographic record
UVB Dose
Protection used (ocular, genital or facial)
Side effects
Cumulative dose
Total number of sessions
Response obtained

phototherapy and, in the absence of response, oral PUVA photochemotherapy is instituted (Table 3).

The UVB_1 source was a Waldmann UV 7001K (PUVA/TL01) booth. The protocol followed was 200-300 mJ/cm^2 as the starting dose depending on the patient's skin phototype, with 100 mJ/cm^2 increases each session. Treatment was performed 3 times per week on alternate days.

The maximum dose per session was 1800 mJ/cm^2 in patients classified as skin phototypes II and III, and 3000 mJ/cm^2 in skin phototypes IV.

In order to assess clinical response to treatment, a complete response was defined as more than 95% clearance of lesions, partial response as 50%-95% clearance, and no response as less than 50% clearance.

Results

All the patients completed the study. A complete response was obtained in 57% of patients (n = 13). Mean disease duration was 7 years. A partial response was obtained in 35% (n = 8) of patients, with a mean disease duration of 11.75 years and there was no response in 8% of the patients (n = 2), with a mean disease duration of 2 years.

Table 4. Previous Studies on Mycosis Fungoides Treated With Narrowband UVB

UVB1	*Number of patients*	*Stage*	*Complete Response, %*	*Partial Response, %*
Hofer et al[7]	6	IA, IB	83	17
Clark et al[8]	8	IA, IB	75	25
Gathers et al[9]	24	IA, IB	54.2	29.2
Diederen et al[10]	21	IA, IB	81	19
Ghodsi et al[11]	16	IA, IB	75	18.75
Kural et al[12]	23	IA, IB	83	17
El-Mofty et al[13]	20	I, IIA	70	30
Boztepe et al[15]	14	I, IIA	78	
Coronel Pérez et al (present study)	23	IB	57	35

There was a mean of 43 UVB_1 sessions in patients with a complete response, 34 in patients with a partial response, and 25 where no response occurred.

The mean cumulative UVB_1 dose was 64.84 J/cm^2 in patients with a complete response.

Side effects included pruritus (n = 6), erythema (n = 7), seborrheic dermatitis (n = 1), and bromhidrosis (n = 1), although none of these led to treatment being stopped. No effect associated with UVB_1 treatment occurred in the remaining patients.

The 1-year follow-up period was completed by 41.6% of the patients with a complete response, half of whom presented recurrence.

Discussion

There are few studies on mycosis fungoides treated with UVB_1 and most address patients with stage I disease (Table 4). The mechanism of action of UVB_1 is not well understood, although it could act on immune system regulation, given that in vitro studies have found a reduced activation of Langerhans cells and their antigen-presenting capacity, as well as increased production of interleukin-2, interleukin-6, and tumor necrosis factor by keratinocytes. Furthermore, UVB_1 may also inhibit neoplastic T cell function and lead to apoptosis.

The unwanted effects of UVB_1 therapy are similar to those of broadband UVB therapy. Although not yet confirmed, it appears to have a weaker carcinogenic effect than PUVA or broadband UVB therapy due to lower cumulative doses of UV radiation; in addition, few mutagenic wavelengths are found between 290 nm and 310 nm.

Hofer et al[7] studied 20 patients, 6 with early-stage mycosis fungoides and 14 with small-plaque parapsoriasis, demonstrating a histopathologically confirmed complete response in 19 cases, after a mean of 20 sessions. The mean time to recurrence was 6 months after stopping phototherapy.

Clark et al[8] observed a complete response in 6 out of 8 patients with patch-stage mycosis fungoides (75% of cases), after a mean of 26 treatment sessions (20-37 sessions), that is, 9 weeks of treatment. Pathological findings suggested that the partial improvement in lesions was associated with early recurrence. Half the patients remained disease-free 20 months after stopping treatment.

Gathers et al[9] assessed the results of UVB_1 therapy in 24 patients with mycosis fungoides (12 with stage IA and 12 with stage IB disease). There was a complete response in 54.2% of patients, partial response in 29.2%, and no response in 16.7%. The mean number of sessions was 52.2 in patients with a complete response and 38.8 in the group with no response to treatment. Half of the patients were classified as having skin phototypes I-III and the other half as having skin phototypes IV-VI, which are more resistant to the effects of UV radiation. This could be responsible for the difference in response when compared to other studies, which only included light-skinned phototypes. Patients with hypopigmented mycosis fungoides also responded poorly.

Diederen et al[10] conducted a retrospective study comparing UVB_1 and PUVA therapy in 56 patients with early-stage mycosis fungoides. There was a complete response in 81% of the 21 patients treated with UVB_1 and in 71% of the 35 patients treated with PUVA, with a mean disease-free period of 24.5 and 22.8 months, respectively. The mean total dose of UVB_1 and UVA was 31.8 J/cm^2 and 283.2 J/cm^2, respectively. Even though the efficacy of UVB_1 therapy is slightly greater, the authors suggest employing it in early-

stage mycosis fungoides, reserving UVA for more advanced stages or in cases where there is no response.

In 2005, Ghodsi et al[11] published a study including 16 patients with early-stage mycosis fungoides treated with UVB_1. There was a complete response in 75% of them after a mean number of 27.9 sessions (range: 13-48) and a mean cumulative dose of 26 J/cm^2. There was recurrence at a mean of 4.5 months. Improvement was confirmed in the 11 patients who agreed to undergo biopsy. There was partial response in 18.75% of the patients and no response in 1 patient (6.25%).

A recently published study of 23 patients (10 cases stage IA and 13 stage IB) with mycosis fungoides[12] treated with UVB_1 reported a complete response in 83% of the patients after a mean of 26 sessions. The mean dose administered was 22.4 J/cm^2 and pathological findings demonstrated the absence of disease. A partial response was obtained in the remaining 17% of patients after a mean of 52 sessions. The response obtained was lower in those patients who had had the disease for a longer period. The mean disease-free period was 16 months (3-36 months) and recurrence was associated with stage IB disease.

Treatment with UVB_1, PUVA, and $PUVB_1$ seems to achieve similar results in stages IA, IB, and IIA of mycosis fungoides.[13] The response was similar (complete response in approximately 70% of patients) and so was the time required to induce the therapeutic effect or reach maximum effectiveness. The only observed difference was later recurrence in those treated with PUVA phototherapy.

Our study included 23 patients in stage IB—the largest series of patients with this stage of mycosis fungoides treated with UVB_1. The outcomes were good, with complete response in 57% of patients after a mean of 43 sessions. This figure is slightly lower than in other published studies, perhaps due to the type of patient included, since all of them had stage IB disease. No patient with stage IA disease was included. Furthermore, skin phototype may have influenced the response, as most patients were classified as type III and IV, whereas there were only 2 skin phototype II patients.

Unlike other studies, there were more partial responses. Adherence to therapy has been considered a determinant in the treatment of prurigo nodularis with UVB_1. There was a high level of adherence to therapy among our patients which may explain the good results.[14]

Although it has been suggested that UVB_1 phototherapy is effective only in the early forms of mycosis fungoides, our series confirms that it is a good choice for stage IB disease. Furthermore, a study including 14 patients demonstrated similar efficacy for stage I and IIA disease, although the latter required more sessions.[15] The disease-free period was also longer in our study than that reported in other studies, a fact which may be related to the maintenance phototherapy that some patients received.

In conclusion, we once again propose UVB_1 phototherapy as first-line treatment for stages IB, IIA, and IA of mycosis fungoides,[1] due to the rapid improvement in lesions, the fact that it is better tolerated, and the long remission period. The need for fewer sessions and the appearance of fewer long-term side effects encourages patient adherence. Furthermore, it is the therapy of choice in women of a child-bearing age because it does not have teratogenic effects.

Nevertheless, long-term prospective studies and randomized studies are needed to confirm these findings as well as to identify the optimal treatment protocol and the best maintenance therapy to extend the remission phase of the disease.

Conflicts of Interest

The authors declare no conflicts of interest.

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