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ORIGINAL ARTICLES

Use of Psoralen Plus UV-A Therapy in the Autonomous Community of Valencia, Spain

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Abstract. *Background.* Photochemotherapy with 8-methoxypsoralen and long-wavelength UV-A (PUVA) has been extensively used for the treatment of various skin diseases since its approval in 1982 by the US Food and Drug Administration.

Methods. A retrospective study was performed of patients treated with PUVA, including topical and systemic treatment, over a period of 14 years. All patients were treated using a standard PUVA therapy regimen.

Results. A total of 877 patients were analyzed for the period 1982 to 1996. Forty-one skin diseases were treated, including 341 cases of psoriasis and 71 cutaneous T-cell lymphomas. The aim of the study was to describe the characteristics of the patients treated with PUVA therapy during that period and compare the results with those observed in other regions.

Conclusions. Although PUVA therapy is widely used in a large number of countries for the treatment of various skin diseases, few studies have described the characteristics of the patients and the differences in the parameters of PUVA according to the disease.

Key words: psoralen psoralen UV-A therapy, psoriasis, epidemiology.

ESTUDIO EPIDEMIOLÓGICO DE LA PUVATERAPIA EN LA COMUNIDAD VALENCIANA

Resumen. *IIntroducción.* La fotoquimioterapia con 8-metoxipsoraleno y radiación ultravioleta de longitud de onda larga A (PUVA) es frecuentemente utilizada para el tratamiento de diferentes enfermedades cutáneas desde que en 1982, la *Food and Drug Administration* aprobase su uso.

Métodos. En este estudio retrospectivo se han analizado los pacientes tratados con PUVA, incluyendo tratamiento tópico y sistémico durante 14 años. Todos estos pacientes recibieron un régimen de terapia PUVA estándar.

Resultados. Durante el período de 1982 a 1996 se analizaron 877 pacientes. Un total de 41 dermatosis recibieron el tratamiento entre las que destacamos 341 casos de psoriasis y 71 casos de linfomas cutáneos de células T. El trabajo tiene como finalidad describir las características de los pacientes tratados con terapia PUVA durante estos años y comparar los resultados con los procedentes de otros ámbitos.

Conclusiones. Aunque la terapia PUVA está ampliamente distribuida en un gran número de países para el tratamiento de diferentes enfermedades cutáneas, existen pocos estudios que indiquen las características de estos pacientes y las variaciones en los parámetros de PUVA dependiendo de las diferentes enfermedades.

Palabras clave: puvaterapia, psoriasis, epidemiología.

Introduction

Psoralen plus UV-A (PUVA) therapy involves the combination of a chemical substance derived from furocoumarins present in certain plants (psoralens) with UV-A radiation.[1-4] The most widely used chemical derivative in this type of treatment is 8-methoxypsoralen (8-MOP). Since its approval by the US Food and Drug Administration in May 1982, PUVA therapy (8-MOP) has been used in many countries to treat a variety of skin diseases, notably, moderate to severe psoriasis, mycosis fungoides, and vitiligio.[5,6] Only a few articles, however, have been published on the use of PUVA therapy to treat different diseases.[7-11] In the present study, we describe the epidemiological features of patients who received PUVA therapy at Hospital General

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Universitario de Valencia, Spain, between 1982 and 1996, placing particular emphasis on more common skin diseases such as psoriasis and mycosis fungoides. We also compare our findings to those from other countries.

Material and Methods

We retrospectively reviewed the medical records and treatment reports of all the patients treated by the phototherapy unit at our hospital between 1982 and 1996.

The following information was recorded for each patient: sex, age at which PUVA therapy was started, and disease being treated.

For the 412 patients who had been treated for psoriasis or mycosis fungoides, we also recorded skin phototype, number of sessions completed, total cumulative dose in J/cm^2, maximum PUVA dose, and adjuvant therapies.

All the patients that received systemic PUVA therapy had been treated using a standard regimen consisting of the oral administration of 8-MOP (0.5-0.6 mg/kg of body weight) 2 hours prior to radiation. The initial UV-A dose was 0.3-1.5 J/cm^2, and the dose regimen was based on skin type rather than on minimal phototoxic dose. The initial treatment phase consisted of 4 sessions per week, in which the radiation dose was incremented in each session by 0.5-1 J/cm^2 until the lesions cleared. This was followed by a maintenance regimen consisting of 1-2 weekly sessions for 1 to 2 months. Where necessary, patients were administered new treatment cycles during the period analyzed.

UV-A radiation was delivered using lamps that emitted UV light at wavelengths in the range of 320 to 380 nm. A maximum wavelength intensity of around 365 nm was used, and the intensity of the lamps was measured regularly using a PUVA-meter. Treatment was administered in a special booth (PUVA 6002; H. Waldmann GmbH & Co, Villingen-Schwenningen, Germany), and dark, UV-protection glasses were used to shield the eyes. Patients were instructed to wear eye protection and avoid exposure to sunlight for 24 hours after treatment.

The topical PUVA regimen consisted of the application of 8-MOP at 0.1% for approximately 20 minutes prior to radiation. The patients completed 3 sessions per week involving both dose and time increments. The UV-A light was produced using a PUVA 200 lamp (H. Waldmann GmbH & Co, Villingen-Schwenningen, Germany).

We analyzed the data collected to determine if there were any significant differences between the study variables according to sex, PUVA therapy regimen (systemic or topical), and disease type (psoriasis and mycosis fungoides).

Frequency tables were generated for the descriptive analysis of qualitative variables and means (SD) were calculated for quantitative variables.

We used the #c^2 test to compare qualitative variables between different study groups and the Fisher exact test to analyze the 2 #x 2 contingency tables.

Statistical significance was set at a value of P<.05 in all cases.

Results

A total of 1012 patients were treated with PUVA therapy at our hospital between 1982 and 1996, and data had been correctly recorded for 877 (86.6%) of those (449 men and 428 women). The mean age at which therapy had been started was 41.49 (17.16) years (44.06 years for men and 39.05 years for women). Although many different skin diseases were treated (see Table 1), the most common ones were psoriasis, hand eczema, and mycosis fungoides (parapsoriasis).

Of the 877 patients analyzed, 198 (22.7%) had undergone topical PUVA therapy, whereas 679 (77.3%) had undergone systemic PUVA therapy.

The mean age at which therapy had been started was 39.82 years for patients with psoriasis, 54.74 years for patients with mycosis fungoides, 38.36 for patients with polymorphic light eruption, 36.74 years for patients with actinic dermatitis, 38.67 years for patients with pityriasis lichenoides, and 26.62 years for patients with alopecia. When analyzed by sex, the mean age at which therapy had been started for psoriasis was 43.06 years for men and 37.48 years for women; for mycosis fungoides, the mean age was 58.28 years for men and 49.56 years for women; and for actinic dermatitis, it was 38.1 years for men and 35.4 years for women.

A total of 412 patients had either psoriasis or mycosis fungoides. Specifically, 341 had psoriasis (192 men [56.3%] and 149 women [43.7%]), and 71 had mycosis fungoides (40 men [56.3%] and 31 women [43.7%]). The most common skin phototype was type III (63.3%), followed by type II (23.5%) and type IV (13.2%). None of the patients had skin phototype I or V. The mean age at which PUVA therapy had been started in the subgroups of patients with psoriasis and mycosis fungoides was 40.44 and 54.24 years, respectively. The differences between the mean ages calculated for the above subgroups and for the entire group (877 patients) were not significant. The mean age at diagnosis was 29.59 and 50.33 years for patients with psoriasis and mycosis fungoides, respectively.

Of the patients with psoriasis, 22.3% received concomitant treatment with methotrexate. Other adjuvant therapies included tar (24.6%), oral retinoids (30.1%), cyclosporine A (16.8%), and UV-B light (2.7%). Of the patients with mycosis fungoides, 27.3% were also treated with interferon, 7.3% with oral retinoids, 5.5% with methotrexate, 1.8% with cyclosporine A, and 1.8% with UV-B light. None of the patients received x-ray therapy or arsenic.

Table 1. Disease Type and Frequency

Disease	*Frequency, n*	*Percentage*	*Valid, %*	*Cumulative %*
Psoriasis 341	38.9	38.9	38.9	
Eczema, hand/palmoplantar/dyshidrotic	100	11.4	11.4	50.3
Parapsoriasis, mycosis fungoides	71	8.1	8.1	58.4
Polymorphic light eruption	65	7.4	7.4	65.8
Psoriasis, hand/palmoplantar	62	7.1	7.1	72.9
Pityriasis lichenoides	40	4.6	4.6	77.4
Atopic dermatitis, atopic eczema	27	3.1	3.1	80.5
Vitiligio	26	3.0	3.0	83.5
Keratosis pilar and other skin diseases with eczema-like lesions	20	2.3	2.3	85.7
Alopecia	19	2.2	2.2	87.9
Lichen planus	17	1.9	1.9	89.9
Pruritus	12	1.4	1.4	91.2
Photosensitivity	11	1.3	1.3	92.5
Solar urticaria	11	1.3	1.3	93.7
Lymphomatoid papulosis	7	0.8	0.8	94.5
Hepatic/uremic pruritus	6	0.7	0.7	95.2
Keratosis palmoplantaris	6	0.7	0.7	95.9
Mastocytosis	4	0.5	0.5	96.4
Urticaria	4	0.5	0.5	96.8
Follicular mucinosis	3	0.3	0.3	97.1
Seborrheic dermatitis	2	0.2	0.2	97.4
Granuloma annulare	2	0.2	0.2	97.6
Acne	2	0.2	0.2	97.8
Aquagenic pruritus	2	0.2	0.2	98.1
Pityriasis versicolor (pigmented)	2	0.2	0.2	98.3
Folliculitis	1	0.1	0.1	98.4
Amyloidosis	1	0.1	0.1	98.5
Miliaria	1	0.1	0.1	98.6
Melanosis	1	0.1	0.1	98.7
Pemphigoid	1	0.1	0.1	98.9
Lymphocytic infiltration	1	0.1	0.1	99.0
Actinic reticuloid, actinic dermatitis	1	0.1	0.1	99.1
Aleukemic leukemia cutis	1	0.1	0.1	99.2
Graft-versus-host disease	1	0.1	0.1	99.3
Impetigo	1	0.1	0.1	99.4
Toxic dermatitis	1	0.1	0.1	99.5
Purpura	1	0.1	0.1	99.7
Sarcoidosis	1	0.1	0.1	99.8
Morphea, scleroderma	1	0.1	0.1	99.9
Pityriasis rubra pilaris	1	0.1	0.1	100.0
Total	877	100.0	100.0	

The mean total cumulative dose per patient was 748 J/cm^2 for psoriasis and 971.97 J/cm^2 for mycosis fungoides. The corresponding doses in men and women were 841.17 and 722.88 J/cm^2, respectively. The mean number of sessions was 59.05 for psoriasis and 76.37 for mycosis fungoides. The mean maximum dose was 17.65 J/cm^2 for psoriasis and 14.26 J/cm^2 for mycosis fungoides, and the corresponding figures for men and women were 17.6 and 16.3 J/cm^2, respectively.

On comparing the data for psoriasis and mycosis fungoides, we found statistically significant differences for the following:

1. The mean age at which PUVA had been started (higher for mycosis fungoides)
2. The mean age at diagnosis (higher for mycosis fungoides)
3. The mean maximum dose (higher for psoriasis)

We found no statistically significant differences for total cumulative dose, number of sessions, sex, or skin phototype.

When we analyzed male patients separately, we found statistically significant differences for the mean age at which PUVA therapy had been started (43.06 years for psoriasis and 58.28 years for mycosis fungoides); the mean age at diagnosis (33.46 years for psoriasis and 54.9 years for mycosis fungoides); and the mean maximum dose per session (18.52 J/cm^2 for psoriasis and 13.68 J/cm^2 for mycosis fungoides). We observed no statistically significant differences for skin phototype, number of sessions, or total cumulative dose. On analyzing female patients separately, we found statistically significant differences for the mean age at which PUVA therapy had been started (37.48 years for psoriasis and 49.56 years for mycosis fungoides); the mean age at diagnosis (25.36 years for psoriasis and 45.04 years for mycosis fungoides); the total cumulative dose (641.4 J/cm^2 for psoriasis and 1110.7 J/cm^2 for mycosis fungoides); and the total number of sessions (54.4 for psoriasis and 84.2 for mycosis fungoides). We found no statistically significant differences for skin phototype or mean maximum dose (although this was higher in patients with psoriasis than in those with mycosis fungoides [16.6 J/cm^2 vs 14.9 J/cm^2]) (Table 2).

We found statistically significant differences between men and women in the subgroup of patients with psoriasis (n=341) for the following parameters:

1. The mean age at which PUVA therapy had been started (43.06 years for men and 37.48 years for women)
2. The mean age at diagnosis (33.46 years for men and 25.36 years for women)
3. The mean maximum dose (18.5 J/cm^2 for men and 16.6 J/cm^2 for women)
4. Adjuvant therapy with oral retinoids (38% of men and 21% of women)

We found no statistically significant differences between men and women for total cumulative dose (although the mean dose was 841.02 J/cm^2 for men and 641.4 J/cm^2 for women) or for the mean number of sessions (63.07 for men and 54.46 for women).

In the subgroup of patients with mycosis fungoides (n=71), there were no statistically significant differences between men and women with respect to the mean age at which PUVA therapy had been started, the mean age at diagnosis, the mean total cumulative dose, the mean number of sessions, the maximum dose received, skin phototype, or adjuvant therapies.

Table 2. Evaluation of Different Variables by Sex and Disease Type[a]

		Age at Diagnosis, y	*Age at iInitiation of PUVA Therapy, y*	*Total Cumulative Dose, J/cm^2*	*Maximum Dose, J/cm^2*	*No. of Sessions*
Men	Psoriasis	33.46[b]	43.06[b]	841.02	18.52	63.07
	Mycosis fungoides	54.9[b]	58.28[b]	856.35	13.68	69.59
Women	Psoriasis	25.36[b]	37.48[b]	641.4[b]	16.65	54.46[b]
	Mycosis fungoides	45.04[b]	49.56[b]	1110.71[b]	14.96	84.24[b]
Psoriasis	Men	33.46[b]	43.06[b]	841.02	18.52[b]	63.07
	Women	25.36[b]	37.48[b]	641.4	16.65[b]	54.46
Mycosis Fungoides	Men 54.9	58.28	856.35	13.68	69.59	
	Women	45.04	49.56	1110.71	14.96	84.24

Abbreviation: PUVA, psoralen-UV-A.
[a]Data are expressed as means
[b]Statistically significant differences

In the subgroup of patients with psoriasis, 198 (77.3%) had received less than 1000 J/cm^2 and 58 (22.7%) had received greater than 1000 J/cm^2. The corresponding figures for the group of patients with mycosis fungoides were 37 (67.3 %) and 18 (32.7 %), respectively. In total, 235 patients (75.6%) had received less than 1000 J/cm^2 and 76 (24.4 %) had received greater than 1000 J/cm^2. When analyzed by sex, 122 men (72.7%) had received less than 1000 J/cm^2 and 45 (27.2 %) had received more than 1000 J/cm^2, while the respective figures for women were 113 (78.4%) and 31 (21.5 %).

We found no statistically significant differences between patients who received greater than 1000 J/cm^2 and patients who received less than 1000 J/cm^2 in terms of type of disease (psoriasis or mycosis fungoides), sex, or skin phototype. We did, however, find significant differences between the 2 groups in terms of the percentage of patients who had received adjuvant therapy: 48.7% in the group that had received a total cumulative dose of less than 1000 J/cm^2 and 62.3% in the group that had received a cumulative dose of more than 1000 J/cm^2. On analyzing the adjuvant therapies separately, we found statistically significant differences between patients who had received less than 1000 J/cm^2 and those who had received greater than 1000 J/cm^2 for methotrexate (15.6 % vs 31.1% in patients receiving greater than and less than 1000 J/cm^2, respectively); oral retinoids (20.7 % vs 41.5%); and cyclosporine A (9.7% vs 27.2%). We found no such differences for tar, UV-B therapy, or interferon (Table 3).

Table 3. Patient Characteristics According to Total Cumulative Dose

	<1000 J/cm²	*>1000 J/cm²*
Patients, No.	235	76
Men, No. (%)	122 (73)	45 (27)
Women, No. (%)	113 (78.4)	31(21.5)
Skin phototype II, %		25 18
Skin phototype III, %	64 62	
Skin phototype IV, %	11 19	
Mycosis fungoides, No. (%)	37 (67.2)	18 (32.7)
Psoriasis, No. (%)	198 (77.3)	58 (22.6)
Adjuvant therapy, %	48.7	62.3
Sessions, No.[a]	36.08	142.29
Maximum dose, J/cm²[a]	15.17	22.87
Total cumulative dose, J/cm²[a]	355.83	2107.5
Age PUVA therapy started, y[a]	43.43	41.44
Age at diagnosis, y[a]	34.09	31.88
Duration of PUVA therapy, d[a]	376.3 (1 y)	1715.64 (4.7 y)

Abbreviation: PUVA, psoralen-UV-A
[a]Data are expressed as means.

Discussion

In our study, psoriasis, followed by palmoplantar eczema, was the most common of all the skin diseases treated with PUVA therapy. This finding coincides with those of Lindelöf et al[7] in Sweden but contrasts with those of Tran et al[8] in Singapore, where vitiligo was found to be the most common reason for treatment. This highlights the fact that the prevalence of these skin diseases varies from one geographic region to the next. In our study, for example, mycosis fungoides accounted for 8.1% of all the skin diseases analyzed, while in the studies of Lindelöf et al and Tran et al, in Sweden and Singapore, it accounted for just 3% and 3.5%, respectively.

Our findings with respect to the differences between topical and systemic PUVA therapy were very similar to those of Lindelöf et al[7] (Table 4).

The proportion of female/male patients who received PUVA therapy in the study by Lindelöf et al[7] and in ours was also similar (49%/51% compared with 51%/49% in the Swedish study and our study, respectively), and there was only a slight difference in the mean age at which treatment had been started (35-40 years and 41.5 years in the Swedish study and our study, respectively).

Table 4. Differences in Topical and Systemic Psoralen-UV-A Therapy in Studies Performed in Sweden and Spaina

	Sweden[7]	*Spain*[b]
Systemic PUVA therapy	70.6%[c]	77.3%
Topical PUVA therapy	29.4%[c]	22.7%

[a]Data are expressed as percentages of total study groups
[b]Present study
[c]Includes several patients who received both topical and systemic PUVA therapy
Abbreviation: PUVA, psoralen-UV-A

Table 5. Differences in Skin Phototype in Studies Performed in Sweden and Spain

Phototype	*Sweden*[7]	*Spain*[a,b]
I and II	32%	23.3%
III and IV	68%	76.7%

[a]Present study
[b]Data refers to patients with psoriasis and mycosis fungoides only

The findings of the 2 studies with respect to skin phototype differed considerably (Table 5), possibly reflecting population differences between Spain and Sweden.

Table 6. Comparative Analysis of Different Studies[a]

	Spain[b,c]	Singapore[8]	North America[9]	Europe[10]
Sessions, No.	59	20	25	20
Total cumulative dose, J/cm^2	748	316	96	245

[a]Data are expressed as means
[b]Present study
[c]Data correspond to 412 patients with psoriasis and mycosis fungoides

Table 6 shows how our findings compare with those of studies conducted in other geographical areas[8-10] with respect to mean number of sessions and total cumulative dose received by patients following a systemic PUVA therapy regimen.

Our study found a higher total cumulative dose and number of sessions than did the studies conducted in the United States of America[9] and Europe,[10] as was also true of the total cumulative dose in the study of Tran et al[8] undertaken in Singapore, possibly because of a greater number of patients with skin phototypes III and IV in these 2 studies.

Our results show that 41 different skin diseases were treated with PUVA therapy during the study period (1982-1996). The most common disease, both in men and in women and in each of the years analyzed, was psoriasis, followed by hand, palmoplantar, and/or dyshidrotic eczema. The second most common disease treated by systemic PUVA therapy was mycosis fungoides. Psoriasis was diagnosed at an older age in men than in women (average difference of 8 years), and therapy was started at an earlier age in women than in men for all diseases. The most common skin phototype in our group—for both men and women—was type III, followed by types II and IV.

Over half of the patients in the psoriasis subgroup received adjuvant therapy. The most common carcinogenic agent used to treat patients with psoriasis was tar, followed by methotrexate. Retinoids were administered as adjuvant therapy more frequently in men than in women, possibly due to the associated risk of teratogenic effects in the latter. Patients who had received a mean total cumulative dose of greater than 1000 J/cm^2 had been administered a greater number of adjuvant therapies than those who had received less than 1000 J/cm^2, a difference that was found to be statistically significant.

Patients with mycosis fungoides required a higher mean total cumulative dose and number of sessions than did patients with psoriasis. The mean maximum dose, however, was lower for mycosis fungoides than for psoriasis. Women with psoriasis or mycosis fungoides underwent fewer sessions and received a lower mean total cumulative dose than did men.

We found statistically significant differences between patients with psoriasis and those with mycosis fungoides for the age at which PUVA therapy had been started, the age at which the presenting disease had been diagnosed (higher for mycosis fungoides), and the mean maximum dose received (higher for psoriasis).

Conflicts of Interest

The authors declare no conflicts of interest.

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