Comparison of psoralen-UVB and psoralen-UVA photochemotherapy in the treatment of psoriasis

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Background: PUVA treatment of psoriasis is usually given with broad-band fluorescent UVA lamps. Narrow-band UVB exposure after oral methoxsalen has been shown to achieve a greater therapeutic response in psoriasis than identical UVB exposure given without psoralen.
Objective: The purpose of this study was to compare conventional PUVA with psoralen-UVB therapy in psoriasis.
Methods: We studied 100 patients with plaque-type psoriasis who were randomly selected to receive either conventional psoralen-UVA or psoralen-UVB treatment.
Results: No significant difference was found between the two treatments in the proportion of patients whose skin cleared during treatment or in the number of exposures required for clearance of psoriasis. As expected, the cumulative UV dose for clearance was smaller in the group treated with UVB compared with those receiving UVA. Side effects and disease status at 3 months after the end of treatment were similar for the two groups.
Conclusion: Psoralen-UVB treatment of psoriasis is as effective as conventional PUVA. The mechanism of psoralen–311 nm UVB action on psoriasis requires study to predict the long-term safety of this treatment.
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The combination of oral methoxsalen followed by UVA (320 to 400 nm) irradiation (PUVA) is an established therapy for psoriasis.[1] Broad-band sources of UVA have conventionally been used, that is, lamps with a fluorescence spectrum extending from 320 to 400 nm, and peak emission between 350 and 360 nm. A narrow-band lamp (TL-01; Philips) with 83% of its UV emission at 311 ± 2 nm has been developed for UVB (290 to 320 nm) phototherapy of psoriasis.[2] We[3] and others[4] have shown that narrow-band UVB exposure, given after oral methoxsalen, results in a greater therapeutic response in psoriasis than identical UVB exposure given without psoralen. We now report the results of a randomized trial in patients with plaque-type psoriasis comparing conventional PUVA with psoralen-UVB therapy.

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PATIENTS AND METHODS

Patients

We studied 100 adults with chronic plaque-type psoriasis who had been referred to a "PUVA clinic." Sample size estimation was based on the number of exposures until clearance, which preliminary analysis suggested was well approximated by the use of a Weibull distribution with shape parameter 2. To have 80% power to detect a decrease in median exposure of 25%, two groups of 50 patients would be required. Patients receiving other systemic treatment of psoriasis, such as acitretin or methotrexate, were excluded, as were those who had received any form of UV therapy within the preceding 6 months. Emollient alone was used as therapy in the 4 weeks before beginning treatment. In an earlier trial[5] we found that plaque size and skin type influenced the response to PUVA. To ensure matching for these variables in the two groups, patients were stratified according to predominant plaque size (> 3 cm, < 3 cm) and skin type (type I/II or type III/IV). Treatment allocation (with the use of sealed envelopes) was based on randomized permuted blocks within strata.

Table I. Allocation of treatment, psoralen-UVA or psoralen-UVB, according to skin type and predominant plaque size (> 3 cm, < 3 cm)

	Skin type			
	I	II	III	IV
Small plaque psoriasis				
UVA	0	9	9	4
UVB	2	5	9	6
Large plaque psoriasis				
UVA	1	14	6	7
UVB	2	13	9	4

Phototesting

Patients were given oral methoxsalen in a microcrystalline formulation (Promedica, Levallois-Perret, France); a dosing system based on body surface area (25 mg/m^2) was used.[6] Actual doses of methoxsalen ranged from 30 to 60 mg (median, 40 mg). Minimal phototoxic dose (MPD) testing was performed on the volar aspect of the forearm 2 hours after ingestion of methoxsalen on the first day of treatment. A phototesting template allowed simultaneous exposure of four 1 cm diameter sites.[7] PUVA phototesting was performed with a cylindrical array[8] of 15 standard UVA fluorescent lamps (Philips TL-09R), with a maximum test dose of 10 J/cm^2. Psoralen-UVB phototesting was performed with a horizontal array[3] of six narrow-band UVB lamps (Philips TL-01), and a maximum test dose of 2 J/cm^2. The MPD, defined as the smallest dose of radiation required to achieve just detectable erythema, was judged visually 72 hours after irradiation.

Treatment

Patients were treated twice weekly according to our standard protocol[5] with whole-body exposure units fitted with 40 fluorescent lamps, either TL-09R or TL-01. Measurements of irradiance were made weekly with a radiometer (IL 700; International Light) in conjunction with either a UVA or UVB sensor, as appropriate. Both sensors were calibrated spectroradiometrically and statements of dose (measured in joules per square centimeter) refer to unweighted spectrally integrated energy between 280 and 400 nm. The first treatment dose was given on the day of phototesting, with the test arm protected from further exposure with a tubular bandage, shown to have negligible (<0.1%) UV transmission. A dose of 2.5 J/cm^2 (UVA) or 0.6 J/cm^2 (UVB) was given initially unless previous PUVA history or experience of sunburn cautioned otherwise. The dose was then increased if tolerated in equal steps to the previously determined MPD, given on the third and fourth treatment days, or to a maximum of 6 J/cm^2 (UVA) or 1.5 J/cm^2 (UVB). These maximum doses were chosen to reduce any risk of burning attributable to variation in photosensitivity achieved by the psoralen on successive treatment days. Thereafter, weekly dose increments were used starting with 40% for UVA and 10% for UVB, reducing stepwise to 10% for UVA and 2.5% for UVB by the sixth week. If erythema developed during treatment, depending on the severity, planned dose increments were postponed or treatments missed, until the erythema resolved.

Assessment

Clinical response was assessed by a clinician unaware of treatment allocation. Clearance was registered when all exposed lesions of psoriasis above the knees had healed. Although this often coincided with clearance below the knees, lesions of psoriasis on the lower part of the legs were excluded from assessment because of the unpredictable rate of clearance and because patients were not matched for involvement at this site. Patients were discharged from treatment with follow-up arranged at 3 months and only emollient to use in that period. At the follow-up visit, the degree of relapse of psoriasis was graded as none (still clear), minimal, moderate, or complete relapse.

Five outcome measures were considered: (1) whether clearance of psoriasis was achieved, (2) number of exposures for clearance, (3) cumulative dose for clearance, (4) side effects, and (5) disease status at 3 months after treatment was stopped. Outcomes (2) and (3) were analyzed by fitting a Weibull distribution[9] using GLIM4,[10] with the values from those patients whose skin did not clear considered to be censored observations.

RESULTS

Of the 100 patients studied, 50 received treatment with conventional UVA lamps and 50 with narrow-band UVB lamps. The two groups were well matched with regard to skin type and plaque size (Table I). Of the patients allocated to treatment with UVA, 35 of 50 (70%) had received PUVA previously, compared with 32 of 50 (64%) allocated to UVB. In the group of patients with a history of previous PUVA treatment, the median (interquartile range) time elapsed since the last course of PUVA was 24 (24) months for UVA and 24 (21) months for UVB. The two groups were also well matched with regard to age; mean age (±standard deviation) for the UVA group was 41.7 ± 16.6 years and 39.8 ± 15.0 years for UVB.

The MPD values ranged from 1.25 to more than 10 J/cm^2 (median, 5 J/cm^2) for UVA and from 0.5 to more than 2 J/cm^2 (median, 1 J/cm^2) for UVB.

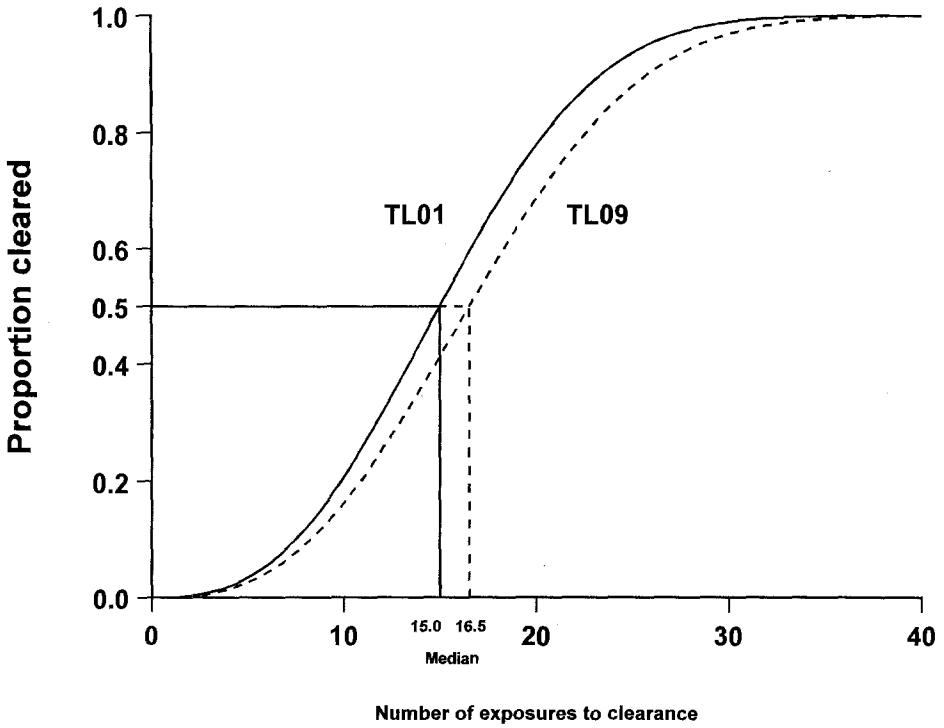

Fig. 1. Clearance of psoriasis according to the number of exposures from the two types of lamp.

Clearance

Clearance of psoriasis was achieved in 43 of 50 patients treated with UVB compared with 37 of 50 treated with UVA. The odds ratio for clearance with UVB relative to UVA was 2.16 (95% confidence interval, 0.78, 5.98; $p = 0.069$), with little change if the analysis was repeated using logistic regression to allow baseline information on skin type and plaque size to be taken into account, or if previous use of PUVA was considered. Of the patients whose psoriasis was not cleared during the trial, treatment was stopped because of poor response in four who received UVB and in 10 who received UVA. In the remaining six patients (three for each lamp type) treatment was stopped before clearance for other reasons, such as intercurrent medical or domestic problems precluding attendance. Any decision to stop treatment was made without knowledge of the lamp type used.

Number of exposures for clearance

The median number of exposures for clearance was 16.5 for UVA and 15.0 for UVB (Fig. 1). There was no evidence of a significant difference in medians ($p = 0.24$; 95% confidence interval for ratio of medians (UVA/UVB) is 0.94, 1.30.

Cumulative dose for clearance

With a Weibull distribution model the median cumulative dose for clearance was found to be 19.1 J/cm^2 for UVB and 72.1 J/cm^2 for UVA (dose ratio, 3.73; 95% confidence interval, 2.81, 4.96) (Fig. 2).

Side effects

Erythema was documented at some stage during the course of treatment in 22 of 50 patients receiving UVB and 23 of 50 receiving UVA. The erythema was of sufficient intensity to require one or more treatments to be missed in five patients receiving UVB and 10 patients receiving UVA (odds ratio, 2.3; 95% confidence interval, 0.7, 7.1; $p = 0.16$). In one of the patients receiving UVB painful blistering occurred within lesions of psoriasis and treatment was stopped as a result. No other significant side effects of treatment were noted.

Disease status at 3 months after the end of treatment

The results of clinical assessment at 3 months are shown in Table II. Of the patients who were clear of psoriasis at the end of the treatment course, 17 of 43 (40%) of the UVB-treated group and 12 of 37 (32%) of the UVA-treated group remained clear at 3

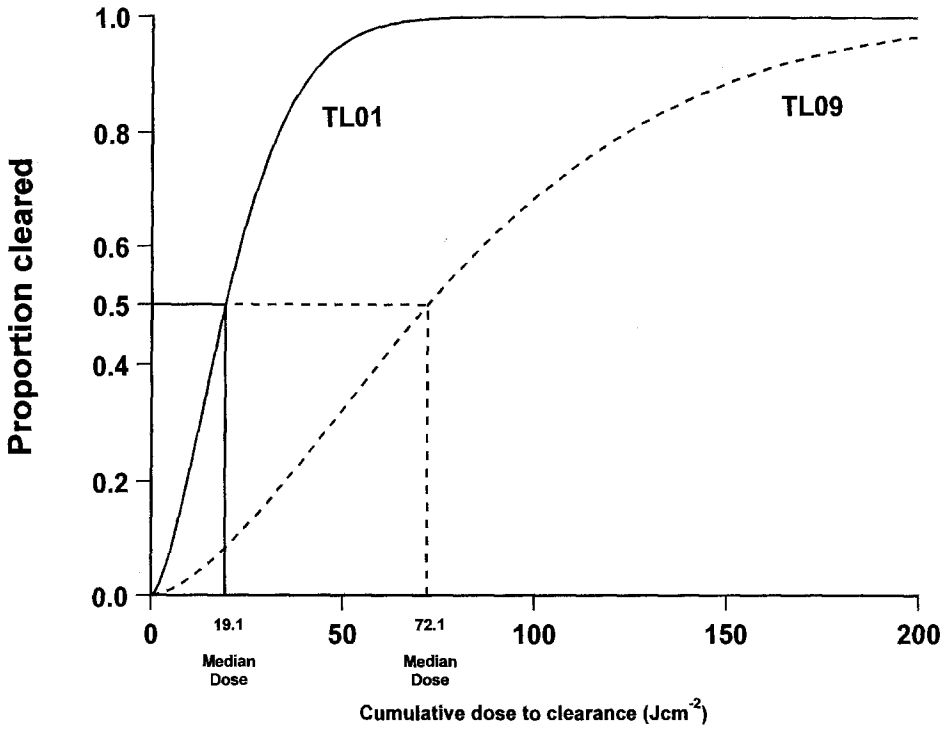

Fig. 2. Clearance of psoriasis according to the cumulative dose from the two types of lamp.

Table II. Extent of relapse of patients with psoriasis at follow-up assessment

	Extent of relapse 3 mo after cessation of treatment				
	Still clear	Minimal	Moderate or complete	Failed to attend at 3 mo	Never cleared
UVA	12	8	14	3	13
UVB	17	8	9	9*	7

*Includes one patient who died before follow-up.

months. This difference is not significant (odds ratio, 1.36; $p = 0.51$; 95% confidence interval, 0.54, 3.42). This comparison is not between the treatment groups as randomized and should be interpreted with caution. However, similar results are obtained by comparing the proportions of all patients in each randomized group who were clear at 3 months.

The remaining patients had a relapse to a variable extent or failed to attend the follow-up assessment (Table II).

DISCUSSION

This trial has shown that response of plaque-type psoriasis is similar with either conventional PUVA treatment or psoralen/narrow-band UVB treatment.

The method of treatment allocation ensured that the two groups were well matched. No important differences were observed between the two groups with regard to achievement of clearance or degree of relapse at the assessment 3 months after treatment was stopped. The design of the trial, with MPD testing, ensured that patients in the two groups received equal erythemal doses of radiation irrespective of the lamp type used for treatment. The cumulative dose for clearance was significantly smaller for the UVB-treated patients compared with the UVA-treated group (Fig. 2). This was an expected finding, given the shape of the action spectrum for UV-induced erythema with[11] or without[12] oral psoralen administration and should not be taken to imply that psoralen-UVB is likely to be safer in the long term than conventional PUVA. Because of the steeper dose-response curve for UVB-induced erythema compared with PUVA-induced erythema,[8] to maintain an equal erythemal dose, smaller percentage dose increments were used for the UVB-treated group than for those receiving UVA. That this was achieved is shown by the similar proportion of patients in whom erythema developed during the trial (22 of 50 for UVB and 23 of 50 for UVA). The more prolonged time course of PUVA-induced erythema, reaching a maximum at or beyond 72 hours after ir-

radiation[1,8] compared with the shorter lasting psoralen-UVB response, may account for the greater number of treatments missed because of erythema within the PUVA group. A blistering response within areas of psoriasis occurred in one UVB-treated patient. This phenomenon has been reported previously in patients treated with TL-01 lamps without psoralen.[13]

A previous study involving 10 patients with psoriasis found no difference in response between conventional PUVA treatment given to one half of the body and narrow-band UVB phototherapy (without psoralen) given to the other half.[14] Clearance of psoriasis was not assessed in this study; response was compared on each side of the body for up to four weeks of treatment (eight exposures). However, our own observations in a within-patient comparison are that addition of psoralen to narrow-band UVB treatment enhances therapeutic response.[3] Similar findings were reported by Ortel et al.[4] The psoralen-enhanced therapeutic response to UVB is likely to be dependent on wavelength; Morrison[15] recently reported no additional benefit in psoriasis from psoralen use in combination with UVB exposure from fluorescent sunlamps (FS40), a radiation source in which erythema is achieved principally by UVC and short-wave (< 310 nm) UVB.

It seems likely that the mechanism of action of psoralen-UVB therapy is both through a direct therapeutic effect of 311 nm radiation on psoriasis as well as through psoralen-mediated photochemical responses. A study is required to delineate clearly the magnitude of the additional therapeutic effect achieved by combining psoralen and narrow-band UVB. The carcinogenic risk of conventional PUVA treatment is well established[16] and is attributed to the effects of psoralen on DNA. The exact mechanism of psoralen–311 nm UVB action on psoriasis requires study to predict the long-term safety of this new treatment.

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