Randomized Double-blind Trial of the Treatment of Chronic Plaque Psoriasis

Efficacy of Psoralen–UV-A Therapy vs Narrowband UV-B Therapy

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**Objective:** To compare the efficacy of oral psoralen–UV-A (PUVA) therapy with that of narrowband UV-B (NB-UVB) therapy in patients with chronic plaque psoriasis.

**Design:** Double-blind randomized study.

**Setting:** Phototherapy unit in a university hospital.

**Patients:** Ninety-three patients with chronic plaque psoriasis.

**Interventions:** Twice-weekly NB-UVB or PUVA therapy, starting at 70% of the minimum phototoxic or erythema dose, with 20% incremental increases. Patients were treated until clearance, up to a maximum of 30 sessions; those with clearance were followed up until relapse or for 12 months.

**Main Outcome Measures:** Proportion of patients achieving clearance, number of treatments to clearance, and, among those with clearance, the proportion remaining in remission at 6 months.

**Results:** Patients with skin types V and VI had a lower rate of clearance than those with skin types I through IV (24% vs 75%; P = .001). In patients with skin types I through IV, PUVA was significantly more effective than NB-UVB at achieving clearance (84% vs 65%; P = .02). The median number of treatments to clearance was significantly lower in the PUVA group (17.0 vs 28.5; P < .001). More patients treated with PUVA vs NB-UVB were reported to have erythema at some stage during treatment (49% vs 22%; P = .004), although this difference may have been due to ascertainment bias. Six months after the cessation of therapy, 68% of PUVA-treated patients were still in remission vs 35% of NB-UVB–treated patients.

**Conclusion:** Compared with NB-UVB, PUVA achieves clearance in more patients with fewer treatment sessions and results in longer remissions.

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**METHODS**

**PATIENTS**

This trial was approved by the Research Ethics Committee at St Thomas’ Hospital (London, England), and all the patients gave informed and signed consent. Sample size calculations suggested that for 90% power to detect a 25% decrease in the median number of exposures at the 5% significance level, 80 patients with psoriasis were needed. Therefore, to allow for dropouts, 93 patients with psoriasis were recruited from among those attending the Phototherapy Clinic of St John’s Institute of Dermatology.

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of Dermatology between April 1, 2002, and March 31, 2004; given the 12-month follow-up period, the study terminated March 31, 2005. The inclusion criterion was chronic plaque psoriasis with at least 8% body surface area involvement as assessed by the rule of nines and with a Psoriasis Area and Severity Index (PASI) score of at least 8; this corresponds to moderate-to-severe disease. Exclusion criteria included being younger than 18 years or older than 70 years, previous skin malignancy, photo(chemo)-therapy in the preceding 3 months or more than 150 sessions in the patient’s lifetime, administration of a drug known to frequently cause photosensitization, topical antipsoriatic treatment in the previous 4 weeks or systemic antipsoriatic treatment in the previous 3 months, pregnancy, lactation, renal or hepatic disease, and a history of photosensitivity.

ADMINISTRATION OF ORAL PSORALEN OR PLACEBO

After study enrollment, patients were randomly allocated to either NB-UVB or PUVA therapy by means of a sequentially numbered list. The dermatologist conducting the assessments was blinded to the treatment allocations; nursing and pharmacy staff conducting the treatment were necessarily aware of it. To ensure full patient blinding, the phototherapy cabinet labels were concealed, and all the patients ingested identical-appearing tablets 2 hours before treatment: the NB-UVB group received placebo and the PUVA group received 10-mg 8-methoxypsoralen tablets (Deltapsoralen; Crawford Pharmaceuticals, Milton Keynes, England). The dose of the latter was determined by patients’ body surface area, namely, 25 mg/m2, and ranged from 30 to 60 mg. All the patients were advised that nausea could occur with use of the medication. During the study, patients intolerant of 8-methoxypsoralen because of nausea were insted given 20-mg 5-methoxypsoralen tablets (Pentaderm; Crawford Pharmaceuticals) at a dose of 50 mg/m2 3 hours before phototherapy, with doses ranging from 60 to 120 mg.

UV SOURCES

The PUVA therapy was given in a Waldmann 6002 cabin containing 40 Waldmann 100-W UV-A fluorescent tubes (Waldmann Medizintechn, Villingen-Schwenningen, Germany). The UV-A irradiance at the surface of the patient’s skin was approximately 17.4 mW/cm2. The NB-UVB treatments were given in a Waldmann UV5000 cabin containing 24 Philips 100-W NB-UVB fluorescent tubes (Waldmann) emitting predominantly in the wavelength range of 311 to 313 nm. The UV-B irradiance in the cabin at the surface of the patient’s skin was typically 7 to 8 mW/cm2. The exact irradiance of both sources was checked monthly.

MINIMUM ERYTHEMA DOSE AND MINIMUM PHOTOTOXIC DOSE TESTING

The minimum erythema dose (MED) and minimum phototoxic dose (MPD) were assessed on unaffected upper buttock skin. In the NB-UVB group, the doses tested were 100, 140, 200, 280, 390, 550, 770, and 1100 mJ/cm2; in the UV-A group, the doses were 0.5, 1.0, 1.5, 2.0, 3.0, 5.0, 7.0, and 9.0 J/cm2. The first 6 doses were used for skin types I and II and the last 6 for types III through VI. The MED and MPD were defined as the lowest dose that caused just-perceptible erythema 24 hours (NB-UVB) and 96 hours (PUVA) after exposure; all the patients were checked at both times to maintain blinding.

<table>
<thead>
<tr>
<th>Table 1. Definitions and Management of Erythema*</th>
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<tr>
<td>Grade</td>
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<tr>
<td>-------</td>
</tr>
<tr>
<td>1</td>
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<td>2</td>
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</table>

*Erythema was defined according to the maximum erythema that had occurred since the previous session and was determined by asking the patient and by examination. The increment was reduced by moving 1 point down the following scale: 20% to 10% to 5% to 0%. Episodes of erythema localized to small areas (eg, the face) were not included and were managed by shielding during treatments until settled, and then during part of the duration of subsequent exposures. There were no recorded erythematous episodes of severity greater than grade 2.

TREATMENT

Patients were treated twice weekly, initially with a radiation dose corresponding to 70% of the MED or MPD, followed by 20% incremental increases at each visit, if tolerated. No further incremental increases were applied once a dose of 5 J/cm2 (NB-UVB) or 15 J/cm2 (PUVA) was reached. Doses were, however, adjusted according to the occurrence of any erythema after treatments (Table 1).

All the patients were instructed to apply aqueous cream (30% emulsifying ointment, 1% phenoxethanol) twice daily and to use a bath emollient (Hydromol; Ferndale Pharmaceuticals Ltd, Thorp Arch Estate, England) (13% isopropyl myristate, 37.8% light liquid paraffin) daily throughout therapy and follow-up. For 12 hours after treatment, all the patients were eye protection as for oral PUVA therapy. During treatment sessions, unaffected skin was covered as far as practically possible with clothing, and male patients were genital protection.

ASSESSMENTS, TERMINATION OF THERAPY, AND FOLLOW-UP

All the patients were assessed immediately before the commencement of treatment and after 8, 16, 24, and 30 sessions. Between assessments, if nursing staff noted at routine examination before exposure that a patient was clear of psoriasis, the subsequent assessment by the study investigator was brought forward. All assessments were made by a blinded investigator (S.S.Y.) and consisted of estimation of the PASI score and of the Physician’s Global Evaluation score as indexes of psoriasis severity. The latter is a 7-point scale (6=severe, 5=moderate to severe, 4=moderate, 3=mild to moderate, 2=mild, 1=almost clear [minimum residual activity, with all lesions flat and free of scale], and 0=clear). In addition, patients completed the Dermatology Life Quality Index (DLQI) and a visual analog scale. The latter was a visual scale from 0 to 10 prefixed with the following question: “At the moment, how would you grade or rate your psoriasis on a scale from 0 to 10? Please circle as appropriate between 0 (no psoriasis) and 10 (the worst psoriasis you have ever had).”

Treatment was terminated in the event of any of the following: clearance of psoriasis (a Physician’s Global Evaluation score of 0 or 1, ie, either complete clearance or minimum residual activity), absent or minimal improvement after 16 treatments or very slow progress thereafter, intolerance to therapy, or the completion of 30 treatments.
Patients who began treatment using a skin type–based starting dose, which ranged from 100 to 500 mJ/cm² (NB-UVB), but this difference was not statistically significant ($\chi^2 = 2.1; P = .15$). Clearance rates among those who had been previously treated and those who had not were similar (69% and 63%, respectively; $P = .56$). Before the commencement of treatment, 3 patients did not have their MPD checked and 3 did not have their MED checked for the following reasons: assessment of erythema is difficult in patients with skin types V and VI (n=3), logistic factors (n=2), and the absence of unaffected skin in the area of testing (n=1). These patients began therapy using a skin type–based starting dose, which ranged from 100 to 500 mJ/cm² (NB-UVB) and from 0.5 to 3.0 J/cm² (PUVA).
ity (PUVA and NB-UVB), age, MPD or MED group, previous phototherapy, and sex as predictor variables for clearance of psoriasis; the latter 4 factors were not, however, significant predictors and were sequentially removed from the model. Skin type (P=.001) and modality (P=.02) had significant effects on clearance rates. Of the 71 patients with skin types 1 through IV, PUVA achieved clearance in 31 (84%) of 37 compared with 22 (65%) of 34 using NB-UVB; the median number of treatments to clearance was 17.0 in the PUVA group and 28.5 in the NB-UVB group (Z = −3.7; P < .001).

In the 71 patients with skin types 1 through IV, the median PASI score at baseline in the PUVA group was 11; this score declined to 4.2 after 8 sessions. Corresponding scores for the NB-UVB group were 9.6 and 5.7. These reductions were significantly greater in the PUVA group (Z = −3.2; P = .001) (Figure 2A). Similarly, after 8 sessions, there were significantly greater reductions in Physician’s Global Evaluation scores (Z = −3.2; P = .001), visual analog scale scores (Z = −2.5; P = .01), and DLQI scores (Z = −2.4; P = .02) (Figure 2B) for patients undergoing PUVA therapy compared with NB-UVB therapy.

There was no evidence that the superiority of PUVA over NB-UVB varied according to the severity of the initial psoriasis; in the 44 patients with an initial PASI score below 10.8, the clearance rate was 79% with PUVA and 52% with NB-UVB, whereas in those with an initial PASI score of 10.8 or greater, clearance rates were 79% and 50%, respectively.

ADVERSE EFFECTS

In patients treated with PUVA, low skin types had a higher incidence of the development of erythema during the study (P = .005) (Table 2). In patients treated with NB-UVB, we did not detect a corresponding significant effect (P = .45) (Table 2). In a binary logistic model (incorporating skin type as a potentially confounding variable), modality (P = .004) and age (P = .04) were significant predictors of the development of erythema during therapy, with patients treated with PUVA and older individuals being more likely to develop erythema. Twenty-one (49%) of 43 patients treated with PUVA compared with 10 (22%) of 45 treated with NB-UVB experienced erythema (of either grade) at some stage during treatment. Considering only grade 2 erythemas, the corresponding figures were 14% and 7%. Two patients changed from taking 8-methoxypsoralen to taking 5-methoxypsoralen during the study because of nausea.

RE rural

The 57 of 88 patients whose psoriasis cleared were followed up until relapse or for a maximum of 12 months, except for 3 who were lost to follow-up and were not included in the analysis of relapse. Binary logistic regression showed that at 6 months, the only significant predictor of remission was treatment modality (P = .02), with more patients treated with PUVA still having clearance (23/34; 68%) than patients undergoing NB-UVB therapy (8/23; 35%). Kaplan-Meier survival analysis also showed that patients treated with PUVA had significantly longer remissions (P = .03), with the median time to relapse being 8 months vs 4 months among patients treated with NB-UVB (Figure 3).

QUALITY OF LIFE

At baseline, PASI scores were not correlated with DLQI scores (ρ = 0.10; P = .35), but after phototherapy, quality of life was correlated with the extent of improvement in PASI scores resulting from the phototherapy (DLQI score compared with reduction in PASI score: ρ = −0.43; P < .001). Furthermore, at the time of relapse, quality of life was lowest in patients with the greatest deterioration in PASI scores (DLQI score compared with increase in PASI score: ρ = 0.52; P < .001).

COMMENT

To our knowledge, this is the first double-blind randomized trial of oral PUVA vs NB-UVB for the treatment of chronic plaque psoriasis. Oral PUVA was superior to NB-UVB in all the main outcome measures: clearance rate (among patients with skin types I-IV: 84% for PUVA and
frequency because in a randomized trial of 113 patients also used NB-UVB twice per week, an acceptable frequency because PUVA erythema peaks at approximately 96 hours; it has been shown that thrice weekly administration may produce unacceptable burning episodes. Therefore, to enable effective masking of group allocation, we administered PUVA twice a week rather than more frequently because any differences in degree or type of pigmentation, or erythema, were not discernable to the investigator, who himself, therefore, remained blinded to group allocation. This is further expected in that observer blinding was successful in 3 previous comparisons of PUVA and NB-UVB. In 2 of those studies, comparisons were made between 2 sides of the same patient, maximizing the chance of detecting differences, which were nevertheless not noticed.

We used MED and MPD testing to ensure that both treatments were given as effectively as possible. We administered PUVA twice a week rather than more frequently because PUVA erythema peaks at approximately 96 hours; it has been shown that thrice weekly administration may produce unacceptable burning episodes and does not seem to be more effective. Therefore, to enable effective masking of group allocation, we also used NB-UVB twice per week, an acceptable frequency because in a randomized trial of 113 patients concerning NB-UVB frequency, the mean number of treatments to clearance in those treated twice weekly was 24.4 and in those treated thrice weekly was 23.0, a difference that was not statistically significant. Treatment with NB-UVB 5 times weekly is not more effective than thrice weekly. It might, despite this, be argued that we administered NB-UVB at a suboptimal frequency, but this seems unlikely to have affected our conclusions because of the large difference between PUVA and NB-UVB in the median number of treatments to clearance.

Among patients who undergo phototherapy, those that have been treated with phototherapy in the past could perhaps be considered more likely to respond well than those who have never had phototherapy, and our PUVA group had a slightly higher proportion of patients who had previously been treated (44% vs 29%). In fact, however, the clearance rates between previously treated and untreated patients were only minimally dissimilar (69% and 63%, respectively), and in the binary logistic regression model, previous phototherapy was not a predictor of clearance, so this issue is not relevant in the interpretation of the results.

The results presented herein and in previous randomized between-patient comparison studies on the treatment of chronic plaque psoriasis are highly consistent with each other (Table 3). In all 4 studies, the median number of treatments to clearance with PUVA was 16 to 19 and with NB-UVB was 25 to 28, and in 3 the clearance rates were 84% to 85% with PUVA and 60% to 65% with NB-UVB. In contrast, within-patient side-to-side comparison studies have had more equivocal results (Table 3). In such studies, it is possible that the effect of treatment on one side is transmitted to the other, thereby minimizing the difference between the 2 sides, but any such effect is likely to be small. One of these studies found slight differences in favor of PUVA, but they were not statistically significant. Another study, in which bath PUVA was used, showed a higher clearance rate with NB-UVB, although the median number of treatments to clearance was lower in the PUVA group. The third study included only 10 patients. Overall, therefore, PUVA seems to be more efficacious than NB-UVB in the treatment of chronic plaque psoriasis.

Forty-nine percent of the patients treated with PUVA vs 22% of those treated with NB-UVB experienced erythema at some stage during treatment. This occurred despite that both groups were following the same dose protocol (70% of the MPD or MED followed by 20% incremental increases). Although the assessment of erythema involves not only examination of the patient but also inquiry of the patient regarding any redness since the preceding visit, in practice, this inquiry is unlikely to be 100% sensitive. Therefore, more erythematous episodes may have been recorded with PUVA use because of bias in that PUVA erythema persists for much longer (approximately 96 vs 12-15 hours) and, therefore, is more likely to be evident at the time of examination at the subsequent treatment session. Also, the absorption of psoralen and the timing of its administration may vary, leading to subsequent erythema. However, only 1 patient treated with PUVA withdrew because of burning, and it is probably acceptable for 49% of patients to...
develop mild erythema at some stage during treatment; indeed, some regimens deliberately try to provoke mild erythema.1,2

We found a much lower clearance rate for patients with skin types V and VI compared with types I through IV (24% compared with 75%). This may well be because the development of facultative pigmentation, most marked (24% compared with 75%). This may well be because the skin types V and VI, may interfere with efficacy by causing, in effect, underdosage.19 However, we did not detect differences between skin types in rates of erythemal episodes that would have supported this hypothesis.

The existence of a perhaps surprisingly weak association between the clinician’s assessment of severity and the DLQI score has previously been reported,20 and before phototherapy, we could not detect any association at all. However, after phototherapy, quality of life was correlated with the extent of psoriasis improvement, suggesting that, at least in the context of phototherapy, quality of life may be associated more with recent changes in psoriasis severity than with the severity of psoriasis itself.

Both NB-UVB and broadband UV-B offer definite advantages over oral PUVA that make these modalities preferable for many patients. In particular, PUVA may cause nausea, requires the use of eye protection after treatment sessions, cannot be used during pregnancy, is contraindicated in patients with significant hepatic impairment or taking warfarin or phenytoin, and requires the data and accuracy of the data analysis.

Table 3. Comparative Studies of PUVA vs NB-UVB for the Treatment of Chronic Plaque Psoriasis

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients Analyzed, No.</th>
<th>Weekly Frequency of Treatment, PUVA/NB-UVB</th>
<th>Clearance Rate, PUVA vs NB-UVB</th>
<th>Treatments to Clearance, PUVA vs NB-UVB, Median No.</th>
<th>Patients Experiencing Erythemal Episodes, PUVA vs NB-UVB</th>
<th>Remain in Remission at 6 mo, PUVA vs NB-UVB</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Weelden et al, 1990</td>
<td>10</td>
<td>2/2</td>
<td>Not treated to clearance</td>
<td>Not treated to clearance</td>
<td>Treatments aimed at mild erythema</td>
<td>Not studied</td>
<td>Observer masked; equal efficacy in 5 patients; PUVA superior in 3; NB-UVB superior in 2</td>
</tr>
<tr>
<td>Tanew et al, 1999</td>
<td>21</td>
<td>3/3</td>
<td>After a maximum of 18 sessions: 43% vs 33%</td>
<td>Not stated</td>
<td>Treatments aimed at mild erythema</td>
<td>Not studied</td>
<td>Analysis of PASI suggested PUVA possibly superior; not statistically significant</td>
</tr>
<tr>
<td>Dave et al, 2003</td>
<td>28</td>
<td>2/3</td>
<td>54% vs 75% (P = .03)*</td>
<td>19 vs 24.5 (P = .01)†</td>
<td>57% vs 75% (P = .10) (grade 1 erythemas)</td>
<td>15% vs 15% (approx)</td>
<td>Observer masked; bath PUVA; results possibly influenced by 36% withdrawal rate; after treatment, 83% of the patients had a preference for NB-UVB</td>
</tr>
</tbody>
</table>

Abbreviations: approx, approximately; NB-UVB, narrowband UV-B; PASI, Psoriasis Area and Severity Index; PUVA, psoralen–UV-A.

*Comparison showing the superior efficacy of NB-UVB.

†Comparisons (statistically significant at the 5% level) showing the superior efficacy of PUVA.

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Author Contributions: Dr Yones had full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. Study concept and design: Yones, Garibaldinos, and Hawk. Acquisition of data: Yones and Hawk. Analysis and interpretation of data:
Yones and Palmer. *Drafting of the manuscript: Yones and Palmer. Critical revision of the manuscript for important intellectual content: Yones, Palmer, Garibaldinos, and Hawk.*

Statistical analysis: Yones and Palmer. *Obtained funding: Yones. Administrative, technical, and material support: Yones and Hawk. Study supervision: Hawk.*

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**REFERENCES**


**Correction**

**Error in Figure.** In the Study by Freeman et al titled “UV Tanning Advertisements in High School Newspapers,” published in the April issue of the ARCHIVES (2006;142:460-462), an editorial error was introduced by the journal in the Figure on page 461. In the Figure, the third box down should have read “37 With Newspapers” instead of “3 With Newspapers.” The corrected **Figure** is reproduced herein.

**Figure.** High school newspaper collection.

63 High Schools Telephoned

57 Accepted Contact by Telephone (3 Attempts)

37 With Newspapers

34 With Newspapers Accepting Commercial Advertisements

23 High Schools Provided Newspapers With Commercial Advertisements (n=131 Newspaper Issues)

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