

# Comparison of Oral Psoralen–UV-A With a Portable Tanning Unit at Home vs Hospital-Administered Bath Psoralen–UV-A in Patients With Chronic Hand Eczema

## *An Open-Label Randomized Controlled Trial of Efficacy*

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**Objective:** To study whether oral psoralen–UV-A (PUVA) with a portable tanning unit at home is as effective as hospital-administered bath PUVA in patients with chronic hand eczema.

**Design:** Open-label randomized controlled trial, with a 10-week treatment period and an 8-week follow-up period.

**Setting:** Two university hospital dermatology departments in the Netherlands, specializing in hand eczema.

**Patients:** One hundred fifty-eight patients with moderate to severe chronic hand eczema (more than 1 year in duration).

**Interventions:** Oral PUVA using methoxsalen capsules and a simple portable commercial facial tanning unit, or hospital-administered bath PUVA with trioxsalen.

**Main Outcome Measures:** The primary outcome was

clinical assessment by a hand eczema score (evaluation of desquamation, erythema, vesiculation, infiltration, fissures, itch, and pain, each on a 4-point scale) after 10 weeks of treatment. The secondary outcome was hand eczema score at 8 weeks of follow-up, after completion of treatment. The tertiary outcome was travel cost and time off work.

**Results:** Both groups showed a comparable and substantial decrease in hand eczema score (meaningful clinical improvement). This decrease was maintained during the follow-up period. Patients treated with oral PUVA at home had lower travel costs and less time off work.

**Conclusions:** Oral PUVA at home has a clinically relevant efficacy, similar to that of hospital-administered bath PUVA. This effect was maintained during an 8-week follow-up period. It resulted in lower travel costs and less time off work.

*Arch Dermatol.* 2004;140:1463-1466

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**Financial Disclosure:** None.

**T**HE TERM *HAND ECZEMA* implies an inflammation of the skin (dermatitis) that is confined to the hands. It tends to run a long-lasting and chronic relapsing course. Hand eczema is considered a common condition, with a 1-year prevalence of about 10% among adults in the general population.<sup>1,2</sup> It is more common in women than in men, with a female-male ratio of around 2.<sup>2,3</sup> The reasons for this sex difference are unknown, although the greater exposure of women to wet work is probably significant. Water is a contact irritant and thereby an exogenous factor contributing to hand eczema. An atopic diathesis is a major endogenous factor.<sup>4</sup>

Because of this high prevalence, most practicing dermatologists are consulted every day by patients with hand eczema, and

every day these dermatologists have to make a decision about the available treatment options. One treatment option is psoralen–UV-A (PUVA): administration of psoralen, either oral or local (as a hand-bath soak, or applied as a gel or cream), and subsequent irradiation with UV-A. The PUVA treatment is well established, and its efficacy in hand eczema has been demonstrated by randomized controlled trials.<sup>5-9</sup> Its effect results from inhibition of DNA synthesis due to photoadducts between psoralen and pyrimidine bases.<sup>10-12</sup>

The availability of cheap, portable UV-A tanning units, and the presumed convenience of PUVA treatment at home, with less interference in daily activities, less time off work, and less travel cost, prompted us to study the efficacy of this modality in comparison with conventional hospital-

administered bath PUVA among patients with chronic hand eczema. We expected to demonstrate equal clinical efficacy.

The protocol, including the dosage schedule, for the home PUVA treatment had been established as a successful modality in a large regional hospital with a specialized hand eczema clinic.

## METHODS

### INCLUSION AND EXCLUSION CRITERIA

In 2 university hospital outpatient clinics, all consecutive adult patients seen during an 18-month period who met the following criteria were eligible for randomization into the trial: (1) chronic bilateral or unilateral hand eczema of at least 1 year's duration, (2) at least 2 relapses or more than 3 consecutive weeks with visible signs in the last 3 months, and (3) moderate to severe hand eczema with a hand eczema severity score at the start of the study of at least 6 (sum of severity ratings of 0 to 3 on the following aspects of hand eczema: vesicles, erythema, desquamation, infiltration, fissures, itch, and pain; range, 0-21; higher score indicates more severe hand eczema).<sup>5</sup>

Exclusion criteria were as follows: (1) active eczematous lesions on other parts of the body; (2) unallowed concurrent medication, such as medication causing photosensitivity and anti-coagulants; (3) unallowed past medication, such as treatment with cytostatics or ionizing radiation or PUVA of the hands less than 6 months before the start of the study; (4) other forms of photosensitivity; (5) alcohol abuse; (6) liver dysfunction, renal dysfunction, congestive heart failure, hypertension, or epilepsy; (7) malignant or premalignant skin tumors; and (8) pregnancy or planning to become pregnant.

The patients' dermatologists enrolled the patients and referred them to one of the trial's dermatologists.

Written informed consent was obtained from all patients. This trial was approved by both hospitals' medical ethics committees and was conducted in compliance with the Declaration of Helsinki.

### RANDOMIZATION

On the basis of equal efficacy (not exceeding a 1-point difference),  $\alpha = .05$ ,  $\beta = .20$ , the sample size was calculated to be 140. Patients were randomly assigned by the trial's dermatologists to either of 2 treatments: 78 to oral PUVA at home (the "home" group) and 80 to hospital-administered bath PUVA (the "hospital" group). Computer-generated randomization lists with blocks of 4 were created by a secretary. Consecutive patients were given consecutive numbers on the list and randomized accordingly by the trial's dermatologists. The randomization sequence was kept concealed by the secretary until the end of the trial.

### TREATMENT

The home group received 30 irradiation treatments, thrice weekly for 10 weeks, 2 hours after oral ingestion of methoxsalen, 0.6 mg/kg. A UV-A facial tanning unit (Philips HB171 or HB172; light intensity, 9 mW/cm<sup>2</sup>; Royal Philips Electronics, Eindhoven, the Netherlands) at 15-cm distance and UV-protective eye goggles were used. The starting dose was 0.54 J/cm<sup>2</sup> (1 minute), increasing in 15 steps to a maximum of 8.1 J/cm<sup>2</sup> (15 minutes). To avoid toxic effects from sunlight, ingestion of methoxsalen and irradiation took place during the evenings. This procedure was performed by patients at home.

Detailed written instructions were given to the patients, who were instructed to mail on a weekly basis a form listing the irradiation dose they applied, as well as any side effects. When necessary, patients were contacted.

The hospital group received 20 biweekly irradiation treatments during 10 weeks, preceded by a 15-minute soak of the hands in a bath with trioxsalen, 0.2 mg/L. Subsequent UV-A irradiation of the hands was performed with a Waldmann PUVA 180 for the palms or a Waldmann PUVA 200 for the dorsa (Herbert Waldmann GmbH & Co KG, Villingen-Schwenningen, Germany). Starting dose depended on the minimal phototoxic dose or skin type, with a maximum of 0.59 J/cm<sup>2</sup>, and was increased in increments of 10% to 20%, depending on the individual's response, to a maximum dose of 20 J/cm<sup>2</sup>. Protection of the hands from sunlight was mandatory on the day of treatment. This procedure was performed by nurses at the outpatient clinic.

In both groups, only emollients were allowed as concomitant medication. Irrespective of the allocation to a treatment group, all patients received instruction and written information on hand care and avoidance of irritants.

### OUTCOME AND ASSESSMENT OF OUTCOME

Hand eczema severity was assessed by one of the unblinded trial's dermatologists (trained in assessment of hand eczema). Patients were examined on 6 occasions: at randomization (T1), at 3 weeks of treatment, at 6 weeks of treatment, at the end of the 10-week treatment period (T2), at 4 weeks of follow-up, and at 8 weeks of follow-up (T3).

The primary outcome was observer-rated clinical assessment by means of a hand eczema score (evaluation of desquamation, erythema, vesiculation, infiltration, fissures, itch, and pain, each on a 4-point scale)<sup>5</sup> after 10 weeks of treatment. The secondary outcome was hand eczema score at 8 weeks of follow-up after completion of treatment. The tertiary outcome was travel cost and time off work, which were analyzed separately.

### SAMPLE SIZE AND STATISTICAL ANALYSIS

The sample size of 158 patients was more than sufficient to ensure 80% power with an error risk of 5%. The statistical analysis was based on the intention-to-treat principle, using the "last value carried forward" method.

It was decided a priori that the observer-rated hand eczema scores in the 2 treatment groups at the end of the treatment would be compared by unpaired *t* test or, in case of a non-symmetric distribution, by a nonparametric test.

## RESULTS

### PATIENTS

A total of 158 patients, 88 men (56%) and 70 women (44%), were randomized during an 18-month period: 70 (44%) from Amsterdam and 88 (56%) from Groningen. Average age was 42 years (range, 18-70 years; SD, 14 years; SE, 1.1 years). After randomization, 78 patients (49%) were assigned to the home group and 80 (51%) to the hospital group. A participant flow chart is provided in the **Figure**, as recommended by the CONSORT (Consolidated Standards of Reporting Trials) statement.<sup>13</sup>

At the time of randomization (T1), the hand eczema score showed a normal distribution. The differences in hand eczema score between the groups at this point were

small and not statistically significant ( $P = .88$ ; 95% confidence interval [CI],  $-0.85$  to  $0.73$ ): home group, 8.1 (range, 6.0-17.0; 95% CI, 7.6-8.7); hospital group, 8.1 (range, 6.0-15.0; 95% CI, 7.5-8.7).

During the treatment period, 33 subjects (21%) dropped out: 15 in the home group and 18 in the hospital group ( $P = .66$ ; 95% CI,  $-0.17$  to  $0.11$ ). The difference in hand eczema score at T1 between those who dropped out in the treatment period (8.8; 95% CI, 7.9-9.8) and the remainder (7.9; 95% CI, 7.5-8.3) was small and not statistically significant ( $P = .057$ ; 95% CI,  $-0.027$  to  $1.9$ ). The dropouts in the hospital group had on average a higher, but not statistically significantly different, hand eczema score than those in the home group: 9.6 vs 8.0 ( $P = .09$ ; 95% CI,  $-0.24$  to  $3.4$ ). During the follow-up period, 8 additional subjects dropped out. Their mean hand eczema score at the end of treatment (T2) (4.9; 95% CI, 1.6-8.2) was comparable with the mean score of the remainder: 4.2 (95% CI, 3.6-4.8), with  $P = .60$  (95% CI,  $-1.9$  to  $3.2$ ). In addition, their effect of treatment (as expressed in mean reduction of hand eczema score from T1 to T2) was comparable: 3.3 (95% CI,  $-1.2$  to  $7.7$ ) vs 3.7 (95% CI, 3.0-4.4), with  $P = .75$  (95% CI,  $-2.3$  to  $3.2$ ). Additional features of the dropouts are presented in the "Comment" section.

Side effects occurred in both groups, such as temporary nausea in the home group and mild stinging in the hospital group. Only side effects that were a reason to discontinue were analyzed: 3 in the home group (all temporary nausea) and 1 in the hospital group (burn).

#### MAGNITUDE OF THE EFFECT

The average hand eczema score at T2 for the home group was 4.8 (95% CI, 3.9-5.6), and for the hospital group, 5.6 (95% CI, 4.7-6.4). The mean reduction in hand eczema score (clinical improvement) in the home group from T1 to T2, ie, during the treatment period, was 3.3 or 41% (95% CI, 2.4-4.1); the mean reduction for the hospital group was 2.5 or 31% (95% CI, 1.7-3.2). These reductions were statistically significant for both groups ( $P < .001$ ). In addition, there was no statistically significant difference between them ( $P = .15$ ; 95% CI,  $-0.31$  to  $2.0$ ).

Between T1 and T2, 56 (72%) of the subjects in the home group improved their hand eczema score (for the individual patients, the reduction ranged between 0.5 and 11 points). In the hospital group, this number was 49 (61%) (a range of 0.5-11 points of reduction).

An analysis of the outcome in the patients who completed the follow-up, ie, ignoring the intention-to-treat principle, gave similar results: a significant improvement in both treatment groups, without a significant difference between the groups.

#### FOLLOW-UP

Average hand eczema score at T3 for the home group was 5.0 (95% CI, 4.2-5.8), and for the hospital group, 5.4 (95% CI, 4.5-6.3). Between T2 and T3, the average hand eczema score barely changed: the home group showed an increase of 0.19 (95% CI,  $-0.57$  to  $0.94$ ), and the hospital group, a reduction of 0.19 (95% CI,  $-0.34$  to  $0.73$ ).

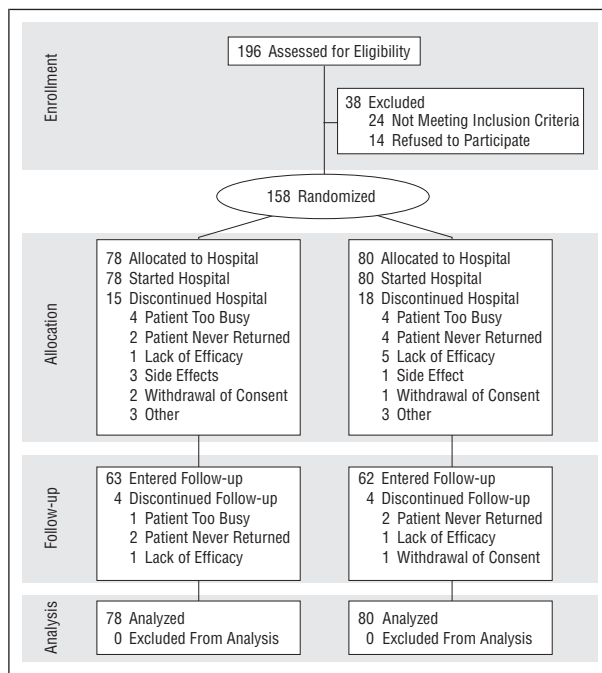


Figure. Participant flowchart.

These changes were not statistically significant for both groups: home group,  $P = .63$ ; hospital group,  $P = .48$ . In addition, there was no statistically significant difference between them ( $P = .41$ ; 95% CI,  $-1.30$  to  $0.54$ ). However, individual changes could be large. The range of change in hand eczema score was  $-16.0$  to  $11.0$  in the home group and  $-7.0$  to  $6.5$  in the hospital group. In the home group, 15 (19%) showed an improvement of more than 1 point, and 18 (23%) worsened more than 1 point. These numbers were 15 (19%) and 14 (18%), respectively, for the hospital group.

An analysis of our data without the intention-to-treat principle resulted in similar findings: on average, minimal changes occurred during the period between T2 and T3 for both groups. There were no statistically significant differences over time and between groups.

#### COMMENT

#### METHODS

Two articles, describing nonrandomized controlled trials, have dealt with UV treatment of hand eczema at home.<sup>14,15</sup> It has proved to be effective, safe, easy, and inexpensive. A self-performed telephone questionnaire among 37 private and university dermatology clinics in the Netherlands, mainly located in the Amsterdam and Groningen areas, disclosed that bath PUVA was used in 28 centers (76%). Therefore, bath PUVA was chosen as the comparator.

Blinding of the patient and the outcome assessor was not practically feasible: patients are aware of their treatment modality and assessors can easily identify a hand treated with bath PUVA because of its rim of pigmentation.

The irradiation dosages and schedules of the 2 groups were different; other (equal) dosages might have had a

different impact. Our aim, however, was to compare 2 established protocols, not the possible variants of dosage. The 20 hospital treatments and 30 hospital treatments were existing standard protocols for the treatment of hand eczema. In addition, in an unpublished pilot study we found that 30 home treatments had the same efficacy as 20 hospital treatments.

### DROPOUT RATES

The dropout rates between the groups were comparable. Also, no statistically significant differences could be found between dropouts and the remainder of the patients with regard to severity of hand eczema or effect of treatment. There were, however, differences in the reasons for dropping out. There was a higher dropout rate owing to a lack of efficacy in the hospital group (5 patients vs 1), and a higher rate in the home group because of side effects. The most frequently reported side effect was the well-known temporary nausea from ingestion of psoralens.<sup>16</sup> In addition, 1 patient experienced transient but severe influenzalike symptoms.<sup>17</sup> Treatment with PUVA can cause burning of the skin; this was a reason to discontinue treatment for 1 patient in the hospital group. We believe the dropout rate does not impair the ability to extend the findings of the study to a larger population. First, the dropout rates of both groups were comparably high. Second, we performed an intention-to-treat analysis, which, with regard to the efficacy measures, did not change our results.

### EFFICACY

In comparing hospital-administered bath PUVA with oral PUVA at home, both had a similar decrease in hand eczema score (clinical improvement) at the end of treatment. This effect was maintained during an 8-week follow-up period after completion of the treatment. The decrease in eczema severity score can be considered clinically relevant, because it was substantial and because it resulted in a lower hand eczema score than was required for inclusion in the trial (the threshold). In addition, patients treating themselves at home had substantially lower travel costs and substantially less time off work.<sup>18</sup>

### CONCLUSIONS

This study has demonstrated the efficacy of oral PUVA at home with the use of methoxsalen capsules and a portable commercial facial tanning unit, during a 10-week treatment period and an 8-week subsequent follow-up period. By performing treatment in the evening, the methoxsalen-associated sensitivity to sunlight was avoided. Its efficacy was comparable with that of the routinely practiced hospital-administered bath PUVA with

trioxsalen. In addition, oral PUVA at home resulted in substantially lower travel costs and substantially less time off work.<sup>18</sup>

Accepted for Publication: June 30, 2004.

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Funding/Support: This study was supported in part by the Netherlands Healthcare Insurance Board, Amstelveen, the Netherlands.

Acknowledgment: H. B. van der Walle, MD, PhD, Rijnstate Hospital, Arnhem, the Netherlands, pioneered the use of the portable UV-A facial tanning unit.

### REFERENCES

1. Meding B, Swanbeck G. Prevalence of hand eczema in an industrial city. *Br J Dermatol*. 1987;116:627-634.
2. Meding B, Järvholm B. Hand eczema in Swedish adults: changes in prevalence between 1983 and 1996. *J Invest Dermatol*. 2002;118:719-723.
3. Meding B, Swanbeck G. Epidemiology of different types of hand eczema in an industrial city. *Acta Derm Venereol*. 1989;69:227-233.
4. Coenraads PJ, Diepgen TL. Risk for hand eczema in employees with past or present atopic dermatitis. *Int Arch Occup Environ Health*. 1998;71:7-13.
5. Rosén K, Mobacken H, Swanbeck G. Chronic eczematous dermatitis of the hands: a comparison of PUVA and UVB treatment. *Acta Derm Venereol*. 1987;67:48-54.
6. Sheehan-Dare RA, Goodfield MJ, Rowell NR. Topical psoralen photochemotherapy (PUVA) and superficial radiotherapy in the treatment of chronic hand eczema. *Br J Dermatol*. 1989;121:65-69.
7. Grattan CEH, Carmichael AJ, Shuttleworth GJ, Foulds IS. Comparison of topical PUVA with UVA for chronic vesicular hand eczema. *Acta Derm Venereol*. 1991;71:118-122.
8. Simons JR, Bohnen IJWE, Van der Valk PGM. A left-right comparison of UV-B phototherapy and topical photochemotherapy in bilateral chronic hand dermatitis after 6 weeks' treatment. *Clin Exp Dermatol*. 1997;22:7-10.
9. Grundmann-Kollmann M, Behrens S, Peter RU, Kerscher M. Treatment of severe recalcitrant dermatoses of the palms and soles with PUVA-bath versus PUVA-cream therapy. *Photodermatol Photoimmunol Photomed*. 1999;15:87-89.
10. Musajo L, Lodighiero G, Dall'Aqua F. Evidences of a photoreaction of the photosensitizing furocoumarins with DNA and with pyrimidin nucleosides. *Experientia*. 1965;21:24-25.
11. Baden HP, Parrington JM, Delhanty JDA, Pathak MA. DNA synthesis in normal and xeroderma pigmentosum fibroblasts following treatment with 8-methoxy-psoralen and long wave ultraviolet light. *Biochim Biophys Acta*. 1972;262:247-255.
12. Walter JF, Voorhees JJ, Kelsey WH, Duell EA, Arbor A. Psoralen plus black light inhibits epidermal DNA synthesis. *Arch Dermatol*. 1973;107:861-865.
13. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet*. 2001;357:1191-1194.
14. Epstein E. Home PUVA treatment for chronic hand and foot dermatoses. *Cutis*. 1989;44:423-427.
15. Sjövall P, Christensen OB. Treatment of chronic hand eczema with UV-B Handy-lux in the clinic and at home. *Contact Dermatitis*. 1994;31:5-8.
16. Wolff K, Fitzpatrick TB, Parrish JA, et al. Photochemotherapy for psoriasis with orally administered methoxsalen. *Arch Dermatol*. 1976;112:943-950.
17. Van Coevorden AM, Coenraads PJ. Severe influenzalike symptoms associated with methoxsalen photochemotherapy. *Arch Dermatol*. 2002;138:840-841.
18. Van Coevorden AM, Coenraads PJ, Stant AD, Duizendstraal A. *Thuisbehandeling van handeczeem met PUVA (THP)*. Diemen, the Netherlands: Healthcare Insurance Board; 2002. Report No. VAZ/CVZ 99252.