UV-B Phototherapy Clears Psoriasis Through Local Effects

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Objective: To determine if UV-B phototherapy clears psoriasis through systemic effects.

Design: Randomized, within-subject comparison of change in psoriasis in 3 plaques in patients attending for whole-body UV-B therapy. Change in patients’ psoriasis plaques covered during UV-B treatment was compared with plaques in an untreated control group.

Setting: University hospital phototherapy unit.

Patients: The study population comprised 17 patients with chronic plaque psoriasis treated with UV-B and 24 psoriasis control patients awaiting UV-B phototherapy.

Interventions: Treatment with a standard 3-times weekly narrowband TL-01 UV-B regimen. Three similar plaques were randomly allocated to be covered every treatment, covered for 2 of 3 weekly treatments, and exposed to local UV-B every treatment. Similar plaques were selected in control patients (awaiting but not yet started UV-B therapy). Severity of psoriasis plaques was assessed using a scaling, erythema, and induration (SEI) scoring system.

Main Outcome Measures: Change in SEI score of the selected plaques over the complete treatment course for UV-B–treated patients and change over 3 weeks in SEI score of plaques covered during UV-B treatment compared with that of plaques in controls.

Results: There was a significant ($P < .001$) difference in how much the SEI score changed in the 3 plaques in UV-B–treated patients. It fell by a mean of 7.6 for uncovered plaques compared with 3.2 for plaques covered during each UV-B exposure (95% confidence interval for difference, 3.0 to 5.8). In patients awaiting UV-B, SEI score of plaques fell by a mean of 0.4 over 3 weeks, compared with a mean fall of 1.4 for covered plaques in UV-B–treated patients (95% confidence interval for difference in means, 0.1 to 2.0).

Conclusions: If UV-B therapy has any systemic effect capable of improving psoriasis, this effect is small and unlikely to be of clinical importance. It is insufficient to alter interpretation of findings of within-subject comparative phototherapy studies. UV-B phototherapy works for chronic plaque psoriasis through local effects.

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Does UV-B phototherapy clear psoriasis through direct local effects, systemic effects, or a combination of both? The answer to this has implications for the interpretation of within-individual comparisons of different phototherapy regimens. It should also contribute to our attempts to understand how UV-B works.

Conceivably, UV-B may work to clear psoriasis on sites not directly irradiated. Ultraviolet B has various effects on parameters of immune function detectable in the circulating blood. Whole-body broadband UV-B treatment of humans has effects on the function of blood neutrophils, and narrowband TL-01 UV-B reduces circulating natural killer cell activity. In mice, systemic inhibition of induction of delayed type hypersensitivity appears to be mediated by UV radiation–induced interleukin 10 release. According to findings from laboratory studies, UV-B may have anti-inflammatory effects resulting from the release of neuropeptides from the skin into the circulation. In healthy human volunteers, systemic effects of UV-B on nonimmunological responses to benzoic acid and methyl nicotinate have been reported. Also, increased activity of interleukin 6 and tumor necrosis factor α may be important in systemic symptoms associated with sunburn, and therapeutic broadband UV-B leads to increased interleukin 1 activity. Such demonstrated systemic effects could possibly be relevant in psoriasis clearing.

Other treatments have been reported to have a systemic effect on psoriasis clear-
PARTICIPANTS AND METHODS

STUDY PROTOCOL

Design and Patients

This study was a prospective, randomized, controlled, interventional study approved by the Tayside Committee on Medical Research Ethics. Consecutive patients with chronic plaque psoriasis referred to the phototherapy unit at Ninewells Hospital and Medical School (a university hospital serving Tayside, Scotland) between April 1998 and June 2000 were invited to participate. Exclusion criteria were age younger than 18 years; a history of skin cancer or solar keratoses; or phototherapy, psoralen–UV-A therapy, or systemic therapy for psoriasis within the preceding 3 months. The enrollment criteria for patients treated with phototherapy during the study and the concurrently recruited control group (awaiting but not yet started phototherapy) were identical.

Treatment Regimen

Ultraviolet B phototherapy was administered according to our standard regimen. The starting dose was 70% of each individual’s minimal erythema dose, with 20% increments, reduced to 10% according to erythemal response. Either a Waldmann UV5000 cabinet (Herbert Waldmann GmbH & Co KG, Villingen-Schwenningen, Germany) fitted with 24 Philips 100W TL-01 lamps (Philips, Eindhoven, the Netherlands) or a cabinet constructed at the Ninewells Medical Physics Department with 50 Philips 100W TL-01 lamps was used.

Adjunctive therapy was limited to emollients known not to significantly impede UV transmission and standard topical treatments for scalp, face, and flexures. End points for stopping therapy were, as in our routine practice, clearance (no palpable psoriasis remaining) or “minimal residual activity,” defined as trace disease, below knees or on sacrum only. To give all patients a chance of achieving complete clearance, treatment was stopped either at clearance or after the fourth treatment at which minimal residual activity was documented, whichever came first. The control patients awaiting phototherapy were permitted the same topical therapy (emollients and scalp and flexure treatments) as those treated with UV-B.

Study Interventions

For the group attending for phototherapy, 3 similar plaques on the trunk or limbs were selected before treatment was started. Only plaques above the knees were selected on lower limbs. These were assessed for scaling, erythema, and induration scores (see “Outcome Measures”) and randomly allocated (as described under “Assignment”) to the following interventions: 1 was covered with Tegaderm dressing (3M Health Care, St Paul, Minn) with backing kept on (which allowed no UV radiation transmission when assessed with Hitachi U-3210 [Tokyo, Japan] double-beam reflectance spectrophotometer) during each treatment, 1 was kept uncovered (ie, exposed normally during treatment), and 1 was covered for 2 of the 3 treatments delivered each week (and treated independently following the same standard regimen as for whole-body exposure). This once-weekly exposed plaque was included because we hypothesized that systemic effects might only significantly influence psoriasis clearing in conjunction with some “priming” UV-B exposure.

For the control group, a single plaque, similar to the selected plaques in the patient group receiving phototherapy, was chosen in each of 24 patients referred for, but not yet receiving, phototherapy. Topical therapies for these patients were limited to the same preparations as were allowed for the phototherapy patient group. Scaling, erythema, and induration score for this plaque was recorded at baseline and 3 weeks later (or as soon after as feasible).

Outcome Measures

The within-patient study design (ie, comparing one phototherapy regimen to one area [usually half] of each patient’s body with another regimen to another area) has been widely used to compare different TL-01 UV-B regimens and to compare TL-01 UV-B with other phototherapies. This design has the major advantage of ensuring that all variables that might influence clearing of psoriasis, apart from the one being studied, are the same. However, if TL-01 UV-B exerts an important systemic effect on psoriasis clearance, even if this effect might only be apparent in psoriasis that also receives some local UV radiation, it is possible that the results of some of these studies were misleading. For example, following a comparison of 3-times weekly with 5-times weekly TL-01 UV-B treatment for psoriasis, we favored 3-times weekly treatment, but could a systemic effect of the 5-times weekly treatment to 1 body half have aided clearing on the 3-times weekly side?

RESULTS

PARTICIPANT FLOW AND FOLLOW-UP

Seventeen patients attending for UV-B phototherapy and 24 control patients awaiting phototherapy participated in the present study (Table). All those attending for UV-B phototherapy completed the study. Of the control patients, 5 did not complete the study: 3 withdrew (1 to start UV-B immediately, 1 used a coal tar solution cream, 1 moved and started UV-B therapy elsewhere), and 2 did not have their selected plaques assessed at their second (pre-UV-B therapy) visit.

Phototherapy patients and controls were similar in age, sex ratio, and skin phototypes (Table). Within these...
indicated by the almost identical treatment numbers and groups, the psoriasis responded to a similar degree, as clear by the end of most patients each treatment and neighboring exposed psoriasis was evidenced in clinical appearance of psoriasis covered during treatments per week, or exposed during treatment). The mean plaques (covered during treatment, covered for 2 of 3 treatments vs plaques covered vs plaques not covered during UV-B. Variation (SD, 1.3) of within-patient difference in amount of change in SEI score was derived from an 8-patient pilot study. For the within-patient comparisons, repeated measures analysis of variance was used to look for any difference across the 3-plaque treatment allocation groups. This was followed by the Tukey wholly significant difference pairwise comparison procedure, using the variance measure derived from the analysis of variance model. For the comparisons between patients (covered phototherapy patient plaques and untreated patient plaques), the unpaired t test was used. Not all control patients were assessed at exactly 3 weeks, and therefore we corrected SEI scores to those that would have been expected at 3 weeks after baseline, assuming that the rate of change for each plaque would follow the slope of a simple linear regression model (based on all the control patient plaque scores at the second visit plotted against days since baseline). When comparing demographic and treatment course data for the phototherapy patients and control (awaiting phototherapy) patients, the \( \chi^2 \) test and the unpaired t test (with log transformation when appropriate to ensure approximation to a Gaussian distribution and using the Satterthwaite method when the requirement for equality of variances was not met) were used. Stata (Intercooled Stata for Windows, release 7; Stata Corp, College Station, Tex, 2001) statistical software and a user-written macro for pairwise comparisons were used.

**Analysis and Statistical Methods**

The main end points were based on change in SEI scores for the selected plaques. We planned to compare the amount of change from baseline to end of treatment course between the 3 within-patient selected plaques and compare the change over 3 weeks between the selected control patient plaques and the plaques covered during UV-B treatment. A secondary end point was comparison of area under the psoriasis severity score time curves for plaques covered every treatment, covered for 2 treatments per week (ie, exposed to local irradiation only once weekly), and plaques exposed normally during treatments 3-times weekly.

We estimated that we would require at least 16 patients to have 90% power to detect (as significant at the 5% level) a difference of 1.5 in mean change in SEI score for plaques covered vs plaques not covered during UV-B. Variation (SD, 1.3) of within-patient difference in amount of change in SEI score was derived from an 8-patient pilot study. For the within-patient comparisons, repeated measures analysis of variance was used to look for any difference across the 3-plaque treatment allocation groups. This was followed by the Tukey wholly significant difference pairwise comparison procedure, using the variance measure derived from the analysis of variance model. For the analysis of treatment courses in the 3–times weekly exposed plaques (95% CI, −0.8 to 2.0). The markedly greater decline in mean SEI score throughout the treatment courses in the 3–times weekly exposed plaques compared with the covered and once-weekly–exposed plaques is shown in Figure 3.

**Control Group**

Initial comparison of change in SEI score over 3 weeks for covered plaques in phototherapy patients with change from baseline to second assessment (≥3 weeks [mode, 3½ weeks; median, 4 weeks]) for control patient plaques showed no significant difference. The mean score for covered plaques in phototherapy patients fell by 0.4 (95% CI, −0.4 to 1.3) more than the mean control patient plaque score. When the change in score for control plaques was corrected (to allow a fairer comparison, since control plaques were assessed at intervals up to a maximum of 7 weeks after initial assessment), the difference remained small and of no likely clinical importance, although it was unlikely to have occurred by chance. The mean SEI score...
for covered plaques in phototherapy patients fell by 1.0 (95% CI, 0.1-2.0) more than it fell over 3 weeks in control patient plaques (Figure 4).

There were no differences in variables that might influence response of the 3 plaques in patients receiving phototherapy. Prognostic features attributable to the patient as a whole were of course identical, and by random allocation of intervention to the individual plaques, we minimized the possibility that the plaques (allocated to any 1 of the 3 interventions) would be expected to be more or less likely to improve. We attempted to ensure that the plaques in control patients would have similar prognostic variables to the covered plaques in the pho-

Figure 1. Within-subject comparisons in phototherapy patients (n=17). Change in scaling, erythema, and induration (SEI) score (from beginning to end of UV-B course) in plaques covered during UV-B, plaques exposed once weekly only, and plaques exposed normally 3 times weekly. The hatched line indicates mean change in SEI score.

Figure 2. This photograph, taken at end of treatment course, shows the clear cutoff in clearing response to UV-B therapy between part of plaque directly exposed (E) and covered plaque (C).

Figure 3. Mean scaling, erythema, and induration (SEI) score at each weekly assessment of plaques in 17 patients receiving UV-B therapy. AUC indicates area under the psoriasis severity time curves, which were calculated separately for each individual’s selected plaques.

Figure 4. Change in scaling, erythema, and induration (SEI) score over 3 weeks (with correction of scores to 3-week values for control patients who were assessed later than 3 weeks) in plaques covered during UV-B treatment in phototherapy patients compared with that in plaques in control patients awaiting UV-B treatment. The hatched line indicates mean change in SEI score.
totherapy patients by selecting a control group of patients referred for phototherapy for chronic plaque psoriasis, that is, a group expected to have similarly severe psoriasis. In practice, this group showed similar responses to treatment when they received phototherapy after the study (Table).

The present study has shown that narrowband TL-01 UV-B phototherapy does not have a clinically important systemic effect contributing to its ability to clear psoriasis. It also showed that once-weekly treatment for up to 10 weeks has little effect on psoriasis. If, as we had hypothesized, UV-B therapy cleared psoriasis through a combination of systemic effects and minor local exposure, then we would have expected a much greater reduction of psoriasis severity in the once-weekly-treated plaque. Incidentally, this study makes it clear that once-weekly treatment of psoriasis would be inappropriate; even if once-weekly treatment might eventually clear psoriasis, it would be unacceptably slow.

To our knowledge, there has been no previous study attempting to determine whether systemic effects of UV-B, or any other form of phototherapy, contribute to psoriasis clearance. One earlier study assessed the possible systemic effect of dithranol treatment.11 That study did not include a control group, although the magnitude of improvements in plaques not directly treated suggested a systemic effect, possibly related to effects resulting from clearing of psoriasis elsewhere rather than directly due to dithranol application. We included a control group in our study because we expected some improvement in the study plaques, regardless of the presence or absence of systemic UV-B effects. Such improvement, as observed in the covered plaques of the phototherapy patients in our study (Figure 3), was expected as a result of the following:

- The regression to the mean phenomenon. These patients were all seen when their psoriasis was likely to be worse than usual (to enter the study they had to have sufficiently severe psoriasis to require referral for UV-B). We could anticipate, regardless of any medical intervention, a fall in psoriasis severity from baseline as a result of simple random fluctuation in severity with a downward tendency toward the mean population severity.
- The effects of allowed treatment other than UV-B, that is, the emollients and the encouragement to apply these and possibly the psychological support associated with 3-times weekly attendance.

We aimed to recruit a control group with similar psoriasis to those attending for phototherapy. This meant asking patients with chronic plaque psoriasis referred for UV-B phototherapy to participate. We considered it inappropriate to withhold treatment from such patients for 10 weeks (the maximum duration of a normal treatment course). So, we did not recruit the ideal comparison group of patients requiring, but not yet receiving, UV-B therapy and willing to be treated with emollients alone, while attending for review 3-times weekly for 10 weeks. Although it would have been possible to recruit patients with psoriasis not requiring UV-B as such a control group, it would not have been appropriate. Such patients might be expected to have milder psoriasis and more likely to respond well to emollients and encouragement of regular review alone, so use of such a control group might have hidden a systemic effect of UV-B on the plaques of patients attending for phototherapy. Our compromise was to ensure our control group was similar by recruiting those referred for UV-B therapy, but accepting that we could only ask them to do without treatment for 3 weeks (not unreasonable, since we then had such a waiting list to start treatment) and not insisting on them making extra visits 3 times weekly while not being treated.

As not all control patients were assessed at 3 weeks, we corrected their second SEI score to that expected at 3 weeks, making the assumption that control patient plaques showed an equal rate of decline in SEI score. If we did not do this and compared the change over 3 weeks in phototherapy patients, there would be no significant difference, but with correction for the fact that several control patients had longer than 3 weeks to improve, the SEI score fell significantly more in the covered plaques of UV-B treated patients. However, it should be noted that this difference in fall in SEI scores was small, and although unlikely to be a chance finding, was not large enough to be clinically important. It is probable that such a small difference in decline in SEI score can be explained by the fact that the patients receiving phototherapy were encouraged to apply emollients during their 3-times weekly visits, while the controls were not. It remains possible that a systemic UV-B effect contributed to this slightly greater improvement in the covered UV-B–treated patient plaques, but such an effect would have to be minor.

We conclude that UV-B has no clinically important systemic effect on psoriasis clearance and that the possibility of what seems to be at most a minor systemic effect should not influence our interpretation of within-subject study comparisons of UV-B phototherapy regimens for psoriasis. Ultraviolet B phototherapy works for psoriasis through local effects.

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