A Randomized Comparison of Methods of Selecting Narrowband UV-B Starting Dose to Treat Chronic Psoriasis

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Objectives: To compare narrowband UV-B (TL-01 lamp) phototherapy for psoriasis with individual patient starting doses based on minimal erythema dose (MED) determination vs a standard fixed starting dose and to compare the efficacy of 70% of MED vs 50% of MED starting dose regimens.


Setting: Department of Dermatology, Ninewells Hospital and Medical School, Dundee, Scotland.

Patients: A total of 210 adult patients (207 of skin phototypes I to III) referred for narrowband UV-B to treat chronic psoriasis. The study was designed to have 90% power to detect a difference of 3 or more treatments to clearance and/or minimal residual activity (MRA) between groups.

Interventions: Narrowband UV-B phototherapy was given according to 3 standard regimens, differing only by starting dose selection method. The randomly allocated starting doses were (1) a fixed starting dose, (2) 70% of individual MED, and (3) 50% of individual MED. All patients were MED tested to ensure blinding and for safety reasons.

Main Outcome Measures: The number of treatments to clearance and/or MRA of psoriasis was the primary efficacy outcome measure, with changes in Psoriasis Area and Severity Index and Psoriasis Disability Index scores as secondary measures. Adverse effects were recorded.

Results: There were no significant differences in the number of treatments to clearance and/or MRA across all 3 groups or in the percentages achieving clearance in each group. More uncomfortable erythemas occurred in the 50% of MED starting dose group (39%) than in the 70% of MED starting dose group (24%) or the fixed starting dose group (24%) (P = .07).

Conclusions: The methods of determining the starting dose in this predominantly skin phototype I and II population, treated 3 times weekly, with a 20% followed by 10% incremental reduction in dose, did not significantly influence the effectiveness of treatment. Had there been a clinically important difference in efficacy, we would have expected to identify this. Thus, basing starting dose on individual MED assessments may not influence the treatment’s efficacy in a skin phototype I to III population, although it remains important for patient safety. It remains possible that in populations containing individuals with a broader range of erythemal sensitivity, basing the starting dose on MED testing could have an important impact on treatment effectiveness.

Trial Registration: isrctn.org Identifier: ISRCTN84614024


WHEN TOPICAL THERAPIES alone are insufficient, the standard next-line therapy for psoriasis in many centers is narrowband UV-B (NB–UV-B). This is more effective than broadband UV-B sources, even with a treatment regimen intended to be suberythema- genic. An individual patient assessment of threshold eryhemogenic dose, the minimal erythemal dose (MED), is frequently used to guide the NB–UV-B starting dose. This ensures that the starting dose is not too high and identifies patients with previously unsuspected severe photosensitivity, as well taking into account possible drug-induced photosensitivity. However, it is not known whether the method of determining the starting dose influences treatment efficacy. In our predominantly skin phototype I to III population, we have previously examined some aspects of treatment methodology. Based on these studies
addressing different methodological aspects of NB–UV-B phototherapy (Table 1). Our standard regimen to treat psoriasis is now a 3-times-weekly treatment with a 20% followed by a 10% incremental reduction in dose after an MED-based starting dose.

A test exposure of a small area is an uncontroversial safety measure. However, whether basing the starting dose on MED measurement influences treatment efficacy is unknown. In general, skin phototype–based starting doses tend to risk being “too low” for the majority in order to minimize the risk of developing erythema in a minority of patients after the first dose. An Austrian study compared 2 different starting doses: 35% of MED vs 70% of MED. The authors of this half-body comparison concluded that because the lower starting dose regimen cleared psoriasis with a median of “only” 4 extra treatments, there was no important advantage in using the higher starting dose. However, the allocated treatments were only continued until there was a “marked clinical difference” between body halves, and thereafter the 2 treatment regimens were gradually “equalized” by increasing the dose on the body half treated with the lower starting dose until it reached that of the other side. That leaves open the possibility that had each regimen been continued until clearance and/or minimal residual activity (MRA), a greater difference in efficacy might have been detected.

A survey compared outcomes of phototherapy in a hospital where an MED-based starting dose was used with outcomes in a hospital where a skin phototype–based starting dose was used. No major differences were detected, but additional factors other than starting dose selection method were likely to have affected outcomes. Another nonrandomized study, also reported in an abstract only, suggested that an MED-based starting dose might make treatment more effective, with a mean of 26 treatments required in the MED-based starting dose group compared with a mean of 29 treatments in the skin type–based starting dose group (95% confidence interval [CI] around this mean difference of 3 treatments from −2 to 8 treatments; P = .25).

We performed a randomized, quadruple-blinded (patient, assessor, treatment nurse, and data analyst) parallel group comparison of NB–UV-B given according to a standard regimen (3 times weekly, with a 20% followed by a 10% incremental reduction) but with 3 different methods of allocating the starting dose: (1) 70% of MED starting dose (70% MED), (2) 50% of MED starting dose (50% MED), or (3) a fixed starting dose (non–MED-based) for all skin phototype I to IV patients. Our main aim was to compare efficacy of the different regimens.

### METHODS

#### PATIENTS

All patients referred for NB–UV-B phototherapy for chronic (lasting >1 year) psoriasis from our catchment area were considered for inclusion. Age younger than 16 years and receipt of systemic immunosuppressant therapy or retinoids within the preceding 3 months were exclusion criteria. The study was approved by the Tayside Committee on Medical Research Ethics and followed the protocol considered by NHS Tayside Research and Development.

#### STUDY INTERVENTIONS (CHOICE OF STARTING DOSES)

The MED-based starting doses were selected on the basis that both are frequently used. The choice of 140 mJ/cm² as the non–MED-based starting dose was based on this being the dose used for all skin phototype I to IV patients attending 2 phototherapy centers in Scotland that did not then conduct MED test-

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**Table 1. Randomized Studies Comparing Different Intensity Regimens of Narrowband UV-B for Psoriasis**

<table>
<thead>
<tr>
<th>Source</th>
<th>More-Intense Regimen</th>
<th>Less-Intense Regimen</th>
<th>Efficacy</th>
<th>Important Erythema Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hofer et al, 1998</td>
<td>Starting dose at 70% of MED, 40% → 10% incremental reduction</td>
<td>Starting dose at 35% of MED, 40% → 10% incremental reduction</td>
<td>More-intense regimen achieved “satisfactory” response with a median of 4 fewer treatments</td>
<td>Not reported</td>
</tr>
<tr>
<td>Dave et al, 1998</td>
<td>Starting dose at 70% of MED, 5 × weekly, 20% → 10% incremental reduction</td>
<td>Starting dose at 70% of MED, 3 × weekly, 20% → 10% incremental reduction</td>
<td>More-intense regimen achieved clearance and/or MRA more quickly but with more treatments</td>
<td>15 Of 16 patients experienced uncomfortable erythema episodes with a more-intense regimen compared with 3 or 16 with a less-intense regimen</td>
</tr>
<tr>
<td>Wainwright et al, 1998</td>
<td>Starting dose at 70% of MED, 40% → 20% incremental reduction</td>
<td>Starting dose at 70% of MED, 20% → 10% incremental reduction</td>
<td>Median number of treatments to clearance and/or MRA marginally (but P &lt; .005) fewer with more-intense regimen</td>
<td>3 Times as many uncomfortable erythemas with the more-intense regimen</td>
</tr>
<tr>
<td>Cameron et al, 2002</td>
<td>Starting dose at 70% of MED, 3 × weekly, 20% → 10% incremental reduction</td>
<td>Starting dose at 70% of MED, 2 × weekly, 20% → 10% incremental reduction</td>
<td>More-intense regimen cleared psoriasis in two-thirds the time it took with the less-intense regimen</td>
<td>25% (95% CI, 7%-43%) More patients treated with the more-intense regimen had at least 1 well-demarcated erythema episode Not reported</td>
</tr>
<tr>
<td>Kleinpenning et al, 2009</td>
<td>Starting dose at 70% of MED, then 40% increments, 3 × weekly</td>
<td>Starting dose 35% of MED, then 20% increments, 3 × weekly</td>
<td>Mean 3.5 (95% CI, 0.5-6.5) fewer treatments to achieve PASI 90% with the more-intense regimen</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; MED, minimal erythemal dose; MRA, minimal residual activity; PASI, Psoriasis Area and Severity Index.
ing. We routinely perform MED testing for patient safety reasons, so we considered that we could not withhold this testing from study participants. Also, such testing of all study patients was necessary to ensure blinding (see “Blinding” subsection in this section). Our phototherapy nurses could not ethically expose patients to doses that might risk uncomfortable erythema, so patients allocated to a 140 mJ/cm² starting dose were instead treated with approximately 90% (rounded to nearest est value that patients in the 50% or 70% MED groups could receive, to help ensure blinding) of their MED if 140 mJ/cm² was greater than 90% of their individual MED.

RANDOMIZATION AND CONCEALMENT OF RANDOM ALLOCATION

A blocked (with variable block size) random allocation sequence was generated by computer using "ralloc" user-written command implemented in Stata 8 statistical software (StataCorp, College Station, Texas). The allocation interventions (method of determining starting dose) were concealed in sequentially numbered opaque envelopes.

BLINDING

Patients, phototherapy nurses, and physicians were all kept blind to treatment allocation. Part of this blinding process involved MED assessments for all patients to ensure that they had MED test sites visible on their backs. When results were analyzed, the treatments were coded to ensure that the person analyzing the data did not know the nature of each intervention.

NB–UV-B PHOTOTHERAPY REGIMEN

Narrowband UV-B was given according to our standard protocol (Photonet [Scottish Managed Clinical Network for phototherapy] protocol for treatment of psoriasis with NB–UV-B, http://www.photonet.scot.nhs.uk/documents/pdf/treatment_protocols_june08.pdf), with a 20% incremental reduction after the starting dose (followed by a 10% incremental reduction and no reduction depending on erythema responses), apart from the starting dose that was allocated randomly. Concomitant therapy with emollients, as per standard practice, was encouraged. Other concomitant topical treatments were limited to scalp and flexures.

MED TESTING

The NB–UV-B MED was determined for all patients, including for the non–MED-based treatment group. Minimal erythemal dose testing was routinely performed on back skin, but if this was not possible (because of extensive psoriasis) it was performed on forearm skin. Doses administered were 25, 50, 70, 100, 140, 200, 280, and 390 mJ/cm² for skin phototypes I and II, and for skin phototype III patients the first 2 doses of this series were omitted and doses of 350 and 770 mJ/cm² added. The MED was taken as the lowest dose that produced just-perceptible erythema at 24 hours.

EQUIPMENT AND DOSIMETRY

Treatment was delivered in either a Waldmann UV 5000 cabinet (Herbert Waldmann GmbH, Villingen-Schwenningen, Germany) fitted with 24 Philips 100-W TL01 lamps (Koninklijke Philips Electronics NV, Eindhoven, the Netherlands) or a Ninewells Medical Physics Department–constructed cabinet fitted with 50 Philips 100-W TL01 lamps was used. Minimal erythema dose testing irradiations were delivered with a separate calibrated bank of TL01 lamps, with a UV-impermeable cloth template used to expose different MED test dose site squares. Dosimetry was determined through monthly irradiance measurement using an IL1400A meter (International Light Inc, Newburyport, Massachusetts) calibrated for NB–UV-B irradiation in our Photobiology Unit’s optical radiation laboratory.

ASSESSMENTS

The main outcomes were based on standard assessment of clearance and/or MRA and routine recording of grades of erythema. In our unit MRA is defined as “trace disease, below knees or on sacrum only.” To give all patients a chance of achieving complete clearance, treatment was stopped at either clearance or after the fourth treatment at which MRA was documented, which ever came first. We also assessed the Psoriasis Area and Severity Index (PASI) score (based on scaling, erythema, and induration and estimated skin surface affected by psoriasis) at baseline (before first treatment), at the 15th treatment, and at the end of the treatment course. The Psoriasis Disability Index (PDI) was used as a measure of disease-related quality of life.

STATISTICAL ANALYSIS

Selection of Sample Size

We estimated (based on raw data of a previous study in our center) that 70 patients in each group would give 90% power to detect a mean difference of 3 or more treatments to clearance and/or MRA between 2 regimens.

Analysis of Study Results

The main outcomes of interest were, first, comparison of the 2 MED-based regimens and then comparison of MED regimens with the non–MED-based regimen. Analyses were performed on an intention-to-treat (as randomized) approach except when otherwise specified. The primary outcome measure was taken as number of treatments to clearance and/or MRA as determined by treating nurses blind to treatment group. Statistical comparisons were conducted within the framework of a Cox proportional hazards regression model. Secondary outcome measures were proportions of patients in each group reaching clearance and/or MRA and change in disease-related quality of life (measured by PDI). Exploratory outcome measures were proportions of patients reaching a 75% reduction in PASI (PASI 75) and a 90% reduction in PASI (PASI 90). As the primary adverse effect outcome measure we compared frequency of episodes of uncomfortable and painful erythema across the different starting dose allocation groups. P<.05 was considered statistically significant. Statata statistical software (StataCorp) versions 8 to 10 was used.

RESULTS

PATIENT FLOW THROUGH STUDY

A total of 210 patients entered the study between December 2003 and October 2007 (Figure 1). Most (74%) potential study participants who were approached participated, making up 30% (210 of 704) of patients starting whole-body NB–UV-B treatment for psoriasis in our Ninewells Hospital Photobiology Unit during this period.

As shown in Figure 1, of the 70 patients allocated to the non–MED-based starting dose (140 mJ/cm²), 16 were in fact treated with a lower starting dose than the fixed
Dose, for ethical reasons, as required by our study protocol. Of these 16 patients, 9 started treatment at 100 mJ/cm², 6 at 70 mJ/cm², and 1 at 50 mJ/cm².

One non–MED-based starting dose patient was found to have an MED below the lowest MED test dose (25 mJ/cm²), and this dose caused erythema and edema at the test site. Subsequent investigation showed that he had chronic actinic dermatitis.

TABLE 2. Basic Demographic Data of Participating Patients in Each Study Group

<table>
<thead>
<tr>
<th>Starting Dose Group</th>
<th>70% of MED</th>
<th>50% of MED</th>
<th>140 mJ/cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No.</td>
<td>70</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Women</td>
<td>41 (59)</td>
<td>35 (50)</td>
<td>38 (54)</td>
</tr>
<tr>
<td>Age at recruitment, mean (SD) [range], y</td>
<td>41.6 (15.6)</td>
<td>42.7 (16.8)</td>
<td>41.5 (17.1)</td>
</tr>
<tr>
<td>Sun-reactive skin phototype</td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>10 (14)</td>
<td>29 (41)</td>
<td>31 (44)</td>
</tr>
<tr>
<td></td>
<td>6 (9)</td>
<td>36 (51)</td>
<td>26 (37)</td>
</tr>
<tr>
<td></td>
<td>8 (11)</td>
<td>33 (47)</td>
<td>28 (40)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>2 (3)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

DEMOGRAPHIC DATA AND ACTUAL STARTING DOSES

The participants' ages, sex ratio, and skin phototypes are summarized in Table 2. The majority had chronic plaque psoriasis, with only 7% with guttate psoriasis. Baseline psoriasis severity, as indicated by PASI and PDI scores and previous treatments used, was similar across each of the study groups (Table 3).

The actual starting doses administered differed across the groups as expected (P = .04), but the magnitude of difference between the groups was not great (Figure 2).

TREATMENTS TO CLEARANCE AND/OR MRA (PRIMARY EFFICACY OUTCOME)

The median number of treatments to clearance and/or MRA were 31 treatments for the 70% MED group, 29 treatments for the 50% MED group, and 32 treatments for the non–MED-based starting dose group (Figure 3). The hazard ratio (HR), with values lower than 1 meaning greater...
probability of clearance per treatment, for MED-based starting dose allocation compared with non-MED–based starting dose allocation was 0.96 (95% CI, 0.67-1.38; \( P = .83 \)).

For the 70% MED group compared with the 50% MED group, the HR was 1.01 (95% CI, 0.83-1.23; \( P = .94 \)). Similarly, there were no large differences between groups in time to clearance and/or MRA, with the median time to clearance and/or MRA of 78 days for the 70% MED group, 81 days for the 50% MED group, and 88 days for the fixed starting dose group (\( P = .71 \)). Exploratory analysis (excluding the 16 patients treated with less than the 140 mJ/cm\(^2\) non–MED-based starting dose) produced similar findings (data not shown).

**UNCOMFORTABLE AND PAINFUL ERYTHEMA EPISODES (PRIMARY ADVERSE EFFECT OUTCOME)**

Grade 2 (well-demarcated, uncomfortable) erythema or worse (grade 3 [painful] or grade 4 [painful, blistering]) erythema was reported at least once (in the majority of courses it was only 1 episode) during the treatment course for 17 of 70 (24%) of those in the 70% MED group, 27 of 70 (39%) of those in the 50% MED group, and 17 of 70 (24%) of those in the non–MED-based starting dose group (\( P = .29 \), \( \chi^2 \) test). Compared with the non–MED-based starting dose group, 8% (95% CI, from 21% fewer to 7% more; \( P = .30 \)) fewer patients in the MED-based starting dose group experienced at least 1 grade 2 or worse erythema episode. Compared with the 70% MED group, 15% more (95% CI from 1% fewer to 29% more; \( P = .07 \)) patients in the 50% MED group had at least 1 episode of grade 2 or worse erythema. No patients were recorded to have a grade 2 or worse erythema episode during the first 5 treatments of a course; there was no clear difference between groups in when (after which treatment) these erythema episodes occurred.

Only 3 grade 4 (blistering) erythema episodes were recorded: all were localized (to hands, along pant line, and to psoriatic plaques), and all occurred in those in the 70% MED group.

**SECONDARY EFFICACY OUTCOME MEASURES**

There were no detectable differences in the proportions of patients reaching clearance and/or MRA or PASI 75 or PASI 90 across the 3 starting dose allocation groups (Table 4). Of those allocated to an MED-based starting dose, 100 of 140 (71%) reached clearance and/or MRA, compared with 43 of 70 (61%) of those allocated to the non–MED-based starting dose (95% CI for difference, −1.4% to 24.2%; \( P = .09 \)). There was no detectable difference between groups in change in PASI from baseline to the 15th treatment visit (\( P = .74 \)), or in change in PASI from baseline to the end of the treatment course (\( P = .39 \)). There was no detectable difference between groups in change in quality of life measured by the PDI (\( P = .82 \)). As for analysis of numbers of treatments to clear, we found no important differences when we analyzed on a per-protocol basis.
ADVERSE EFFECTS OTHER THAN ERYTHEMA

The only adverse effect other than erythema to be recorded was polymorphic light eruption, which was seen in 13 patients (3 in the 70% MED group and 5 in each of the other starting dose allocation groups).

COMMENT

We did not detect any important difference in efficacy between the different starting dose regimens compared in this study. We had hypothesized that starting at a lower dose might lead to greater induction of tolerance ("hardening") that might reduce efficacy, while protecting against erythema, over subsequent treatments. This study failed to support this hypothesis. Also, we did not detect any definite differences between regimens in important erythema episodes occurring during treatment. There was a suggestion (P=.07) that important (uncomfortable to painful) erythema occurred more with the regimen involving a 50% of MED starting dose than with the 70% of MED starting dose. Perhaps this was just a chance finding. However, possibly, starting treatment with a lower dose, on the initial flatter part of the sigmoidal erythema dose response curve,17,18 leads to less production of higher doses given mid course (when most important erythema reactions occur) than does starting at a higher dose.

An important limitation of our study was that 16 patients allocated to the fixed starting dose were actually started, on the basis of their MED results, at lower doses than would have been allocated had our study protocol not required MED testing for all study subjects. We performed MED testing on all patients for 2 reasons: (1) to ensure blinding (so that all patients would have MED test sites visible when put into the treatment cubicle) and (2) for ethical reasons. When designing the study we decided that we could not reasonably expose patients to whole-body starting doses close to or above their MEDs, hence the study protocol requirement that we had to give lower doses than allocated if the non–MED-based starting dose turned out to be greater than 90% of an individual’s MED. Exploratory per-protocol analyses (excluding the 16 non–MED-based starting dose group patients with a starting dose less than the allocated dose) did not give findings importantly different from intention-to-treat analyses. However, it is possible that our findings (both efficacy and safety outcomes) might have been different had we not conducted MED testing and acted on this for safety reasons in the fixed starting dose group.

Previous studies suggest that lower-intensity regimens, whether lower starting dose, lower incremental doses during a course, or lower frequency, appear slightly less effective than higher-intensity regimens (Table 1).5-10 However, the magnitude of greater benefit with the more-intense regimens was, in all but 2 studies,9,10 considered insufficient to justify the more frequent uncomfortable erythemas of the more-intense regimens. This is why standard phototherapy regimens, such as the regimen offered by the Scottish Managed Clinical Network for Photo-therapy (established 2002), recommend relatively low-intensity regimens (http://www.photonet.scot.nhs.uk/).

In conclusion, this study suggests that choice of starting dose method is not highly important for the efficacy of NB–UV-B for chronic psoriasis in predominantly skin phototype I to III Scottish adults. However, the single patient, with previously unsuspected severe photosensitivity due to chronic actinic dermatitis, who would likely have had a severe reaction had we not conducted MED testing, emphasizes the need for some form of small area testing before proceeding with whole-body NB–UV-B.3 For now, we continue to conduct MED testing routinely before treatment, although it could be argued that some other form of small-area test irradiation could be used instead. We cannot extrapolate the findings of this study to populations that include a broader range of skin phototypes and MEDs.

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Author Contributions: Dr Dawe had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Dawe, Cameron, Yule, Ibbotson, and Ferguson. Acquisition of data: Dawe, Cameron, Yule, and Ibbotson. Analysis and interpretation of data: Dawe, Ibbotson, Moseley, and Ferguson. Drafting of the manuscript: Dawe. Critical revision of the manuscript for important intellectual content: Dawe, Cameron, Yule, Ibbotson, Moseley, and Ferguson. Statistical analysis: Dawe. Administrative, technical, and material support: Moseley. Study supervision: Dawe, Ibbotson, and Ferguson.

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REFERENCES

Comparative Effectiveness Research

Comparative effectiveness research expands the scope of clinical research to compare different therapies against one another as a means to improve delivery of value-based health care. Typically, outcomes analysis of quality of life, disability, and death are used to compare the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor dermatologic conditions. Traditional efficacy research, used for approval of pharmaceuticals or devices, compares 1 or more treatment alternatives with placebo in a carefully selected population cared for in an ideal setting, thus answering the question of whether the intervention is effective and safe for human use.

In contrast, comparative effectiveness research seeks to answer a different set of questions including: (1) when to use the treatment (appropriate time), and (2) who should receive the intervention (proper patient selection). This research also considers patients from populations that are under less than ideal conditions. Thus, comparative effectiveness research seeks to replace the physician’s informed intuition of case management with data-driven, scientifically derived, “best-treatment” protocols. We at the Archives are interested in comparative effectiveness research using observational and clinical trial methods comparing different strategies provided by dermatologists in heterogeneous patient populations and heterogeneous health care settings.

The Archives of Dermatology, along with JAMA and other Archives Journals, will publish a theme issue devoted to comparative effectiveness research in early 2012. Priority will be given to studies using rigorous methodological designs that are generalizable beyond a single institution. Authors should consult the Instructions for Authors at http://www.archdermatol.com for guidelines on manuscript preparation and submission. Manuscripts must be received before October 1, 2011, to allow for appropriate consideration.

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Associate Editor


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