

CLINICAL REPORT

A Randomized Comparison of Acitretin-narrow-band TL-01 Phototherapy and Acitretin-Psoralen plus Ultraviolet A for Psoriasis

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The combination of retinoids with phototherapy enhances the efficacy of phototherapy and reduces the cumulative ultraviolet dose and duration of the therapy needed to treat chronic plaque psoriasis. Although TL-01 phototherapy has been used widely, there are few data about the effectiveness of the combination of acitretin with TL-01 in treatment of the disease. The aim of this study was to compare acitretin-narrow-band TL-01 phototherapy with acitretin-psoralen plus ultraviolet A (acitretin-PUVA) in psoriasis. We studied 60 patients with moderate to severe plaque psoriasis who were randomly allocated to three times weekly treatment acitretin-narrow-band TL-01 or acitretin-PUVA. The efficacy of treatments was assessed using the Psoriasis Area and Severity Index by a blinded observer. Clearance of psoriasis was achieved in 56.6% of patients treated with acitretin-narrow-band TL-01 and in 63.3% of those treated with acitretin-PUVA. All of these patients remained clear of psoriasis 3 months after finishing the treatments. Mucocutaneous side-effects, such as dry lips and mouth, were the most common complaints in both groups. In conclusion, acitretin-narrow-band TL-01 is an effective and well-tolerated treatment for moderate to severe plaque psoriasis, with a therapeutic effect equal to that of acitretin-PUVA. Key words: phototherapy; psoriasis; retinoid; re-TL-01; re-PUVA.

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Retinoids are used widely in many dermatological diseases. Oral retinoids or their combination with psoralen plus ultraviolet A (PUVA)/UVB (acitretin-PUVA and acitretin-UVB) have been used with varying success in the treatment of psoriasis. Acitretin, a second-generation aromatic retinoid, is a carboxylic acid and active metabolite of etretinate. Etretinate has been replaced by acitretin and is no longer available. The pharmacokinetic properties of acitretin are much more favourable than those of etretinate. It has a less terminal elimination half-life than etretinate (1, 2). The therapeutic profile of acitretin in the treatment of psoriasis is similar to that of etretinate.

Several studies have shown that the effectiveness of a combination of acitretin with PUVA or UVB is higher than that of acitretin, PUVA or UVB alone (3–5).

A comparison of etretinate-TL-01 and etretinate-PUVA has been reported in only one study (6). This randomized, but not observed, masked study did not detect any clinically important difference between the two treatments with respect to efficacy. Although some series with chronic plaque psoriasis vulgaris treated with acitretin-PUVA/UVB combination have been reported in the literature, acitretin-narrow-band TL-01 (re-TL-01) has not been reported as a therapeutic combination in the disease to date, except for a retrospective study (7).

In the present study, the efficacy of re-TL-01 in moderate to severe plaque psoriasis was investigated and compared with acitretin-PUVA (re-PUVA) in a randomized and observer-masked trial.

MATERIALS AND METHODS

Study design

This prospective study was designed to be randomized and blinded. In- and out-patients of both sexes with moderate to severe plaque-type psoriasis were enrolled into the study, which was approved by the institutional ethics committee, and all subjects signed an informed consent form. All patients were recruited from our dermatology departments. Recruitment took place during a 16-month period from August 2005 to December 2006. All patients had Fitzpatrick's skin type II–IV. Female patients of child-bearing potential were admitted only if a beta-human chorionic gonadotrophin (hCG) slide test for pregnancy proved negative and the use of effective contraceptives during the treatment was agreed. The patients were advised to continue contraception for 2 years after the treatment. All patients had psoriatic lesions on more than 20% of their total body surface area and a minimum Psoriasis Area and Severity Index (PASI) of 10. All patients had been treated previously with phototherapy or systemic medication or topical agents. Patients had stopped all topical therapy at least 4 weeks before and all systemic therapies for at least 6 months before initiating the study protocol.

Exclusion criteria were: age <18 years, a history of skin cancer or solar keratoses, or phototherapy, localized palmo-plantar psoriasis, pregnancy, lactation, renal or liver diseases, hyperlipoproteinaemias, and severe cardiac and neurological diseases. Patients receiving other systemic therapy for psoriasis, such as acitretin or methotrexate, were excluded, as were those who had received any form of UV therapy within the preceding 6 months. Additionally, enrolment excluded patients with guttate, erythrodermic or pustular psoriasis. During the study and the follow-up period, additional therapy was restricted to the use of emollients that were applied once daily in the evening.

Randomized assignment of the two treatments was performed by asking the patients to throw a dice without knowing the underlying allocation criteria (numbers 1–3 = re-TL-01; numbers 4–6 = re-PUVA).

For TL-01 UVB and UVA, a Daavlin UV 311/350 cabinet (Daavlin, California, USA) fitted with 12 Philips 100 W TL-01 and 12 Philips 100 W UVA lamps (Philips Co., Eindhoven, The Netherlands), were used. TL-01 and UVA irradiances were checked every 3 months. During the first week, patients received 0.3–0.5 mg/kg/day low-dose acitretin. TL-01 or PUVA therapies were started in the second week. Minimal erythema dose (MED) and minimal phototoxic dose (MPD) were done on upper back skin before the treatments. These tests were carried out on the volar aspect of the forearm in 5 patients, because of their disease distribution or severity. If erythema developed during the treatments, depending on the severity, planned dose increments were postponed or treatments missed, until the erythema resolved.

Re-TL-01

The dose used at the start of the course of treatment was 70% of the MED and was subsequently increased by 10–20% increments at each phototherapy session, providing there were no side-effects. Patients were treated three times weekly with whole-body exposure units.

Re-PUVA

Two hours before irradiation 0.6 mg 8-methoxypsoralen/kg body weight was administered. Treatment was started with 70% of the MPD, with 20% increments weekly. UVA was given three times weekly using whole-body exposure units.

Clinical assessment

The treatment period lasted 8 weeks. The patients underwent physical examination after the first and second weeks and every 2 weeks thereafter. At each visit one independent observer (BE) assessed the patient's lesion using the PASI (8). The mean reduction in the PASI score after 56 days of treatment was considered the primary outcome measure. An adequate response was defined as a 75% reduction in the PASI score from when treatment started (PASI 75). The total number of irradiations and the total TL-01 and UVA exposures were recorded in J/cm². Using the PASI score, patient responses were classified at the end of the treatments as exacerbation (>5% increase over enrolment PASI), unchanged (<5% improvement), slight (5–25% improvement), moderate (>25–50% improvement), marked (>50–75% improvement) and complete improvement (>75% improvement). The final overall efficacy assessment in the patients withdrawn from the study before treatment completion was accepted as unchanged.

Treatments were discontinued when neither improvement nor exacerbation was seen after 6 weeks, or when severe side-effects occurred or laboratory analyses showed abnormalities. All patients whose skin cleared were followed up for 3 months after stopping treatment. Patients were then graded as clear (no psoriasis or trivial lesions) or relapsed (an increase in global score to 50% of that at baseline). All patients were monitored for adverse effects at each visit using a standardized questionnaire. Overall assessment of tolerability was made at the end of the treatments by the observer and patients according to a 4-level rating scale: "very good", "good", "moderate" and "poor". The tolerability assessment in the patients withdrawn from the study before treatment completion was accepted as poor. Laboratory analyses, including total blood count, urinalysis, liver function

tests (AST, ALT), serum triglycerides, cholesterol and creatinine were performed before, during and at the end of the treatment.

Statistical analysis

The study was designed to have a power of 0.80 to detect a difference of two treatments. Assumption included $\alpha = 0.05$, and estimated of within-patient standard deviations were based on a previous study (9). We calculated that we required 22 patients, on the assumption that 80% would complete treatment within the study. The main target variable (PASI changes) was analysed on an intention-to-treat (ITT) basis using baseline PASI score and last available PASI score of all randomized patients. The PASI changes with time were evaluated as areas under the curve (AUC). The AUC was calculated using the trapezoidal method. The paired *t*-test was used to compare change (beginning to end of the treatment course) in PASI score. Adequate response rates (PASI decrease $\geq 75\%$) were compared using the χ^2 test and 95% confidence intervals (95% CI) were calculated for response rates. Distribution of age, sex and duration of the disease was analysed by Student's *t*-test, χ^2 and the Mann-Whitney *U* test, respectively. Statistical analyses were performed on an ITT basis.

RESULTS

A total of 60 patients were enrolled in the trial, all of them received the investigational drug on day 0, and TL-01 or PUVA on day 8. Of the 60 patients, 52 completed the trial. Five patients discontinued treatment before the end of the treatment protocol in re-PUVA due to reasons independent of the trial, such as severe nausea resulting from 8-methoxypsoralen and severe headache resulting from acitretin. Of the re-TL-01 withdrawals, 2 patients failed to attend for treatment and one developed severe erythema (Fig. 1). Baseline demographics and disease characteristics were similar to that of the two treatments groups and are summarized in Table I. The mean number of TL-01 exposures in the re-TL-01 group was 20.7 ± 5.1 days and the total TL-01 dose was 13.7 ± 4.4 J/cm². In the re-PUVA group, the mean number of UVA exposures was 20.4 ± 6.5 and the total UVA dose was 38.4 ± 14.1 J/cm². Due to social problems, TL-01 and PUVA were given two times weekly in 1–3 weeks in 7 and 11 patients, respectively.

Both treatment combinations were effective in the treatment of psoriasis. In re-TL-01 patients, the mean PASI was 15.5 (range 11.2–33) before treatment and 3.9 (range 1.3–17.4) after treatment. In re-PUVA patients, the corresponding values were 16.8 (range 11.2–29.3) and 4.2 (range 1.7–11.8). There was no significant difference in the decrease in PASI score at the end of treatment between the two groups ($p = 0.83$). There was no significant difference between the mean fall in PASI score for re-TL-01 vs. re-PUVA (95% CI –7.16 to 5.44) (Fig. 2). Similarly, the response rate (PASI decrease $\geq 75\%$) was 17 out of 30 (56.7%, 95% CI 37.9–75.5) in re-TL-01 group (Fig. 3) and 19 out of 30 (63.3%, 95% CI 45.0–81.6) in re-PUVA groups ($p = 0.59$). The final

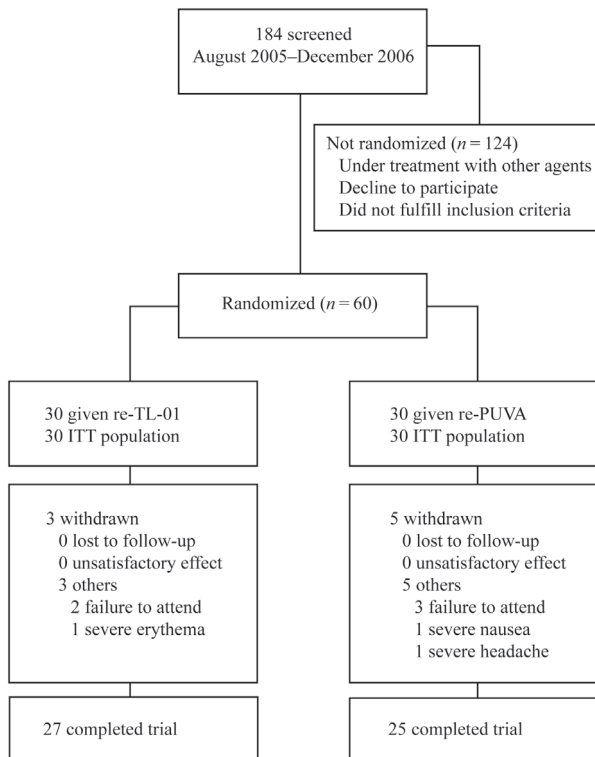


Fig. 1. Flow diagram. Intention-to-treat (ITT) population indicates all randomized patients who have received acitretin-narrow-band TL-01 (re-TL-01) or acitretin-psoralen plus ultraviolet A (re-PUVA) and from whom at least one post-baseline Psoriasis Area and Severity Index (PASI) score was available. Withdrawn; patients who were lost to follow-up, or discontinued study because of unsatisfactory outcome or other reasons.

overall efficacy and overall tolerability assessments in the treatment groups are shown in Table II.

Adverse effects due to acitretin were frequent in both treatment groups. Mucocutaneous symptoms, such as dry lips, mouth, skin and nose, were the most common complaints in both treatment groups. Other complaints were joint pain, nose bleeding, pruritus, taste loose, hair

Table I. Baseline characteristics of the two treatment groups

| | Re-TL-01 (n=30) | Re-PUVA (n=30) | p-value |
|--|--------------------|-------------------|---------|
| Sex (male/female), n | 16/14 | 18/12 | 0.59 |
| Age (years), mean±SD | 37.2±11.6 | 36.1±9.9 | 0.70 |
| Body mass index (kg/m ²), mean±SD | 25.4±4.5 | 24.5±2.3 | 0.34 |
| Duration of disease (years)* | 13 (4–40) | 14 (3–35) | 0.61 |
| Baseline PASI score* | 15.5 (11.2–33) | 16.5 (11.2–29.3) | 0.54 |
| Skin type, n | | | |
| Type 2 | 2 | 1 | |
| Type 3 | 17 | 20 | |
| Type 4 | 11 | 9 | |

*Median (minimum–maximum).

PASI: Psoriasis Area and Severity Index; SD: standard deviation; re-PUVA: re-acitretin-psoralen plus ultraviolet A; re-TL-01: acitretin-narrow-band TL-01.

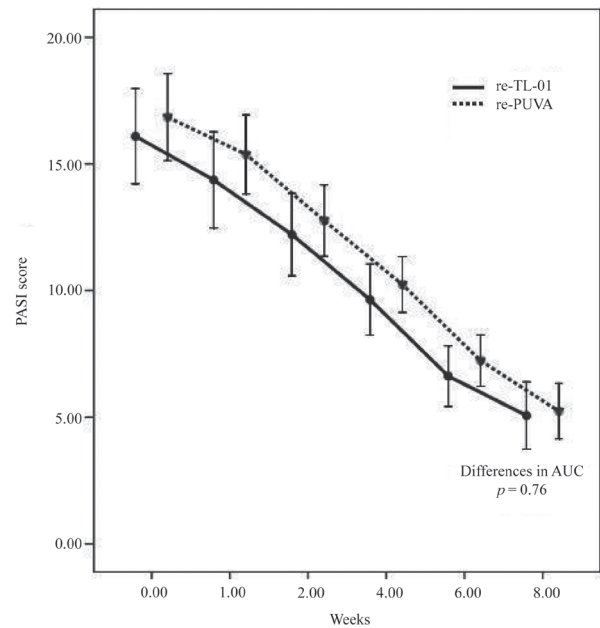


Fig. 2. Mean Psoriasis Area and Severity Index (PASI) score in patients treated with acitretin-narrow-band TL-01 (re-TL-01) or acitretin-psoralen plus ultraviolet A (re-PUVA). AUC: area under the psoriasis severity time curves. Differences in AUC $p=0.76$.

loose, muscle pain, paronychia, xerophthalmia, nail fragility, headache and gastrointestinal events. For those complaints, emollients, anti-analgesics and anti-pruritics were prescribed. One patient in re-PUVA group did not tolerate acitretin, because of severe headache, and the treatment was stopped by the patient. Increased liver enzymes or triglycerides levels that necessitated stopping the treatments were not detected in any patients. Erythema was detected at some stage during the course of treatment in 37% of the patients receiving re-TL-01 and in 28% of the patients receiving re-PUVA. Planned dose increments were postponed or treatments missed in those patients. Severe erythema developed after 3 TL-01 exposures in one patient who had skin type 2 and the treatment was discontinued. Various degrees of nausea occurred in 76% of the patients treated with re-PUVA. The treatment was stopped in one of those patients, due to severe nausea.

Patients who completely cleared in the two treatment groups (17 patients in the re-TL-01 group, and 19 patients in the re-PUVA group) remained clear of psoriasis 3 months after finishing treatments. Psoriasis improvement was maintained in 5 patients with marked improvement (3 patients in the re-TL-01 group, 2 patients in the re-PUVA group) after treatment and clearance of psoriasis was seen in these patients at 3 months after finishing treatments. Relapse occurred in a total of 11 patients in the two groups. Marked to slight improvement was achieved in these patients during the treatment period.



Fig. 3. Three patients before (upper panel) and after (lower panel) acitretin-narrow-band TL-01 (re-TL-01) treatment. The post-treatment photographs were taken after 8 weeks.

DISCUSSION

The results of this study show that re-TL-01 is as effective as re-PUVA in the treatment of plaque type psoriasis. The combination of acitretin and TL-01 enhances the therapeutic efficacy of TL-01. Although the percentage response was higher in re-PUVA than in re-TL-01, no significant difference was detected in the PASI decrease in the two groups. Equal therapeutic effectiveness of PUVA and TL-01 treatment in psoriasis has been shown in several previous reports (10,

11). However, these results were not confirmed by a subsequent study (12). We found that these treatments combined with acitretin had similar therapeutic effectiveness. Our results showed that a combination of these treatments with acitretin continued equal effectiveness of these treatments in psoriasis. Because acitretin can cause thinning of the stratum corneum, re-TL-01 may be more effective than using TL-01 alone.

TL-01 and its combination with topical or systemic agents are used as a standard treatment for chronic plaque and guttate psoriasis. The effectiveness of this treatment has been reported in many studies to date (13, 14). It is also effective in producing histological resolution of psoriasis and improves the quality of life in patients with psoriasis (15, 16). In addition, a recent quantitative review suggests that TL-01 is much more effective than broadband UVB for treatment of psoriasis (17). The combination of acitretin with broadband UVB has been shown to be more effective in the treatment of psoriasis than acitretin or broadband UVB alone (3–5). Although the effectiveness of re-UVB in psoriasis treatment has been showed in several studies, there are two studies in re-TL-01 for psoriasis. However, one of these studies was randomized but used etretinate as the retinoid agent and the other study was retrospective (6, 7).

In this randomized study of TL-01 with and without systemic etretinate in 45 patients with chronic plaque or guttate psoriasis, no real advantage was determined for combination treatment. A reduction in the cumulative UVB dose was found, but there was no effect on overall numbers of treatments, and an increased relapse rate was seen in the retinoid treatment group (6). In the retrospective study, a marked improvement (greater than 75%) has been reported in 72.5% of 40 patients with psoriasis

Table II. Final overall efficacy and overall tolerability assessments in the treatment groups

| | Re-TL-01 (n=30) | | Re-PUVA (n=30) | |
|--|-----------------|------|----------------|------|
| | n | % | n | % |
| <i>Overall efficacy assessment</i> | | | | |
| Complete improvement | 17 | 56.6 | 19 | 66.6 |
| Marked improvement | 4 | 13.3 | 4 | 13.3 |
| Moderate improvement | 4 | 13.3 | 1 | 3.3 |
| Slight improvement | 2 | 6.6 | 1 | 3.3 |
| Unchanged | 3 | 10 | 5 | 16.6 |
| Exacerbation | 0 | 0 | 0 | 0 |
| <i>Overall tolerability of treatment (O)</i> | | | | |
| Very good | 17 | 56.6 | 13 | 43.3 |
| Good | 5 | 16.6 | 8 | 26.6 |
| Moderate | 3 | 10 | 3 | 10 |
| Poor | 5 | 16.6 | 6 | 20 |
| <i>Overall tolerability of treatment (P)</i> | | | | |
| Very good | 16 | 53.3 | 12 | 40 |
| Good | 4 | 13.3 | 7 | 23.3 |
| Moderate | 5 | 16.6 | 5 | 16.6 |
| Poor | 5 | 16.6 | 6 | 20 |

O: observer; P: patient; re-TL-01: acitretin-narrow-band TL-01; re-PUVA: acitretin-psoralen plus ultraviolet A.

who were refractory to treatment with broadband UVB, monotherapy with TL-01, monotherapy with acitretin, or the combination of acitretin and broadband UVB (7). Although the phototherapy regimes were not directly comparable because the incremental doses were weekly for PUVA and daily for TL-01, re-TL-01 showed a similar effectiveness to that of re-PUVA in moderate to severe plaque psoriasis and PASI 75 was achieved in 56% of the patients treated with re-TL-01 in our randomized study. In addition, we found that the duration of remission of psoriasis at 3 months with re-TL-01 treatment was not different from that with re-PUVA treatment.

Acitretin enhances the efficacy of PUVA and reduces the number, duration and cumulative dose of treatments necessary to effect clearing. Likewise, several studies demonstrated that re-PUVA is highly effective in the treatment of psoriasis (4, 5). However, in particular, nausea and sunlight protection for 8–12 h due to the use of psoralens are some of the problematic aspects of this treatment, and these may affect treatment adaptation and tolerability in many patients. In addition, cumulative UVA may lead to an increase in the risk of skin cancer (18). Although the chronic side-effects of treatment with TL-01 have not yet been established, re-TL-01 may be a good alternative treatment in psoriatic patients who would normally be treated with re-PUVA.

Many patients with chronic plaque psoriasis do not heal with UVB, PUVA or acitretin treatment alone. Re-TL-01 is an effective and well-tolerated treatment in moderate to severe plaque psoriasis. Apart from protecting against the potential side-effects, low-dose acitretin is sufficient to enhance the efficacy of TL-01. This combination may reduce the side-effects of TL-01, by enabling the use of a lower cumulative dose of UVB or number of treatments (18, 19). In addition it may offer an additive or synergistic effect in the treatment of psoriasis. In conclusion, we suggest that re-TL-01 is an effective and safe treatment for psoriasis.

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