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NON-INVASIVE EVALUATION OF TACALCITOL PLUS PUVA VERSUS TACALCITOL PLUS UVB-NB IN THE TREATMENT OF PSORIASIS: "RIGHT-LEFT INTRA-INDIVIDUAL – PRE/POST COMPARISON DESIGN"

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Photochemotherapy with psoralen plus ultraviolet A (PUVA) and phototherapy with UVB narrow band (UVB-NB) are used in the treatment of psoriasis. Numerous studies have shown that the additional administration of either topical or systemic antipsoriatic agents may effectively increase the efficacy of these therapies. This study aimed to compare through objective data the efficacy of topical tacalcitol in combination with PUVA or UVB-NB versus PUVA and UVB-NB monotherapy in the treatment of mild to moderate chronic plaque psoriasis. Modified Psoriasis Area and Severity Index (PASI) score, transepidermal water loss (TEWL) and stratum corneum hydration were used to monitor the restoration of skin barrier in the psoriatic plaques of 40 patients during photochemotherapy. The study was a right-left, intra-individual, pre/post comparison trial. PUVA and UVB-NB treatments were given three times a week. On those plaques localized on the right side of the body tacalcitol ointment was applied once a day, in the evening. Corneometry, TEWL and modified PASI score were used to evaluate the response to the treatment at baseline, one month and two months. Thirty-six of the forty enrolled subjects completed the study. The comparison between combination treatments and the PUVA/UVB-NB monotherapy showed no significant differences with regard to modified PASI index. However, significant differences were recorded with regard to TEWL and corneometry. The combination of tacalcitol plus PUVA or tacalcitol plus UVB-NB restored epidermal barrier functions as well as skin hydration faster than PUVA or UVB-NB monotherapy (TEWL: p=0.0050 and corneometry: p=0.003). The combination of tacalcitol plus UVB-NB allowed a better restoration of skin barrier functions than tacalcitol plus PUVA (p=0.013). In conclusion, the combination of tacalcitol plus PUVA or plus UVB-NB improves the therapeutic result. In addition, the data from TEWL and skin hydration suggest a means in which tacalcitol plus UVB-NB induces a better normalization of skin biophysical parameters.

Photochemotherapy with psoralen plus ultraviolet A (365nm) (PUVA) and phototherapy with UVB narrow band (311nm) (UVB-NB) are widely used in the treatment of psoriasis (1). Numerous studies have shown that the additional administration of topical or systemic antipsoriatic agents may serve as an effective means to increase the efficacy of these therapies and to reduce possible long term risks of cutaneous malignancies (2). Tacalcitol (1α,24-dihydroxyvitamin D3) is a synthetic analogue of calcitriol, the most active metabolite of vitamin D (3). The biological action of tacalcitol includes the regulation of

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epidermal cell proliferation and differentiation, the inhibition of angiogenesis, and the modulation of cytokine production. Several studies (4) have shown its efficacy in the treatment of psoriasis. However, little data exist on the role of tacalcitol used with photo-photochemotherapies (5-6).

The purpose of this study was to compare, through objective data, the efficacy of topical tacalcitol in combination with PUVA or UVB-NB in the treatment of mild to moderate chronic plaque psoriasis. Transepidermal water loss (TEWL) and stratum corneum hydration (corneometry) were objectively used to monitor the restoration of skin barrier in psoriatic plaques. Data were compared to more subjective evaluations using the modified PASI index of the same area. The study was a right-left intra-individual – pre/post comparison trial.

MATERIALS AND METHODS

Patients

A total of 40 consecutive out-patients (age: 18-65; mean age: 47) with chronic, stable plaque-type psoriasis encompassing a large symmetrical distribution entered the study after giving their informed consent. They were not receiving any other treatment for psoriasis and they had discontinued all other topical or systemic therapy one month before the beginning of the study.

The following exclusion criteria were applied: pregnant or lactating women, patients with a history of abnormal UVA/UVB sensitivity, patients taking photosensitizing drugs, patients needing systemic or topical treatment that might influence psoriasis (eg. Lithium, β-blockers or systemic steroids, tacrolimus), patients with renal or liver dysfunction, patients with ocular diseases, patients with hypersensitivity to tacalcitol or 8-methoxypsoralen, and patients unable to follow the protocol.

Treatment protocol

Two symmetrical lesions of similar size (4-10 cm in diameter) and severity located on knees or elbows were selected on each patient for clinical and instrumental follow-up evaluations.

Tacalcitol ointment (4 mcg/g) was applied once a day in the evening on those plaques localized on the right side of the body. White petrolatum, one of the base ingredients without active substance, (hereafter referred to as placebo) was applied once a day on those plaques localized on the left side of the body. Emollients were the only topical agents allowed. The topical treatment was started on the first day of PUVA or UVB-NB therapy. Lesions were treated until cleared, but for no more than 8 weeks.

The severity of erythema, infiltration, and scaling of the selected plaques was clinically evaluated by the investigators and scored on a scale ranging from 0 to 4 (0=none, 4=extremely severe) (modified PASI score, visual score). The final sum gave the total score for erythema, infiltration and scaling.

Modified PASI score and instrumental score (TEWL and corneometry) assessed the response to treatment at the beginning of the therapy, at one month, and at 2 months.

Adverse side effects

Adverse side effects were minimal. Only one patient showed mild erythema, which disappeared after application of emollient and mild topical steroids for two days. In this case the irradiation dose was held constant until resolution of the symptoms. Phototoxic or photoallergic reactions were not observed.

Instrumental measurements

TEWL, as indicator of the stratum corneum integrity, was measured with an evaporimeter (Tewameter TM 210, Courage-Khazaka Electronic GmbH., Köln, Germany).

Electrical capacitance, as indicator of the stratum corneum hydration (corneometry), was measured in duplicate with a capacitance meter (Corneometer CM 825 PC, Courage & Khazaka Electronic GmbH. Cologne, Germany). TEWL and corneometry measurements were conducted at ambient conditions (45-65% relative humidity, 20-22°C): subjects rested at least 15 minutes before measurements were taken.

Photo-photochemotherapy

Treatment allocation (PUVA or UVB-NB) was based on a randomized selection: the first group of twenty patients was treated with PUVA and the second group of twenty patients was treated with UVB-NB.

UVB-NB treatment

UVB irradiation at 311nm was administered three times a week; the light source was a Waldmann Lichttechnik booth, containing a bank of 8 fluorescent bulbs (Philips TL-01). The starting dose was 180-200 mJ/cm^2, depending on skin type with increments of about 50 mJ/cm^2 each treatment up to the maximum tolerable dose. All subjects wore protective goggles during exposure.

PUVA treatment

Oral 8-methoxalen was given at the dose of 0.6 mg/kg two hours before therapy three times a week. The light source was a Waldmann Lichttechnik mod. PUVA 6001 booth with 40 conventional fluorescent PUVA lamps

(Waldmann mod. F85/100W-PUVA). The starting dose was 0.5-1J/cm², depending on skin type, previous PUVA history, and experience of sun burn. The dose was increased of 0.5-1 J/cm² for each treatment up to the maximum tolerable dose. All subjects wore protective goggles during exposure and sunglasses on the day of PUVA therapy.

Statistical methods

UVB-NB plus tacalcitol or PUVA plus tacalcitol were compared with monotherapy by a student T-test for paired data. A $p<0.05$ was considered significant. All tests were performed with Statistica 99 edition software (StatSoft, Inc Tulsa OK).

RESULTS

Of the 40 patients, 36 completed the study. Two subjects were excluded for evaluation because of irregular attendance for treatment and two subjects defaulted for reasons unrelated to treatment (Table I). Psoriasis cleared in all subjects and a significant decrease of the PASI score was documented at the end of the therapy. The comparison between the combination treatments (tacalcitol plus PUVA or UVB-NB) and the PUVA/UVB-NB monotherapy (placebo plus PUVA or UVB-NB) however, showed no significant differences in the visual scores. In contrast, significant differences were recorded with regard to TEWL and corneometry. All the treatments induced a significant decrease of TEWL and a significant increase of corneometry, but the combination treatments restored barrier function (Fig.1) (TEWL: $p=0.0050$) and improved skin hydration (Fig.2) (corneometry: $p=0.003$) faster if compared with PUVA and UVB-NB monotherapy. The comparison of baseline and week 8 mean values between tacalcitol plus PUVA and tacalcitol plus UVB-NB with the monotherapies showed a better restoration of skin barrier function (TEWL) with tacalcitol plus UVB-NB ($p=0.013$) (Table II). Corneometry mean values at baseline and week 8 did not show significant differences.

DISCUSSION

In recent years the vitamin-D-analogue tacalcitol has been marketed as an effective novel agent for the topical treatment of psoriasis (7-9). Besides its proven efficacy as monotherapy and adjunctive treatment to photo-photochemotherapy, little information exists on its use and comparative efficacy in combination with PUVA or UVB-NB (5-6,10).

In this study, the method of paired comparison right-left intra-individual pre/post treatment automatically eliminates the differences between patients and allows us to directly test the differences between the two therapeutical procedures. With this design, a large number of patients is not required.

On clinical evaluation, both tacalcitol plus PUVA or UVB-NB and PUVA/UVB-NB monotherapy

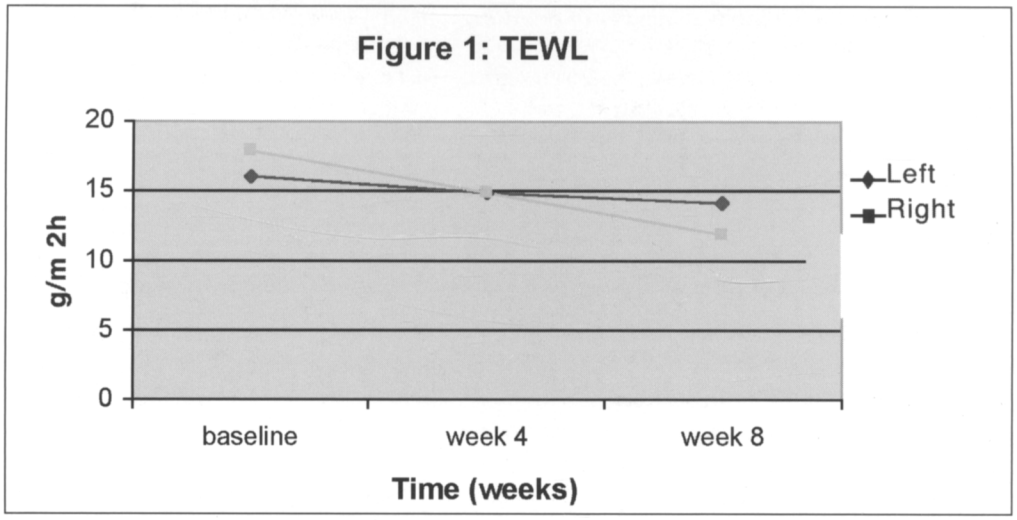

Fig. 1. *Direct comparison between the combination therapies (PUVA/UVB-NB plus tacalcitol, right) and monotherapy (PUVA/UVB-NB plus placebo, left). Significant differences were recorded at week 8 ($p=0.0050$).*

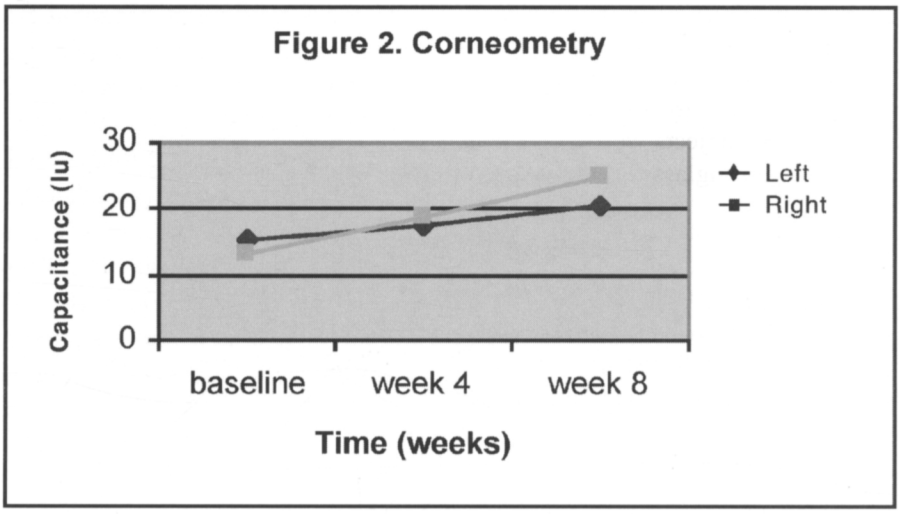

Fig. 2. *Corneometry: direct comparison between the combination therapies (PUVA/UVB-NB plus tacalcitol, right) and monotherapy (PUVA/UVB-NB plus placebo, left). Significant differences were recorded at week 8 (p=0.003).*

	N° patients	Total UV dose, J/cm^2 ± d.s. (range)	N° of exposures ± d.s. (range)
UVB-NB	18	19.00 ± 0.78 (17.6-20.01)	21.07 ± 1.66 (19-24)
PUVA	18	113.95 ±12.25 (94-136)	19.55 ± 2.83 (15-24)

Table I. *Total UV dose and number of exposure of photo/photochemotherapy.*

	Tacalcitol (mean values, g/m^{2}h ± d.s.)	Placebo(mean values, g/m^{2}h ± d.s.)	p
UVB-NB	8.46 ± 10.1	2.55 ± 3.6	0,013
PUVA	3.58 ± 6.63	2.01 ± 6.8	NS

Table II. *TEWL: Comparison between the combination therapies PUVA and UVB-NB with the monotherapies PUVA and UVB-NB respectively (the data are the result of the difference between week-8 and baseline mean values). A significant difference is evident with tacalcitol/UVB-NB with a better restoration of barrier functions (p=0.013) in comparison with the monotherapy.*

resulted in a significant improvement of psoriatic plaques. No significant differences were detected between the treatments. PUVA therapy was on average as effective as UVB-NB (both as monotherapies and as combination therapies); however the post-treatment assessment and the period of remission were not studied. The median UV dose (J/cm^2) for clearance was lower for UVB-NB than for PUVA, as described in literature (1).

In contrast, significant differences were recorded for the restoration of skin barrier in psoriatic plaques using an objective procedure. Specifically, both treatments (PUVA/UVB-NB plus tacalcitol and PUVA/UVB-NB monotherapy) induced a significant decrease in TEWL and an increase in corneometry during the 8 weeks. The comparison between the combination therapies and the monotherapies showed a better restoration of skin barrier with the former treatments (TEWL p=0.0050, corneometry p=0.003). Moreover, the comparison between tacalcitol plus PUVA and tacalcitol plus UVB-NB showed a better restoration of skin barrier function with tacalcitol plus UVB-NB (TEWL p=0,013).

The difference between PUVA and UVB-NB plus tacalcitol that has been observed may be related to different mechanisms. Both therapeutic and natural UV radiation cause DNA injuries repaired by specific processes (11). Cell injury is unavoidable in UVB phototherapy and it is the initial step in the therapeutic event. The subsequent decrease of DNA synthesis that normalizes the kinetics of epidermal cells (12) is considered the final therapeutic process. Under the influence of UVA radiations, PUVA therapy creates bonds between psoralens and DNA strands thereby inhibiting DNA synthesis and cell division. These reasons seem to explain the delayed restoration of the epidermal barrier observed in those patients treated with PUVA therapy (13).

Moreover, it is known that UVB- and UVA-irradiated skin is more resistant to irritants, which indicates an improved barrier function. The barrier improvement is correlated with a broad UVR-induced increase in the amount of stratum corneum lipids, including ceramides, cholesterol, and free fatty acids. In particular, the increase in ceramides can be attributed to the ability of UVB to induce both the activity and mRNA levels serine palmitol-transferase, the rate-limiting enzyme in sphingolipid synthesis (14).

In their study on vitamin D metabolism in psoriasis before and after photo-photochemotherapy, Guilhou et al. (15) demonstrated an increase in serum 1,25 (OH)^2 D during UV therapy occurring only in psoriatic patients and significant only for UVB therapy. An increase in epidermal 1,25 (OH)^2 D could be responsible for the regulation of mitotic activity and the differentiation of psoriatic keratinocytes, which enhance the therapeutic action of tacalcitol.

In conclusion, the combination of tacalcitol with PUVA or UVB-NB improves the results of these therapies. In particular, the objective data of TEWL and skin hydration show a better normalization of skin biophysical parameters with tacalcitol plus UVB-NB, which enhance the beneficial effect of UVB-NB on the psoriatic skin.

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