2 SYNOPSIS

Study code: MC 9308 FR.

Title:

Objectives:
The primary objective was to compare the efficacy of the combination calcipotriol ointment + narrow-band UVB (TL-01) phototherapy and placebo ointment (vehicle of calcipotriol) + narrow-band UVB (TL-01) phototherapy in patients with psoriasis vulgaris.

The secondary objectives were to compare the safety, tolerability of calcipotriol ointment + narrow-band UVB (TL-01) phototherapy in the above group of patients.

Study design:
This study was a multicentre, prospective, randomised, double-blind, vehicle-controlled, right-left comparison of the following treatments:

- narrow-band UVB (TL-01) phototherapy given 3 times weekly with calcipotriol ointment (50 µg/g) applied twice daily,
- narrow-band UVB (TL-01) phototherapy given 3 times weekly with placebo ointment (vehicle of calcipotriol) applied twice daily.
This study was divided in 2 phases:

Phase I: wash-out/qualification of 2 weeks
During this phase, the patient used only an emollient as required.

Phase II: randomised, active treatment for up to 8 weeks
During this phase the patient was given double-blind treatment.

Sample size calculation:
Based on similar experiment with coal tar + narrow-band UVB (TL-01) phototherapy versus vaseline + narrow-band UVB (TL-01) phototherapy, the standard deviation of the differences of amelioration between the two hemibody was supposed to be close to 15%. Each total sign score (sum of score for redness, thickness and scaliness) was previously divided by its baseline value. In this experiment a difference of amelioration of 10% between the two hemibody was reached after 20 UVB exposures.

For this study, a sample size of approximately 51 patients was required to allow detection of such difference, with type I error of 0.05 ($\alpha = 5\%$) and type II error of 0.10 ($\beta =10\%$). It was decided to include 60 patients in this study to ensure the required number of analysable patients.

Source of patient:
Out-patient seen by a dermatologist in a general practice.

Patient group studied:
Included were out-patients of either sex, aged more than 18 years, with a clinical diagnosis of extensive and symmetrical body psoriasis ($\geq 20\%$ to $\leq 50\%$ body
surface area), who had skin type II, III or IV and who had given their signed informed consent.

Excluded were patients whose psoriasis markedly deteriorated or spontaneously improved before randomisation, patients whose psoriasis was predominantly located on the face and/or scalp and/or genital areas and/or flexures, patients who had used systemic anti-psoriatic treatment or phototherapy within 8 weeks prior the study, patients with hypercalcaemia, impaired renal function, previous or current carcinoma. Patients were not permitted to take other topical or systemic medication that could affect the course of their psoriasis.

Investigational products used:

Patients who fully complied with the inclusion/exclusion criteria were included in the wash-out/qualification period. During this period, the patients were allowed to use the emollient cream Danatekt® only if it was required.

Patients who fully complied with the protocol's eligibility criteria were randomly assigned to treatment with placebo ointment (vehicle of calcipotriol) on one side of the body and calcipotriol ointment 50 μg/g on the other side of the body. A thin layer was applied to psoriatic lesions twice daily. A maximum of 3 tubes of 30 g ointment (calcipotriol or vehicle) was provided per 2 weeks.

All randomised patients received narrow-band UVB (TL-01) phototherapy 3 times weekly regularly spaced. The starting narrow-band UVB was determined by skin type:
- skin type II and III : 200 mJ/cm²,
- skin type IV : 300 mJ/cm².
The narrow-band UVB doses were gradually increased by 20% at every irradiation until:
- clearance of psoriatic lesions for at least one body side was obtained or,
- 90% ± 5% reduction in PASI score for at least one body side was obtained or,
- the maximum UVB dose was reached (1400 mJ/cm² for skin II and III or 1700 mJ/cm² for skin type IV).

When the maximal UVB dose was reached the same dose was repeated for the next irradiations until the end of the study.

The narrow-band UVB dose was not to be increased or was decreased if any following adverse event appeared:
- slight erythema,
- minor, mild and severe burning.

On days of narrow-band UVB phototherapy the ointment should be applied no later than 2 hours prior to exposition.

**Efficacy, tolerability and safety parameter:**
The two treatments were compared with respect to percentage change in PASI from baseline to the end-point. The end-point was the visit when the patient reached the clearance of psoriasis or at least 90% ± 5% reduction in PASI score (on one side or both body sides) or withdrawn of the study or at visit 6 (end of the study).
The secondary response criteria were:
- change in the various clinical parameters (redness, thickness, scaliness and extent) from baseline to end-point,
- percentage of patients who achieved the target treatment response,
- duration (in days) of treatment from visit 2 (baseline) to achieve the target treatment response,
- to compare the treatment response on the two body sides from investigator's and patient's grading of the overall assessment,
- to compare the clinical adverse events recorded on the two body sides,
- to present any within-patient changes in the laboratory parameters from baseline to each subsequent visit.
Study procedures:

<table>
<thead>
<tr>
<th>VISITS</th>
<th>PHASE I Wash-out qualification</th>
<th>PHASE II Calcipotriol/placebo ointment and narrow-band UVB (TL-01)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2 3 4 5 6</td>
</tr>
<tr>
<td>Weeks</td>
<td>-2</td>
<td>0 2 4 6 8</td>
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<tr>
<td>Medical history</td>
<td>*</td>
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<td>Randomisation to calcipotriol or placebo</td>
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<tr>
<td>Investigator clinical assessment (PASI)</td>
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<tr>
<td>Patient and investigator overall assessment</td>
<td>* * * *</td>
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<tr>
<td>Recording of adverse events</td>
<td>* * * *</td>
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</tbody>
</table>

Laboratory examination(1):

Haematology:
- B-haemoglobin * *(2)
- B-red blood cells count * *(2)
- B-white blood cells count * *(2)
- B-differential WBC * *(2)
  (if WBC in abnormal)
- B-platelets * *(2)

Biochemistry 1:
- S-total-calcium * *(2)
- S-albumin * *(2)

Biochemistry 2:
- ALAT/ASAT * *(2)
- S-phosphate * *(2)
- S-creatinine * *(2)

Pregnancy test(3) *

Supply of study medication * * * *

Collection of unused and used study medication * * * *

Emollient *

(1) In case any abnormality occurred, the examination was repeated until normalisation
(2) Or earlier in case of withdrawal
(3) In female patients of child-bearing potential
Efficacy results:
Six French centres recruited 61 patients with 59 qualifying for randomisation. This randomised population included 46 males (78.0 %) and 13 females (22.0 %), with a mean age of 43.9 years (range 18-70), with the following skin types: 20.3 % (n=12) skin type II, 44.1 % (n=26) skin type III and 35.6 % (n=21) skin type IV. The mean duration of psoriasis was 15.3 years (range 1-42) and 41 % (n=25) had been using antipsoriatic therapy within the last 2 weeks prior to wash-out/qualification phase.

All the randomised patients fulfilled the major protocol's eligibility criteria and were included in the per-protocol population. For 2 patients, the data analysed for efficacy were those of their visit before the last visit attended, because of important deviation from the treatment schedule defined as lack of ointment application and narrow-band UVB phototherapy exposure between two consecutive visits.

The mean reduction in PASI score was statistically significantly greater at the end-point in calcipotriol + narrow-band UVB phototherapy body side compared to the body side treated with narrow-band UVB phototherapy + vehicle.

<table>
<thead>
<tr>
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<th>Calcipotriol + UVB body side</th>
<th>Vehicle + UVB body side</th>
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<tbody>
<tr>
<td>Mean PASI at baseline</td>
<td>21.09</td>
<td>21.01</td>
</tr>
<tr>
<td>Mean PASI at end-point</td>
<td>2.75</td>
<td>4.22</td>
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<tr>
<td>Relative change in mean PASI from baseline to end-point</td>
<td>86.35 %</td>
<td>78.86 %</td>
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<td></td>
<td>p &lt; 0.001</td>
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</table>

The mean difference between the two treatment groups for all the signs of the psoriatic lesion (extent, severity, thickness, scaliness) was significantly in favour of the calcipotriol + UVB body side.
Investigators' and patients' assessments were significantly in favour of the body side treated with calcipotriol + narrow-band UVB phototherapy. At the end-point, calcipotriol + narrow-band UVB phototherapy body side was judged as "cleared" or "marked improvement" by 89.9 % of patients and 94.9 % of investigators when the opposite side had the similar judgement by 72.9 % of patients and 81.4 % of investigators.

![Graph showing "Cleared" or "Marked improvement" at end-point](image)

The onset of this action ("cleared" or "marked improvement") was significantly more rapid in calcipotriol + narrow-band UVB phototherapy body side with better efficacy.
"Clearance" or at least 90 % ± 5 % reduction in PASI score on one or both sides was achieved by 50 patients (84.75 %), 16 on calcipotriol plus narrow-band UVB phototherapy treated side only, 2 on vehicle plus narrow-band UVB phototherapy treated side only and 32 with the both treatments. This status was reached by 29 patients (49.2 %) before 4 weeks of treatment and by 46 patients (78.0 %) before 8 weeks of treatment.

Safety results:
Of the 59 randomised patients, 26 patients (44.1 %) reported a total of 43 adverse events, of which 18 were judged to be "possibly" or "probably" related to the use of medication. The most commonly reported adverse events were in the WHO group "Skin and appendage disorders" reported by 19 patients (32.2 %). In this group, 18 patients (30.5 %) reported "lesional/perilesional irritation". There were no drug related serious or unexpected adverse event reported during the trial.
No case of hypercalcaemia or other significant laboratory abnormalities were recorded.
Conclusion:
In this study, calcipotriol ointment plus narrow-band UVB phototherapy three time weekly has been shown to be an effective and safe combination treatment when treating extensive psoriasis.
Calcipotriol ointment plus narrow-band UVB phototherapy gave a response in reduction in PASI score earlier than vehicle ointment plus narrow-band UVB phototherapy. This improvement in favour of calcipotriol ointment plus phototherapy was found by the patients and the investigators. Each of them judged the improvement after 2 weeks of treatment.
Calcipotriol potentialises the effect of narrow-band UVB phototherapy.