Treatment of vitiligo with narrowband-UVB (TL01) combined with tacrolimus ointment (0.1%) vs. placebo ointment, a randomized right/left double-blind comparative study

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Abstract

Background Only a few, small double-blind clinical trials have been reported for the treatment of vitiligo. Narrowband-ultraviolet B (NB-UVB) is an established form of treatment for this condition. Tacrolimus ointment is assumed to have an effect in some patients.

Objectives To assess the additive effect of tacrolimus ointment (0.1%) once daily in vitiligo patients treated with NB-UVB.

Methods In a randomized double-blind trial, patients with stable symmetrical vitiligo were treated half-side with tacrolimus ointment (0.1%) and half-side with placebo ointment. Whole body NB-UVB was given twice or thrice weekly for at least 3 months. As a morphometric device, Visitrak™ was used to measure the area of the vitiligo target lesions.

Results Of 40 patients, 27 had a better effect on the tacrolimus side. The degree of improvement was significantly better on the tacrolimus side (P = 0.005). The median reduction in the target lesion areas was 42.1% on the tacrolimus side and 29% on the placebo side. There was a correlation between the effect and the number of topical tacrolimus applications (P = 0.044), but there was no correlation with the number of UV treatments given; neither any significance of gender, age, skin type, duration of disease, familial occurrence of vitiligo nor presence of other autoimmune disease or atopy was observed. We found a significant reduction in the patients’ subjective disease impact during the treatment period (P < 0.001).

Conclusion According to this study, the combination of NB-UVB and tacrolimus ointment (0.1%) is more effective than UV treatment alone in patients with vitiligo. The effect is tacrolimus total dose-dependent.

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Conflict of interest

The study was initiated and carried out independently by the authors. Apart from supply of the topical medications, the study was accomplished without influence or any form of investigator compensation from Astellas Pharma.

Introduction

Several treatment modalities have been used to achieve repigmentation in vitiligo. A meta-analysis showed the most effective and safe therapy for localized vitiligo to be potent corticosteroids and for generalized vitiligo to be ultraviolet B (UVB) therapy.1 Narrowband (NB)-UVB has been reported to be advantageous to psoralen plus ultraviolet A with respect to efficacy and pigment stability.2 Various topical agents have been combined with phototherapy for treatment of vitiligo.3 Tacrolimus has been reported to induce repigmentation in vitiligo, and an enhanced improvement has been demonstrated by combining tacrolimus and UVB therapy.4

We performed a randomized and controlled double-blind study comparing NB-UVB combined with tacrolimus ointment (0.1%) and NB-UVB combined with placebo ointment. The aim of this study was to assess the additive effect of tacrolimus ointment in vitiligo patients treated with NB-UVB.

Materials and methods

This study was approved by the local ethics committee for medical research. Patients were recruited at the Department of Dermatology, Ullevaal university hospital in Oslo during September 2006–April 2007. We had to stop the inclusion in April to avoid outdoor sun exposure from interfering with the UV treatment. Patients
aged above 18 years having Fitzpatrick skin type II–VI with stable, symmetrical vitiligo were invited to take part in this study. They were consecutively included following signed informed consent. Pregnant or breast-feeding women were excluded.

Symmetrical vitiligo target lesions were selected in every patient, taking care to avoid cross-contamination of the medications applied. The total vitiligo area was assessed using the palm and thumb method on 1% of the skin surface. The area of the target lesions was recorded precisely using Visitrak™ (Smith & Nephew Inc., Largo, FL, USA). An inter-observer comparison and a reproducibility test for 10 patients showed a variation of less than 5% for both tests. A visual analogue scale [(VAS) 1–10] was used to measure the patients’ subjective impact of living with vitiligo.

Whole-body phototherapy was given with NB-UVB (Waldmann 1000; Phillips TL 100W/01) two or three times a week for at least 3 months with a 3-month follow-up. The skin area affected with vitiligo changed from a median of 6% (range 0.25–90%) to 4.9% (range 0–67%) throughout the study period (P = 0.001). The median reduction in the target lesion area on the tacrolimus side was 42.1% compared to 29% on the placebo side (Table 1). The patients with at least 20% better effect on the tacrolimus side were counted as high-responders, and those with less advantage of tacrolimus as low-responders (Table 2). The clinical improvement is exemplified in Fig. 1.

There was a statistically significant correlation between the reduction in the target lesion areas and number of tacrolimus applications (Fig. 2), but no correlation with the number of UV treatments (Fig. 3). There was an equal distribution of gender, duration and degree of disease, autoimmunity, atopy and family occurrence between responders to tacrolimus and non-responders.

There was no correlation between skin type and the effect of treatment. The impact of vitiligo measured on a visual analogue scale of 1–10 varied considerably. A significant change from mean 5.9 to 4.9 was seen throughout the study period (P < 0.001). There was no correlation between the disease impact measure and the treatment effect. However, even patients with only slight effect of the treatment reported increased coping ability during the course of the study.

At follow-up time, the median total affected area was 4.41% (range 0–66%), hence there was no major relapse.

### Statistical analysis

The initial power calculation estimated was based on an additional effect of tacrolimus in the order of 10% with a standard deviation of 7.3. This gave a sample size of 50 patients. Throughout this study, the change in percentage of the vitiliginous area and the target lesion areas was assessed and analysed by non-parametric Wilcoxon tests. Pearson correlation coefficient was used to assess the relationship between treatment effect (percentage reduction of target lesion areas) and number of treatments or duration of disease. Comparison between responders and non-responders was done with Mann–Whitney or chi-squared tests as appropriate. Change in VAS scores of the patients during treatment was tested with a pair-wise t-test. All statistical analyses were performed with SPSS version 16.0 (SPSS Inc., Chicago, IL).

### Results

The patients had 17–68 UV treatments (mean 46). Three patients had less than 25 treatments. The number of topical treatments carried out varied from 33 to 221 (mean 148) and all, except three patients, were compliant with every night application. Two patients applied the ointment on the target lesions only, and only these vitiliginous areas were recorded in those patients. The duration of the treatment was 89–252 days (mean 177). The follow-up time after the last treatment was 42–297 days (mean 138) for 34 patients. Six patients were lost to follow-up.

### Side-effects

There were no phototoxic events or persistent erythema during the study, but some reactions to the ointments. Perioral dermatitis

### Table 1 Percentage reduction in target lesion areas, n = 40

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Range</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Tacrolimus side</td>
<td>42.1</td>
<td>(−73) – (+100)</td>
<td></td>
</tr>
<tr>
<td>Placebo side</td>
<td>29.0</td>
<td>(−71) – (+100)</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>13.1</td>
<td>0.005</td>
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</tbody>
</table>

### Table 2 Tacrolimus response categories, n = 40

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-responders</td>
<td>9</td>
<td>22.5</td>
</tr>
<tr>
<td>Low-responders</td>
<td>19</td>
<td>47.5</td>
</tr>
<tr>
<td>Non-responders</td>
<td>12</td>
<td>30.0</td>
</tr>
</tbody>
</table>

*No higher reduction in target lesion area on the tacrolimus side than on the placebo side.
arose in one patient affecting the vitiliginous skin. The condition was most pronounced on the tacrolimus side. Several patients found the ointment quite greasy to apply, especially if the areas were extensive or hair-covered, and this was the reason why two of the patients treated the target lesions only. No hyperpigmentation was noticed on the tacrolimus side.

Discussion

Vitiligo is a treatment-resistant disease, and to achieve repigmentation, various strategies have been tried. Corticosteroids may be effective, but the long-term use is restrained by the side-effects. In a combination study, betamethasone dipropionate (0.05%) in the morning and calcipotriol ointment (0.005%) in the evening were reported to be better than any of the treatments in localized vitiligo.\(^5\) In 2002, tacrolimus ointment was, for the first time, reported to induce repigmentation in vitiligo.\(^6\) Tacrolimus inhibits T-cell activation, and thereby blocks the production and release of proinflammatory cytokines.\(^7\) A comparative study revealed tacrolimus ointment (0.1%) to be almost as effective as clobetasol propionate cream (0.05%) for the treatment of childhood vitiligo, and tacrolimus is concluded to be favourable in younger individuals and in sensitive areas as it does not induce atrophy.\(^8\)

Phototherapy is widely used in the treatment of vitiligo. Topical tacrolimus has been combined with NB-UVB or 308 nm excimer laser, and has been shown to enhance the effect of the UV source, but only small double-blind studies have been presented to confirm this.\(^8,9\) According to a recent Cochrane review, the benefit of topical tacrolimus in conjunction with UV light has limited evidence, but more robust randomized controlled trials are requested to establish fully the efficacy and safety of currently used interventions.\(^10\)

This double-blind study is one of few performed in treating a greater number of vitiligo patients. It confirms the conclusion of previous reports that tacrolimus ointment enhances the effect of NB-UVB.
Evaluation of treatment effects may be measured in many ways. Other authors have used semi-quantitative methods for evaluating vitiligo treatment response. A vitiligo area scoring index has been described.\textsuperscript{10,11} We wanted to use a quantitative morphometric method, and found the Visitrak\textsuperscript{TM} useful for this purpose.

The treatment effects found in our study were of limited degree. Just a few patients regained full repigmentation with a symmetrical response. We found a reduction in vitiligo target lesions to be 42.1% on the tacrolimus side and 29% on the placebo side. However, the target lesions chosen were not necessarily representative for the treatment effect. The dorsal aspects of hands were used in several patients due to practical considerations (Fig. 1), but the distal parts of extremities are known to respond less to different treatment modalities.\textsuperscript{12} In several previous studies, tacrolimus ointment was applied twice daily.\textsuperscript{6,7} If we had done so, it might have augmented the tacrolimus effect, especially as we found a significant correlation between the effect and the number of applications. Surprisingly, we found no increasing effect with increasing number of UV treatments, which may be due to a small number of treatments. According to clinical experience, the effect of UV treatment may show up late in the treatment course. This might also be the explanation why the effect gained by NB-UVB monotherapy on the placebo side was less than reported by other authors.\textsuperscript{3} In other reported studies, the patients received a far higher number of NB-UVB treatments, such as three times weekly for 1 year.\textsuperscript{13} This is three-fold more than the mean number of treatments given to our patients.

The follow-up period was too short for evaluation of the durability of the effect. It is known that the repigmentation obtained during NB-UVB treatment is unstable in several patients. A previous study revealed lasting pigmentation in only 16% of the patients, 2 years after termination of NB-UVB treatment.\textsuperscript{13}

The patients in this study reported only slight subjective side-effects of the ointments. Mild burning, stinging, dryness, erythema, scaling and pruritus from tacrolimus have been experienced by other patients.\textsuperscript{8} Concern about a photo-carcinogenic effect of tacrolimus ointment has been raised, but so far, the combination of NB-UVB and tacrolimus is considered a safe therapeutic option.\textsuperscript{14} The depigmentation in vitiliginous skin is, by nature, completely different from depigmented skin seen in albinos. Development of sun damage and skin malignancies in vitiligo patches is extremely rare.\textsuperscript{15}

In conclusion, NB-UVB combined with tacrolimus ointment (0.1%) once daily may be a favourable treatment option for vitiligo, especially if the distribution is limited. Further studies are required, also focusing on the optimal duration of therapy and long-term follow-up results.

Acknowledgements
We thank Astellas Pharma for providing the topical medications for the study.

References