Clinical and patient reported outcomes in vitiligo
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A RANDOMISED COMPARISON OF EXCIMER LASER VERSUS NARROW-BAND ULTRA VIOLET B PHOTOTHERAPY AFTER PUNCH GRAFTING IN STABLE VITILIGO PATIENTS

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SUMMARY

Background: Ultraviolet radiation following punch grafting may stimulate the migration of melanocytes from the grafts into the vitiliginous skin, thereby increasing the rate of repigmentation. We compared the effects of the 308-nm xenon chloride excimer laser (EL) versus Narrow-Band Ultraviolet B (NB-UVB) after punch grafting in patients with vitiligo.

Objective: The aims of this study were to evaluate 1) repigmentation (%), 2) treatment satisfaction and 3) patient preferences for EL versus NB-UVB therapy after punch grafting in vitiligo.

Methods: Fourteen patients were treated with the punch grafting technique on two symmetrical vitiligo patches. Starting 1 week after the punch grafting, the vitiligo patches were treated twice a week during 3 months, with EL on one side and with NB-UVB on the other side. Repigmentation (%) was measured by a digital image analysis system. Patients’ satisfaction with and preference for treatment were also assessed.

Results: Whereas both treatment modalities induced repigmentation, no statistically significant difference was found in grade of repigmentation after 3 months. With EL, 71.4% lower cumulative dose was reached. Patients were significantly more satisfied with NB-UVB and preferred it over EL.

Conclusions: The choice between EL and NB-UVB cannot solely be based on repigmentation, but rather on other factors, such as patients’ preferences. However, given the lower UV dose of EL, we recommend its use in vulnerable populations, such as small children and patients with sun-damaged skin with a history of long-term UVB treatment.
INTRODUCTION

Vitiligo is a common skin disorder, characterized by the appearance of milky white maculae, due to a loss of melanocytes. Non-surgical and surgical therapies are available for vitiligo. Surgical therapies can be considered for stable vitiligo patches that are resistant or respond unsatisfactorily to non-surgical therapies.

In the Netherlands Institute for Pigment Disorders (NIPD) we routinely use the autologous punch grafting technique as a surgical therapy. This technique is relatively simple and has shown to be effective for stable localised and generalized vitiligo. After punch grafting, we treat our patients with narrow band ultraviolet B (NB-UVB) to stimulate further repigmentation. Monotherapy with NB-UVB was introduced in 1997 as an effective treatment for generalized vitiligo, with better repigmentation and fewer adverse effects than topical photo chemotherapy (PUVA).

In 2002, the 308-nm xenon chloride excimer laser (EL) was introduced as a treatment for vitiligo. In vitiligo EL treatment was compared with NB-UVB treatment. A higher efficacy of EL was found as it produced more rapid repigmentation. Another advantage of EL over NB-UVB is selective targeting which spares non-affected skin and reduces the cumulative UV dose. Punch grafting followed by either EL or NB-UVB was found to be effective in inducing repigmentation in vitiligo patients. In these studies, repigmentation was assessed by independent investigators who rated photographs of the treated skin.

To our knowledge, no studies have compared the efficacy of EL versus NB-UVB after punch grafting in vitiligo patients. The aim of this study was to evaluate percentage of repigmentation, treatment satisfaction and patient preferences regarding EL versus NB-UVB therapy as a post-treatment regimen in vitiligo patients who underwent punch grafting.

METHODS

We employed a prospective, single blinded, randomized within-patient controlled study design. The trial was approved by the local research ethics committee and was recorded in the trial register (www.trialregister.nl, NTR789).

Patients

Consecutive adult patients (18 years or older) attending the NIPD, with stable generalized vitiligo were invited to participate in the study. Stable vitiligo was defined as no progression of existing lesions or no appearance of new lesions during the previous 6 months, absence of the Koebner phenomenon and a positive minigrafting test. An additional inclusion criterion was the presence of two symmetrical vitiligo patches on the extremities or the trunk, to reduce exposure to sunlight. Exclusion criteria included a history of hypertrophic scarring and/or keloid, allergic/phototoxic reaction (Lidocaine, Tegaderm, Suture strips, and sunlight), a personal or family history of skin cancer or photosensitivity and/or
photo toxicity disorders, Skin type I (according to Fitzpatrick classification I-VI), pregnancy, use of medications known to cause photosensitivity and/or photo toxicity and other skin diseases that would impair evaluation of repigmentation or local immunosuppressive treatment within 6 weeks prior to enrolment.

**Treatment**

*Selection of treatment sites and randomization*

In each patient we selected two treatment areas that were similar in size, colour and body location. The site of treatment with EL and NB-UVB was randomly assigned with a randomization computer program (Graphpad Software Inc., La Jolla, CA, USA). Treatment allocation was blinded for the physicians, not for the patients.

*Punch grafting*

The two lesions were treated with punch grafts in the same distribution pattern. The punch grafting method consists of harvesting small 1.5 mm full thickness punch grafts from normally pigmented donor sites (such as hip, buttocks and outer thigh). These were subsequently transplanted to the two depigmented acceptor sites in which similar punches were taken and removed. The procedure was performed using local infiltration anaesthesia. The grafts were placed 5 mm apart and were covered with suture strips and a transparent adhesive tape (Tegaderm) during 7 days. The donor site was also covered with a transparent adhesive tape (Tegaderm). Lesions treated on the extremities were covered with an elastic bandage for 1 week to give compression and fixation on the grafted site.

*Post-treatment phototherapy*

After 7 days, the grafted areas were irradiated during 3 months with EL at one side and NB-UVB on the other side: twice a week, on non-consecutive days amounting to 24 treatments. Patients started their treatment at the beginning of September and the last treatment was given in July.

*308-nm EL*

A 308-nm xenon chloride gas EL (Talos®; Wavelight Laser Technology AG, Erlangen, Germany; 308 nm, 10 or 20 mm spot size, 200 mW/ cm², 60 ns, 200 Hz) was used. The initial dose was 0.05 J/ cm², independent of the skin type. Sequential doses had an increment according to the manufacturer’s guidelines, with a range of 0.025- 0.10 J/ cm². Doses were not increased if there was erythema lasting for 24 hours or more. If painful erythema, such as burning, pain, or blistering developed, the treatment was withheld until this erythema disappeared. The subsequent dose was decreased by 0.05 J/ cm². Possible presence of painful erythema was checked by the treating dermatologist. The cumulative UV dose was measured at the end of the treatment. The eyes of the patient and nurse were protected by UV-blocking goggles during the treatment session.
UVB (311nm) phototherapy (NB-UVB)
The treated vitiligo patches were locally irradiated based on our own guidelines for NB-UVB in vitiligo patients of the NIPD. The initial irradiation dose was 0.25 J/cm², independent of the skin type. Irradiation dose was increased by 50 mJ/cm² each subsequent treatment when minimal erythema occurred in the lesions, which means an erythema vanishing within 24 hours. If the erythema was lasting for 24 hours or more the dose was held constant for the subsequent treatment. If painful erythema developed, the treatment was withheld until the painful erythema was relieved and the subsequent dose was decreased by 20%. The cumulative UV dose was measured at the end of the treatment. The eyes were protected by UV-blocking goggles during the treatment.

For both treatment modalities, the patients were asked to protect their skin from sun exposure during treatment and to apply sunscreen in case sun exposure of the treated skin was unavoidable.

Assessment of therapy outcomes

Repigmentation. Clinical photographs of the treated lesions were taken with a Canon Power Shot G6 digital camera, prior to punch grafting and after every six treatments with EL and NB-UVB. Conditions were standardized throughout the study, including the room, lighting, background and distance between camera and patient.

Objective measurement of the grade of repigmentation was performed by a digital image analysis system. To assess the size of the vitiligo lesion the contours of the lesion were copied on a transparent sheet before and after treatment. This technique has the advantage that the curvature of the body surface will not bias the measurement. Afterwards these sheets were scanned using a predefined resolution. Digital image analysis involved an application based on Matlab (Math works, Inc, Natik, MA, USA). By comparing pre- and post-treatment pictures we computed the relative surface showing repigmentation expressed in percentages.

Treatment satisfaction. A study-specific questionnaire consisting of two questions on satisfaction with each treatment modality: (i) How do you appreciate the results of punch grafting with the EL (or NB-UVB) and (ii) Would you recommend this treatment to other patients? Answers were given on a 7-point scale running from ‘very good’ to ‘very poor’, and ‘yes, certainly’ to ‘no, certainly not’ respectively. Administration took place after 3 months treatment.

Patient preference. A study-specific questionnaire consisting of two questions on preference: (i) If you will be treated again with punch grafting, which treatment do you prefer? and (ii) Can you report the reason for this preference? Optional answers to the first question were: EL, NB-UVB, I don’t know, no preference. Optional answers to the second question were: more repigmentation, a faster rate of repigmentation, no colour difference, faster treatment, other....
Statistical Analysis

On the basis of the results of a pilot study, including 20 patients, we estimated that EL would lead to 15% more repigmentation after 3 months than NB-UVB. A sample size of 16 patients would have a power of 80% with $\alpha$ of 0.05 to detect this difference, assuming a standard deviation of 20%. Paired Student’s t-test was used for the statistical evaluation of the differences in percentage of repigmentation. The Wilcoxon signed ranks test was used for the difference in patient satisfaction between the two treatment modalities. All analyses were conducted using SPSS (for Windows version 12.01; SPSS Inc., Chicago, IL, USA). The level of significance was set at P<0.05.

RESULTS

Patient characteristics

A total of 16 patients were included in the study. Two of these patients did not finish the study (after 8 and 13 treatments) because of private problems unrelated to the study. These patients were not included in the statistical analysis. One patient only completed 21 out of the 24 treatments and another patient completed 22 treatments because of health problems unrelated to the vitiligo treatment. These patients were included in the statistical analysis. All participants gave informed consent. The 14 patients suitable for analyses consisted of nine female and five male patients, with a mean age of 44.2 years (SD 16.4, median 47.2) (Table 1). None of the patients experienced painful erythema during therapy and 3 months after the EL and NB-UVB.

Repigmentation

The mean degree of repigmentation attained after EL treatment was 31% compared to 38% for NB-UVB treatment [$t (df = 13) = 2.11; P<0.06$]. More than 75% repigmentation was obtained in two patients after EL versus three patients after NB-UVB. The cumulative UV dose for lesions treated with EL was $7.3 \pm 3.5 \text{ J/cm}^2$ and $7.8 \pm 3.6 \text{ J/cm}^2$ for NB-UVB.

Table 1. Patients characteristics

<table>
<thead>
<tr>
<th>N=14</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
</tr>
<tr>
<td>Female</td>
<td>9</td>
</tr>
<tr>
<td>Age</td>
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<tr>
<td>Median</td>
<td>47.2</td>
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<tr>
<td>SD</td>
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</tr>
<tr>
<td>Disease duration</td>
<td></td>
</tr>
<tr>
<td>1-5 years</td>
<td>4</td>
</tr>
<tr>
<td>&gt; 10 years</td>
<td>10</td>
</tr>
<tr>
<td>Skin type</td>
<td></td>
</tr>
<tr>
<td>I-III</td>
<td>4</td>
</tr>
<tr>
<td>IV-VI</td>
<td>10</td>
</tr>
</tbody>
</table>
for NB-UVB 25.6 ± 11.6 J/cm². With EL 71.4% lower cumulative dose was reached (Table 2). For both treatment modalities, there was no further pigmentation of the punch grafts on the feet (n=3).

Treatment satisfaction
Seven patients (50%) reported to be satisfied with the results of EL treatment, whereas 11 (79%) patients indicated to be satisfied with the results of NB-UVB treatment \[z (df=13)= 2.41; P=0.02\]. Patients were found to be comparable with respect to recommending a treatment modality to another patient: eight patients vs. nine patients would recommend treatment with EL vs. NB-UVB. Moreover, three patients would possibly recommend either modality whereas two patients were not able to make a choice. Finally one patient would not recommend EL.

Patient preference
Seven patients (50%) preferred NB-UVB to EL because of more and more rapid repigmentation while two patients (14.3%) preferred EL because it was less time consuming. Five patients did not have a preference for treatment (35.7%).

DISCUSSION
To our knowledge, this is the first randomized controlled trial of EL versus NB-UVB treatment after punch grafting in vitiligo patients. Contrary to our expectation, EL did not result in a higher degree of repigmentation than NB-UVB, but rather led to comparable results. Interestingly patients favoured the NB-UVB treatment as they were more satisfied with it and preferred it over EL.

Our results run counter to two previous studies that compared EL with NB-UVB in vitiligo patients who did not undergo punch grafting. In a group of eight vitiligo patients, Hong et al\(^{15}\) found that EL was more effective than NB-UVB as it produced more rapid and profound repigmentation. Another study comparing EL with NB-UVB in 21 patients, also found that EL was more effective because of faster repigmentation.\(^{16}\) In these studies, physicians assessed repigmentation based on clinical examination and evaluation of photographs. Conversely, we used a digital image analysis system, which is a more objective and reliable scoring method, perhaps explaining, in part, the difference in results.

We noticed a remarkable dispersion of repigmentation irrespective of the type of phototherapy. This is partly a result of the inclusion of locations that are known to react poorly, such as the feet. However, it also indicates that intrinsic patient-related factors may be more important than post-treatment procedures for the results of punch-grafting in vitiligo as was suggested recently.\(^{21}\) As it is known that stability is a lesion-specific phenomenon in many patients, the area based variable status of stability may account for some variation in matched pairs.

The used treatment doses merit attention. We treated our patients according to the NIPD guidelines and started with an initial dose of 0.25 J/cm² for the
NB-UVB and 0.05 J/cm² for EL. These dosages are within the wide range reported in the literature. For NB-UVB therapy initial doses range from 0.10 J/cm²-0.74 J/cm² or 70% of the minimal erythema dose (MED). For EL, initial doses are much lower and range from 0.05 J/cm²-0.60 J/cm², depending on the body site, or 75% the MED. Whereas we used the lowest reported initial dose of EL, we found this was warranted because most patients reported a mild short-lived erythema on the treatment day on both treated sites. Consequently, the comparable repigmentation induced by EL was achieved by a lower cumulative dose, i.e. 71.4% less than that of NB-UVB treatment.

The choice for either EL or NB-UVB cannot be made on the percentage of repigmentation but needs to be based on other factors, such as patients’ preferences, cumulative dose, availability, ease of administration and costs. NB-UVB is the preferred choice of patients, and it is more feasible, less time consuming and cost-effective. However, the cumulative dose is substantially higher than that of EL, and it may affect surrounding tissue possibly resulting in long-term side effects, such as increased carcinogenicity. As we lack insight into

### Table 2. Treatment outcomes

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>Treated lesion</th>
<th>Skin type (II-VI)</th>
<th>Repigmentation After excimer laser (%)</th>
<th>Repigmentation After NB-UVB (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>18,5</td>
<td>Arms</td>
<td>V</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>18,8</td>
<td>Trunk</td>
<td>IV</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>48,9</td>
<td>Arms</td>
<td>IV</td>
<td>56</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>52,9</td>
<td>Arms</td>
<td>IV</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>37,9</td>
<td>Feet</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>6¹</td>
<td>F</td>
<td>63,8</td>
<td>Legs</td>
<td>IV</td>
<td>65</td>
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<tr>
<td>7</td>
<td>F</td>
<td>42,7</td>
<td>Legs</td>
<td>II</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>54,1</td>
<td>Trunk</td>
<td>V</td>
<td>59</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>45,5</td>
<td>Feet</td>
<td>IV</td>
<td>6</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>62,1</td>
<td>Trunk</td>
<td>III</td>
<td>22</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>27,1</td>
<td>Trunk</td>
<td>II</td>
<td>15</td>
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<tr>
<td>12</td>
<td>M</td>
<td>69,1</td>
<td>Legs</td>
<td>II</td>
<td>17</td>
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<tr>
<td>13</td>
<td>M</td>
<td>50,0</td>
<td>Legs</td>
<td>IV</td>
<td>5</td>
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<tr>
<td>14</td>
<td>F</td>
<td>27,0</td>
<td>Feet</td>
<td>IV</td>
<td>5</td>
</tr>
</tbody>
</table>

Mean (SD)

¹ patient with 21 treatments, ² patient with 22 treatments
the prevalence and severity of long-term side effects of vitiligo treatment with EL or NB-UVB, future studies are needed on this point.

A number of limitations of this study merit attention. Firstly, the sample size is relatively small. Our sample size analysis indicated that inclusion of 16 patients would be sufficient to achieve significant differences. However, as two patients dropped out of the study prematurely, we have results of 14 patients instead of the intended 16. This number appeared to be sufficient to draw clear conclusions as the percentage of repigmentation of EL was not higher but lower than that of NB-UVB, albeit insignificantly. More importantly, we found statistically significant differences between the treatment modalities with respect to patients’ treatment satisfaction.

Secondly, this study only focused on short-term effects of 24 treatments. We therefore have no information on the effects of longer treatments or on long-term follow-up effects.

Our study has a number of strengths. The within-patient study design where EL and NB-UVB were randomly allocated to skin patches at either side of the body, allowed for direct comparison between the two treatment modalities. An additional major strength is the objective and reliable assessment of the percentage of

<table>
<thead>
<tr>
<th>Cumulative dose EL (J/cm²)</th>
<th>Cumulative dose NB-UVB (J/cm²)</th>
<th>Difference in cumulative dose (J/cm²)</th>
<th>Patient Satisfaction EL</th>
<th>Patient Satisfaction NB-UVB</th>
<th>Treatment Preference</th>
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<tr>
<td>9.45</td>
<td>29.47</td>
<td>20.02</td>
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<td>EL</td>
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<tr>
<td>5.69</td>
<td>16.73</td>
<td>11.04</td>
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<tr>
<td>2.30</td>
<td>8.52</td>
<td>6.22</td>
<td>Rather good</td>
<td>Very good</td>
<td>NB-UVB</td>
</tr>
<tr>
<td>3.29</td>
<td>14.41</td>
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<td>13.97</td>
<td>49.31</td>
<td>35.34</td>
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<td>Rather good</td>
<td>NB-UVB</td>
</tr>
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<td>10.67</td>
<td>33.24</td>
<td>22.57</td>
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<td>Good</td>
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<tr>
<td>10.50</td>
<td>36.17</td>
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<td>14.11</td>
<td>9.70</td>
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<td>5.20</td>
<td>23.68</td>
<td>18.48</td>
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<td>NB-UVB</td>
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<tr>
<td>10.25</td>
<td>34.05</td>
<td>23.80</td>
<td>Good</td>
<td>Good</td>
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<td>6.56</td>
<td>23.83</td>
<td>17.27</td>
<td>Rather bad</td>
<td>Rather good</td>
<td>NB-UVB</td>
</tr>
<tr>
<td>8.40</td>
<td>23.90</td>
<td>15.50</td>
<td>Not good not bad</td>
<td>Not good not bad</td>
<td>NB-UVB</td>
</tr>
</tbody>
</table>

Mean (SD)

7.32 (3.50) 25.60 (11.62) 18.27 (8.34)
repigmentation. Moreover, we asked patients systematically about their satisfaction with and preference for either treatment. Whereas these questions needed to be tailored to the study treatments, they were, by definition, study-specific and unstandardized. However, they were simple and straightforward.

In conclusion, both EL and NB-UVB achieve comparable degrees of repigmentation after punch grafting, whereas patients were significantly more satisfied with the results of NB-UVB treatment and preferred it more than EL.

However, given the large variation in results, we strongly recommend shared decision making by the dermatologist and the patient, on the treatment modality of choice. In vulnerable populations, such as small children and patients with sun damaged skin and/or with a history of long-term UVB treatment, EL should be given serious consideration because of its lower UV dose.

**REFERENCE LIST**


