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Treatment of Vitiligo by 308-nm Excimer Laser: An Evaluation of Variables Affecting Treatment Response

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Background and Objectives: To determine the true efficacy of the 308-nm excimer laser for the treatment of vitiligo, while taking into account confounding factors such as anatomic site of treatment, age, sex, skin type, MED, and duration of evolution of the vitiligo.
Study Design/Materials and Methods: Thirty-five patients with vitiligo were included. Each lesion was treated twice a week by the 308-nm excimer laser for a maximum of 24 sessions. Efficacy was blindly evaluated by two independent physicians.
Results: Repigmentation was noted in 46 plaques/52 (88.5%). Repigmentation rate (75%) was obtained in 14 (26.9%). In "UV sensitive" areas (face, neck, trunk), 8/14 lesions (57.1%) had a repigmentation rate, 75% versus 6/38 (15.8%) in "UV resistant" areas (bony prominences and extremities) ($P = 0.031$). No relationship could be established between response to the treatment and the following variables: age, sex, skin type, MED, and duration of evolution of the vitiligo (respectively, $P = 1$, 0.666, 0.566, 0.628, 0.521).
Conclusions: An aesthetically reasonable result is achieved essentially in "UV sensitive" areas, thus appearing to be the appropriate places of choice for this treatment. Lasers Surg. Med. 35:152–156, 2004. © 2004 Wiley-Liss, Inc.

Key words: vitiligo; 308-nm excimer laser

INTRODUCTION

Vitiligo is an acquired cutaneous disorder of pigmentation, with a 1–2% incidence worldwide, without predilection for sex or race. People affected by vitiligo have a vast reduction of quality of life, caused by the color contrast between healthy pigmented skin and the depigmented vitiligo patches, which may cause psychological problems to the patients [1,2]. First line of non-surgical therapy includes topical corticosteroid therapy and phototherapy (solar exposition, Psoralen+UVA (PUVA), narrowband UVB (NB-UVB)) [3–5]. Thanks to its relatively good efficacy and its excellent tolerance, the NB-UVB is now considered as the best treatment for extensive vitiligo vulgaris. However, treating a vitiligo that spreads on less than 10% of the total body surface by NB-UVB unnecessarily exposes healthy areas to radiation. Contrary to the majority of laser devices, the 308-nm excimer laser is not a "destructive" form of therapy but induces photobiological effects similar to selective UVB phototherapy (311–312 nm). As for UVB phototherapy, it could be judged that the efficiency of the 308-nm excimer laser in treating vitiligo depends on immunomodulatory effects (induction of the secretion of cytokines, T-lymphocytes apoptosis) and stimulation of melanocyte migration and proliferation from the niche located in hair follicles.

Thanks to the use of a hand-piece, the 308-nm excimer laser allows a selective treatment of the lesions. This device has already shown interesting results in post-resurfacing leukoderma [6]. To date, three studies have evaluated the effectiveness of the 308-nm excimer laser in the treatment of vitiligo. The first two pilot studies clearly demonstrated the validity of this technique and its good tolerance [7,8]. However, these studies have included a limited number of patients and lesions, and they treated almost exclusively "UV sensitive" areas such as face, neck, arm, and leg, excluding extremities and bony prominences which are usually resistant to phototherapy. The third and last study published provided two interesting pieces of data [9]. First, this study shows that continuation of treatment beyond 40 sessions does not provide further improvement. Second, a clear difference appears between effectiveness on face and axillae when compared to hands or feet. These results suggest heterogeneity of response depending on the localization of the treated areas. Unfortunately, the relatively small number of treated plaques does not justify drawing definitive conclusions.

As the usefulness of the 308-nm excimer laser for treating vitiligo was demonstrated, it became necessary to determine its true efficacy in a controlled study by taking into account the possible effects of confounding factors like age, sex, skin type, duration of disease, and localization. Thus, we conducted a prospective intra-individual study including enough treated lesions to present a statistical analysis of the results.

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MATERIALS AND METHODS

Patients

Thirty-five patients (28 women and 7 men) were included. Criteria for inclusion were age above 12 years, development of vitiligo before the last 3 months, presence of at least two symmetrical patches of vitiligo with surfaces of at least 4 cm^2, and understanding the information and signature of written consent. Criteria for non-inclusion were pregnant or breastfeeding women, personal history of hypertrophic scarring, melanoma or other skin cancer, immunosuppresion or taking immunosuppressive or photosensitizing drugs, and phototherapy or any other vitiligo treatment during the last 3 months. For each patient age, gender, skin type, date of onset of lesions, prior treatments for vitiligo with their results, and finally the localization of the patches of vitiligo were noted.

Treatment

The laser used was the 308-nm Xenon-Chloride excimer laser TALOS©, WaveLight Laser Technology AG, Erlangen, Germany. The fixed technical parameters were pulse frequency 200 Hz, pulse width 60 nanoseconds, and distal pulse energy 4.6 mJ/cm^2. Beam transmission was achieved by an articulated arm with changeable distal heads of 15-, 20-, and 25-mm diameters for the spot sizes. For each patient, two to six target lesions were chosen (one to three vitiligo plaques treated by the laser and one to three untreated control plaques of vitiligo on the opposite side). A maximum number of lesions localized in usually "UV resistant" areas were chosen in order to evaluate precisely the efficacy of 308-nm laser radiation on these difficult areas. All the patients were treated during winter. They were asked to apply a photo-protective cream on the areas exposed to sunlight. No local anaesthetic was used. Lesions were treated twice weekly for a maximum of 24 sessions. Initial fluence was 50 mJ/cm^2 less than minimal erythematous dose (MED) for vitiliginous skin, and fluence was increased by 50 mJ/cm^2 every two sessions. In the presence of vesicles or bullae or erythema lasting more than 8 hours beyond the treated lesions, session treatment was withheld, and the treatment was resumed after resolution at the last dose without side effects. Each treated lesion had an untreated control target lesion on the opposite side.

Assessment

Tolerance was evaluated using a visual analog scale (0: poor to 10: excellent) and side effects were recorded at each session. Efficacy was blindly evaluated by two independent physicians on tracing paper and direct light photographs (Fujifilm Finepix S1 pro©) taken before, at the end of treatment, and for the last time 1 month after the end of the sessions. Repigmentation was graded on a 6-point scale (0—no repigmentation, 1—repigmentation 1–24%, 2—repigmentation 25–49%, 3—repigmentation 50–74%, 4—repigmentation 75–99%, and 5—total repigmentation). In the case of disagreement between the two physicians, a second evaluation was done in common. If the disagreement persisted, the lowest evaluation was chosen. At the final visit, the patients' opinions about treatment effectiveness and their degree of satisfaction were recorded (excellent, good, moderate, poor).

Statistical Analysis

The efficacy of the 308-nm excimer laser was first compared to the control symmetrical plaques. Efficacy was measured in two different ways: (i) no repigmentation versus repigmentation, (ii) repigmentation $<75\%$ versus repigmentation $\geq 75\%$. The last measurement was used to evaluate the aesthetic result. Mc Nemar's χ^2 was used to compare dichotomous variables on matching series. Then the potential confounding factors were studied in single variable analyses using χ^2 and Fisher's exact tests for categorical variables and the Kruskal–Wallis test for continuous ones. All the tests were considered significant at a 5% type I error rate ($P < 0.05$). Statistical analyses were performed using SPSS© version 11.0 (Statistical Package for Social Sciences, SPSS, Inc., Chicago, IL).

RESULTS

The characteristics of the study population are summarized in Table 1. Thirty patients had already tried one or more other therapies for vitiligo (PUVA in 6, NB-UVB in 20 and antioxidant therapies in 12). None of these treatments produced a repigmentation rate of at least 75%. Four patients (11%) discontinued their treatments before the end of the 24th visit because of the following reasons. One patient was satisfied by the result obtained after 15 sessions and decided to stop the treatment. On the other hand, another one gave up due to the absence of repigmentation after nine sessions. Two other patients left the study because of a change in their professional activity. A disagreement between the two observers occurred only once and the lowest evaluation was chosen.

Fifty-two patches of vitiligo were treated. Only 14 patches were chosen in the "UV sensitive" areas (face, neck, trunk, lower and upper limbs, with the exception of bony prominences and extremities), whereas 38 patches were selected in the "UV resistant" areas (cf., Table 2). Repigmentation was observed on 46 plaques (88.5%) after

TABLE 1. Characteristics of the Study Population

	n	%
Number of patients	35	100.0
Age [mean (range)]	43.9	(11–74)
Gender		
Male	7	21.9
Female	28	78.1
Fitzpatrick skin type		
II	5	14.3
III	17	48.5
IV	12	34.3
VI	1	2.9
Duration of disease (y)		
Mean (range)	12.3	(1–41)
Sites treated (mean per patient, range)	1.6	(1–3)

Values are n, %, or mean (range) as appropriate.

TABLE 2. Description of the Anatomic Sites of Treatment

Anatomic sites of treatment	
UV sensitive	14
Face	8
Neck	2
Back	1
Breast	1
Arm	2
UV resistant	38
Knee	6
Elbow	15
Wrists	12
Hand	2
Ankles	2
Feet	1

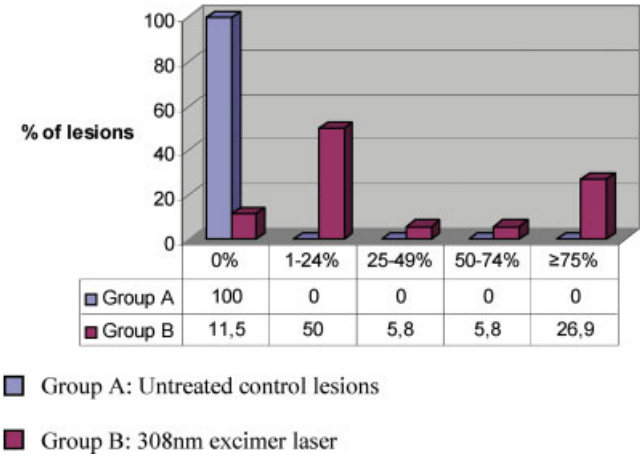

Fig. 2. Global repigmentation after 24 sessions.

the 24 sessions. No untreated control lesions were repigmented. Repigmentation rate (75%) was obtained with 14 plaques (26.9%) (cf., Fig. 1). When we compare the treatment by 308-nm laser excimer with therapeutic abstention, the laser is statistically superior to abstention when taking as the criteria of effectiveness the presence of repigmentation or repigmentation at least equal to 75% ($P < 0.0001$ in both cases). In "UV sensitive" areas, 8 lesions of 14 (57.1%) had a repigmentation, 75% (including 6 of 8 (75%) on the face) while this percentage was only 15.8% (6 lesions of 38) in usually "UV resistant" areas (cf. Figs. 2–4). The total cumulative dose went from 2.6 to 15.3 J/cm^2 (average 9.8 J/cm^2). The beginning of repigmentation was observed by the 15th session on average (range 4–22). The cumulated doses for a beginning of repigmentation were 0.9–12.8 J/cm^2 (average 5.6 J/cm^2).

No relationship could be established in single variable analysis between the response to the treatment and the following variables: age, sex, skin type, MED, and duration of evolution of the vitiligo ($P = 1$, 0.666, 0.566, 0.628, and 0.521, respectively). On the other hand, the response to the treatment is related to the localization of the treated lesion. In special, "UV sensitive" areas responded better than "UV resistant" areas ($P = 0.031$). Subsequently, we performed a more detailed analysis by comparing the response inside the "UV sensitive" and the "UV resistant" areas. In "UV sensitive" areas, no statistically significant difference could be found between face and neck on one hand and back,

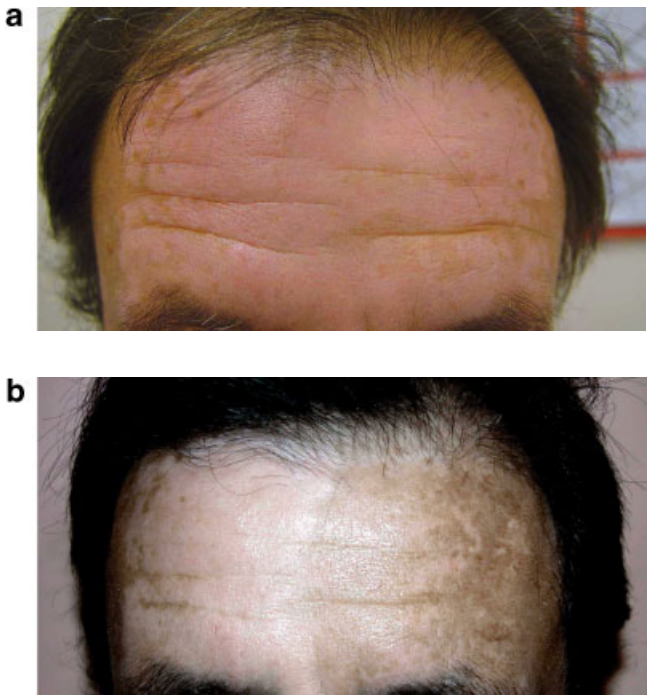

Fig. 1. Vitiligous plaque of the face (**left side**: treated area; **right side**: untreated control area). **a**: Before treatment; (**b**) after 24 sessions. [Figure can be viewed in color online via www.interscience.wiley.com.]

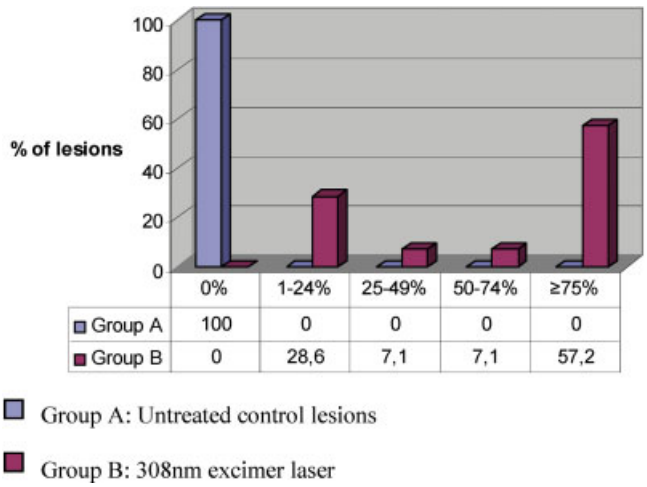

Fig. 3. Repigmentation in "UV sensitive" areas after 24 sessions. [Figure can be viewed in color online via www.interscience.wiley.com.]

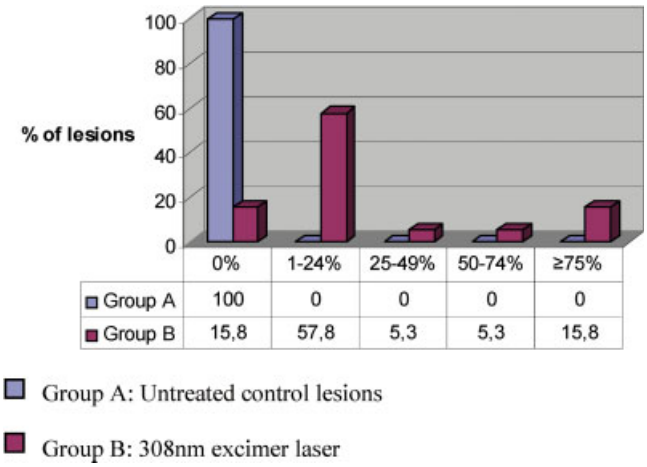

Fig. 4. Repigmentation in "UV resistant" areas after 24 sessions. [Figure can be viewed in color online via www.interscience.wiley.com.]

breast, and arms on the other hand ($P = 0.245$). However, in "UV resistant" areas, the effectiveness of the laser on knees, elbows, and wrists was significantly higher than on hands, ankles, and feet ($P = 0.001$).

Side effects were limited to mild to moderate erythema (observed at least one time in all patients) and localized bullae in five patients (15.6%). Each of these side effects occurred just once for each patient. Tolerance was evaluated by the patients at 7.6/10. No peri-lesional hyperpigmentation was noted. We have not observed any return of depigmentation on the treated lesions within 1 month after the end of the sessions. Subjectively, the degrees of patient satisfaction were excellent (26%), good (22%), moderate (40%), and poor (12%). Moreover, patients' opinions of the treatment efficacy at the end of the 24th session were always better than the objective assessments given by our two independent physicians.

DISCUSSION

Two major parameters must be taken into account in order to evaluate a new treatment for vitiligo. These two parameters, which are the reflection of an improvement of quality of life, are the percentage of repigmentation and the subjective assessment of the patients. On visible areas, such as face and neck, the results are excellent (six of eight plaques on face and two of four plaques on neck, back, and breast achieved at least 75% of repigmentation). For these localizations, all the patients assessed the technique as good or excellent. On the other hand, for "UV resistant" areas the results were not aesthetically acceptable (only 15.8% of the lesions achieved at least 75% of repigmentation) although the response rate was high (84.2%). Thus, for these localizations, more than 70% of the patients have assessed the efficacy as moderate or poor.

In a meta-analysis of the literature assessing the effectiveness and the safety of non-surgical vitiligo repigmentation therapies, class 3 topical corticosteroids and NB-UVB appeared as the best choices for localized and for generalized vitiligo, respectively 10. When regarding percentage of lesions achieving at least 75% of repigmentation, class 3 corticosteroids showed 56% (95% CI, 50–62%) in localized vitiligo and NB-UVB showed 63% (95% CI, 50–76%). Compared to these data, the result obtained in this study is quite poor (27%). However, two important points have to be taken into consideration. First, the total duration of our treatments was shorter than in previous studies (3 months vs. on average 5–8 months) [10]. It is highly probable—as it is the case with other therapies for vitiligo—that increase of treatment duration will increase the percentage of patients reaching at least 75% of repigmentation. Secondly and probably most importantly, only a few studies have addressed criteria such as age, skin type, and above all, localization of vitiliginous lesions. Contrary to most previous reports, a high proportion (73%) of the lesions was localized in usually resistant areas in our study. We have demonstrated the predominant role of the localization of lesions here. Therefore, treating a high percentage of "UV resistant" areas induces a decrease of the results in terms of efficacy. All these considerations show the difficulties in comparing different studies.

The predominant role of the topographical factor in the treatment response in vitiligo has been reported by many authors (including phototherapy). Due to the relatively high number of treated lesions in this study, we could statistically demonstrate the importance of the localization of the treated lesions. Moreover, to reinforce our clinical impression, we showed the heterogeneity of response within the "UV resistant" areas. Thus elbows, knees, and wrists have a statistically higher rate of response than hands, ankles, and feet. These differences are difficult to explain. The density of the hair follicles, which represents the source from which differentiation and then migration of melanocytes could occur, is certainly an important factor but it is probably not the only one. By the same token, no statistical difference could be shown within the "UV sensitive" areas (between neck and face on the one hand, and back, trunk, and arms on the other hand). This absence of difference does not corroborate our clinical impression and could be explained by the limited number of lesions in "UV sensitive" areas in our study. Such analyses have a real practical interest. Indeed, according to these results, we should use the 308-nm excimer laser only in "UV sensitive" areas. For plaques, which are localized on knees, elbows, and wrist, the treatment could be proposed but patients should be informed that the success rate was poorer and the number of sessions necessary could be greater. Finally, according to the actual data, the 308-nm excimer laser should not be used in monotherapy for hands, ankles, and feet. Among the other potential confounding factors, none has statistically influenced the response to the treatment. However, the limited number of children and dark-skinned types of patients in our study do not justify making definitive conclusions as to the influence of age and skin type. Finally, even if the 308-nm excimer laser has provided very interesting results, this study was not designed to evaluate the long-term efficacy of this technique and a long-term follow-up of these patients is now needed.

Last but not least, tolerance and side-effects must be taken into consideration. In this study, the progressive increase of fluencies in every two sessions has prevented the burn reactions sometimes observed in the treatment of psoriasis by this same laser. Even if erythema was always observed, no pain was reported by the patients. The tolerance of the treatment was good, which increased the overall satisfaction of the patients. Moreover, the selective treatment of the vitiliginous lesions has prevented peri-lesional hyperpigmentation, which is sometimes observed with conventional phototherapy. Long-lasting side-effects using this technique are not known. Photo-ageing and increase of skin cancer risk are possible as in all UVB phototherapies. However, the cumulative doses were relatively low and unlike conventional phototherapy, the selectiveness of the treatment clearly decreases these risks by sparing the non-affected areas. This gives the 308-nm excimer laser a real advantage over NB-UVB for treating localized vitiligo.

In conclusion, the 308-nm excimer laser is an effective treatment for stable and localized vitiligo. The treatment is well tolerated and side-effects are limited. Long-lasting lesions could be treated as well as more recent ones. The localization of the treated lesions clearly appears to be a limiting factor and only those lesions affecting face, neck, back, trunk, and lower and upper limbs, excepting extremities and bony prominences, should be treated.

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