STUDY

Topical Tacrolimus and the 308-nm Excimer Laser

A Synergistic Combination for the Treatment of Vitiligo

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Objective: To compare the efficacy of combined tacrolimus and 308-nm excimer laser therapy vs 308-nm excimer laser monotherapy in treating vitiligo.

Design: Comparative, prospective, randomized, intraindividual study.

Patients: Fourteen patients, aged 12 to 63 years, with Fitzpatrick skin types II to IV.

Intervention: For each patient, 4 to 10 target lesions were chosen. The treatment applied to each target lesion was randomized by drawing lots. Each lesion was treated twice a week by the 308-nm excimer laser, for a total of 24 sessions. Initial fluences were 12 mcal/cm^2 (50 mJ/cm^2) less than the minimal erythemal dose in vitiliginous skin. Then, fluences were increased by 12 mcal/cm^2 every second session. Moreover, topical 0.1% tacrolimus ointment was applied twice daily on target lesions receiving the combined tacrolimus and excimer laser treatment (group A). Group B target lesions received only excimer laser monotherapy. For each treated lesion, the untreated lesion on the opposite side served as the control. Tolerance was evaluated by a visual analog scale, and secondary events were recorded at each session.

Main Outcome Measure: Treatment efficacy, which was blindly evaluated by 2 independent physicians by direct and polarized light photographs taken before and after treatment.

Results: Forty-three lesions were treated (23 in group A and 20 in group B). All patients completed the study. Repigmentation was observed in all group A lesions (100%) and in 17 (85%) of the 20 group B lesions. Repigmentation was not observed in the untreated lesions (control group). A repigmentation rate of 75% or more was obtained in 16 (70%) of the 23 group A lesions and in 4 (20%) of the 20 group B lesions. In UV-sensitive areas (the face, neck, trunk, and limbs, with the exception of bony prominences and extremities), 10 (77%) of 13 group A lesions had a repigmentation rate of 75% or more vs 4 (57%) of 7 group B lesions. In classically UV-resistant areas, 6 (60%) of 10 group A lesions had a repigmentation rate of 75% or more vs 0 of the 13 group B lesions. The mean number of sessions necessary for an improvement of repigmentation was 10 in group A and 12 in group B. Adverse effects have been limited, and tolerance was excellent.

Conclusions: The combination treatment of 0.1% tacrolimus ointment plus the 308-nm excimer laser is superior to 308-nm excimer laser monotherapy for the treatment of UV-resistant vitiliginous lesions ($P<.002$). The efficacy and the good tolerance of the 308-nm excimer laser in monotherapy for treating localized vitiligo were also confirmed, but this treatment regimen should be proposed only for UV-sensitive areas.

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VITILIGO IS AN ACQUIRED CUtaneous disorder of pigmentation with a 1% to 2% incidence worldwide without sex or race predilection. The clinical presentation is characterized by well-circumscribed white cutaneous macules with absence of melanocytes. People affected by vitiligo have a vast reduction of quality of life caused by the color contrast between healthy pigmented skin and the depigmented vitiliginous patches that give the patients psychological problems.[1,2] The first line of nonsurgical therapy includes topical corticosteroid therapy and phototherapy (solar exposition, psoralen–UV-A therapy, and narrowband UV-B [NB–UV-B] therapy).[3-5] However, to our knowledge, no treatment provides truly satisfactory results.

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Because of its relatively good efficacy and its excellent tolerance, NB–UV-B

therapy is considered the best treatment for extensive vitiligo vulgaris. The mechanism of action of the UV-B therapy on the vitiligo is still uncertain. Stimulation of melanocytic migration and proliferation starting from the niches located in the hair follicles are certainly leading factors. This stimulation probably involves the direct action of UV therapy on the melanocytes, and the action of the cytokines secreted by the keratinocytes. Recent studies on the autoimmune origin of vitiligo also emphasize the probable implication of the immunosuppressive action of UV therapy in the repigmentation of vitiliginous plaques. This immunomodulating photobiological action of the UV therapy involves the withdrawal of Langerhans cells and the decrease of their antigen presentation function, the keratinocytic cytokines, and moreover the apoptosis of the activated T lymphocytes.[6] Recently, the 308-nm excimer laser, a new technique allowing for targeted phototherapy, was used to treat localized plaques of vitiligo.[7-10] On the other hand, tacrolimus, a new topical immunosuppressive drug developed for the treatment of atopic dermatitis, has shown some interesting results in treating vitiligo in 2 prospective studies.[11,12] However, although the repigmentation rate was high, the percentage of patients achieving at least 75% repigmentation was low. Interestingly, patients with the best likely treatment response benefited from concomitant natural sunlight exposure.

We hypothesized that the combined action of the 308-nm excimer laser and topical tacrolimus could be synergistic, thus providing better results in the treatment of vitiligo. Therefore, we performed a prospective, randomized, left/right comparison pilot study to evaluate the efficacy of the association of 0.1% tacrolimus ointment plus the 308-nm excimer laser compared with 308-nm excimer laser monotherapy in the treatment of vitiligo.

METHODS

PATIENTS

Fourteen patients were included in this comparative, prospective, randomized study. The criteria for selection were as follows: older than 12 years, the development of vitiligo before the past 3 months, the presence of at least 2 pairs of symmetrical patches of vitiligo (with surfaces of at least 4 cm^2), and an understanding of all information given by signing a written consent form. Exclusion criteria were as follows: pregnant or breastfeeding women; personal history of a hypertrophic scar, melanoma, or other skin cancer; immunosuppression or taking immunosuppressive or photosensitizing drugs; and undergoing phototherapy or other vitiligo treatment during the past 3 months. For each patient, age, sex, skin type, date of onset of lesions, prior treatments for vitiligo with their results, and the localization of the patches of vitiligo were noted. The characteristics of the 14 patients (2 males [14%] and 12 females [86%]) are summarized as follows. Their mean age was 36.6 (range, 12-63) years, their mean disease duration was 18.1 (range, 3-33) years, and the mean number of sites treated per patient was 3 (range, 2-5). The Fitzpatrick skin type of the patients was as follows: type II, 5 patients (36%); type III, 8 patients (57%); and type IV, 1 patient (7%). All patients but 1 had already tried 1 or more other therapies for vitiligo (psoralen–UV-A therapy in 8, NB–UV-B therapy in 3, and antioxidant therapies in 9). None of these treatments had produced a repigmentation rate of at least 75%, except for NB–UV-B therapy in 1 patient.

TREATMENT

The laser used was a 308-nm xenon-chloride excimer laser (TALOS; WaveLight Laser Technology AG, Erlangen, Germany). The fixed technical variables were as follows: pulse frequency, 200 Hz; pulse width, 60 nanoseconds; and distal pulse energy, 1.1 mcal/cm^2 (4.6 mJ/cm^2). Beam transmission was achieved by an arm with moveable joints and changeable distal heads of 15-, 20-, and 25-mm diameters for the spot sizes. For each patient, 4 to 10 target lesions were chosen (2-5 vitiliginous macules treated by either the combination therapy or laser monotherapy and 2-5 untreated vitiliginous macules on the opposite side). The treatment applied to each target lesion was randomly selected by drawing lots. Lesions were treated twice weekly, for a maximum of 24 sessions. Initial fluences were 12 mcal/cm^2 (50 mJ/cm^2) less than the minimal erythemal dose in vitiliginous skin, and fluences were increased by 12 mcal/cm^2 every 2 sessions. In the presence of a vesicle, a bulla, or an erythema lasting more than 8 hours over the treated lesions, treatment was withheld and then resumed, after resolution, at the last dose without any adverse effect. Topical 0.1% tacrolimus ointment was applied twice daily on the target lesion receiving 308-nm excimer laser therapy plus tacrolimus treatment (group A). Group B target lesions received only 308-nm excimer laser monotherapy. Each treated lesion had an untreated control target lesion on the opposite side.

ASSESSMENT

Tolerance was evaluated by a visual analog scale, and secondary events were recorded at each session. Efficacy was blindly evaluated by 2 independent physicians (N.O. and W.Z.) using direct and polarized light photographs (Fuji FinePix S1 pro; Fuji Photo Film USA, Inc) taken before and at the end of treatment. Repigmentation was graded on a 6-point scale (0 indicates no repigmentation; 1, repigmentation of 1%-24%; 2, repigmentation of 25%-49%; 3, repigmentation of 50%-74%; 4, repigmentation of 75%-99%; and 5, total repigmentation). In the case of disagreement between the 2 physicians, a second evaluation was done together. If the disagreement persisted, the lowest evaluation score was chosen. At the final visit, the patients' opinions about treatment efficiency and the degree of satisfaction were recorded (excellent, good, moderate, or poor).

STATISTICAL ANALYSIS

The efficacy of combination treatment (excimer laser therapy plus 0.1% tacrolimus ointment) and excimer laser therapy alone was first compared with the symmetrical control plaques. Efficacy was measured in 2 different ways: (1) no repigmentation vs repigmentation and (2) repigmentation of less than 75% vs repigmentation of 75% or more. The latter was used to consider the aesthetic result. The McNemar χ^2 test was used to compare dichotomous variables on matching series. Then, the comparability between the 2 treatment groups and the relationships between repigmentation of less than 75% vs 75% or more and the treatments were studied in single-variable analyses using χ^2 and Fisher exact tests for categorical variables and the Kruskal-Wallis test for continuous variables. Analysis with the potential confounding factors was performed with the same statistical tests. Finally, the relationship between treatments and repigmentation was also studied after adjustment to localization using the Mantel-Haenszel test. All the tests were considered significant at a 5% type I error rate ($P<.05$). Statistical analyses were performed using a commercially available software program (SPSS for Windows, version 11.0; SPSS Inc, Chicago, Ill).

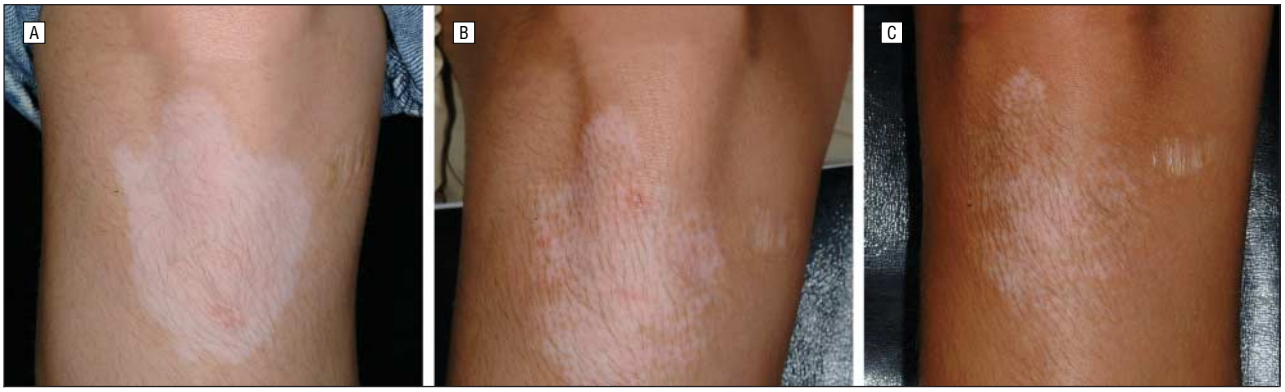

Figure 1. Vitiliginous plaque of the knee by direct light photographs before treatment (A), after 24 sessions (B), and 1 month after the end of treatment (C).

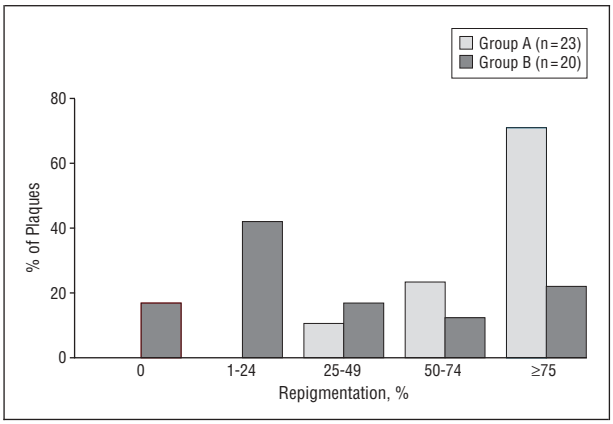

Figure 2. Global repigmentation. Group A indicates those persons who were treated with the combination of the 308-nm excimer laser and 0.1% tacrolimus; group B, those persons who were treated with 308-nm excimer laser monotherapy. In group A, 0 patients achieved 0% to 24% repigmentation, 2 (9%) achieved 25% to 49% repigmentation, 5 (22%) achieved 50% to 74% repigmentation, and 16 (70%) achieved 75% or more repigmentation. In group B, 3 patients (15%) achieved 0% repigmentation, 8 (40%) achieved 1% to 24% repigmentation, 3 (15%) achieved 25% to 49% repigmentation, 2 (10%) achieved 50% to 74% repigmentation, and 4 (20%) achieved 75% or more repigmentation. (Percentages may not total 100 because of rounding.)

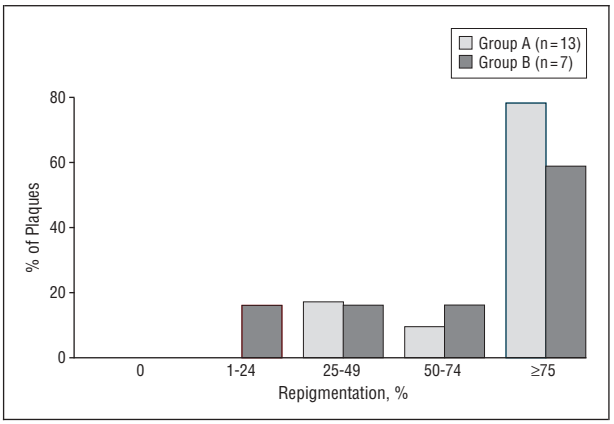

Figure 3. Repigmentation in UV-sensitive areas. Groups A and B are described in the legend to Figure 2. In group A, 0 patients achieved 0% to 24% repigmentation, 2 (15%) achieved 25% to 49% repigmentation, 1 (8%) achieved 50% to 74% repigmentation, and 10 (77%) achieved 75% or more repigmentation. In group B, 0 patients achieved 0% repigmentation, 1 (14%) achieved 1% to 24% repigmentation, 1 (14%) achieved 25% to 49% repigmentation, 1 (14%) achieved 50% to 74% repigmentation, and 4 (57%) achieved 75% or more repigmentation. (Percentages may not total 100 because of rounding.)

RESULTS

Forty-three lesions were treated (23 in group A and 20 in group B). All the patients completed the study. The degree of concordance between the 2 observers was excellent, as disagreement was noted for only 2 plaques. Repigmentation was observed in all group A lesions (100%) and in 17 (85%) of the 20 group B lesions (**Figure 1**). Repigmentation was not observed in any untreated control lesions. When considering the criterion presence of repigmentation, both treatment regimens—combined laser and tacrolimus therapy and laser therapy alone—showed an efficacy statistically superior to untreated control lesions ($P<.001$ each). A repigmentation rate of 75% or more was obtained in 16 (70%) of the 23 group A lesions and in 4 (20%) of the 20 group B lesions (**Figure 2**). When considering the criterion presence of repigmentation of at least 75%, only the laser and tacrolimus combination was statistically superior to untreated control lesions ($P<.001$ for group A and $P=.15$ for group B). In UV-sensitive areas (the face, neck, trunk, and limbs, except the bony prominences and extremities), 10 (77%) of 13 group A lesions had a repigmentation rate of 75% or more vs 4 (57%) of 7 group B lesions (**Figure 3**). In classically UV-resistant areas, 6 (60%) of 10 group A lesions had a repigmentation rate of 75% or more vs 0 of 13 group B lesions (**Figure 4**).

The study of the comparability between the 2 treatment groups for clinical variables (age, sex, skin type, duration of disease, and localization) showed no statistical differences. Thus, the comparison of the 2 treatment regimens using the criterion repigmentation of at least 75% suggests a statistically significant superiority of the combination treatment over laser monotherapy ($P<.001$). In single random variable analyses, we found no associations between response to treatment and the following variables: age, sex, skin type, and minimal erythemal dose ($P=.73$, $P=.39$, $P=.17$, and $P=.72$, respectively). However, response to treatment was associated with the lesion's localization. Special UV-sensitive lesions (in the face, neck, trunk, and limbs, except for the bony prominences and extremities) responded better than UV-resistant lesions (in the bony prominences and extremities) ($P=.004$). The relationship be-

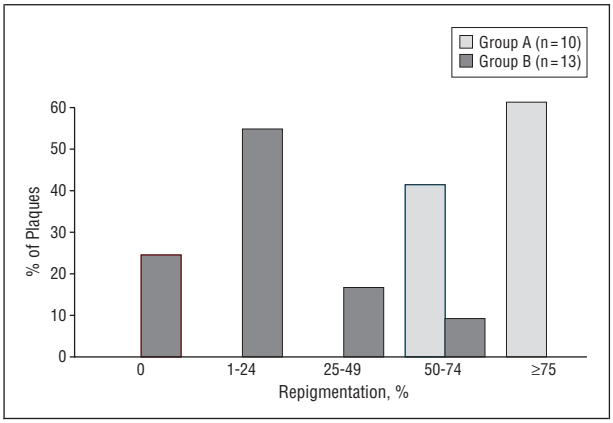

Figure 4. Repigmentation in UV-resistant areas. Groups A and B are described in the legend to Figure 2. In group A, 0 patients achieved 0% to 49% repigmentation, 4 (40%) achieved 50% to 74% repigmentation, and 6 (60%) achieved 75% or more repigmentation. In group B, 3 patients (23%) achieved 0% repigmentation, 7 (54%) achieved 1% to 24% repigmentation, 2 (15%) achieved 25% to 49% repigmentation, 1 (8%) achieved 50% to 74% repigmentation, and 0 achieved 75% or more repigmentation.

tween response to treatment and treatment groups has been further studied, adjusting it to the lesion's localization. In UV-resistant areas, combination treatment was statistically superior to laser monotherapy ($P<.002$), but no statistical difference has been shown in UV-sensitive areas ($P=.61$).

Cumulative doses ranged from 0.45 to 4.16 (mean, 2.01) cal/cm^2 (1.9-17.4 J/cm^2) in group A and from 0.79 to 4.83 (mean, 2.56) cal/cm^2 (3.3-20.2 J/cm^2) in group B. Treatment was stopped at the 15th and 16th sessions for 2 lesions in group A and at the 16th session for 1 lesion in group B because of achievement of 100% repigmentation. On average, the onset of repigmentation was observed at session number 10 in group A (range, 4-15) vs session number 12 in group B (range, 5-24). Cumulative doses before the onset of repigmentation were 0.69 (range, 0.17-1.27) cal/cm^2 (2.9 J/cm^2; range, 0.7-5.3 J/cm^2) in group A and 1.00 (range, 0.19-2.68) cal/cm^2 (4.2 J/cm^2; range, 0.8-11.2 J/cm^2) in group B. Adverse events were quite similar in both groups: moderate to severe erythema (observed at least 1 time in all the patients) and localized bullous eruptions in 4 lesions (2 in group A and 2 in group B). However, stinging was reported by 5 patients in group A vs 0 in group B. Tolerance was evaluated by the patients at 8.9 of 10 in group A vs 9.2 of 10 in group B, on average. Finally, the degree of patient satisfaction was excellent for 10 patients in group A and 0 in group B, good for 3 patients in group A and 7 in group B, moderate for 1 patient in group A and 5 in group B, and poor for 0 patients in group A and 2 in group B.

COMMENT

Our results demonstrate that the combination treatment of 0.1% tacrolimus ointment plus 308-nm excimer laser and 308-nm excimer laser monotherapy are effective for the treatment of vitiligo. However, in this study, only the combination treatment showed statistically significant efficacy compared with controls for achieving a repigmentation rate of at least 75%. Laser monotherapy showed a nonnegligible rate of response of at least 75%, but the rather small size of the sample probably explains the absence of statistical significance. Interestingly, localization seems to be clearly associated with the response to treatment, whereas factors such as age, sex, skin type, and minimal erythemal dose are not. When adjustment is made for localization, combination treatment is clearly superior to laser monotherapy when treating UV-resistant areas, confirming our initial hypothesis. On the other hand, no statistical difference can be found between the 2 treatments when treating UV-sensitive areas. For technical reasons, it was impossible to also evaluate the efficiency of tacrolimus ointment alone in this study. The results of previous studies[11,12] suggest that tacrolimus ointment alone can induce repigmentation. This repigmentation is clearly more observed in UV-exposed areas and is less important compared with that obtained with combination treatment. However, a comparative study between combination treatment and tacrolimus ointment alone is necessary to confirm these results.

To date, NB–UV-B therapy is one of the most effective treatments for extensive vitiligo vulgaris. However, the 308-nm excimer laser presents many advantages compared with NB–UV-B therapy for treating localized vitiligo. Photobiological effects seem more effective because the induction of lymphocyte apoptosis is superior.[13] Moreover, the articulate arm can reach any kind of localization and selectively target vitiliginous lesions while sparing the healthy skin. The results obtained in group B (308-nm excimer laser monotherapy) confirm the efficacy of this technique. Repigmentation has been observed in most of the lesions by the end of the sessions. However, because aesthetic results are expected, we have focused on the percentage of targeted plaques achieving at least 75% repigmentation. Therefore, when regarding aesthetic results, the overall efficacy is clearly less important, yet remains interesting. Differences between classic UV-sensitive and UV-resistant areas are marked, and are comparable to those observed using other phototherapy techniques. Even if it was not statistically proved, a marked difference depending on localization has also been noted in the latest study[10] evaluating excimer laser efficiency in treating vitiligo. Thus, according to our results, the treatment of bony prominences and extremities by the 308-nm excimer laser induces only few aesthetic good results. In UV-sensitive areas, our results are comparable to those obtained in the 3 previous reports,[8-10] confirming the medical interest of this technique in the treatment of localized vitiligo. Interestingly, a pilot study[14] performed with localized high-intensity UV-B phototherapy (B Clear) and tacrolimus ointment reports similar conclusions as ours and suggests that tacrolimus ointment and UV therapy could be synergistic in the treatment of vitiligo.

The tolerance of both treatments was good and adverse effects were not significant. Erythema was constant, but bullous lesions were rare. Adjunction of twice-daily application of 0.1% tacrolimus only induces a moderate stinging (noted in 5 [36%] of the 14 patients). This study was not designed to determine if the use of an immunosuppressive drug plus UV exposure can in-

duce long-term adverse effects. Minimizing or avoiding natural or artificial sunlight exposure during tacrolimus ointment treatment is recommended. The restriction of UV exposure during local treatment with tacrolimus results from the increased risk of cutaneous cancers observed in patients who have undergone organ transplantation and have been treated with systemic tacrolimus. However, the barrier function of vitiliginous skin is normal. This results in poor penetration of tacrolimus ointment within the interfollicular epidermis. Furthermore, recent studies[15] in mouse skin have shown that tacrolimus applications protect UV-induced damage on DNA. Moreover, the UV exposures and tacrolimus applications are limited in duration and surface area, which limits the risk of inducing carcinogenic mutations. However, this combination treatment should be used with caution and limited to controlled studies or short treatments.

Finally, it is difficult to compare the 308-nm excimer laser with other vitiligo treatments. In a meta-analysis[16] of the literature assessing the effectiveness and the safety of nonsurgical vitiligo repigmentation therapies, class 3 topical corticosteroids and NB–UV-B therapy seemed the best choices for localized and generalized vitiligo, respectively. When regarding the percentage of lesions achieving at least 75% repigmentation, class 3 corticosteroids showed 56% (95% confidence interval, 50%-62%) for localized vitiligo and NB–UV-B therapy showed 63% (95% confidence interval, 50%-76%) for generalized vitiligo. Compared with these data, the results obtained with combined treatment (70%; 95% confidence interval, 51%-88%) are good, but the results obtained with the 308-nm excimer laser alone are poor (20%; 95% confidence interval, 6%-44%). However, 2 important facts have to be considered. First, the total duration of our treatments was shorter than that in previous studies (3 months vs 5-8 months, on average).[16] It is highly probable, as is the case with other therapies for vitiligo, that an increased duration of treatment will increase the percentage of patients achieving at least 75% repigmentation. In addition, with the 308-nm excimer laser, the continuation of repigmentation has been observed up until 40 sessions in the study by Taneja et al.[10] Second, and probably most important, only a few studies have addressed criteria such as age, skin type, and localization of vitiliginous lesions. In our study, and contrary to findings in most previous reports, there was a high proportion of lesions localized in usually resistant areas (in 10 [43%] of 23 patients in group A and in 13 [65%] of 20 patients in group B). We have demonstrated the predominant role of the localization of the lesions. Thus, treating a high percentage of UV-resistant areas induces a decrease of results in terms of efficacy. Moreover, within the UV-resistant areas, heterogeneity is also observable. Even if the number of localizations treated is too small in our series to show statistically significant differences, knees, elbows, and the dorsal surfaces of the hands and feet seem to respond better than the tips of the fingers and toes, the ankles, and the wrists. All these data make any comparison of treatments difficult, and stress the importance of comparing laser therapy with those treatments of reference noted within the same study, especially now that the effectiveness of the 308-nm excimer laser has been demonstrated.

In conclusion, the efficacy of the 308-nm excimer laser for the treatment of localized vitiligo is confirmed, but should be proposed only for UV-sensitive areas. The combination of 0.1% tacrolimus ointment applied twice daily and 308-nm excimer laser therapy performed twice a week gives excellent results on UV-sensitive and UV-resistant areas. The treatment was well tolerated, and the patients were satisfied. A monitored study (with controls) on a larger population would be in order to confirm these encouraging preliminary results.

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