Original Article

Does Pimecrolimus Cream Enhance the Effect of Excimer Laser on Eyelid Vitiligo?

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Abstract:

Introduction: Vitiligo is a cutaneous disorder of pigmentation, for which, there are some proven modalities of treatment. In this study, we evaluated the efficacy of the addition of topical pimecrolimus to 308nm Excimer laser in reducing treatment duration and improving the response rate of eyelid vitiligo, compared with 308nm Excimer laser monotherapy.

Methods: Fifty two symmetrically localized lesions of eyelid vitiligo in 26 patients were observed. Each of vitiliginous patches was treated with 308nm Excimer laser twice a week for a total of 30 sessions. Topical pimecrolimus 1% cream was applied to the patches of right eyelid(group A lesions) and eucerine cream as a placebo to the left side patches(group B lesions)twice daily, throughout the study. Photographs were taken at baseline, 6 and 15 weeks after starting the treatment.

Results: Twenty two patients (44 lesions) completed the study. Repigmentation was appeared in all (100%) of groups A and B lesions. A 75% or more repigmentation was achieved in 17(78%) of group A versus 14 (64%) of group B lesions. The average number of sessions needed for the appearance of repigmentation was 8 for group A lesions and 12 for group. The repigmentaion of 50% or more in patients with disease duration of 2 years or less and those with more than 2 years duration ere 100% and 59.2%, respectively.

Conclusions: Repigmentation rate obtained by the combination therapy of eyelid vitiligo with 308nm Excimer laser and topical Pimecrolimus 1%cream is significantly higher, and obtained in fewer sessions in comparison with 308nm Excimer laser and placebo combination therapy.

Keywords: Pimecrolimus; Lasers, Excimer; Vitiligo, Eyelid; Clinical Trial; Laser Therapy

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Introduction

Vitiligo is a disorder in which, owing to disappearance of melanocytes from the skin, symmetrically arranged, white patches develop. The condition occurs in about 1-2% of the world population, mostly between the ages 10-30 years and with no predilection in males and females. The ethiology of vitiligo is unknown, but it seems to have genetic, autoimmune, neurological and extrinsic factors, involved in its pathophysiology(1).

Treatment modalities that are currently used for vitiligo include topical corticosteroids, topical calcineurin inhibitors, ultraviolet light(PUVA or NBUVB), psudocatalase cream, surgery/

transplantation, depigmentation therapy, and immunomodulators like cyclosporine and levamisole(2). The 308nm Excimer laser is an effective and well tolerated mode of phototherapy in vitiligo treatment, which should be proposed for limited vitiligo and essentially of UV-sensitive areas(2).

Recently, topical calcineurin inhibitors like Tacrolimus (FK506,protopic,Astellas) and Pimecrolimus (SDZASM981,Elidel,Novartis)have been introduced in the treatment of vitiligo. They are immunomodulators approved for the treatment of atopic dermatitis and alopecia areata by topical administration. Pimecrolimus 1% cream is a topical immunomodulating macrolactam that works as a calcineurin inhibitor and inhibits the maturation of various Tcell inflammatory cytokines(IL-2, IL-3, IL-4, IL-5, IL-10, GM-CSF, IFN-γ and TNF-α) that are postulated to be involved in the destruction of melanocytes in some vitiliginous lesions(3,4).

Most of clinical trials have evaluated the efficacy of topical immunomodulators alone or in combination with different types of phototherapy methods in treatment of vitiligo. However, research for evaluating newer, more efficacious, and well-tolerating therapeautic modalities with minimum side effects in treatment of vitiligo continues. Regarding to inadequacy of data on this issue, we decided to study the role of topical Pimecrolimus 1% cream in enhancing and accelerating the efficacy of 308nm Excimer laser in the treatment of eyelid vitiligo through this trial, a site rarely investigated specifically in previous trials.

Methods

A prospective, placebo-controlled study was conducted in Tehran`s Behsima skin and laser center, on 26 patients with eyelid vitiligo, in a 15 weeks long trial. All patients were informed of the process of treatment and signed informed consent. Four patients stopped treatment due to personal reasons. Demographic data of the patients was collected via a questioner by a trained physician. The mean age of the patients recruited, was 31.8(range, 17-50) years, with mean disease duration of 12.3(range, 1.5-24) years. All the participants had chronic (>1 year), stable (not expanding during the last year) and symmetrical vitiliginous lesions on their eyelids, with mean surface area of 5.6 cm². Patients with accompanying diseases, immunosuppressive conditions(due to underlying disease or using immunosuppressive drugs), pregnant women, breast feeding mothers, and patients that had received other treatment modalities previously (in the last 3 months) were excluded from the trial.

The laser used, was 308nm Excimer laser, operated by (XTRAC XL Plus Excimer Laser System, Photomedex, Inc. USA). Lesions were treated twice weekly, for a maximum of 30 sessions. Initial fluencies were 100 mj/cm²(less than the minimal erythemal dose in vitiliginous skin), increasing by 50 mj/cm² every 2 sessions, until reaching to an unusual erythema. (The average of energy used was 300 mj/ cm².)

Topical treatments consisted of Pimecrolimus 1%cream (Elidel) and eucerine cream as placebo.

Patients were asked to apply topical Pimecrolimuc 1% cream, twice daily, on the right eyelid vitiliginous patches (lesions group A), and eucerine cream on the left eyelid patches (lesions group B).The amount of topical cream, applied, was defined equal for both Pimecrolimus and placebo creams.

Follow up visits were arranged to be on week 5, 10, and 15(at the end of treatment). Assessment of the grade of repigmentation achieved was held by direct and polarized light photographs, evaluated by two independent dermatologists.

At first, the efficacy of combination treatment with 308nm Excimer laser and topical Pimecrolimus 1% cream was compared with combination treatment with308nm Excimer laser and placebo cream, in each person. Then, overall repigmentation grade of the lesions group A and B were compared with each other. Repigmentation was graded as: grade0=0%, 1=1-24%, 2=25-75%, and 3= more than 75%. The comparability between the 2 treatment groups and their relationship to repigmentation less vs more than 75% were studied in single-variable analyses using Fisher exact test for categorical variables, and the Student T test for continuous variables. The software program used for performing Statistical analysis was SPSS for windows, version 15.

Results

Twenty two patients completed the study (14(64%) female, 8(36%) male). Forty four symmetrical lesions were treated (22 lesions in group A, and 22 lesions in group B). Comparison of lesions group A with B in each person from the aspect of response to therapy, demonstrated a higher repigmentation grade and rate obtained in lesions group A. Repigmentation was

Table 1. Repigmentation gradingGul

Repigmentation grade	Group A	Group B
0	0	0
1 (1-24%)	0%	2 (9%)
2 (25-74%)	5 (22%)	6 (27%)
3 (>75%)	17 (78%)	14 (64%)

appeared in all (100%) of 44 lesions group A and B. Grade 3 Repigmentation was achieved in 78% of group A vs 64%of group B lesions (Table 1). Grade 3 repigmentation in lesions group A, were 100% and 59.2%, in disease duration of 2 years or less and more than 2 years, respectively. This response was obtained in 100% and 51.5% of lesions group B. This result suggests that mean disease duration has a role in response to therapy. Comparing the two treatment regimens using the criterion of 75% or more repigmentation shows that the combination of laser and topical pimecrolimus has no statistical difference over the combination of laser and placebo cream. We didn't find any correlation between patients skin type, age, and gender, and response to therapy in both treatment regimens(P values are as follows respectively: 0.24, 0.66, 0.31). But a significant correlation between the repigmintation response rate and disease duration was found, by dividing patients into 2 groups from the aspect of their disease duration (disease duration of ≤2 years, and >2 years) (P=.0.03)

Discussion

Our study confirmed the outcomes obtained by previous reports, and showed that although it was not statistically meaningful but both the rate and grade of repigmentation in treating eyelid vitiligo was superior in combination therapy with 308nm Excimer laser and topical Pimecrolimus 1% cream, comparing with 308nm Excimer laser and placebo(5).

Current treatment modalities for vitiligo suppress the immune response and/or stimulate the proliferation of melanocytes with ultraviolet radiation and most of them have limitations such as inconsistent and incomplete response, and long-term treatment periods that cause intolerance in patients receiving those(6).

Narrow band UVB and psoralens and UVA (PUVA) are the two most important treatments for generalized vitiligo affecting more than 10-20% of the cutaneous surface, and topical corticosteroids or calcineurin inhibitors are the most valuable treatments for localized vitiligo.

In one meta analysis assessing the effectiveness of nonsurgical treatment methods of vitiligo, the percentage of at least 75% repigmentation achieved by class 3 topical corticosteroids in localized vitiligo and NB-UVB therapy in generalized vitiligo has been demonstrated as 56% and 63% respectively(7). In this trial we omitted the role of localization in response to therapy.

The efficacy of calcineurin inhibitors also vary, based on the type of the drug and the UV light combined. With Tacrolimus being more effective with 308nm Excimer laser, Pimecrolimus has been effective with NB-UVB and 308nm Excimer laser on facial vitiligo(7,8).

Concerning the value of topical Pimecrolimus 1% cream in treatment of vitiligo, Boone B. and her colleagues performed a trial(3) on 26 target vitiliginous lesions. In 13 of 26 (50%) evaluated target lesions, repigmentation was noted after a 6 month treatment period with a median percentage of repigmentation of 72.9% (interquartile range: 30.5-98.3%).

Conventional phototherapy delivers UV radiation to affected and unaffected skin over many months of treatment. The possibility of increased risk of skin cancer after phototherapy has been repeatedly raised. Targeted phototherapy with the 308-nm Excimer laser emits UV radiation to only the affected area. So, uninvolved skin is not exposed. Furthurmore, since conventional phototherapy is time consuming, methods like the 308-nm Excimer laser monotherapy or combining it with topical immunomodulators that enhance repigmentation and hasten therapeautic response rate are increasingly focused on topics(9).

In our trial, although, the percentage of response to treatment regimen of group A lesions(78%) is higher than that of group B (64%), but there is no statistical difference between these two treatment modalities that can be justified by either the small sample we investigated, or shortness of the treatment period in our trial. Additionally, it may be related to the localization of vitiliginous lesions that are treated, as repigmentation rate is significantly higher in UV-sensitive areas(such as eyelids), and a statistical difference may not be observed between the 2 treatment regimens. This result is completely comparable to that achieved by Passeron et al. that compared the efficacy of combined Tacrolimus and 308-nm Excimer laser therapy vs 308-nm Excimer laser monotherapy in treating vitiligo in both UV-sensitive and UV-resistant areas(2). The rate of repigmentation of 75% or more, for lesions group

A(receiving combination therapy),was mentioned 60%in UV-resistant vs 77%in UV-sensitive areas and for group B(receiving laser monotherapy) these rates were 0% and 57% respectively. Based on their study Tacrolimus can significantly enhance the response rate of vitiligo to excimer laser in UV-resistant areas.(2) In investigating the efficacy of Excimer laser monotherapy in treatment of vitiligo, when only lesions of UV-sensitive areas like face and trunk were taken into account, a 75% repigmentation rate of 40%(6/15) was found by A Hofer et al(10). and 57%(8/14) by ostovari et al(11). It is probable that by increasing the treatment period and sample size in further trials, a statistical difference be achieved between the two therapeutic modalities. However, the administration of the 308-nm Excimer laser in combination with topical immunomodulators in UV-resistant areas shows a significantly higher statistical difference in comparison with the 308-nm Excimer laser monotherapy ($p<.002$).The average sessions needed for the onset of repigmentation to occur is fewer than that needed for Excimer laser and placebo cream combination (8 vs 12 sessions), parallel to the result obtained in previous reports(8,10). The only side effects encountered with, during our trial was a minimal and transient pruritis that was experienced by 2 of our patients on location of Pimecrolimus application, and didn't cause patients to discontinue the treatment.

In contrary to some trials(11), mentioning that there is no association between disease duration and the degree of response to treatment, we found an apparently evident correlation between disease duration before starting the treatment and repigmentation grade achieved at the end of 30 sessions of treatment($p<0.05$). The only previous research confirming our result is that held by Zhang XY et al(12).

In this study we didn't investigate and compare the efficacy of the two treatment regimens in increasing the stability and consistence of repigmentation achived after the end of treatment. Additionally, in contrary to a pilot study by Adam Z. et al. pathological biopsy and evaluation wasn't performed to estimate repigmentation rate obtained by each of the two treatment regimens administered in our study.

In conclusion, we recommend further trials to be held in larger sample sizes and longer treatment periods in order to assess the efficacy of combining topical drugs and light or laser therapies in achieving repigmentation and to investigate the long-term prognosis/consistence of repigmentation obtained by these methods.

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Declaration of interest

The authors declare that there is no conflict of interest.

References

1. Njoo MD, Westerhof W. Vitiligo. Ned Tijdschr Geneeskd.1997 Apr 19;141(16):759-64.
2. Passeron T.,Ortonne JP. The 308-nm excimer laser in dermatology.Presse Med.2005 Feb 26;34(4):301-9.
3. Boone B.,Ongenae K. Topical pimecrolimus in the treatment of vitiligo.European Journal of Dermatology. 2007 January-February ;17(1):55-61.
4. Ruzicka Th, Assmann T. Tacrolimus. The drug for the turn of the Millennium. Arch Dermatol. 1999;135:574-80.
5. Yang Hui-Lan, Huang Xiao-Yan, Combination of 308-nm excimer laser with topical Pimecrolimus for the treatment of childhood vitiligo. Pediatr Dermatol, 2009 May-june;26 (3):354-6.
6. Grimes PE. Diseases of hypopigmentation. In: Sams WM, Lynch PJ, eds. Principles and Practice of Dermatology,2nd ed. New York: Churchil-Livingstone; 1996. 873-85.
7. Hossani-Madani AR, Halder RM. Topical treatment and combination approaches for vitiligo: new insights, new developments. G Ital Dermatol Venereol. 2010 Feb;145(1):57-78.
8. Njoo MD ,Spuls PI, Bos JD. Nonsurgical Repigmentation therapies in vitiligo. Arch Dermatol 1998;134:1532-40.
9. Kawalek AZ, Spencer JM, Phelps RG. Combined Excimer Laser and topical Tacrolimus for the treatment of vitiligo: A pilot study. Dermatol Surg. 2004;30:130-5.
10. Hofer A, Hassan AS, Legat FJ, Kerl H, Wolf P. The efficacy of excimer laser (308-nm) for vitiligo at different body sites. J Eur Acad Dermatol Venereol. 2006 May;20(5):558-64.
11. Passeron T, Ostovari N, Zakaria W, Fontas E, Larrouy JC, Lacour JP, Ortonne JP. Topical Tacrolimus and 308-nm excimer laser, a synergistic combination combination for the treatment of vitiligo. Arch Dermatol. 2004 Sep;140(9):1065-9.
12. Zhang XY, He YL, Dong J, Xu JZ, Wang J. Clinical efficacy of a 308-nm excimer laser in the treatment of vitiligo. Photodermatol Photoimmunol Photomed. 2010 june;26(3):138-42.