Global Dermatology

Research Article ISSN: 2056-7863

308 nm UV excimer light in monotherapy or combined to topical khellin 4% and/or tacrolimus 0.1% in the treatment of vitiligo

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Abstract

Many therapeutic options have been suggested for the treatment of vitiligo including non-surgical and surgical modalities. Non-surgical modalities, considered the first line therapy, include topical, intra-lesional and systemic corticosteroids, topical and oral psoralen plus ultraviolet A (PUVA), topical khellin 3%-4%-5%, broad-band and narrow-band UVB (311 nm UVB phototherapy), and recently, topical immunomodulators (TIMs. e.g. tacrolimus, pimecrolimus), 308 nm excimer laser and light (MEL, monocheromatic excimer light). Thirtytwo patients affected by vitiligo were selected in this open comparative study: they were subdivided into 4 groups of 8 patients each: Group I (Control Group) included 4 man and 4 women, aged 16-70 years (mean age: 41.2 years), treated with MEL; Group II included 3 man and 5 women, aged 13-70 years (mean age: 37.7 years), treated with MEL associated with topical khellin 4%; Group III included 5 men and 3 women, aged 31-61 years (mean age: 44 years) treated with MEL associated with topical tacrolimus 0.1%; Group IV included 4 men and 4 women, aged 10-72 years (mean age. 45 years) treated with MEL associated with topical khellin 4% and tacrolimus 0.1%.

Results seemed more favourable towards Group III which included patients treated with MEL and topical tacrolimus 0.1% presented an overall best response rate if compared to the other groups. In fact, the results of Group IV-patients treated with MEL combined to topical khellin 4% and tacrolimus 0.1% were not up to the authors higher expectations, taking into account the novel association not yet described in literature.

Introduction

Vitiligo is an acquired depigmentation skin disorder affecting 1-4% of world's population. Its pathogenesis remains obscure and needs to be further investigated to increase therapeutical success. Some authors proposed an autoimmune aetiology because of the presence of autoantibodies and autoreactive T lymphocytes that target melanocytes in some vitiligo patients [1,2]. Moreover, it has been often associated with autoimmune disorders such as thyroid disease, diabetes mellitus, atrophic chronic gastritis, and others [3]. Many therapeutic options have been suggested for the treatment of vitiligo including non-surgical and surgical modalities [4]. Surgical modalities, such as autologous transplantation (split-thickness epidermal grafting, epidermal blister grafting and grafting of cultured of melanocytes) are obviously invasive and not well accepted by most of the patients. Non-surgical modalities, considered the first line therapy, include topical, intra-lesional and systemic corticosteroids, topical and oral psoralen plus ultraviolet A (PUVA), topical khellin 3-5%, broad-band and narrow-band UVB (311 nm UVB phototherapy), and recently, topical immunomodulators (TIMs. e.g. tacrolimus, pimecrolimus), 308 nm excimer laser and light. Furthermore, several recent studies confirm that phototherapy is the most effective treatment option.

Monochromatic excimer light (MEL, Excilite® TM DEKA Medical Lasers, Florence, Italy) is a 308 nm XeCl device that produces a power density of 48 mW/cm^2 at 15 cm distance from the skin level covering an irradiation field of 512 cm^2 [4-9].

Our objective was to evaluate the effectiveness of 308 nm monochromatic excimer light (MEL) on 32 vitiligo patients with multiple stable patches in mono-therapy or associated to topical therapies (e.g. khellin 4% ointment, tacrolimus 0.1% ointment), which might act synergistically and increase the quality of repigmentation and/or the response times.

The aim of the overall study was to find other options for the treatment of vitiligo. The ones reported may represent a key advancement in vitiligo therapy, although the study groups mentioned above should be expanded to include a greater number of subjects with a view to achieving a higher statistical significance.

Patients

Thirty-two patients, 16 man and 16 women, aged 10-72 years (mean age: 41.2 years) affected by generalized vitiligo (acrofacial type and symmetrical/bilateral type) were enrolled in this open prospective pilot study Patients were subdivided into 4 groups of 8 patients each: Group I (Control Group) included 4 man and 4 women, aged 16-70 years (mean age: 41.2 years), treated with MEL; Group II included 3 man and 5 women, aged 13-70 years (mean age: 37.7 years), treated with MEL associated with topical khellin 4%; Group III included 5 men and 3 women, aged 31-61 years (mean age: 44 years) treated with MEL associated with topical tacrolimus 0.1%; Group IV included 4 men and

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Received: February 05, 2015; **Accepted:** March 08, 2015; **Published:** March 11, 2015

4 women, aged 10-72 years (mean age. 45 years) treated with MEL associated with topical khellin 4% and tacrolimus 0.1%.

Patients suffered from a generalized vitiligo, acrofacial type (19 patients. Group I: 4/8 patients; Group II: 4/8; Group III: 7/8; Group IV: 4/8) and symmetrical/bilateral type (13 patients. Group I: 4/8 patients; Group II: 4/8; Group III: 1/8; Group IV: 4/8), presenting multiple stable patches (cutaneous depigmentation present for more than 8 month) covering a body surface between 20% and 55%. The mean duration of vitiligo was 9 years (range: 1-45 years). The sites of the single vitiligo patches were: face (30), neck (13), chest (3), back (6), elbows (13), hands (25), inguinal (3) and axillary's (3) folds, genital area (4), knees (9), and feet (15).

Patients had a Fitzpatrick skin phototype ranging I-IV. Eleven patients (34.4%) presented a positive familiar history for vitiligo. Fourteen patients (43.7%) had an association with autoimmune disorders such as thyroid disease (11 patients), atrophic chronic gastritis (2 patients), diabetes mellitus (1 patient) and celiac disease (1 patient). All patients had a history of previous non-surgical therapies.

Exclusion criteria were: topical, systemic and phototherapy during the previous 3 month; photosensitivity; photomediated disorders; radiotherapy; systemic immunosuppressive treatments; immunosuppressive diseases; history of skin cancer; pregnancy and breast-feeding women; and, age <10 years.

During the initial pre-treatment visit and after 3 month of therapy, patients were submitted to clinical assessment which included physical examinations, photographic documentations (lesional photography), monitoring for adverse events, Vitiligo Disease Activity (VIDA) score, Quality of Life Modified test, blood and urine tests for routine laboratory evaluations (e.g. haemachrome, autoimmunity, renal and hepatic functions). All patients enrolled in the study provided written informed consent.

Assessment of treatment efficacy was based on the percentage of repigmentation in the treated area, evaluated by two independent physicians. The repigmentation score considered 5 grades: "no repigmentation" (score 0), "poor repigmentation" (1%-25%, score 1), "moderate repigmentation" (26%-50%, score 2), "good repigmentation" (51%-75%, score 3), and "excellent repigmentation" (76%-100%, score 4) (Table 1).

The study was approved by the local ethical committee.

Materials and methods

MEL is a 308 nm excimer XeCl device (Excilite® TM DEKA Medical Lasers, Florence, Italy) that releases a power density of 48 mW/cm^2 at the distance of 15 cm^2 from skin and it has an irradiation area of 512 cm^2.

All patients were photo-tested with MEL on normally pigmented and unexposed skin. The Minimal Erythemal Dose (MED) was then determined at increasing light dosage following the initial dose of MEL, which was calculated according to patients photo-type.

Table 1. Repigmentation score and overall results.

Score	Repigmentation	Results obtained
0	None	0/32
1	1-25%	3/32
2	26-50%	10/32
3	51-75%	6/32
4	76-100%	13/32

Therapy was administered once a week. The initial fluency for each patient was 80% of MED. During each MEL application at every other treatment doses were increased of 5-15 seconds. The peripheral area of each single patch was protected from irradiation with a topical sunscreen applied 1-hour prior treatment.

When minimal asymptomatic erythema occurred in the lesion the dose was reduced by 25%. When symptomatic erythema (burning and itching) or blistering occurred treatment was suspended for one week and at the following treatment the last dose was decreased by 25%.

Khellin 4% (dimethoxy-4, 9 methyl-7 oxo-5 5-H-Furo [3,2-G]-4H chromone) is a furanochromone with: vasodilative, spasmolytic, stimulating melanocyte proliferation, inhibiting fibroblast proliferation activities; it is a photosensitiser whose chemical structure closely resembles that of psoralen. Khellin 4% ointment was topically administered once daily (morning) on the single patches of patients included in Group II and IV.

Tacrolimus 0.1% ointment is a novel immunomodulatory agent that modulates the immune system by inhibiting T-cell activation via down-regulation of the transcription genes encoding proinflammatory cytokines (interleukin (IL)-2, IL-3, IL-4, IL-5, interferon-γ, tumor necrosis factor-α, granulocyte-macrophage colony-stimulating factor). It may act synergistically with MEL through activation of pathways influencing the process of melanocyte mitogenesis, melanocyte migration and melanogenesis. Tacrolimus 0.1% ointment was topically administered once daily (evening) on the vitiligo patches of patients included in Group I and IV.

Results

After a time-frame of 3 months, 13/32 (40.6%) achieved an excellent degree of repigmentation between 76%-100% (among this group of thirteen, 9/32 (28.1%) patients achieved a complete response with 100% of repigmentation), 6/32 (18.8%) a good repigmentation between 51%-75%, and 13/32 patients (40.6%) obtained a poor (3/32) and moderate (10/32) degree of repigmentation between 1% and 50%.

In general, 19 patients (59.3%) had a "good-excellent" response (51%-100%).

Considering each study-group the results were as follows: Group I (treated with MEL) showed a poor-moderate repigmentation in 4/8 patients (50%), a good repigmentation in 1/8 patient (12.5%) while 3/8 patients (37.5%) achieved 100% repigmentation; Group II (treated with MEL and topical khellin 4%) showed a poor-moderate repigmentation in 2/8 patients (25%), good repigmentation in 2/8 patients (25%) and excellent repigmentation in 4/8 (50%. Two patients obtained 100% response); Group III (treated with MEL and topical tacrolimus 0.1%) presented moderate repigmentation in 3/8 patients (37.5%), good repigmentation in 1/8 (12.5%) and excellent repigmentation in 4/8 (50%. Three patients achieved 100% response); 4/8 patients had a "good repigmentation" between the 6th and 8th treatment. Group IV (treated with MEL combined to topical khellin 4% and tacrolimus 0.1%) showed moderate repigmentation in 4/8 patients (50%), good repigmentation in 2/8 (25%) and excellent response in 2/8 (25%. One patient obtained 100% repigmentation).

The vitiligo lesions sites with the best response rate were: face, neck, elbows, inguinal fold and knees.

No side effects, such as burning and blistering, were observed in any of the patients treated.

Table 2. Side effects.

Group	Erythema	Burning-pain	Perilesional hyperpigmentation
1	4/8	1/8	2/8
2	5/8	2/8	1/8
3	3/8	1/8	1/8
4	4/8	2/8	2/8

Only the following mild side effects were assessed: symptomatic erythema (50%. Group I: 4/8 patients; Group II: 5/8 patients; Group III: 3/8 patients; Group IV: 4/8 patients); burning/pain (18.7%. Group I: 1/8; Group II: 2/8; Group III: 1/8; Group IV: 2/8); and perilesional hyperpigmentation (18.7%. Group I: 2/8; Group II: 1/8; Group III: 1/8; Group IV: 2/8) (Table 2).

All patients were satisfied with the given therapeutic protocol since it was well tolerated, not time-consuming and easy to administer. Furthermore, patients noted a significant improvement of their quality of life, less embarrassment during relationships, improvement of their body image, and a more optimistic attitude towards life in general and their disease.

Discussion

It is known that many therapeutic options have been suggested for the treatment of vitiligo including surgical and non-surgical modalities. Non-surgical modalities are considered the first line therapy and include topical, intra-lesional and systemic corticosteroids; topical and oral psoralen plus ultraviolet A (PUVA); khellin (topical, oral or associated with UVA); broad-band and narrow-band UVB (311 nm UVB phototherapy); and recently, topical non-steroid immune-modulators (TIMs. e.g. tacrolimus, pimecrolimus) as well as 308 nm excimer laser and 308 nm monochromatic excimer light. Several recent studies confirm that phototherapy is the most effective treatment option. Furthermore, narrow-band UVB (NB UVB) 311 nm phototherapy and excimer laser 308 nm [8-11] showed various advantages compared to other phototherapies, such as rapidity of the onset of repigmentation, good overall response in terms of repigmented area and possibility of a selective irradiation of vitiligo patches without a perilesional skin involvement. Moreover, it is reported that repigmentation induced by khellin plus ultaviolet A (KUVA) may be due to an activation of melanocyte mitogenesis, melanocyte migration and melanogenesis [7].

A recent study of Leone *et al.* [11] demonstrated that 308 nm MEL may be considered a more effective therapy for vitiligo when compared to NB UVB phototherapy based on the rapid repigmentation, shorter treatment time-frames and better compliance of the patients [16,17,25]. In fact, after 3 month of MEL treatment 12/37 patients showed an "excellent repigmentation" (21/37 a "good repigmentation") and after 6 month of therapy patients with an "excellent repigmentation" increased to 18/37. Moreover, their results were similar to other ones recently reported when using a 308 nm excimer laser administered twice a week or once a week for a long period of time (approximately one year) [9].

Our group of patients treated with MEL alone (Group I), after 3 months of treatment, showed a moderate repigmentation in 4/8 patients (50%), a good repigmentation in 1/8 (12.5%) and 3/8 (37.5%) achieved 100% repigmentation; therefore, we confirm data described in literature although the percentage of patients with a good repigmentation was less than the ones with an excellent repigmentation. The results of this study indicate that 308 nm MEL phototherapy is effective also with one single irradiation session a week for a total time-frame of only 3 months. Patients appreciated the lower number of treatments necessary in order to achieve a satisfactory repigmentation.

Khellin (dimethoxy-4, 9 methyl-7 oxo-5 5-H-Furo [3,2-G]-4H chromone) is a furanochromone which induces a photosensitization of defined DNA sequence [6]. Recently it has been proposed as an alternative treatment for vitiligo, alone or combined to phototherapy; in particular, a photobiology study demonstrated that khellin activated by UVA (KUVA) stimulates melanocyte proliferation and melanogenesis [7].

The results of our study on Group II which included patients treated with MEL and topical khellin 4% may be useful to confirm the interpretation of khellin's mechanism of action; also it was showed,similarily to previous studies that the use of topical khellin combined with UV light may predispose the patient to higher photosensitive responses [7].

Tacrolimus is a novel immunomodulatory agent that modulates the immune system by inhibiting T-cell activation via down-regulation of the transcription genes encoding proinflammatory cytokines (IL-2, IL-3, IL-4, IL-5, interferon-γ, tumor necrosis factor-α, granulocyte-macrophage colony-stimulating factor) [18]. It may act synergistically with NB UVB phototherapy through activation of pathways influencing the process of melanocyte mitogenesis, melanocyte migration and melanogenesis [17].

While topical tacrolimus displays a 41% average response in vitiligo lesions after two months of treatment [17] the addition of tacrolimus to NB UVB is another therapy option for vitiligo patients considering its lower cancerogenesis profile compared with systemic administration and its quicker repigmentation effect [12-17]. In fact, Moncada *et al.* [17] showed that after 6 months of NB UVB phototherapy an additional 3 months application of tacrolimus 0.1% induced a further 25% improvement in repigmentation.

Different studies [18-21] reported that vitiliginous patches treated with excimer laser 308 nm, in combination with tacrolimus 0.1% ointment, 50% achieved a successful response (75% repigmentation) at a significant faster rate than of other vitiliginous patches treated with excimer laser and placebo which achieved only 20% successful response.

The results of our study on Group III which included patients treated with MEL and topical tacrolimus 0.1% presented an overall best response rate if compared to the other groups. In fact, the results of Group IV-patients treated with MEL combined to topical khellin 4% and tacrolimus 0.1% were not up to the authors higher expectations, taking into account the novel association not yet described in literature.

The aim of the overall study was to find other options for the treatment of vitiligo. The ones reported may represent a key advancement in vitiligo therapy, although the study groups mentioned above should be expanded to include a greater number of subjects with a view to achieving a higher statistical significance.

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