Broad-band pulsed UVB and topical tacrolimus treatment for localized vitiligo -our experience.

Alexia Díaz Mathé[1], Virginia Mariana González[2], Verónica Llorca[1], Kamelia Losada[3], Paula Luna[2], María Eugenia Abad[2] and Margarita Larralde[4]

ABSTRACT

Background: Present vitiligo therapies require many months of treatment and often result in disappointing outcomes. Several therapies, such as PUVA (psoralen plus UVA) and narrow-band UVB have been used with satisfactory results. Recently, 308-nm excimer laser has been used to treat localized vitiligo with good results. Evidence suggests that broad-band pulsed UVB should have similar biological effects to the latter.

Material and methods: A prospective, descriptive and observational study of 15 patients was performed. 12 had generalized vitiligo, 2 localized vitiligo, and 1 segmental vitiligo. All of them had been previously treated with topical tacrolimus with poor results. Treatment with topical tacrolimus twice a day and broad-band pulsed UVB twice a week during 30 sesions was initiated.

Results: All patients revealed different levels of repigmentation: 12 patients achieved over 75% repigmentation, 2 patients between 50 and 75%, and one patient showed no repigmentation (patient with segmental vitiligo).

Conclusion: The combination of topical tacrolimus and broad-band pulsed UVB is a good alternative for the treatment of vitiligo (Dermatol. Argent., 2011, 17(2):134-139).

Keywords:

broad-band pulsed UVB, tacrolimus, vitiligo.

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[1] 3rd year student of Specialization in Dermatology, UBA
[2] Medical Staff
[3] 2nd year student of Specialization in Dermatology, UBA
[4] Chief of Dermatology Department at Hospital Alemán
Contact: Margarita Larralde: Arenales 2557, 1ª A, Ciudad Autónoma de Buenos Aires, Argentina.
doctoralarralde@gmail.com

Introduction

Vitiligo affects between 0.1 and 2% of the population and compromises their quality of life significantly. The disease is characterized by the destruction of melanocytes, principally of the skin, and gives rise to the appearance of circumscribed achromic macules. Pathogenesis is not very clear but it is believed that, in genetically prone patients, the interaction of immunological, neurogenic and environmental factors causes the development of the lesions[1]. There are various treatments for this pathology which do not always have satisfactory results. In this paper, we report our experience with the combination of topical tacrolimus and broad-band pulsed UVB for the treatment of localized vitiligo.

Material and method

A prospective, descriptive and observational study was carried out which included 15 patients with stable vitiligo. Stable vitiligo was defined as the absence of repigmentation or progression of the disease for at least 8 weeks before the initiation of treatment. All the patients had received previous treatments for the disease and the use of 0.1% topical tacrolimus for at least three months without response was considered a necessary condition for their inclusion in our study.

The exclusion criteria were: more than 20% of body surface involved, personal history of skin cancer, photosensitivity, pregnancy, epilepsy, active infections on the site to be treated, active suntan in the previous month and systemic treatment or phototherapy in the previous two months.

A complete clinical history with the patients' signature for informed consent was made, pictures were taken before the initiation of treatment and every eight exposures, we determined up to what extent the body surface was affected, and we measured the minimum erythematogenic dose (MED) 24 hours before the initiation of treatment on an area not exposed to light. Treatment was also applied on face and neck. We used Harmony de Alma Lasers equipment, which emits ultraviolet radiation between 300 and 380 nm with a peak between 300 and 320 nm. It has a movable head and an articulated arm with a 2 x 4 opening through which light is emitted. Treatment was initiated twice a week at MED and it was increased at 50 mJ/cm^2 per exposure if no adverse effects were evidenced. At the appearance of erythema, treatment was continued at the same dose and if the patient presented blisters, the dose was reduced to the previous one they tolerated. All patients received concomitant treatment with 0.1% topical tacrolimus twice a day. Treatment end point was reached: after 30 sessions, if complete repigmentation of the lesion was achieved or if, after 8 exposures, no modification was noticed.

Results

All 15 patients completed the study. Nine were female and 6 male, between 4 and 70 years old (mean age: 25.7 years). According to the level of involvement of their disease, 12 patients presented generalized vitiligo, 2 localized facial and 1 segmental. The mean time duration of the disease was 9.3 years. The skin phototypes, according to Fitzpatrick's classification, were between II and IV (Table 1). Adherence to treatment was excellent: none of the patients abandoned it although it was applied biweekly. All of them, except for the patient with segmental vitiligo, evidenced different degrees of improvement. The mean number of exposures necessary to observe the first signs of repigmentation was 5. Evaluation of repigmentation was carried out using a scale described on Table 2. Twelve patients reached score 4 after 30 exposures (Photos 2 and 4), while 2 reached score 3 and one patient did not show any repigmentation after 8 exposures (patient with segmental vitiligo).

All patients, except for the one with segmental vitiligo, evidenced some degree of repigmentation after 8 exposures. Oddly enough, those with a diagnosis of vitiligo with a longer course responded earlier (3rd session) than the ones with a recent diagnosis. The 2 patients with a high skin phototype (Fitzpatrick IV) had slower improvement and required a greater number of exposures to achieve changes similar to the rest of the patients.

The type of repigmentation observed in 80% of the cases (12 patients) was perifollicular. The other two patients presented repigmentation from the periphery of the lesions. The lesions which responded earlier were the ones on non-periorificial locations and the perioral lesions showed the most difficult repigmentation.

The only adverse effect observed in just one patient was erythema with a course of less than 24 hours so it was not necessary to interrupt or suspend the treatment. During follow-up, only one patient had a relapse of their disease and it was coincidental with a stressful situation, 6 months after completing treatment. The rest of the patients did not evidence any relapses. Mean follow-up time was 6 months and the longest follow-up time was a year, in three patients.

Discussion

Vitiligo is an acquired disease which affects between 0.1 and 2% of the world's population without predilection for age, sex or race. It is characterized by the destruction

Photo 1: Before initiation of treatment.

Photo 2: After 30 exposures.

of melanocytes and CD8+ T-lymphocytes have recently been involved in their pathogenesis[1,2]. Even though it is an asymptomatic pathology without systemic involvement, its cosmetic and psychological effects may alter the patient's self-esteem and significantly affect their quality of life[3,4]. The most important prognostic factor is the location of the lesions. Facial and neck vitiligo usually respond to topical treatment or phototherapy rapidly. The lesions on trunk and limbs improve partially, whereas segmental vitiligo and the one affecting distal extremities is more difficult to treat[5-7]. Skin phototype, age, sex, duration of the disease and response to previous phototherapy treatments are less predictable prognostic factors[6,8].

Given the fact that its physiopathology is unknown, there are multiple and varied treatments which include corticosteroids, calcineurin inhibitors, vitamin D analogs, phototherapy, surgery and the combination of a topical treatment associated with ultraviolet light.

Phototherapy has been used for many years for the treatment of generalized vitiligo. PUVA (phototherapy with ultraviolet A radiation and an oral psoralen) consists in the administration of 8-methoxypsoralen at a dose of 0.5 mg/kg followed by UVA irradiation 2-3 times a week. The treatment usually lasts several months and the results are not always entirely satisfactory: 30-40% evidence improvement but only 20% achieve complete repigmentation[9]. It has several adverse effects, including: burns, erythema, lentiginosis, pruritus, nausea, eye cataracts and increased risk of cutaneous neoplasias such as squamous cell carcinoma and melanoma[9]. Topical PUVA consists in applying 0.05-0.1% topical 8-methoxypsoralen and then UVA 2-3 times a week. It is useful for localized vitiligo and it has fewer adverse effects, but response is not as good[10].

Narrow-band UVB (NB-UVB) is currently considered the best treatment for generalized vitiligo[4,5 11]. It emits 311-313 nm continuous, incoherent, polychromatic light[12]. Its mechanism of action is not altogether clear: it is believed to act by the stimulation and migration of melanocytes from the hair follicle stem cell niche through direct action of ultraviolet radiation (UVR) over melanocytes, and by the secretion of cytokines of adjacent keratinocytes, such as the fibroblast growth factor and endothelin 1, which stimulate the proliferation of melanocytes[4,13]. Another theory posits that the immunosuppression generated by UVR would reduce the number of Langerhans cells and their capacity to present antigens, and would also generate the apoptosis of activated T-lymphocytes[12,13]. NB-UVB is well tolerated and renders satisfactory results. It may be associated with erythema, pruritus, burns, photoageing and cutaneous neoplasias after prolonged use[14].

There is new phototherapy equipment available which emits higher energy flows, with a small, movable head which allows for a better selection of the target and pre-

TABLE 1: Clinico-epidemiological features and results in our population

	Sex/ Age (years)	Skin phototype (Fitzpatrick)	Type of vitiligo	Course time (years)	Sessions up to repigmentation	Type of repigmentation	Sessions up to score 3	Sessions up to score 4
1	F/16	III	G	12	5	Follicular	24	30
2	F/59	III	G	45	3	Follicular	24	30
3	M/36	II	G	2	5	Follicular	24	30
4	M/11	III	G	1	6	Follicular	24	30
5	F/4	II	G	2	4	Follicular	24	30
6	F/48	III	L	13	3	Follicular	24	30
7	M/16	IV	G	6	8	Perifollicular	30	-
8	M/23	III	L	3	4	Follicular	24	30
9	M/10	III	G	2	5	Follicular	24	30
10	F/7	II	G	1	6	Follicular	24	30
11	F/16	IV	G	5	6	Follicular	30	-
12	F/56	III	G	4	5	Follicular	24	30
13	M/8	III	G	1	6	Perifollicular	24	30
14	F/70	III	G	40	3	Follicular	24	30
15	F/6	II	S	2	-			

Abbreviations

F: female. **M:** male. **G:** generalized. **L:** localized. **S:** segmental

Photo 3: Before initiation of treatment.

serves healthy skin. Excimer laser was first used in 2001 as a new device to treat localized vitiligo[15]. It emits a coherent monochromatic light beam at short, more intense pulses[12]. It induces photobiological effects similar to NB-UVB with a greater apoptosis of T-lymphocytes[12]. Different studies have proved its efficacy [4,15-18]. It is very useful, as it preserves healthy skin from UV radiation.

On the basis of its mechanism and the good results obtained from the treatment with excimer laser and taking into account its high cost, we have tried applying pulsed UVB[7,19,20]. It consists in the administration of a polychromatic, incoherent, pulsed light beam within the UVB range which supplies higher flows of energy over a short time of exposure. It has a movable head which allows for treatment on areas of difficult access. It enables selective treatment of affected skin and ensures the preservation of healthy skin. Asawanonda and colleagues carried out a comparative study between broad-band pulsed UVB and narrow-band pulsed UVB (similar to excimer laser) which did not show any differences as far as therapeutic response is concerned[19].

Several authors have tried to combine different treatments looking for better results. Tacrolimus is an immunomodulating agent capable of inhibiting the activation and maturation of T-cells as it not only blocks the transcription of some cytokines, including interleukin (IL) 2, IL-3, IL-4, IL-5, alpha tumor necrosis factor and gamma interferon but also stimulates the apoptosis of T-lymphocytes in vitro[21]. Its use and approval offered a new treatment alternative for vitiligo[22,23]. Given the fact that the synergy in the combination of UV light and topical tacrolimus has been demonstrated, we have decided to carry out this

TABLE 2: Re-pigmentation score

Score 0	No repigmentation
Score 1	<25% repigmentation
Score 2	26-50% repigmentation
Score 3	51-75% repigmentation
Score 4	>76% repigmentation

study combining both treatments, and we have obtained similar repigmentation percentages to the ones in the literature.

Our experience with pulsed UVB was highly satisfactory. The results obtained are comparable to the results in the literature as 73% of our patients achieved over 75% repigmentation. Contrary to what was found in the bibliography, high skin phototypes (Fitzpatrick IV) did not respond so well to treatment in our study[24]. We highlight the excellent response of patients with long-standing vitiligo. One advantange of pulsed UVB is how rapidly improvement of the lesions is observed, ranging from 4 to 8 exposures according to different authors[6,15]. In our case, there were 2 patients who presented clear repigmentation as from the third exposure.

Pulsed UVB presents an alternative for the treatment of vitiligo and has some advantages over other therapeutic procedures: it does not present any significant adverse effects, it is well tolerated, it may be used in children, it allows treatment in areas of difficult access, it achieves significant repigmentation in a short time and substantially improves the quality of life of the patients.

Photo 4: After 30 exposures.

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