

Phototherapy and Vitiligo Re-pigmentation: From PUVA to Micro-focused Phototherapy

Gianfaldoni S^{1*}, Zarrab Z² and Lotti T³

¹Department of Dermatology, University of Pisa, Italy

²University of Rome "G. Marconi", Rome, Italy

³Chair of Dermatology, University of Rome "G. Marconi", Rome, Italy

*Corresponding author: Gianfaldoni S, Department of Dermatology, University of Pisa, Italy, Tel: 39050992548, +393382248075; Fax: +39050992556; E-mail: serena.gianfaldoni@gmail.com

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Abstract

Vitiligo is a relatively common, emotionally frustrating, skin disorder, which is characterized by the development of white patches related to the progressive loss of melanocytes. Despite the continuous introduction of medical and surgical therapies, photo-therapies still represent the mainstay of vitiligo re-pigmentation. In the last years, this therapeutic field has seen several advances; the most recent is the micro-focused photo-therapy.

Keywords: Vitiligo; Re-pigmentation; PUVA; Narrowband-UVB; Micro-phototherapy; Micro-focused phototherapy

progressive loss of melanocytes from the epidermis and the epidermal appendages.

Introduction

Vitiligo is an acquired chronic pigmentary disorder, often familial, characterized by de-pigmented skin areas, which stem from the

Vitiligo is a relatively common skin disease, affecting 1-2% of world population. Men and women are equally affected, without difference of backgrounds. Half of vitiligo patients have an onset before the age of 20 years.

Medical Therapies	<p>Topical and/or systemic corticosteroids</p> <p>Phototherapy: oral PUVA, topical PUVA, sol PUVA, nb-UVB, microphototherapy</p> <p>Excimer laser</p> <p>Topical immunomodulators: tacrolimus, pimecrolimus</p> <p>Topical Vitamin D analogues (calcipotriol)</p> <p>Pseudocatalase</p> <p>Topical 5-Fluoracil</p> <p>Topical prostaglandin (PGE2) analog</p> <p>Topical curcumis melo extracts</p> <p>Depigmentation therapy</p> <p>Camouflage</p>
Surgical Therapies	<p>Tissue grafting technique: suction blister grafting, split thickness grafting</p> <p>Miniature punch grafting</p> <p>Follicular unit grafting</p> <p>Smash grafting</p> <p>Cellular grafting techniques: non-cultured epidermal suspensions, melanocyte culture</p>

Table 1: Therapeutic options for Vitiligo

The precise etiology and pathobiology of the disease are still unclear [1]. Multiple theories have been proposed, including genetic, neuronal, autoimmune and biochemical mechanisms. Moreover, recent data support that vitiligo is a T-cell mediated autoimmune disease, maybe triggered by oxidative stress [2].

Clinically, vitiligo is characterized by white macules and patches, varying in number, form and distribution, affecting skin, mucous membranes and hair. The color contrast between the healthy-pigmented skin and the vitiliginous patches (leopard-like skin appearance) [3] is an important cause of psychological distress and reduction of the life quality index, of vitiligo patients.

Vitiligo's treatment has two main goals: the first one is to halt the disease progression; the second one is to induce the lesions' repigmentation, achieving an acceptable cosmetic result. In the last years, several therapeutic options, both medical and surgical, have been proposed for vitiligo [4-6] (Table 1). Treatment of vitiligo is based on various factors, such as patient's age and sex, psychological condition and expectation, distribution and extension of skin lesions, type of vitiligo (stable or not), availability of therapeutic options and their cost.

Overall, Ultraviolet Radiations (UVR), both in the range of UVB and UVA, are one of the most appreciated therapeutic options, especially in the treatment of generalized vitiligo [7]. The last four decades have seen significant technological advances in the field of phototherapy, which evolved from PUVA, to the introduction of nb-UVB, and, more recently, to the micro-phototherapy.

Historically, the first photo-therapeutic device, which has been introduced in the vitiligo treatment, was UVA light used alone (broadband UVA) or, more commonly, in association with psoralen (PUVA therapy).

PUVA therapy is a form of photochemical treatment, which consists in the oral intake of a psoralen followed by exposure to photo-activating UVA light (320-400 nm). Psoralens, also known as furocoumarins, are photo-sensitizing chemicals which occur naturally in some plant species. 8-methoxypsoralen (MeoPso) and 4,5',8-trimethylpsoralen (Me3Pso) are two psoralen analogs which are used in the photo-chemo-therapy of some dermatological diseases. In the skin, PUVA therapy inhibits the basal cell division, and stimulates melanocytes. The therapeutic protocol of vitiligo, consists in 2-3 sessions for week, increasing the dose of UVA on the base of patient's response. Because of psoralen's toxicity (e.g. gastric and ocular damage), PUVA therapy could be performed only in adult, with some contraindications. There is not agreement about the rate of repigmentation after oral PUVA. Lesions on extremities are less responsive. The treatment is not safe and side effects are due to both psoralens and radiations. The most common short-time side effects are pruritus, erythema, xerosis and phototoxic reactions. Burns have been described only in patients, who receive incorrect irradiation doses or sunbathed after taking psoralen. Long-term side effects include chronic actinic damages, carcinogenesis (melanoma and non-melanoma skin cancer), and, more rarely, hypertrichosis.

A valid therapeutic option to the oral PUVA therapy is the topical one, which is especially indicated for localized form of vitiligo. Topical PUVA consists in the application of 0.1-0.01% 8-methoxypsoralen (Me₃Pso) in hydrophilic petrolatum or ethanol, onto the depigmented macules, followed by exposure to UVA light (0.12-0.25 J/cm²). The treatment is performed 1-3 times a week, increasing the UVA dose until a mild erythematous reaction will be developed. The clinical results are quite good, but the acute and chronic side effects, due to UV radiations, are well described.

PUVASOL therapy is another photo-therapeutic option [8]. It consists in the psoralen intake and, successively, in the sunlight exposure at home. The treatment is not safe: erythema, pigmentation, blistering, burning and ocular side effects are well-described. On the other hand, PUVASOL could be considered as a therapeutic approach in not-compliant patients to hospital based photo-therapy.

Finally there is the bath-PUVA [9]. After a 10 minutes-bath in a solution containing 0.0002% Me₃Pso, patients is irradiated with UVA. Treatment is performed twice a week for a period of 6 or more weeks.

The more common acute side effects are itching and erythema. Long term side effects are represented by photo-ageing and carcinogenesis.

In the last decades, narrow-band UVB (nb-UVB) has emerged as the treatment of first choice in generalized vitiligo, often preferred to PUVA. It consists in the exposure to nb-UVB (311 nm) at the starting dose of 0.1 mJ/cm², followed by 20% increments on a weekly basis, according to clinical response. Nb-UVB stimulates melanocytes activity and halts their destruction, mainly by inhibiting the immune activity.

Treatment is done 2-3 times a week, with average treatments lasting between 10 weeks and 2 years. Due to the absence of photosensitizing substances, Nb-UVB therapy could be performed in children, open air workers, patients with liver or kidney failure, and pregnant females. Recent studies support how nb-UVB is superior to PUVA for many reasons, including higher rates of repigmentation and color match with natural skin [10]. Treatment is generally accepted and well-tolerated by most patients. The most common acute side effects are itching, xerosis, erythema, and transient hyperpigmentation. Apart for a supposed photo-damaging, long term side effects are yet to be determined. Keratoacanthoma after narrowband-UVB has been reported as a rare side effect.

Many studies show how nb-UVB, combined with different topical drugs (eg. Corticosteroids, vitamin D analogues, tacrolimus, pimecrolimus), may be more efficient than photo-therapy alone. More recently, further advances in technology have permitted the development of micro-photo-therapy. Micro-photo-therapy consists in the treatment limited to the affected vitiliginous areas, with sparing of uninvolved skin (Table 2). This allows reducing acute and long-term side effects of uninvolved skin. Micro-photo-therapy acts with the same modalities of the classical photo-therapy, but in a more precise and safe way because, treating only skin lesions, the operator can use more appropriate dose of energy. The possibility to deliver higher dose of energy, leads to shorten duration and less frequent treatment sessions, with an increasing of patient's compliance. Micro-photo-therapy is particularly indicated for the treatment of localized vitiligo [11] (< 10% of body surface area), also for lesions localized in skin areas (e.g. Scalp, ear, nose), which could not be treated with conventional devices. Micro-photo-therapy could also be used in pregnant, claustrophobic patients and children, who may be afraid by the large device. In the last years, many different target photo-therapy machines (laser and non-laser) have been introduced in the clinical practice (Table 3), providing good results in term of restoring pigmentation, patients' compliance, and safety. As conventional photo-therapy, the targeted one could be used alone or in combination with different therapies in order to obtain better results and reduce risks in the management of the disease [12].

However, the last frontier of vitiligo therapy is represented by the BIOSKIN EVOLUTION[®] device, an innovative cold light generator micro-focused photo-therapy. The device consists of a short arc lamp generating a beam of visible ultraviolet radiations, filtered in order to obtain only narrowband-UVB. BIOSKIN EVOLUTION[®] provides a spectrum of intensity up to 400 mW/cm² with an emission spectrum ranging from 300 to 320 nm and a peak emission at 311 nm. This specific wavelength has seen to be the most effective in the treatment of vitiligo, because it can stimulate in an optimal way the "silent" melanocytes cells gradually. Moreover, it can act on the modulation of the immune skin system.

Conventional Phototherapy	Microphototherapy
Exposure of affected and unaffected skin areas	Treatment focused on skin lesions and sparing of uninvolved areas
Difficulty in treating certain skin areas (e.g. ear, nose)	Possibility to treat difficult areas thanks to a maneuverable hand piece
Slow delivery system, which needs longer treatment sessions	Quick delivery system. Uninvolved areas aren't treat, operators can also use higher doses of energy, achieving faster response on selected areas
Multiple and frequent visits to clinic	Shorten and less frequent visits
Bulky machines which need large office space	Smaller device
Difficulty in treating claustrophobic patients and children, who may be afraid by the large device	Easy administration of the energy delivery and well tolerate-therapy

Table 2: Main differences between Conventional Phototherapy and Micro-Phototherapy

Monochromatic excimer laser
Intensed pulsed light therapy (IPL)
Light target phototherapy (UVA and/or UVB)
Photodynamic therapy
Low-level laser

Table 3: Micro-Phototherapies

The treatment is limited to the vitiliginous patches, with sparing of uninvolved skin areas. This fact allows the operator to obtain lesional re-pigmentation, without increase in the color contrast between affected and not affected skin. The therapeutic protocols (energy level, spot light, time of emission, number of session) are decided by the dermatologist on the base of the clinical characteristics of the singular patient. The treatment is repeated once every three weeks, with the possibility to effect 1-3 sessions in the same day, in accordance with the patient's therapeutic protocol. Usually, the first clinical results, in term of re-pigmentation's rate, can be described just after 8-10 sessions. Body's areas, such as face, neck, breast, genitals and thighs, re-pigment first than terminal zones (e.g. Finger), which require in general a superior lapse of time.

No adverse effects have been noted with BIOSKIN EVOLUTION[®], neither during the therapeutic sessions nor in the following days. Moreover, because it conveys micro doses of energy limited to lesions, it does not provoke photo ageing of the skin.

Recent data suggest that nb-UVB micro-focused phototherapy could be considered as first-choice therapy for patients affected by localized vitiligo, where it may provide good clinical results in term of restoring pigmentation, patients' compliance, and safety [13].

Conclusion

Vitiligo is one of the oldest skin disorders, affecting 1-2% of the human population. It is characterized by de-pigmented areas varying in number, form and localization, which stem from melanocytes loss or dysfunction. Recent advances in the knowledge of vitiligo's pathogenesis have contributed to find better therapeutic options (both medical and surgical), so that at present many patients find a solution

for de-pigmented skin. Among those, phototherapies, used alone or in combination with different therapies, are considered the mainstay in the treatment of both localized and generalized form of vitiligo.

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