

Vitiligo repigmentation: What's new?

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Abstract

Vitiligo is a relatively common acquired skin disorder, characterized by the progressive loss of melanocytes, which results in white patches. Classically, vitiligo's treatments have been considered unsatisfactory and challenging. Recent advances in the knowledge of vitiligo's pathogenesis have contributed to find better therapeutic options, so that at present many patients find a solution for depigmented skin. The authors show new promising technologies for vitiligo's repigmentation.

Introduction

Vitiligo is an acquired condition, often familial, characterized by progressive loss of melanocytes from the epidermis and the epidermal appendages, resulting in skin areas without pigmentation. Vitiligo is a relatively common skin disease, with an estimated prevalence of 0.5-1% in most populations. It affects people of all backgrounds and both genders. Half of vitiligo patients have an onset before the age of 20 years.

Although the precise etiology of the disease is still unclear [1], recent data support that vitiligo is a T-cell mediated autoimmune disease, maybe triggered by oxidative stress [2].

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

The treatment of vitiligo is aimed at halting disease progression and inducing repigmentation, achieving an acceptable cosmetic result. To date, many medical and surgical treatments are available [3,4] (Table 1). Surgical therapies should be reserved for stable recalcitrant lesions, which did not achieve cosmetically pleasing results with medical treatments. Moreover a wide range of medical treatments are now available, such as steroids, ultraviolet radiations, lasers, calcineurin inhibitors, topical immunomodulators, 5-FU, prostaglandin analogs, topical vitamin D analogues and many others. Among these topical steroids and phototherapy are the more appreciated medical therapeutic options.

Corticosteroids (CSs) act as antiinflammatory and immunosuppressant agents. Treatment with CSs has seen to decrease melanocytes' destruction, to induce their repopulation and pigment production. CSs could be used in a topical or in a systemic way. Topical steroids are considered to be the first-line therapy for localized vitiligo. They could be used alone or combined with light therapy, achieving better clinical results. Steroids are quite safe if used for few weeks, and, under this condition, they could be used also in children. Unfortunately, the treatment should be time-limited (no more than 2-4 months) to avoid percutaneous adsorption and local side effects such as

epidermal atrophy, striae distensae, telangiectasia, hypertrichosis and, more rarely, acneiform eruption. In patients affected by generalized or progressive vitiligo, another therapeutic option is the systemic administration of corticosteroids, also in combination with UV light. While systemic CSs could be useful to stop the progression of the disease and to induce repigmentation, they can induce important side effects (eg. insomnia, acneiform eruption, weight gain, hypertrichosis, menstrual alteration, adrenal insufficiency).

Another mainstay in the treatment of vitiligo, especially for generalized forms, is ultraviolet radiations (UVR), both in the range of UVB and UVA. Phototherapy stimulates melanocytes activity and halts their destruction. Historically, the first phototherapeutic device, which has been introduced in the vitiligo treatment, was UVA light

Table 1. Therapeutic options for vitiligo.

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

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used alone (broadband UVA) or, more commonly, in association with psoralen (PUVA therapy).

PUVA therapy consists of the oral intake of a photosensitizer psoralen followed by exposure to photoactivating UVA light (320-400nm). Treatment is performed 2-3 times a 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. The rate of repigmentation after oral PUVA is different in different studies. Lesions on extremities are less responsive. PUVA therapy is not always safe: side effects are due to both radiations and psoralens. The most common short-time side effects are erythema, pruritus, xerosis and phototoxic reactions. Burns occur in patients, who receive incorrect irradiation doses or sunbathed after intaking psoralen. Long-term side effects include chronic actinic damage, carcinogenesis (melanoma and non melanoma skin cancer), and, more rarely, hypertrichosis.

Topical PUVA consists in the application of 0.1-0.01% 8-methoxypsoralen in hydrophilic petrolatum or ethanol onto the vitiliginous patches, followed by exposure to UVA light (0.12-0.25J/cm²). The treatment is done 1-3 times a week, increasing the UVA dose until mild erythematous reaction develops. The clinical results are quite good, but the acute and chronic side effects, due to UV radiations, are well known.

In the last decades, narrow-band UVB has become an important therapeutic option for vitiligo treatment, often preferred to PUVA. It consist in the exposure to nb-UVB (311nm) at the starting dose of 0.1mJ/cm², followed by 20% increasing dose of UVR on a weekly basis, according to clinical response. Treatment is performed 2-3 times a week, with average treatments lasting between 10 weeks and 2 years. Nb-UVB therapy is generally well-tolerated, and it could be performed in children and pregnant females. Recent data support how nb-UVB produces higher rates of repigmentation than topical and oral PUVA. Moreover, the repigmentation achieved with narrowband UVB is more persistent and more similar to the color of the uninvolved skin [5]. Since oral psoralens are not used, ocular or gastrointestinal side effects are not described with nb-UVB treatment. The commonest 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 nb-UVB has been reported as a rare side effect.

More recently, further advances in technology have permitted the development of target phototherapy. Target phototherapy consists in the treatment limited to the affected vitiliginous areas, avoiding exposure to unaffected skin. This permits to reduce acute and long-term side effects of uninvolved skin. The mechanism of action of target phototherapy are the same of the classical phototherapy, but in a more precise and safe way because, treating only vitiliginous patches, the operator can use more appropriate dose of energy. The possibility to deliver higher dose of energy, leads to shorten time of sessions and duration of cycles, with an increasing of patient's compliance [6-8]. In the last years, many different target phototherapy machines (laser and non laser) have been introduced in the clinical practice (Table 2).

New therapeutic option for Vitiligo repigmentation

Among these the last frontier of vitiligo therapy is represented by the BIOSKIN EVOLUTION® device. It is a cold light generator micro-focused phototherapy, which consists of a short arc lamp generating a beam of visible ultraviolet radiations, filtered in order to obtain only

Table 2. Target therapies.

Monochromatic excimer laser
Intensed pulsed light therapy
Light target phototherapy (UVA and/or UVB)
Photodynamic therapy
Helium neon laser

narrowband-UVB. BIOSKIN EVOLUTION® can provide a spectrum of intensity up to 400 mW/cm² with an emission spectrum ranging from 300 to 320nm and a peak emission at 311nm. This specific wavelength has seen to be the most effective in the vitiligo treatment, because it can stimulate in an optimal way the dormant melanocytes cells gradually. Moreover, it can act on the modulation of the immune skin system.

The treatment is limited to the vitiliginous pathes, with sparing of uninvolved skin areas. This fact allows the operator to obtain lesional re-pigmentation, without increase in the color contrast between healthy skin and vitiligo's pathes. Energy level, spot light, time of emission and number of session are determined by the dermatologist, on the base of the clinical characteristic 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 repigmentation's rate, could be described just after 8-10 sessions. Body's areas, such as face, neck, breast, genitals and thighs, repigment first than terminal zones (eg. Finger), which require in general a superior lapse of time.

The treatment has never highlighted any negative side effects, neither during the therapeutic session nor in the following days. Moreover, because it conveys microdoses 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 [7,8].

While the effectiveness of conventional phototherapies and of the more innovative micro-focused phototherapy, patients' compliance is the major obstacle in obtaining good clinical results. In facts, treatments are usually performed in more session at clinics, so that they require cost and time commitments.

For not-compliant patients, exposure to natural sunlight could be an effective alternative to administer phototherapy. However, sunlight provides narrowband UVB radiation and others non-therapeutic ones, which limit its value's treatment. Recently, an innovative topical cream (PHOTOCIL®) has been introduced to selectively deliver nb-UVB therapy, when exposed to solar ultraviolet irradiation [9]. The composition of the cream is diethylamino hydroxybenzoin hexyl benzoate and alpha-glucosyl hesperidin, a glucosylated derivative of a natural plant flavonoid. These compounds were selected after toxic, allergic reaction and molecular size studies. Skin application is promoted by a water and oil emulsion. As respect to a broadband SPF 50 sunscreen, PHOTOCIL® is applied only on vitiliginous pathes. Recent data support the efficacy of the cream, suggesting that its application, before sunlight exposure, could be a safe and more accepted treatment for vitiligo than the tradition artificial phototherapy [10].

Another important innovation in vitiligo treatments is the use of antioxidant agents. Some evidences support this theory:

- 1) The skin is an organ constantly affected by reactive oxygen

species (ROS) from both endogenous and exogenous sources [11].

2) Plasma advanced protein oxidation or serum catalase levels are altered in vitiligo patients compared with healthy subjects, suggesting oxidative stress as a pathological marker [12].

3) The immunological component of vitiligo is linked with the displacement of redox equilibrium. ROS, besides having a direct melanocytotoxicity, can induce an autoimmune attack against melanocytes. They are involved in specific early events in T-cell activation and antioxidants are involved in reducing T-cell proliferation, IL-2R expression and IL-2 production [13].

4) The activity of tyrosinase, the enzyme expressed by melanocytes and catalyzing the synthesis of melanin, is altered by high levels of the reactive oxygen species (ROS) hydroxide peroxide [14].

ROS affect both melanocyte and keratinocytes functionality [15]. Melanogenesis is finely regulated by a chemical cross-talk of the cellular component of the dermis. In particular keratinocytes, together to melanocytes, form a functional unit deputed to the regulation of skin pigmentation. In vitiligo the impairment of keratinocyte cells removes the functional and trophic support to melanocytes and promotes their consequent death. Recently the modulation of keratinocytes activity of perilesional skin has received more attention. Perilesional skin may be considered as a critical zone where melanocyte death is initiated, with a substantial role played by keratinocytes in the development of disease. An Italian group of study indicated that keratinocytes from perilesional skin are significantly affected by oxidative stress [16]. The natural antioxidant compounds curcumin and capsaicin repressed the intracellular ROS generation and the lipid peroxidation, improved mitochondrial activity and increased the phosphorylation of the antiapoptotic protein ERK.

Recently SIRT1 positive modulation has been highlighted as a preventive therapy able to reduce keratinocyte cell stress reducing the oxidative stress and promoting the activation of antiapoptotic pathways [17]. Sirtuins are a family of seven proteins in humans (SIRT1–SIRT7) that are involved in multiple cellular processes relevant to dermatology. In the cell they work as histone deacetylase and/or adenosine diphosphate ribosyltransferase. Sirtuins are involved in cellular pathways related to skin structure and function, including aging, ultraviolet-induced photoaging, inflammation, epigenetics, cancer, and a variety of cellular functions including cell cycle, DNA repair and proliferation. In human keratinocyte cultures from perilesional skin, resveratrol showed beneficial effects dependent on SIRT1 activation. The natural antioxidant rebalanced the keratinocytes oxidative state through normalizing the superoxide anion levels, the mitochondria depolarization and the mPTP opening. In particular it exerted cytoprotective effects managing the functionality of AKT protein. Among its various cellular functions, there is extensive evidence that Akt plays a central role in regulating growth factor-mediated cell survival and blocking apoptosis. It is important to consider that though resveratrol is the most widely employed natural SIRT1 activator [18], some of their effects (e.g. its antioxidant properties) may be SIRT1-independent. Their protective effects are attributed to the increased expression of protective molecules, including MnSOD, Trx1 and Bcl-xL, and the down-regulation of pro-apoptotic effectors (e.g. Bax). Recent data [19] underlined that the SIRT1 activator, resveratrol, protects against UV- and H₂O₂-induced keratinocytes cell death, whereas SIRT inhibitors such as sirtinol and nicotinamide enhance cell death. In conclusion future studies are needed to elucidate the protective role of SIRT1 activators in the prevention of perilesional

skin keratinocytes. Nevertheless SIRT1 positive modulation could be, in the future, an exploitable pharmacological intervention for the vitiligo treatment.

Conclusion

Vitiligo is one of the oldest skin disorders, affecting 1-2% of the human population. It is characterized by depigmented areas varying in number, form and localization, which stem from melanocytes loss or dysfunction. Because of the aspect of skin lesions, the disease is a psychological burden. Despite the classical idea of unsuccessful vitiligo treatments, recent advances in the knowledge of vitiligo's pathogenesis have contributed to find better therapeutic options, so that at present many patients find a solution for depigmented skin.

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