New Therapies for Vitiligo

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Vitiligo is a depigmenting disorder characterized by amelanotic macules and resulting from a loss of melanocytes. It affects approximately 1% of the worldwide population regardless of race, ethnic background or gender. It is a skin disease that can cause psychological problems since patients with vitiligo experience low self-esteem, depression, job discrimination and embarrassment in social relationships.

Vitiligo usually begins in childhood or young adulthood; half of the patients acquire the disease before the age of 20, and the incidence decreases with increasing age. Vitiligo is seen as acquired white or depigmented macules; progression of the depigmentation is variable. The disease is categorized according to the extent of its involvement and the distribution of depigmentation. Patterns of distribution of the disease include generalized, acral, acrofacial, localized and segmental types. Generalized vitiligo is the most common presentation characterized by bilateral symmetric areas of depigmentation. The universal form of vitiligo is defined as more than 80 percent of depigmentation. Segmental vitiligo is the least common pattern and occurs in a dermatomal distribution.

The cause of vitiligo remains unknown, possibly from multifactorial and overlapping pathogenetic mechanisms.[1] Multiple theories have been proposed for the pathogenesis of vitiligo including autoimmune, neural, biochemical, oxidative stress and autocytotoxic hypothesis. Among these, autoimmunity remains the most well-supported by current data. Autoimmune diseases associated with vitiligo include Hashimoto thyroiditis, Grave's disease, pernicious anemia, diabetes mellitus, alopecia areata and Addison's disease.[2] In a recent survey of 2624 vitiligo Caucasian probands reported by Alkhateeb et al., a significant increase in six autoimmune diseases included vitiligo, thyroid disease predominantly hypothyroidism, pernicious anemia, Addison's disease, systemic lupus erythematosus and inflammatory bowel disease; however, type I diabetes mellitus was not associated with vitiligo in this study.[3] The autoimmune theory was also supported by the findings of antimelanocyte autoantibodies in some vitiligo patients. The neuronal theory was suggested that dermal nerve endings release a chemical, which is toxic to melanocyte. Autocytotoxic theory is proposed that melanocytes destroy themselves due to a defect in the natural protective mechanism that removes toxic melanin precursors. Genetics also play a role in pathogenesis of this disease; family history of vitiligo was reported between 7-24% of cases.[3-5] The genetics of vitiligo cannot be simply explained by Mendelian genetics; it is characterized by incomplete penetrance, multiple susceptibility loci and genetic heterogeneity.

Management for vitiligo

Vitiligo has remained a difficult disease to treat. Previous available therapies are often ineffective. It usually takes several months or years for complete repigmentation and some areas of the body get at best only partial repigmentation. The desire of the patient to undergo therapy varies from patient to patient and it needs to be assessed individually. Several factors should be considered when planning the treatment stratigies including type of vitiligo, site and degree of involvement, skin color, psychological effect, patient compliance, ease to assess to therapy, cost of treatment and social association of the disease.

The goal of the therapy is to restore melanocytes to migrate to depigmented skin. Melanocyte can migrate about 2 to 3 mm from the pigmented edge of a lesion into the depigmented skin. The most important reservoir for melanocytes is in the hair follicles. Mechanism of medical therapies and phototherapy for vitiligo is theorized to stimulate adjacent melanocytes, presumably those persisting within the underlying hair follicles to migrate and repopulate in vitiliginous patches. Generally the face, arms, trunk and legs respond well to therapies. However, grabrous skin on the fingertips and the dorsum of hands and feet is less responsive to therapies because of the absence of a melanocyte reservoir.[6] Importantly, hair-bearing skin in which terminal hairs are totally white is as well less likely to respond to medical or phototherapy. Therefore, the white hair is a clinical sign demonstrated that the reservoir of melanocytes has been destroyed and is a poor prognosis for medical therapies.

Previously therapeutic options for vitiligo have included administration of oral or topical psoralen together with UVA irradiation (PUVA), and topical steroids. However, none of these treatments gives excellent result; in addition, adverse effect could be considerable. Most of patients who are treated with PUVA therapy experience gastrointestinal irritation. Ocular protection is required at least 24 hours after psoralen ingestion. Moreover multiple sessions with high cumulative dose of PUVA therapy increase the risk of cutaneous malignancies. Moreover, prolonged use of topical steroids can result in irreversible skin atrophy, striae and telangiectasia. During the past eight years, there have been several new advanced therapies for vitiligo. These treatments include narrowband ultraviolet B phototherapy (NB-UVB), targeted phototherapy and topical immunomodulators.

New therapy for vitiligo

Narrowband ultraviolet B (NB-UVB) phototherapy

Narrowband UVB involves the use of UV lamps

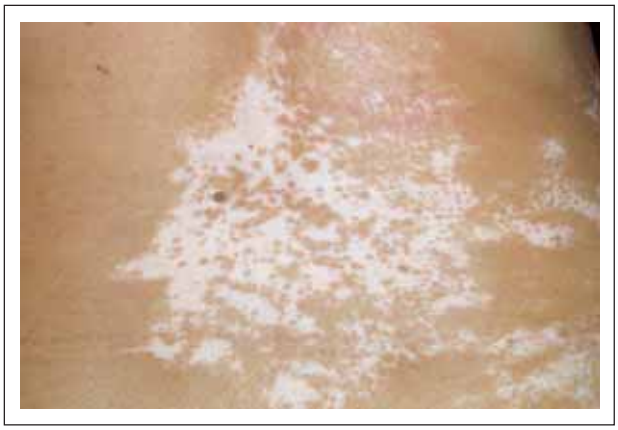

Fig 1. Repigmentation of vitiligo occurs in follicular pattern.

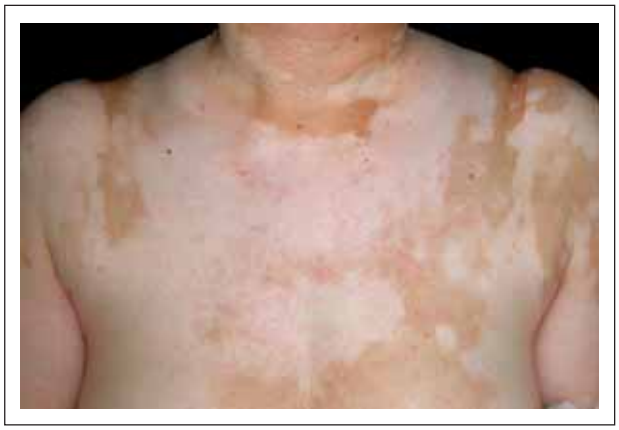

Fig 2A. Generalized vitiligo before NB-UVB phototherapy.

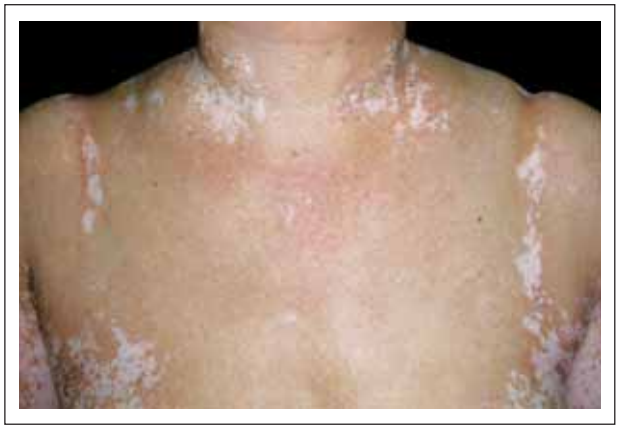

Fig 2B. More than 80% repigmentation after 5-month of NB-UVB phototherapy.

with a peak emission around 311-312 nm. Mechanism of NB-UVB in vitiligo involves local immunosuppression, stimulation of melanocyte-stimulating hormone, melanocyte proliferation and melanogenesis. In an open trial, 51 children with generalized vitiligo were treated twice weekly with NB-UVB radiation. The treatment resulted in more than 75% overall repigmentation in 53% of patients and in stabilization of the disease in 80% of patients.[7]

Retrospective analysis of 69 patients with vitiligo who were treated either with PUVA or NB-UVB demonstrated that NB-UVB was more effective than PUVA. Narrowband-UVB also provided a better stability and color match of repigmentation with surrounding skin.[8] Whereas another study, however, showed no different between NB-UVB 311 nm and PUVA in repigmentary effects.[9] A recent retrospective analysis of 60 Thai patients with recalcitrant vitiligo treated with NB-UVB phototherapy was performed. Forty two percent of patients had more than 50% repig-mentation on face, trunk, arms and legs. The response rate of patients who had never been treated with PUVA was significantly higher than who previously had PUVA. Similar to other studies, hands and feet are the most recalcitrant area of therapies. In this study, no patient had more than 25% repigmentation on their hands and feet.[10]

From our experience at the Phototherpy Unit, Faculty of Medicine Siriraj Hospital, we prefer NB-UVB for patients with generalized vitiligo because of fewer side effects and well tolerate compared to PUVA. Our phototherapy treatment schedule is twice weekly. We start the treatment with a low dose of NB-UVB, and then gradually increase the dose. Patients usually begin to notice follicular repigmentation within the first two months (Fig 1). It takes several months up to two years for complete repigmentation. The areas such as face, trunk, arms and legs respond well to NB-UVB (Fig 2A, 2B). Phototherapy for vitiligo on the acral area, lip or tips of finger are often ineffective.

Targeted Phototherapy

The 308-nm excimer laser is one of the laser devices that emit a monochromatic and coherent beam of light. It can selectively treat a lesion while sparing surrounding normal skin. The 308-nm xenon-chloride excimer laser has the advantage of having ability to deliver higher energy fluences to the target tissue in less time. The degree of repigmentation in a period of 2 to 4 weeks is much higher than that achieved with any other types of vitiligo therapy.[11] A number of study series have shown the efficacy and the good tolerance of the 308-nm excimer laser in the treatment of localized vitiligo. The treatment requires 3 times a week. A drawback of this treatment is time consuming to treat a very large area; therefore it is only appropriate for localized vitiligo. A combination of the 308-nm excimer laser and 0.1% tacrolimus ointment has provided very motivating results, which need to be confirmed in larger series. Targeted phototherapy is a new treatment, even though irradiation is targeted only for depigmented skin but at present it still lacks of actual data concerning the long-term risk for skin cancer after this treatment. Therefore the treatment should be considered with caution.

Topical immunomodulators

Topical tacrolimus (FK-506)

Tacrolimus is a new immunosuppressive agent that acts by inhibiting T-cell activation and cytokine release. It offers a safe and efficacious alternative for many skin conditions. It minimizes the need for topical glucocorticoids and does not cause skin atrophy. Tacrolimus was first reported for treatment of vitiligo in 2002. The underlying mechanism was shown in an in vitro study that topical tacrolimus promoted proliferation of melanocytes and melanoblasts.[12] Recently, a double-blind randomized trial of 0.1% tacrolimus against 0.05% clobetasol for the treatment of vitiligo in children was performed. Both topicals were used for a 2-month period. The mean percentage of repigmentation was 49.3% for clobetasol and 41.3% for tacrolimus. However, few patients using clobetasol got skin atrophy or telangiectasia, while tacrolimus spared

these adverse effects.[13] A combination treatment of 0.1% tacrolimus ointment plus the 308-nm excimer laser is superior to 308-nm excimer laser monotherapy for the treatment of UV-resistant vitiliginous lesions.[14]

Pimecrolimus

Pimecrolimus is one of the calcineurin inhibitors. It derives from ascomycin macrolactam and has immune-modulating and anti-inflammatory properties. A right-left comparison of the effect of pimecrolimus and clobetasol in 10 vitiligo patients was performed recently. Both treatment modalities showed a comparable rate of repigmentation. As other treatments for vitiligo, the degree of repigmentation varied according to the anatomical location of vitiligo lesions.[15]

Surgical Therapies

Vitiligo in some areas of the body is recalcitrant to medical therapies; those areas include lip, tip of fingers, dorsum of hands and feet. When vitiligo fails to respond to medical treatments or phototherapy, surgical therapy by implanting melanocytes on the depigmented areas is a considerable option. These surgical methods include autologous suction-blister grafts, split thickness grafts, punch grafting and transplantation of autologous melanocyte culture. A systematic review of autologous transplantation was carried out by analysis of sixty-three studies. The highest mean success rates (87%) were achieved with split-skin grafting and epidermal blister grafting. Minigrafting had the highest rates of adverse effects but was the easiest, fastest, and least expensive method.[16] Recently, a prospective study of 66 patients with recalcitrant vitiligo undergoing punch graft in combination with NB-UVB phototherapy was performed. Eighty-six percent of patients got successful repigmentation from this combination. This therapy was shown to be an easy, safe, inexpensive, and effective method of repigmenting static and stubborn vitiligo.[17]

Besides specific therapies, patients with vitiligo should be counseled for taking care of themselves. Since a vitiligo lesion can get burnt easily due to lack of melanocyte and melanin in the depigmented lesions, all vitiligo patients should be recommended staying out of the sun at peak periods, wearing protective clothing and regularly applying sunscreen when they are going out.

CONCLUSION

For management of vitiligo patients, each patient should be assessed individually and planned for treatment accordingly. Counseling is an essential part of overall treatment. At present, new therapies together with cosmetic camouflage may help the patient to cope better with this disease.

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