New Insights and New Therapies in Vitiligo

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VITILIGO IS A RELATIVELY COMMON, ACQUIRED PIGMENTARY DISORDER CHARACTERIZED BY AREAS OF DEPIGMENTED SKIN RESULTING FROM LOSS OF EPIDERMAL MELANOCYTES. THE PREVALENCE OF THIS DISEASE VARIES FROM 0.1% TO 2% IN VARIOUS GLOBAL POPULATIONS. ONSET MAY OCCUR AT ANY AGE, BUT THE INCIDENCE USUALLY PEAKS IN THE SECOND AND THIRD DECADES OF LIFE. PATTERNS OF DISTRIBUTION OF THE DISEASE INCLUDE THE GENERALIZED, ACRAL OR ACROFACIAL, LOCALIZED, AND SEGMENTAL TYPES. THE GENERALIZED DISTRIBUTION IS THE MOST COMMON PATTERN AND IS CHARACTERIZED BY SYMMETRICALLY DISTRIBUTED AREAS OF DEPIGMENTATION. SEGMENTAL VITILIGO IS THE LEAST COMMON PATTERN AND OCCURS IN A DERMATOMAL OR QUASI-DERMATOMAL DISTRIBUTION, OFTEN FOLLOWING THE DISTRIBUTION OF THE TRIGEMINAL NERVE. THE COURSE OF THE DISEASE IS UNPREDICTABLE. VITILIGINOUS SKIN LESIONS MAY REMAIN STABLE OR SLOWLY PROGRESS FOR YEARS. IN SOME INSTANCES, HOWEVER, PATIENTS UNDERGO RAPID, COMPLETE DEPIGMENTATION IN 1 TO 2 YEARS.

THE DISEASE SHOWS NO RACIAL, ETHNIC, OR SOCIOECONOMIC PREDILECTION. HOWEVER, GIVEN THE CONTRAST BETWEEN THE DEPIGMENTED AREAS AND HEALTHY SKIN, THE DISEASE IS MOST DISFIGURING IN DARKER RACIAL OR ETHNIC GROUPS. VITILIGO IS ONE OF THE MOST PSYCHOLOGICALLY DEVASTATING SKIN DISEASES.1,2 THE PSYCHOLOGICAL EFFECTS OF VITILIGO ARE INFLUENCED AND EXACERBATED BY SOCIETAL PERCEPTIONS OF SKIN DISFIGUREMENT AND IRRREGULARITIES IN SKIN COLOR.1,2

See also Patient Page.
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Patients with vitiligo experience low self-esteem, job discrimination, depression, and embarrassment in social and sexual relationships.3

Genetic studies support a non-mendelian inheritance pattern for vitiligo and suggest that vitiligo is a multifactorial, polygenic disorder.3,5 Twenty percent to 30% of patients report vitiligo in first- and second-degree relatives. The disease has been associated with specific HLA haplotypes including HLA-DR4, Dw7, DR7, DR1, B13, Cw6, DR33, and A19; however, haplotypes may vary considerably with the population studied.3,6 Recently, a genome-wide linkage scan was performed in 71 white multiplex families with vitiligo.7 Linkage was assessed by a multipoint nonparametric linkage analysis. AIS1 located at 1p31 showed highly significant linkage, suggesting that it is a major susceptibility locus in whites. Additional signals on chromosomes 1, 7, 8, 11, 19, and 22 have met genome criteria for suggestive linkage. Other candidate genes reported to mediate vitiligo susceptibility include the catalase gene, VIT1 at chromosome 2p16, and the guanosine triphosphate cyclohydrolase I gene.8,7

Pathogenesis

Histologically, the predominant finding in the depigmented areas of vitiligo is an absence of epidermal melanocytes (FIGURE 1A and 1B). The precise cause of the loss of these epidermal melanocytes is unknown. Light microscopic and ultrastructural studies have revealed vacuolar degeneration of basal and parabasal keratinocytes and dermal lymphohistiocytic infiltrates. Autoimmune, neural, biochemical, oxidative stress, autocytotoxic, viral, and melanocyte detachment mechanisms have been proposed to explain the pathogenesis of vitiligo.3,8-11 However, the autoimmune hypothesis remains the most well-supported by current data.

Substantial new data further implicate immune mechanisms in the pathogenesis of vitiligo and indicate that vitiligo may share common linkages with other autoimmune diseases. Historically, vitiligo has been reported in association with a number of autoimmune endocrinopathies and autoimmune diseases. Thyroid disorders, in particular Hashimoto thyroiditis and Graves disease, are most commonly associated with vitiligo. Other associated disorders include diabetes mellitus, alopecia areata, pernicious anemia, rheumatoid arthritis, autoimmune polyglandular syndrome, and psoriasis.10-13 In a recent survey of 2624 vitiligo probands in North America and the United Kingdom, a significant increase in 6 autoimmune diseases was reported in vitiligo probands and first-degree relatives.14 These diseases included vitiligo, thyroid disease (predominantly hypothyroidism), pernicious anemia, Addison disease, systemic lupus erythematosus, and inflammatory bowel disease.

Many humoral and cell-mediated immune aberrations have been reported in vitiligo patients. Numerous studies have documented an increased frequency of organ-specific autoantibodies in these patients.15,16 Antithyroid (thyroglobulin-
lin, thyroid microsomal, and thyroid peroxidase), gastric parietal cell, and antinuclear antibodies are the most commonly associated autoantibodies that have been documented. Vitiligo patients with organ specific autoantibodies, unassociated with overt autoimmune disease, have an increased risk of developing subclinical or overt autoimmune disease.15,16 Although there are no established guidelines for laboratory testing in patients with vitiligo, these observations may support routine thyroid function screening tests. Such tests may include obtaining a serum thyroid-stimulating hormone level and a thyroid peroxidase antibody level performed at 1- to 2-year intervals.

The presence of antibodies to surface and cytoplasmic melanocyte antigens in the sera of vitiligo patients lends additional support to the autoimmune hypothesis.8,17-19 These antibodies can induce the destruction of melanocytes grown in culture by complement-mediated lysis and antibody-dependent cellular cytotoxicity.8 In addition, melanocyte antibodies, when passively administered to nude mice grafted with human skin, have a destructive effect on melanocytes within the skin graft.20 Less commonly, antibodies targeting tyrosinase, tyrosinase-related protein 1 and 2, Pmel17 (gp100), and melanin-concentrating hormone 1 (MCHR1) have also been reported in vitiligo patients.8 The transcription factors SOX9 and SOX10 have been identified as melanocytic autoantigens in autoimmune polyendocrine syndrome and idiopathic vitiligo.21 Recent studies have provided additional insights into the role of cell-mediated immunity in the destruction of melanocytes, suggesting that cytotoxic T lymphocytes may play a significant role in melanocyte destruction in vitiligo.8,9 Activated cytotoxic T lymphocytes have been reported in abundance in the perilesional area of the vitiliginous skin, often in apposition to disappearing melanocytes.22 These infiltrating lymphocytes are predominantly cytotoxic CD8+ lymphocytes that express skin homing receptors (ie, CLA+). In addition, other studies have demonstrated the presence of increased numbers of circulating CD8+ cytotoxic lymphocytes that are reactive to the melanosomal proteins MelanA/MART-1, gp100, and tyrosinase in HLA-A2-positive patients with vitiligo.22-25 Several investigations have also addressed the role of peripheral blood and lesional cytokine expression in the pathogenesis of vitiligo. Elevated levels of serum soluble IL-2 receptor, IL-6, IL-8, and elevated lesional tissue levels of IL-2 have been reported in vitiligo patients.26-28 These findings correlate with an increased level of T-cell activation. In biopsies of lesional, perilesional, and healthy skin, significantly lower levels of expression of granulocyte colony-stimulating factor, basic fibroblast growth factor, and stem cell factor were reported in vitiliginous skin, whereas the expression of IL-6 and tumor necrosis factor α (TNF-α) were increased in lesional skin.29 Granulocyte colony-stimulating factor, basic fibroblast growth factor, and stem cell factor are paracrine cytokines secreted by keratinocytes. These paracrine cytokines stimulate melanogenesis and melanocyte proliferation, whereas IL-6 and TNF-α inhibit melanocyte proliferation and melanogenesis.30 Together these findings suggest that keratinocyte function is also impaired in vitiliginous skin.

A subsequent report demonstrated increased expression of TNF-α- and interferon γ (IFN-γ) in the lesional and adjacent healthy skin of patients with vitiligo as compared to the skin of matched controls.31 After 6 months of

Figure 1. Photomicrographs of Vitiliginous vs Healthy Skin

Immunohistochemical staining for melanocytes using an alkaline phosphatase detection kit and a 1:5 dilution of MEL-5 antibody after predigestion for 4 minutes with protease. A, vitiliginous skin; B, healthy skin with scattered cells in the basal layer positive to MEL-5 antibody (red chromogen) (magnification ×20).
treatment with twice-daily application of tacrolimus, a topical immunomodulator, there was a significant depression in the level of TNF-α/H9251 expression in the lesional and adjacent healthy skin as compared with baseline. This observation suggests that suppression of TNF-α may be associated with repigmentation of vitiliginous lesions.31 Whether these immunologic aberrations are primary or secondary events in the destruction of melanocytes in vitiligo remains an intensely debated topic among pigmentation researchers. However, regardless of which event is primary, many of the most effective therapies for vitiligo work via suppression or modulation of the immune response.

Medical Therapies for Vitiligo

Vitiligo has been and remains a difficult disease to treat. Previously, therapeutic options have included administration of oral and topical psoralen photochemotherapy, topical steroids, and depigmentation therapies. At best, none of these treatment options have been optimal.

Study outcomes have varied considerably given differences in inclusion criteria and scoring systems used to assess repigmentation. Recently, a Vitiligo Area Scoring Index was developed as a quantitative tool to evaluate vitiligo responses parametrically.32 The scale is based on the degree of macular repigmentation within lesions over time and was validated against physician and patient global assessments. Additional studies will be necessary to validate this scoring system.

During the past 6 years, there have been several new advances in the treatment of vitiligo. These new treatment options include narrowband UV-B phototherapy, targeted light therapy, topical immunomodulators, and calcipotriol in combination with UV light.

Narrowband UV-B. Historically, topical and systemic psoralen photochemotherapy with UV-A (PUVA) were considered the gold standard for repigmenting vitiliginous skin lesions; however, PUVA-induced–repigmentation rates varied considerably.33,34 In addition, adverse effects could be substantial, including phototoxicity and gastrointestinal irritation, and the treatment requires ocular protection.35

Given the comparable efficacy of narrowband UV-B phototherapy and its lack of systemic adverse effects, it has emerged as the initial treatment of choice for patients with moderate to severe disease (Figure 2A and 2B).35 Narrowband UV-B involves the use of UV lamps with a peak emission around 311 nm.36 These shorter wavelengths provide higher energy fluences and induce less cutaneous erythema. Narrowband UV-B induces local immunosuppression, stimulates the production of melanocyte-stimulating hormone, and increases melanocyte proliferation and melanogenesis. The first major study of narrowband UV-B in patients with vitiligo compared the efficacy of narrowband UV-B to topical PUVA.37 Significantly enhanced repigmentation was achieved in patients treated with narrowband UV-B as compared with those treated with topical PUVA. Adverse effects were minimal in patients treated with the narrowband UV-B group in contrast to the increased phototoxicity observed in the patients treated with topical PUVA.

Subsequent studies have further confirmed the efficacy of narrowband UV-B phototherapy for vitiligo.38-40 The efficacy of narrowband UV-B was recently assessed in 60 Asian patients with recalcitrant vitiligo.40 Forty-two percent of the patients achieved greater than 50% repigmentation of lesions on the face, trunk, arms, and legs. Narrowband UV-B was also used in an open label study to treat 51 children with generalized vitiligo.38 Fifty-three percent of the participants (n=27) achieved greater than 75% repigmentation, 29% (n=15) had 26% to 50% repigmentation, and 18% (n=9) had less than 25% repigmentation. Although these studies suggest that repigmentation achieved with narrowband UV-B is comparable to oral PUVA-induced–repigmentation,35-39 no
direct comparison trials of narrowband UV-B and oral PUVA have been published to date. The major advantages of narrowband UV-B include an established safety profile in both children and adults and lack of systemic adverse effects. Unlike treatment with systemic psoralen phototherapy, narrowband UV-B does not require eye protection beyond treatment exposure time. Beyond isolated case reports and in contrast to the findings reported for psoriasis patients who have undergone this therapy, no studies have documented an increase in squamous cell carcinomas, basal cell cancers, or malignant melanomas in vitiligo patients treated with either PUVA or narrowband UV-B. Recent functional color yeast assays demonstrated overexpression of a functioning wild-type p53 protein in both the depigmented and healthy pigmented epidermis of patients with vitiligo compared with healthy controls. This wild-type p53 overexpression may explain the possible low risk of skin cancers in patients with vitiligo. However, long-term follow-up studies are needed to fully assess the risks of narrowband UV-B.

Targeted Light Therapy. Targeted phototherapy systems have also demonstrated improved efficacy for the treatment of localized vitiligo. These units deliver high-intensity light only to the affected areas, while avoiding exposure of the healthy skin and lowering the cumulative UV-B dose. In 1999, the effectiveness of UV-B radiation microtherapy was first reported for repigmentation of segmental vitiligo in a small series of 8 patients. Five of these patients achieved greater than 75% repigmentation. Subsequent investigations have also documented the benefits of excimer laser systems and targeted phototherapy units. The excimer laser produces monochromatic radiation at a wavelength of 308 nm. An open-label pilot investigation used the excimer laser to treat 29 affected areas of vitiligo in 18 patients. In this study, lesions were treated 3 times weekly for a maximum of 12 treatments. Twenty-three vitiliginous areas on 12 patients received at least 6 treatments. Varying degrees of repigmentation were reported in 57% of the treated areas. Of the 11 affected areas that received all 12 treatments, 87% demonstrated some repigmentation. A newly developed unit with a larger irradiation field was recently used on 37 patients. Compared with other targeted units with small irradiation fields (less than 3 cm), this unit has an irradiation field of 36 cm by 14 cm allowing treatment of larger areas. Forty-three percent of patients treated with this unit had 50% to 75% repigmentation of their lesions and 49% of patients had 76% to 100% repigmentation.

These agents can also work synergistically with other topical therapies. Several studies have assessed the efficacy of combination treatment with an excimer laser and tacrolimus, a topical immunomodulatory agent. In a study of 8 patients with vitiligo, 24 symmetric vitiliginous areas were treated with the excimer laser 3 times/wk for a total of 24 treatments. Topical tacrolimus ointment and a placebo were applied to randomized affected areas twice daily throughout the length of the trial. Fifty percent of the areas treated with the combination excimer laser and topical tacrolimus achieved 75% or greater repigmentation compared with 20% for the placebo group. Subsequently, a randomized prospective right/left comparison study was performed in 14 patients. Twenty lesions were treated with excimer laser monotherapy and 23 lesions were treated with combination excimer laser phototherapy and topical tacrolimus 0.1% twice daily. Twenty percent of patients treated with excimer laser monotherapy achieved greater than 75% repigmentation. In contrast, 70% of patients achieved greater than 75% repigmentation when treated with tacrolimus 0.1% in combination with the excimer laser.

The efficacy of excimer laser monotherapy has also been compared with treatment with the excimer laser in combination with topical methoxsalen. Nine patients were treated with the excimer laser as monotherapy compared with 11 patients who were treated with the excimer laser in combination with topical 8-methoxypsoralen 0.001%. A statistically significant greater degree of repigmentation occurred in patients treated with the combination excimer laser and topical 0.001% methoxsalen. Twenty percent of the excimer laser monotherapy group achieved greater than 50% repigmentation compared with 50% of the patients who were treated with the combination regimen.

These studies suggest that efficacy is enhanced when the excimer laser therapy is combined with a topical therapy such as tacrolimus or topical 8-methoxypsoralen in patients with vitiligo. Given the small numbers of patients enrolled in these trials of targeted light/laser systems and combined excimer laser therapies, additional studies are necessary to elucidate their full potential.

Topical Immunomodulators. Topical immunomodulatory agents such as tacrolimus and pimecrolimus offer several advantages in treating vitiligo. These agents are extremely well-tolerated in children and adults and can be used for long periods without evidence of atrophy or telangiectasias, the common complications associated with long-term steroid use. This is a key advantage in treating a chronic disease such as vitiligo; however, long-term data on the use of these agents for treatment of vitiligo are lacking.

Tacrolimus is a topical immunomodulatory agent that affects T-cell and mast cell functions by binding to cytoplasmic immunophilins and by inactivating calcineurin. Tacrolimus inhibits the synthesis and release of proinflammatory cytokines and vasoactive mediators from basophils and mast cells. Multiple studies have demonstrated its efficacy and safety for treatment of atopic dermatitis. The efficacy of tacrolimus for repigmentation of vitiligo was initially reported in a series of 6 patients with generalized vitiligo. Five of the 6 patients in this study achieved 50% to 100% repigmentation of their affected sites. A subsequent 24-week study assessed the efficacy and safety of tacrolimus oint-
ment in 23 patients with generalized vitiligo.19 Nineteen patients completed the study. At 24 weeks, 89% of patients (n = 19) achieved varying levels of repigmentation and there was a statistically significant decrease in overall disease severity scores at 24 weeks. Maximal repigmentation was observed on the face and neck areas (the areas with greater sun exposure), with 68% of patients (n = 13) achieving greater than 75% repigmentation. Adverse events were minimal throughout the study. Other studies have corroborated these results.51-53

Another double-blind randomized trial compared the efficacy of tacrolimus vs clobetasol, a topical steroid, for the treatment of childhood vitiligo.52 Two symmetrical lesions were treated on each of the 20 patients, 1 with tacrolimus 0.1% and the other with 0.05% clobetasol. The mean percentage repigmentation for the tacrolimus-treated lesions was 41% vs 49% for the clobetasol-treated lesions. However, 3 patients experienced steroid-induced atrophy at their sites treated with clobetasol.

Pimecrolimus, which has a mechanism of action similar to tacrolimus, also can induce repigmentation of vitiliginous skin lesions.54 As with tacrolimus, pimecrolimus induces maximal repigmentation on sun-exposed areas.

It should be mentioned that an increased risk for skin cancer among transplant recipients under immunosuppression with azathioprine or cyclosporine is well-recognized.55,56 and systemically administered tacrolimus is also an effective immunosuppressant used as an antirejection agent in organ transplantation.57 The use of topical tacrolimus, however, has not been associated with systemic immunosuppression or increased risk for skin and other malignancies in clinical trials.58

Calcipotriol. Calcipotriol is a synthetic analog of vitamin D₃. Vitamin D₃ binds to vitamin D receptors in the skin, affecting melanocyte and keratinocyte growth and differentiation. It also inhibits T-cell activation.59 Melanocytes are thought to express 1-α-dihydroxyvitamin D₃ receptors, which may have a role in stimulating melanogenesis. Several studies have assessed the efficacy of calcipotriol in combination with UV light therapy in patients with vitiligo. Some have shown that when used in combination with UV light exposure, calcipotriol may be well-tolerated and efficacious in treating both children and adults with vitiligo.60,61 However, in other controlled studies, minimal repigmentation was observed.62,63 Recently, the efficacy of calcipotriol was reported in combination with clobetasol in a series of 12 patients with vitiligo. Clobetasol was used in the morning and calcipotriol was used in the evening.64 Eighty-three percent of patients (n = 10) responded to treatment with an average 95% repigmentation of affected areas.

Surgical Therapies
Surgical therapies have been used for vitiligo for the past 25 years. Recently, substantial advances have been made in the techniques and protocols for harvesting and transplanting melanocytes. Surgical therapies remain viable options for patients with localized areas that have failed medical intervention. The major advantage of transplantation procedures is the transfer of a reservoir of healthy melanocytes to vitiliginous skin for proliferation and migration into areas of depigmentation. Transplantation procedures are contraindicated for patients with a history of hypertrophic scars or keloids.

Surgical therapies include autologous suction-blast grafts, punch grafts, split-thickness grafts, autologous melanocyte cultures, cultured epidermal suspensions, and single-hair grafts. A systematic review of autologous transplantation methods for vitiligo involved data synthesis of 39 patient series65 and concluded that maximal repigmentation occurred in patients treated with split-thickness grafting and epidermal blister grafting. Both treatment groups achieved success rates of 90% repigmentation.

Recently, 120 patients were treated with cultured pure melanocyte suspensions after carbon dioxide laser ablation. Patients with stable, localized vitiligo experienced the highest percentage of repigmentation with 84% (n = 67) achieving 90% to 100% coverage. Fifty-four percent of patients (n = 14) with stable, generalized vitiligo achieved 90% to 100% coverage, whereas only 14% of patients (n = 2) with active, generalized vitiligo demonstrated good repigmentation.66

A subsequent double-blind, randomized controlled trial in 28 patients assessed the efficacy of autologous transplanted epidermal cell suspensions followed by UV radiation (narrow-band UV-B or PUVA twice weekly for approximately 2 months) after graft healing compared with placebo and UV radiation in symmetrically distributed vitiligo lesions. A statistically significant greater amount of repigmentation was observed at the sites treated via epidermal cell suspensions and UV radiation, compared with placebo and UV radiation treatments. These results suggest that repigmentation was caused by the transplanted melanocytes.67

One hundred seventeen patients were included in a separate study assessing the influences of age, site of lesion, and type of disease on transplantation outcomes.68 In this series, the best results were achieved for patients younger than 20 years and patients with segmental vitiligo. The grafting site did not significantly affect outcome.

Conclusion
Substantial strides have been made in the pathogenesis and treatment of vitiligo. New, more effective therapies provide renewed hope for patients affected by this disease. As clinicians explore these therapies, a new paradigm for vitiligo treatment will be established.

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REFERENCES
NEW THERAPIES IN VITILIGO


