Successful Treatment of Vitiligo With 0.1% Tacrolimus Ointment

Lisa B. Travis, BS; Jeffrey M. Weinberg, MD; Nanette B. Silverberg, MD; St Luke’s-Roosevelt Hospital Center, New York, NY

REPORT OF CASES

CASE 1
A 23-year-old Hispanic woman with Fitzpatrick type IV skin presented with vitiligo vulgaris affecting 75% of her face, including complete depigmentation of the eyelids, chin, cheeks, and perioral skin. This had developed progressively over a 2-year period. As is the standard practice of our vitiligo clinic, thyroid function testing, blood cell counts, and vitamin B12 levels were taken; all were within normal limits. Mometasone furoate ointment was applied twice daily for 3 months with no signs of follicular repigmentation either on visual examination or with the use of the Wood light.

CASE 2
A 24-year-old man with Fitzpatrick type II skin presented with a history of vitiligo vulgaris for 12 years. At the time of presentation, he had depigmentation of 60% of his body surface area, including the eyelids, chin, axillae, elbows, hips, knees, and back. Thyroid function findings, blood cell counts, and vitamin B12 levels were all within normal limits. Topical mometasone furoate cream was applied twice daily for 4 months, during which patient also underwent a course of narrowband UV-B irradiation to the entire body. Despite these therapies, no repigmentation occurred, even under Wood light examination. We believe this was owing to the use of protective eyewear in the phototherapy booth.

CASE 3
A 10-year-old African American boy with Fitzpatrick type VI skin had a history of microcephaly, absence of the radii bilaterally, and learning disabilities. Eight months prior to presentation, he began to develop rapid depigmentation of the forehead, forearms, chest, back, and calves. Thyroid function findings, blood cell counts, and vitamin B12 levels were all within normal limits. Triamcinolone acetonide ointment (0.1%) was tried for 3 months with no repigmentation.

THERAPEUTIC CHALLENGE
The mainstays of vitiligo therapy in children and adults are topical corticosteroids and phototherapy. None of the 3 patients herein responded to midpotency topical corticosteroid therapy after a 3- to 4-month trial. Eyelid and facial skin is thin, and high-potency topical corticosteroids may cause atrophy, dyspigmentation, telangiectasias, and glaucoma if used for an extended period. Phototherapy cannot be administered to the eyelids owing to the need for protective eyewear in the phototherapy booth.

SOLUTION
A trial of topical 0.1% tacrolimus ointment was begun for the face and eyelids in each of these patients. Patients were instructed to apply the medication to the affected areas twice daily on dry skin. Patients were allowed unprotected (no sunscreen) natural sunlight exposure at midday: 5 minutes in the summer and 10 minutes in fall, winter, and spring. They were instructed to apply sunscreens of sun protection factor 30 or higher at all other times. The patient in case 1 developed noticeable follicular repigmentation after 3 weeks of therapy and had complete repigmentation in 4 months (Figure 1). Patient 2 (Figure 2) began to show repigmentation at 6 weeks. He was completely repigmented in 2 months, at which time he showed no Wood light enhancement. His repigmentation persisted 9 months later. Patient 3 demonstrated good facial repigmentation in 4 weeks and complete repigmentation in 2 months. All 3 patients have maintained repigmentation after 6 to 9 months of follow-up, even with discontinuation of treatment. None of the patients had any local adverse effects, including pruritus or erythema.
Vitiligo is an acquired, idiopathic disorder characterized by depigmented macules that result from damage to and destruction of melanocytes. Although the disease can occur at any age, 50% of patients acquire it before age 20 years.1 Two of the major theories of the pathogenesis of vitiligo are the autoimmune theory and the autocytoxicity theory.1,2 The autoimmune theory speculates that patients with vitiligo form autoantibodies against melanocytes. The existence of antimelanocyte surface antigen antibodies has been demonstrated, and the severity of vitiligo has proven to be related to the amount of antibodies present.2 Vitiligo has been associated with antibody-mediated autoimmune diseases such as thyroid disease, pernicious anemia, diabetes mellitus, Addison disease, alopecia areata, and myasthenia gravis.3

The autocytoxicity theory postulates that melanocytes are destroyed either by themselves through self-generation of melanin precursors (or metabolites) or by keratinocytes, which release chemicals that generate oxidative stresses. It is believed that the normal defense mechanisms of melanocytes against oxidative stress and melanin precursors are defective in vitiligo melanocytes.1

Patients have numerous treatment options available, but none is universally effective. Even among patients who respond to treatment there is a high potential for relapse.3 For this reason, most clinicians surveyed do not offer therapy to their patients with vitiligo.4 However, the disease is cosmetically disfiguring and may produce profound adverse psychological effects because it can lower self-esteem and interfere with interpersonal relationships. Support groups and other adjuncts to therapy may be very beneficial and should always be offered to the patient.5

Systemic and topical psoralens with subsequent long-wave UV-A exposure (PUVA) is the most common treatment prescribed.1 Narrowband UV-B irradiation has also demonstrated some success in treating vitiligo.3 Surgical procedures are performed for patients who have not responded well or completely to medical treatments, whose disease is stable, and whose vitiligo is segmental or localized.2 Grafts of autologous epidermal sheets or cultured melanocytes can be surgically placed into areas where PUVA has produced incomplete repigmentation.1,6

Patients with extensive vitiligo vulgaris receive the most benefit from PUVA. Several clinical studies have shown successful repigmentation after long-term PUVA therapy. Despite long-term use of PUVA, the success rate in many studies is only slightly greater than 50%.5,7,8 Furthermore, eyelids cannot be treated because of the need to wear protective eyewear under UV-A irradiation. Up to 75% of PUVA-treated patients may relapse within 1 to 2 years, according to Shaffrali et al.3 The short-term adverse effects of PUVA include pruritis, erythema, hyperpigmentation, hypertrichosis, xerosis, nausea, and

Figure 1. A, Patient 1 prior to therapy. B, The same patient after 4 months of twice-daily topical administration of 0.1% tacrolimus ointment to the affected areas.

Figure 2. A, Patient 2 prior to therapy. B, The same patient 4 months after the completion of a 4-month course of 0.1% topical tacrolimus ointment to the eyelids.
Vitiligo can be devastating for patients and at times, very difficult to treat. As the authors note, corticosteroids and phototherapy have been our mainstays of treatment. Surgical approaches to the disease are less commonly used in the United States than are these other modalities.

The authors describe 3 patients who responded well to therapy with topical tacrolimus. The presumed mechanism of action relates to the drug’s immunosuppressant effects. The therapy was well tolerated in their patients. Most of the adverse effects experienced to date when treating atopic dermatitis relate to skin irritation, burning sensation and pruritus, and folliculitis. No significant blood levels have been detected, even when applying the drug to large surface areas, with the exception of children with Netherton syndrome, as reported by Allen et al16 in the Archives. In addition, the drug has not been found to be phototoxic, photoallergenic, or photosensitizing, which is important when treating depigmented skin. The relatively quick response and lack of adverse effects make this an exciting new option for patients with vitiligo.

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vomiting. Long-term adverse effects include cataracts and skin cancer.

Shephard and Panizzon9 reviewed the literature regarding the carcinogenic risks of bath PUVA therapy compared with oral PUVA and found that both forms that use 8-methoxypsoralen increase the risk of nonmelanoma skin cancer in a dose-dependent manner. The recommended maximum number of total treatments is between 100 and 150, and the maximum cumulative dose for white-skinned patients is between 1000 and 1500 J/cm².

Topical corticosteroids are most effective on small, newly depigmented areas.3 Potent topical corticosteroids can be used on the face, with ultrapotent steroids reserved for the body. Corticosteroids have been shown to be effective in only 57% of adult patients and only 64% of childhood vitiligo patients.10 The long-term use of topical steroids often causes irreversible dermoeidermal atrophy, manifesting with striae and telangiectasias.1

It has been posited that corticosteroids are effective in treating vitiligo because they limit the amount of antimelanocyte autoantibodies produced.11 Other authors have strongly suggested that both cell-mediated and humoral immunity play an important role in generalized vitiligo vulgaris.1

Tacrolimus, a macrolide immunosuppressant that comes from the fungus Streptomyces tsukubaensis, is a novel treatment for vitiligo. The drug is approved by the US Food and Drug Administration for oral prophylaxis of rejection in kidney and liver transplant recipients.12,13 Although it differs structurally from cyclosporine, tacrolimus shares with this drug the ability to inhibit T-lymphocyte activation.14 Tacrolimus binds to an immunophilin, FK-binding protein, located in the cytoplasm of T lymphocytes. The complex formed inhibits the phosphatase calcineurin. This inhibition prevents signal transduction pathways from occurring, which ultimately halts the transcription of cytokines, including interleukin (IL) 2, IL-3, IL-4, IL-5, IL-8, tumor necrosis factor α, and interferon γ. Other actions of tacrolimus include inhibition of histamine release from skin mast cells, impairment of synthesis of prostaglandin D₂, down-regulation of FcER1 on Langerhans cells, and inhibition of CD4+ and CD8+ lymphocyte migration.11-14

Topical tacrolimus has been approved by the US Food and Drug Administration for the treatment of atopic dermatitis. At 0.03% concentration, it has been approved for use in children aged 2 to 15 years, while a 0.1% concentration has been approved for use in adults. Tacrolimus has also been used safely and effectively in immunologically based skin disorders, including psoriasis, pyoderma gangrenosum, and alopecia areata.2,11,13,15

Systemic absorption of topical tacrolimus has been documented to be very limited in trials of topical tacrolimus for atopic dermatitis. High concentrations were seen only in children with Netherton disease,16 which causes a permanent generalized abnormality of the stratum corneum. In patients with atopic dermatitis but without Netherton disease, systemic absorption of topical tacrolimus decreased as eczematous skin lesions resolved, and none of the drug was detected in the serum of the control patients with no skin disease.17 Therefore, the drug likely has limited absorption within vitiliginous lesions because the skin barrier is not broken and there is no inflammation to increase drug absorption.

The photocarcinogenic risk increased in a 52-week animal study when topical tacrolimus was used in conjunction with UV irradiation.18 Human long-term data have not demonstrated any increase in photocarcinogenicity with topical tacrolimus use. However, the manufacturing company generally recommends use of photoprotection while being treated with topical tacrolimus.18

Oral tacrolimus has limited use in skin disorders because of its potentially severe adverse effects, including infections, hypertension, hyperglycemia, hyperkalemia, nephrotoxic and neurotoxic effects, and increased risk of neoplasia.12 The effectiveness of tacrolimus in treating vitiligo, as in other skin disorders, may stem from its suppression of autoantibody recognition of cell-surface melanocyte antigens and inhibition of subsequent cytotoxic T-lymphocyte reactions. Despite the good results achieved by our patients, larger studies that are double-blinded and placebo controlled or half-face studies would be helpful to prove the efficacy of topical tacrolimus in the treatment of vitiligo.

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Corresponding author: Nanette B. Silverberg, MD, Department of Dermatology, St Luke’s-Roosevelt Hospital Center, 1090 Amsterdam Ave, Suite 11D, New York, NY 10025 (e-mail: NSilverberg@slrh.org or NSilverberg@juno.com).

REFERENCES


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