

# Tacrolimus Ointment 0.1% Produces Repigmentation in Patients With Vitiligo: Results of a Prospective Patient Series

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*The cause of the selective melanocyte destruction in vitiligo may be due to an autoimmune disorder. A series of 15 patients with vitiligo were treated with a topical immunomodulator, tacrolimus ointment 0.1%, twice daily for a minimum of 45 days. Thirteen patients (87%) experienced at least partial repigmentation, and 3 of those patients had greater than 75% repigmentation. Patients with the greatest treatment response likely benefited from concomitant natural sunlight exposure. Further studies investigating the safety and efficacy of tacrolimus ointment either as monotherapy or in combination with other therapeutic measures are warranted.*

Vitiligo is a skin depigmentation disorder caused by the selective destruction of melanocytes.<sup>1</sup> The cause of this melanocyte destruction is not known, but it has been suggested that vitiligo may be an autoimmune disorder. The demonstration of abnormal antibodies to melanocytes in patients with vitiligo<sup>2,3</sup> supports this theory, as does the fact that this disorder is associated with a variety of nonspecific immune abnormalities.<sup>1</sup> Also, a high frequency of melanocyte-specific cytotoxic T cells has been demonstrated in vitiligo patients.<sup>4</sup> Lowered CD4:CD8 cell ratios, as well as significantly greater numbers of T cells in feather pulp, have been

seen in Smyth line chickens—an animal model for human vitiligo—before vitiligo development, during vitiligo development, or both.<sup>5</sup> Bursectomy, which inhibits antibody responses, and cyclosporine, which selectively inhibits T cells and their immune response, both delay the onset and reduce the severity of vitiligo in Smyth line chickens.<sup>1</sup> This supports at least a role of T-cell-mediated autoimmunity in vitiligo.

Treatment options for vitiligo are generally unsatisfactory and difficult. Those who do respond are at risk for relapse.<sup>6</sup> Treatments that induce varying degrees of repigmentation in patients with vitiligo are immunosuppressive therapies,<sup>6,7</sup> including topical corticosteroids and photochemotherapy with psoralen-UVA (PUVA), which affects cytotoxic T cells.<sup>8</sup>

Topical tacrolimus has been shown to target T-cell activation, making it effective for the treatment of atopic dermatitis,<sup>9,11</sup> a dermatologic condition believed to be caused by an abnormal T-cell-mediated immune response in the skin.<sup>12</sup> Tacrolimus binds to the intracellular protein FKBP12 and inhibits the phosphatase activity of calcineurin, thereby impairing T-cell activation and the subsequent production and release of cytokines.<sup>12</sup>

## Patients and Results

Fifteen patients with vitiligo on various body surfaces applied tacrolimus ointment 0.1% to depigmented skin twice daily for a minimum of 45 days (range, 45–284 days). Patient demographics are summarized in Table 1.

Ten patients (66%) previously had failed on other vitiligo treatment regimens. To assess the efficacy of topical tacrolimus as monotherapy, concomitant

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vitiligo treatments were not allowed during tacrolimus ointment 0.1% therapy. Safety and efficacy were assessed at approximately every 6 weeks during treatment.

Thirteen patients (87%) experienced at least partial improvement with tacrolimus ointment 0.1%: 3 had greater than 75% repigmentation (Figures 1 through 3), 1 had 50% to 75% repigmentation, and 9 had greater than 0% to 25% repigmentation. Two of the patients had no response to treatment (Table 2). The onset of response generally occurred within 6 to 8 weeks of treatment initiation.

**Comment**

Most patients in this case series experienced at least some repigmentation with tacrolimus ointment 0.1% therapy. Several factors appeared to affect the degree of treatment response, including site of disease, season when treated, darker skin color, and age.

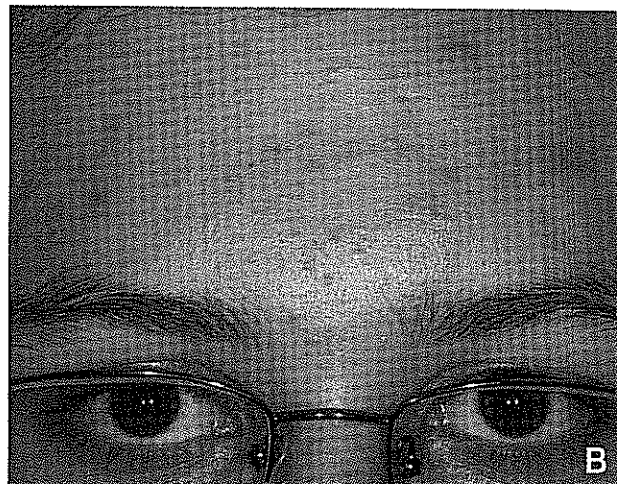
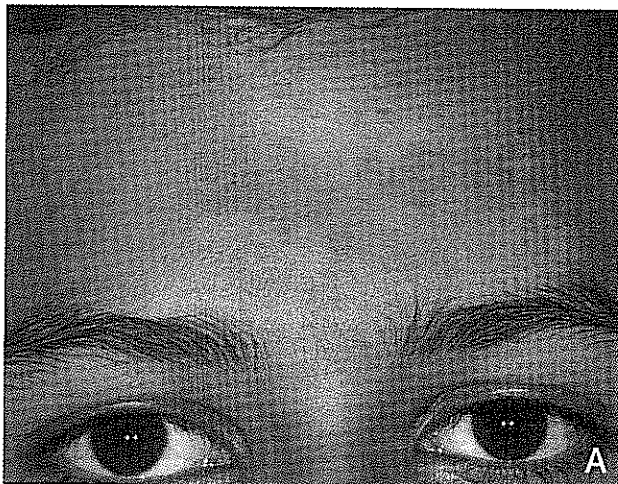
Patients who had casual, daily sun exposure to the application site during treatment experienced the greatest benefit from tacrolimus ointment 0.1%. Patients with darker skin tones, especially those with disease involvement of the head and neck, had the best response. The younger patients in this series also appeared to respond particularly well.

Twice-daily applications of tacrolimus ointment 0.1% for up to 9 months were well tolerated in this treatment group. In previous randomized, double-blind, vehicle-controlled clinical studies of topical tacrolimus for treating atopic dermatitis,<sup>9,10</sup> the most common adverse events were irritation at the application sites, including a burning sensation and pruritus. Such adverse events at the application sites were not reported in this series of patients

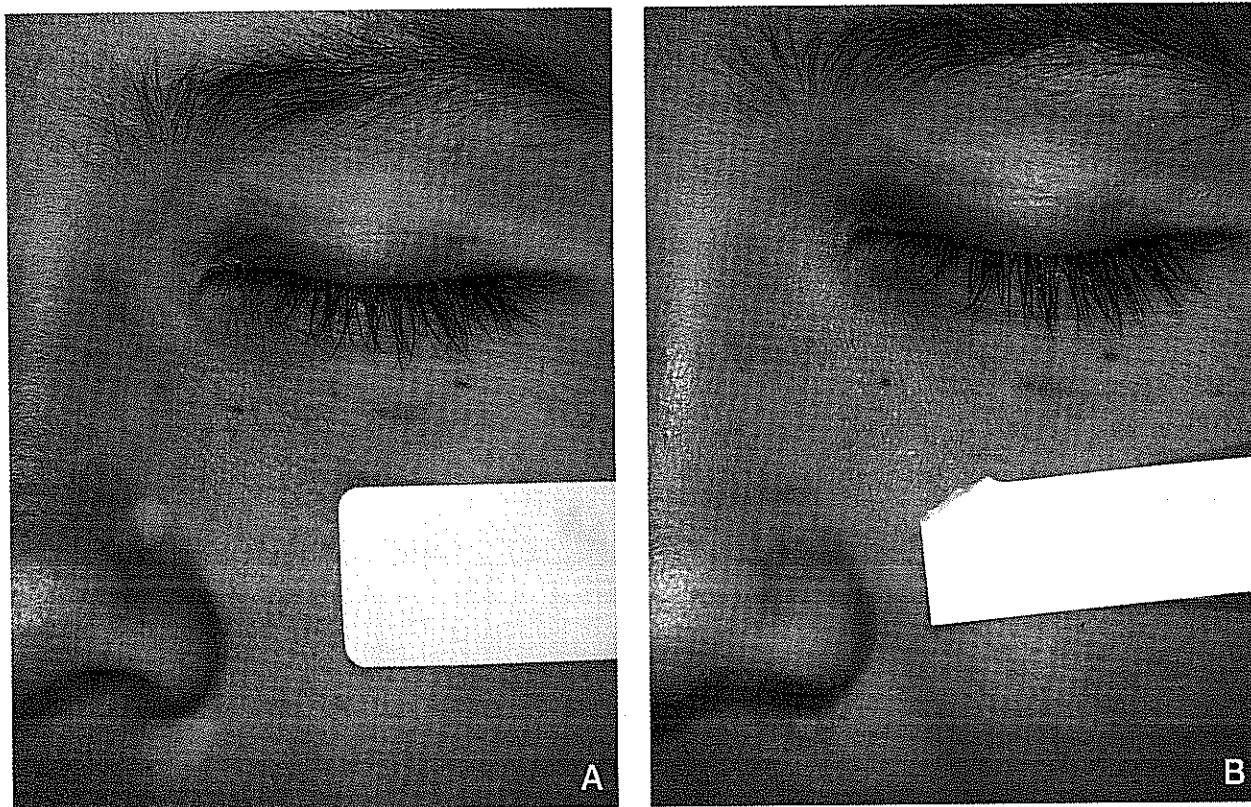
with vitiligo. The discrepancy in side effect profile is probably because the patients with atopic dermatitis in earlier clinical trials had moderate to severe atopic dermatitis, thereby compromising to various degrees the integrity of their skin barrier, whereas the patients with vitiligo described here generally had normal skin-barrier function.

**Table 1.**  
**Patient Demographics**

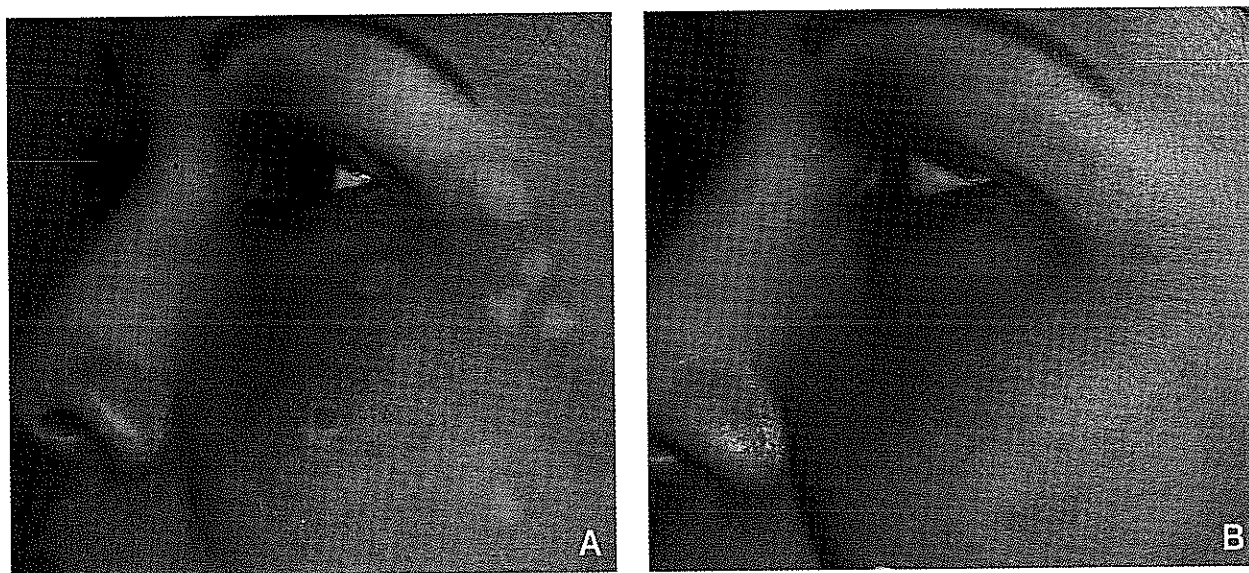
N=15	
<b>Gender, n</b>	
Male	5
Female	10
<b>Race/ethnicity, n</b>	
Asian	3
White	6
Hispanic	6
<b>Age, y</b>	
Mean	32
Median (range)	23 (4-73)
<b>Disease duration, y</b>	
Mean	4.9
Median (range)	3 (1-20)



**Figure 1.** Patient 2 at baseline (A) and with greater than 75% repigmentation after 8.5 months of treatment with tacrolimus ointment 0.1% (B).



**Figure 2.** Patient 6 at baseline (A) and with greater than 75% repigmentation after 2 months of treatment with tacrolimus ointment 0.1% (B).



**Figure 3.** Patient 7 at baseline (A) and with greater than 75% repigmentation after 5 months of treatment with tacrolimus ointment 0.1% (B).

Also important in the treatment of chronic skin disorders and those that require long-term therapy is that no skin atrophy or other significant adverse events have been reported with the use of tacrolimus ointment 0.1%,<sup>10,13,14</sup> even in the long-

term.<sup>15</sup> In addition, only minimal systemic absorption has been observed with topical tacrolimus use,<sup>10,11,14</sup> and no increase in infection or other indicators of systemic immunosuppression have been seen with use in both children and adults with

Table 2.  
Patient Treatment and Outcome Data\*

Patient	Age, y	Lesion Location(s)	Prior Treatment(s)	Tacrolimus Treatment Period	No. of Treatment Days	Treatment Response, † %
1	51	Face, neck	PUVA	Aug-Jan	172	>0-25
2	13	Forehead	Methoxsalen, hydrocortisone butyrate cream	April-Jan	284	>75-100
3	11	Left knee, ankle	Triamcinolone cream	Oct-Jan	119	>0-25
4	23	Hands, knees, elbows	None	Aug-Nov	79	>0-25
5	50	Hands	None	Aug-Sept	45	>0-25
6	13	Face	Hydrocortisone butyrate cream	June-Sept	114	>75-100
7	45	Face, neck	None	July-Dec	180	>75-100
8	4	Right dorsal hand	Fluticasone	June-Nov	176	>0-25
9	42	Face, neck	None	July-Oct	113	>50-75
10	23	Elbows, hands	Dihydroxyacetone, hydrocortisone valerate	Oct-Dec	67	>0-25
11	43	Neck, chest	Trioxsalen, PUVA	Oct-Dec	46	None
12	18	Face	PUVA	Nov-Jan	72	None
13	16	Right hand	Psoralen, topical steroid	Sept-Jan	156	>0-25
14	73	Forehead, face, hands	None	Oct-Dec	63	>0-25
15	61	Forehead, hands	Triamcinolone cream	April-Jan	283	>0-25

\*PUVA indicates psoralen-UVA.

†Percentage repigmentation.

atopic dermatitis for up to 4 years.<sup>16</sup> In contrast, chronic topical steroid therapy carries the risk for a number of potentially serious adverse events, including skin atrophy, striae, and hypothalamic-pituitary-adrenal axis suppression, especially in children or when the high-potency agents are used.<sup>17,18</sup>

Because PUVA has been used with some success in vitiligo treatment, and UV light has been shown to affect immunologic function,<sup>19</sup> these treatment modalities may have additive or synergistic effects if used in conjunction with topical tacrolimus. Therefore, studies should be performed to assess the safety and efficacy of topical tacrolimus in combination with PUVA, narrowband UVB, excimer laser and hand-held narrowband UVB light devices, and sunlight exposure. Although the prescribing information for topical tacrolimus indicates that "patients should minimize or avoid exposure to natural or artificial sunlight,"<sup>20</sup> the enhanced response seen in these vitiligo patients who were exposed to sunlight while using tacrolimus ointment 0.1% makes the implementation of such studies desirable and potentially important to the treatment of vitiligo, as well as other dermatologic conditions.

### Conclusion

Twice-daily treatment of vitiligo with tacrolimus ointment 0.1% produced at least partial repigmentation in the majority of patients in this series. Patients experiencing the greatest treatment response appear to have benefited from concomitant natural sunlight exposure. Further clinical studies are warranted to determine which vitiligo patients are most likely to benefit from topical tacrolimus therapy, and whether the best response is attained with topical tacrolimus monotherapy or with combination therapy using additional treatment modalities. Studies investigating the safety and efficacy of topical tacrolimus in combination with natural sunlight, UV light, excimer laser, and PUVA also are warranted.

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