A Double-blind Randomized Trial of 0.1% Tacrolimus vs 0.05% Clobetasol for the Treatment of Childhood Vitiligo

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Objective: To assess the safety and efficacy of topical 0.1% tacrolimus vs 0.05% clobetasol propionate.

Design: Randomized double-blind trial.

Setting: Department of Dermatology, Hospital Central “Dr Ignacio Morones Prieto,” San Luis Potosi, México.

Participants: From 20 children with vitiligo, 2 symmetrical lesions of about the same size and evolution time were selected. They were devoid of any topical or systemic therapy for 2 months prior to inclusion.

Interventions: Treatment with topical tacrolimus and clobetasol for a 2-month period.

Main Outcomes Measures: The grade of repigmentation was evaluated by color slides at baseline and again at every 2-week visit. The slides were analyzed by 2 clinicians unrelated to the study and by a morphometric digitalized computer program. Characteristics of pigment, time of response, symptoms, telangiectasias, and atrophy were evaluated every 2 weeks.

Results: Eighteen (90%) of the 20 patients experienced some repigmentation. The mean percentage of repigmentation was 49.3% for clobetasol and 41.3% for tacrolimus. Lesions in 3 patients using clobetasol presented atrophy, and 2 lesions incurred telangiectasias; tacrolimus caused a burning sensation in 2 lesions.

Conclusions: Tacrolimus proved almost as effective as clobetasol propionate to restore skin color in lesions of vitiligo in children. Because it does not produce atrophy or other adverse effects, tacrolimus may be very useful for younger patients and for sensitive areas of the skin such as eyelids, and it should be considered in other skin disorders currently treated with topical steroids for prolonged periods.

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VITILIGO IS a common idiopathic, acquired, depigmenting disease of the skin and hair that affects 0.5% of the world’s population. Controversy still exists about its pathogenesis because factors other than immunologic ones have been implicated, such as the early cell death of vitiligo melanocytes related to their increased sensitivity to oxidative stress. The idea that nitric oxide could lead to autodestruction of melanocytes resulting in skin depigmentation has been raised. Also, the monoaminergic system has been implicated because of increased activity of some of its components and higher levels of catecholamine and its metabolites. Neuropeptide Y may play certain roles in the pathogenesis of vitiligo via neuroimmunity mechanisms or neuronal effects on the melanocytes. More recently, reports of the participation of 1,25-dihydroxy-vitamin D₃ in the regulation of melanin synthesis and the demonstration of the receptors in the melanocytes for this vitamin have opened a new direction in therapy.

See also pages 571 and 651

However, experimental evidence shows that abnormal humoral and cell-mediated immune mechanisms are probably the most commonly involved aspect of pathogenesis in this disease. The relative success of clinical use of topical corticosteroids (a widespread therapeutic approach with response rates between 50% and 70%) supports this theory. Tacrolimus is an immunosuppressor macrolide lactone capable of inhibiting the activation and maturation of T cells by means of blocking the action of calcineurin and interleukin (IL) 2, IL-4, and IL-5 transcription. It also enhances T-cell apop-
tosis in vitro and down-regulates IL-8 keratinocyte surface receptors.\textsuperscript{14} Systemic tacrolimus has been used in a number of applications, particularly to avoid graft rejection.\textsuperscript{15} Topical tacrolimus is a safe and effective treatment for inflammatory skin diseases, particularly atopic dermatitis, psoriasis, pyoderma gangrenosum, alopecia areata, and other illnesses with immunologic disarrangement.\textsuperscript{16}

Limited data are available about topical bioavailability in humans when tacrolimus is applied to normal skin, although a number of studies have assessed blood levels following application to diseased skin. In a phase 1 study of patients with atopic dermatitis, the topical absorption of 0.3% tacrolimus ointment was found to be less than 4% of an equivalent oral dose given for immunosuppression. Pruritus, burning sensation, and erythema are the adverse reactions observed from topically applied tacrolimus.\textsuperscript{17}

We hypothesized that given its immunomodulatory properties and safer profile than corticosteroids, tacrolimus ointment might carry an improved benefit–toxic effect ratio\textsuperscript{18} and provide a new therapeutic alternative to topical corticosteroids in children with vitiligo. We know from experience that clobetasol is the most effective topical corticosteroid for vitiligo because it very often produces pigmentation where other topical steroids have failed. For that reason we selected clobetasol propionate rather than other midpotency steroids for this trial.

### METHODS

#### PATIENTS

Twenty patients younger than 18 years with vitiligo but otherwise healthy were selected for the study. They all had a vitiligo index of disease activity (VIDA) greater than 3; VIDA is a useful measure to assess the activity of the disease and takes into account recentness or remoteness of the onset of lesions (a VIDA of +4 indicates a lesion duration of 6 weeks; +3, a duration of 3 months; +2, six months; and +1, one year).\textsuperscript{19} Our patients had not had any vitiligo therapy for 2 months prior to the study. Patients with segmental and mucosal vitiligo were excluded.

A total of 20 patients were recruited; there were 16 girls and 4 boys. Only 2 patients had a positive family history. The mean age was 9.5 years (range, 4–17 years). The mean duration of disease was 2.2 years. The mean percentage of total area affected by vitiligo was 12.2%. The localization of vitiligo was variable. Fifteen patients (75%) had a VIDA of +4, and the other 5 had a VIDA of +3.

#### RESULTS

Information collected in the routine clinical history included patient sex, location and distribution of the disease, percentage of depigmentation, age at onset, family history, and disease activity. Informed consent was obtained from all patients, and the study was approved by the local institutional review board.

Two lesions similar to each other in size and time of evolution were selected to apply either 0.1% tacrolimus ointment (Protopic Ointment, Fujisawa Healthcare Inc, Deerfield, Ill) or 0.05% clobetasol propionate (Lobevat Cream; Stiefel Laboratories Inc, Coral Gables, Fla) twice a day, in a double-blind randomized way. The medications were in exactly the same containers, packed by a person unaware of the study. The total amount of medication used ranged between 20 and 40 g. Patients were evaluated every 2 weeks, and repigmentation and adverse effects were recorded.

Color slides of the lesions were taken at the beginning and end of the treatment period. The slides were analyzed visually by 2 clinicians not involved in the study and by computer using Corel Draw, version 9.0 (Corel Corporation, Ottawa, Ontario). For the computer analysis, each of the digitalized pictures was subjected to morphometry analysis (Figure 1). The entire lesion was given a 0% score at the beginning of the study to indicate a baseline of no repigmentation. A second percentage value was assigned at the end of the study to represent the level of repigmentation. The categories of repigmentation were as follows: none (0%), poor (1%-29%), moderate (26%-50%), good (51%-75%), and excellent (>75%).\textsuperscript{20}

#### STATISTICAL ANALYSIS

To assess the size of the sample, we hypothesized that 95% of patients using clobetasol and 40% of patients using tacrolimus would reach some degree of repigmentation; using these figures, we determined that we needed 20 subjects.\textsuperscript{21} The method of randomization was the technique of permuted block randomization for right or left selection.\textsuperscript{22} Evaluation of the new pigment was done by the Kolmogorov-Smirnov test for clinical observation and the paired t test for digital observation. We compared the clinicians’ visual evaluations and the digitalization-morphometry findings using the χ test of consistency.\textsuperscript{23} The error differences between the medications had a normal distribution (W=0.965; P=.65); then a paired t test was applied (P<.005).\textsuperscript{24}
Betasol was 49.3% vs 41.3% with tacrolimus. With both treatments, the new pigment was conserved and the best effects of repigmentation were observed in the face and areas with greater density of hair follicles. Neither treatment produced pigment on the dorsum of the hands or areas devoid of hair follicles.

With clobetasol, perifollicular islands of pigment were observed after 3 weeks; more than 75% overall repigmentation was seen in 5 (25%) of the clobetasol-treated patients. Of these, none showed complete repigmentation. Most of the patients using clobetasol (40%) experienced from 51% to 75% repigmentation in areas such as the axillae, legs, and abdomen—areas where clobetasol showed an advantage over tacrolimus. No change of coloration was observed in 2 patients (10%); these 2 cases involved the dorsal hand areas.

Tacrolimus produced more than 75% repigmentation in 5 patients, most of this on facial areas (Figure 3). Two patients (10%), the same 2 who showed no repigmentation from clobetasol, showed no change of pigmentation with tacrolimus. For those patients who experienced repigmentation, it first appeared after the third week, and the new pigment color was a mix between the color of the patient’s normal skin and the color of the lesion. It was homogeneous and in centripetal form (Figure 4).

Clinical evaluation of the results showed no statistically significant differences between treatments ($P > .05$, Kolmogorov-Smirnov test). However, computorized morphometric evaluation showed that tacrolimus was a significantly more effective treatment ($P = .005$, paired $t$ test). The results obtained by the 2 clinicians not related to the study were compared and subjected to the test of consistency, with the following results: $\kappa = 0.70$ for clobetasol; $\kappa = 0.64$ for tacrolimus. To prove the dependability of the computer program, the results of these 2 clinicians were compared against the computer results, with the following outcome: $\kappa = 0.93$ and 0.79 for clobetasol; $\kappa = 0.74$ and 0.51 for tacrolimus. These data show agreement for both kinds of observations.

Atrophy was reported in 3 patients (15%) and telangiectasias in 2 (10%) after the eighth week of treatment with clobetasol, when approximately 20 to 30 g of medication had been consumed. Burning sensations (that did not preclude continuation of therapy) were reported in 2 (10%) of the patients treated with tacrolimus during the first 2 weeks of treatment (Table).

**COMMENT**

For the past 2 decades, monotherapy with topical steroids has been the most common treatment for vitiligo in children. The range of response has been between 20% and 90% improvement, usually not a complete
cure. Adverse effects and poor efficacy have led to the search for new alternatives. While treatment with combinations of steroids and retinoids can avoid atrophy, retinoids are not well tolerated by children because of skin irritation. Therapy with systemic psoralens and UV-A irradiation is not used in children, and the topical variant is cumbersome and carries some risk. The new phototherapeutic approach with narrow-band UV-B irradiation may prove useful for children with vitiligo.

The search for substances with the benefits of topical steroids but without the well-known adverse effects seems to be producing results: calcipotriol for psoriasis and tacrolimus and other macrolides for inflammatory dermatoses. Calcipotriol has also been shown to be 77% effective in treating adults with vitiligo, but there are no data for children with this disease.

In our study, the results were evaluated by digital morphometry, which we believe provides a high degree of certainty. Pigment obtained in the study was sustained throughout the period of observation. It remains to be seen whether the newly formed color remains over the long term. We believe that the present study is the first to show the usefulness of tacrolimus in treating vitiligo in children. It would be interesting to see whether longer periods of therapy, combinations of tacrolimus with other topical agents, or increased concentrations of tacrolimus could produce better results than those obtained in this series and whether the negative results obtained in acral areas could be overturned with any of these approaches.

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### REFERENCES


### Table: Characteristics of Patients, Repigmentation, and Adverse Effects

<table>
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<tr>
<th>Sex/Age, y</th>
<th>Total Body Involvement, %</th>
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<th>Evolution Time</th>
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Abbreviation: VIDA, vitiligo index of disease activity.

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