The Safety and Efficacy of Tazarotene Gel, a Topical Acetylenic Retinoid, in the Treatment of Psoriasis

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Objective: To determine the safety and efficacy of topically applied tazarotene gel in the treatment of mild to moderate psoriatic plaques.

Design: Two multicenter, double-blind, randomized studies of 6- and 8-week duration, with an 8-week follow-up in the second study.

Setting: Medical center outpatient dermatology services.

Participants: One hundred fifty-three adults with 2 bilateral target plaques on the trunk, legs, or arms.

Interventions: Vehicle gel or 0.01% and 0.05% tazarotene gel administered twice daily to 45 patients (study A), or 0.05% and 0.1% tazarotene gel administered either once or twice daily to 108 patients (study B).

Main Outcome Measures: Treatment success and plaque elevation, scaling, and erythema vs time.

Results: The 0.01% tazarotene gel showed minimal efficacy. Applications of 0.05% and 0.1% tazarotene gels administered once or twice daily, resulted in significant improvements in plaque elevation, scaling, erythema, and overall clinical severity as early as 1 week. Treatment success rates (defined as ≥75% improvement from baseline) were 45% with 0.05% tazarotene gel vs 13% with vehicle gel after 6 weeks of treatment (P<.05; study A) and ranged from 48% to 63% with the various tazarotene treatment regimens after 8 weeks of treatment (study B). These improvements were evident at the 8-week follow-up. Treatment-related adverse effects were generally limited to mild or moderate local irritation and were less frequent with the treatment regimen administered once daily.

Conclusion: The 0.05% and 0.1% tazarotene gels demonstrated significant efficacy in the treatment of mild to moderate psoriatic plaques that persisted after cessation of treatment.

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The initial management of mild to moderate cases of psoriasis usually involves topical treatments with corticosteroids, calcipotriene, coal tar preparations, anthralin, and keratolytic agents. Although these treatments are generally effective, many cases do not respond to these treatments and for others the treatments cease to be effective. Thus, new and effective topically applied agents are needed.

Retinoids have been used to treat a variety of skin disorders, including psoriasis and acne. They appear to act by reducing epidermal proliferation, normalizing aberrant epidermal differentiation, and inducing significant immunomodulatory effects.

Second-generation retinoids (e.g., etretinate and acitretin) administered systemically have proved effective in treating certain forms of psoriasis. However, the adverse effects of orally administered retinoids are frequently severe and include both dermatologic and systemic effects. Additionally, there is concern about the teratogenic potential of these compounds. These characteristics emphasize the need for topical retinoids that do not cause these systemic adverse effects.

Tazarotene is a novel third-generation acetylenic retinoid that is being investigated as a topical treatment for psoriasis. This article presents the outcome of 2 phase-2 studies. The first study (study A) was a vehicle-controlled evaluation of 2 low-dose (0.01%, 0.05%) aqueous tazarotene gel formulations applied to psoriatic plaques twice daily. The second study (study B) was a dose-ranging study to determine the safety and efficacy of 2 tazarotene gel concentrations (0.05%, 0.1%) applied either once or twice daily.
PATIENTS AND METHODS

DESIGN OF STUDIES

Both studies followed a double-blind, randomized design. Patients 18 years of age or older with mild to moderate psoriatic plaques were eligible for enrollment. Each patient was required to have at least 2 bilateral psoriatic plaques on the trunk, legs, or arms; only these target plaques were treated. In study A, the size of the selected plaques was between 2.5 and 4.0 cm in diameter. Irrespective of size, the treatment was limited to an area 2.5 cm in diameter (marked with indelible ink). In study B, at least 50% of the target plaques selected for study were located in areas other than the knees and elbows, and each target plaque (measuring at least 3 x 3 cm but not >10 x 10 cm) was treated.

To minimize center differences, a defined 9-point scale was used for evaluating plaque elevation, erythema, and scale. These were anchored at 5 defined points (0, 1, 2, 3, and 4) with worded descriptions; increments of 0.5 were permitted. For entry, the sum of the baseline scores for elevation, scale, and erythema for each plaque was required to be less than or equal to 6. This ensured that only plaques of mild to moderate severity were selected for study.

Investigators also made global evaluations of the treated plaques using the following 6-point scale: 1, complete clearing except for possible residual discoloration; 2, excellent response with the plaques almost cleared (90% improvement); 3, good response with significant improvement (75% improvement); 4, fair response with intermediate improvement (50% improvement); 5, poor response with some improvement (25% improvement); and 6, no change or condition of plaques worse. Treatment success was defined as a global evaluation that placed the treated lesion in the good, excellent, or complete clearing category.

The safety of the test medications was evaluated at each visit by both the patient and physician. Patients were permitted to use an emollient on the nontarget areas as needed. Women who were pregnant, nursing, or of childbearing potential were not eligible for inclusion in the studies. Patients were also ineligible if they had used topical agents that might have altered the clinical condition within 2 weeks of enrollment, ever received systemic retinoids, been treated with UV phototherapy, or received systemic antipsoriasis drugs within 4 weeks of the entry date. All patients were required to have normal baseline laboratory values (urinalysis, multichemistry profile, and complete blood cell counts). Written informed consent was obtained from each participant.

STUDY A

Patients were randomly assigned to receive 2 of 3 possible test medications: vehicle gel, 0.01% tazarotene gel, or 0.05% tazarotene gel. Medication tubes were labeled as left or right, and patients were instructed to apply a small pea-sized amount (250 mg) of the gel to the respective plaque twice a day for 6 weeks.

Evaluations were made on day 3 and at weeks 1, 2, 3, 4, and 6, and laboratory tests were repeated at weeks 1, 3, and 6.

STUDY B

Study B was conducted using a similar study design and the same scoring system. A vehicle gel control was not used. Patients were randomly assigned to treatment groups, such that the treatment regimen used on the left plaques was not the same as the treatment regimen used on the right plaques. There were 6 treatment groups: (1) 0.1% tazarotene gel twice daily; and 0.1% tazarotene gel once daily; (2) 0.1% tazarotene gel twice daily and 0.05% tazarotene gel once daily; (3) 0.1% tazarotene gel twice daily and 0.05% tazarotene gel once daily; (4) 0.1% tazarotene gel once daily and 0.05% tazarotene gel twice daily; (5) 0.1% tazarotene gel once daily and 0.05% tazarotene gel once daily; or (6) 0.05% tazarotene gel twice daily and 0.05% tazarotene gel once daily.

The duration of treatment in study B was 8 weeks, with clinical evaluations scheduled at weeks 1, 2, 4, 6, and 8. Laboratory tests were performed at entry and at weeks 4 and 8. The study also included an 8-week follow-up period during which no therapy, other than emollient cream, was allowed. The patients' plaques were evaluated at weeks 10, 12, and 16 for safety criteria and evidence of relapse.

STATISTICAL ANALYSIS

Statistical analyses were carried out using an analysis of variance model for randomized, incomplete-block designs. If error terms were not normally distributed, the Durban-Watson nonparametric test was used. The analysis of treatment success rates was performed using an extension of the Cochran-Mantel-Haenszel test for randomized, complete-block designs.

RESULTS

Forty-five patients were enrolled in study A, and 108 patients were enrolled in study B. Within each study, demographics did not differ among the treatment groups. Plaques selected for treatment were similar in clinical features between treatment groups within each study and between the 2 studies.

STUDY A

In 1 patient in study A who was treated with both 0.05% and 0.01% tazarotene gel formulations, pruritus developed over the whole body after 3 weeks of treatment, and the patient was withdrawn from the study. All 45 patients in study A (90 plaques) were included in the evaluation of safety and efficacy. The patients with evaluable plaques were predominantly men (84%) and ranged in age from 23 to 83 years (mean, 50 years).

Treatment Success Rate

A primary measure of efficacy in this study was the treatment success rate. Treatment success rates for study A are presented in Figure 1. For the series of plaques treated with 0.05% tazarotene gel twice daily, the success rate was 30% after 2 weeks of treatment. This increased to 45% by the end of the study. The success rates in this
treatment group were significantly better at weeks 2 through 6 when compared with the success rates using the vehicle gel alone and significantly better at week 4 when compared with the success rate in the plaques treated with 0.01% tazarotene gel twice daily.

Response of Individual Signs and Symptoms

After 1 week of treatment and continuing for the duration of the study, plaque elevation and scaling scores were lower ($P < .05$) for plaques treated with 0.05% tazarotene gel twice daily than for those treated with 0.01% tazarotene gel or vehicle gel.

Safety

Treatment-related adverse effects were reported in 30 (33%) of the 90 plaques at some time during the study. Most were mild or moderate in severity. The most common adverse events were erythema and pruritus. Severe erythema and pruritus developed in 1 plaque treated with 0.05% tazarotene gel twice daily. In 1 patient, who was treated with both 0.05% and 0.01% tazarotene gel formulations, pruritus developed over the whole body after 3 weeks of treatment, and the patient was withdrawn from the study. No clinically significant changes in laboratory values and no drug-related systemic effects were noted in any of the patients.

STUDY B

The greater efficacy demonstrated with 0.05% tazarotene gel twice daily, in study A suggested that a higher concentration should be tested. However, the relatively high (30 [33%] of 90) incidence of treatment-related adverse events indicated that once daily and twice daily treatment regimens should be compared. In addition, it was determined that a higher dose, a longer drug-treatment phase, and a follow-up after drug cessation were indicated.

Of the 216 plaques initially selected for inclusion in the study, 210 (97.2%) were evaluable for efficacy, and 152 (70.4%) of these were observed for the entire study period. Two patients were unavailable for follow-up, and 1 patient was disqualified because the baseline laboratory values were abnormal. Treatment was withdrawn in 11 plaques (5.1%) because of adverse experiences and in 10 plaques (4.6%) because of lack of efficacy. All plaques were included in the safety analysis. The patients with evaluable plaques were predominantly men (81%) and ranged in age from 25 to 82 years (mean, 53 years).

Treatment Success Rate

The treatment success rate increased steadily for all 4 treatment regimens during the treatment phase (Figure 2). During the 8-week follow-up period, treatment success rates remained similar to rates observed after 8 weeks of treatment. There were no significant differences in treatment success rates between any of the treatment groups during the 8-week treatment phase or the 8-week follow-up phase. However, during the follow-up phase, several patients continued to show improvement. At the end of study, 4 plaques were in the completely clear category; this number increased to 16 during the 8 weeks without therapy.

Response of Individual Signs and Symptoms

Significant improvements in plaque elevation and scaling were noted after 1 week of treatment with 0.05% tazarotene gel twice daily, and the mean change in severity scores was similar to that observed in study A after 1 week when compared with the baseline. Similarly, significant reductions in plaque elevation and scaling were observed with 0.05% tazarotene gel once daily, and 0.1% tazarotene gel, administered either once daily or twice daily within the first week of treatment. In the 8-week period following the cessation of treatment, the score for
the severity of scaling was sustained at final treatment levels. Plaque elevation also continued to be significantly reduced vs baseline throughout the posttreatment period. There was some indication of decline in efficacy by the end of the follow-up period, particularly in plaques treated with either 0.05% or 0.1% tazarotene gel once daily. Significant decreases in erythema were observed after 1 week of treatment with 0.05% tazarotene gel once daily, and after 4 weeks of treatment with 0.1% tazarotene gel once daily. Continued improvements were evident at each subsequent visit during the treatment phase. Similar improvements were observed in plaques that were treated twice daily.

Safety

Treatment-related adverse effects occurred in 48 (22.2%) of the 216 plaques selected for treatment. The incidence of adverse effects was related to the dose of tazarotene gel and the frequency of dosing. Adverse effects were reported in 7 (13%) of 52 plaques treated with 0.05% tazarotene gel once daily, whereas adverse effects were reported in 16 (30%) of the 53 plaques treated with 0.1% tazarotene gel twice daily. Adverse effects were typical of those associated with topical application of retinoids. The most common of these were mild to moderate burning, pruritus, stinging, and erythema. In most instances, erythema was the manifestation of this mild to moderate irritation. As many as half of the plaques had erythema of the surrounding skin, the incidence tending to increase with the duration of the application and the dosage of tazarotene. Severe burning or stinging occurred in 6 plaques, and severe skin irritation (dermatitis) developed in 2 additional plaques. Adverse events associated with tazarotene (generally, local irritation) resulted in cessation of treatment in 11 plaques (5.1%): 4 plaques in the group that received 0.1% tazarotene gel twice daily; 1 plaque in the group that received 0.1% tazarotene gel once daily; 4 plaques in the group that received 0.05% tazarotene gel twice daily; and 2 plaques in the group that received 0.05% tazarotene gel once daily. As in study A, no significant changes in laboratory values and no drug-related systemic effects were observed.

The results from study A demonstrated that 0.05% tazarotene gel twice daily was more effective than vehicle gel and 0.01% tazarotene gel. The erythema scores between the active treatment and vehicle groups were similar, suggesting that the double-blinding was not compromised because of the erythema induced by the tazarotene use.

In study B, 4 dosage regimens, ranging from 0.05% tazarotene gel once daily to 0.1% tazarotene gel twice daily, led to significant reductions in plaque elevation and scaling of lesions of psoriasis. There were no significant differences in success rates among the 4 treatment regimens at either the end of the 8-week treatment period or the 8-week follow-up period. However, 0.05% tazarotene gel once daily, was less effective than the other treatment regimens. The maintenance of the therapeutic effect in treated plaques and the continued improvement observed in some of the treated plaques after treatment was discontinued were interesting.

Although there was no vehicle control in study B, 0.05% tazarotene gel administered twice daily was used in both studies. The 4-week efficacy assessment was the latest assessment shared by both studies. A comparison of the 4-week results for 0.05% tazarotene gel administered twice daily, in both studies indicated comparable treatment success rates: 52% for study A and 41% for study B. This suggests that the results obtained in study B were not compromised by the lack of vehicle control.

Tolerability and safety profiles were acceptable, particularly for treatments administered once daily, and treatment-related adverse events (mostly mild to moderate burning, pruritus, or erythema) were similar in nature and frequency to those reported for other topically applied retinoid treatments.

The results obtained in the treatment of single plaques cannot necessarily be extrapolated to the treatment of large skin areas. However, the efficacy demonstrated by tazarotene gel in the treatment of mild to moderate psoriatic plaques, with therapeutic benefit continuing to accrue even after cessation of treatment for periods as long as 8 weeks, and the acceptable safety and tolerability profiles are promising.

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