Dosing With 5% Imiquimod Cream 3 Times per Week for the Treatment of Actinic Keratosis

Results of Two Phase 3, Randomized, Double-blind, Parallel-Group, Vehicle-Controlled Trials

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Objective: To evaluate the efficacy and safety of 5% imiquimod cream compared with vehicle in the treatment of actinic keratosis (AK).

Design: Two phase 3 randomized, double-blind, parallel-group, vehicle-controlled studies.

Setting: Twenty-six ambulatory care offices, including dermatologists in private practice or research centers.

Patients: Four hundred ninety-two patients, 18 years and older, with 4 to 8 AK lesions in a 25-cm² treatment area on the face or the balding scalp were randomized; an additional 162 patients underwent screening but were ineligible.

Interventions: Patients applied 5% imiquimod (Aldara) or vehicle cream to the treatment area once daily, 3 times per week, for 16 weeks, followed by an 8-week posttreatment period.

Main Outcome Measurements: Complete clearance rate (proportion of patients at the 8-week posttreatment visit with no clinically visible AK lesions in the treatment area), partial clearance rate (proportion of patients at the 8-week posttreatment visit with a ≥75% reduction in the number of baseline AK lesions in the treatment area), and frequency and severity of adverse events and local skin reactions were measured.

Results: Complete and partial clearance rates for imiquimod-treated patients (48.3% and 64.0%, respectively) were clinically and statistically significantly higher than for vehicle-treated patients (7.2% and 13.6%, respectively). The median percentage reduction of baseline lesions was 86.6% for the imiquimod-treated group and 14.3% for the vehicle-treated group.

Conclusion: The 5% imiquimod cream dosed 3 times weekly for 16 weeks is safe and effective for the treatment of AK.

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ACTINIC KERATOSES (AKs) are epidermal lesions consisting of dysplastic keratinocytes that generally occur in fair-skinned individuals with long-term exposure to UV radiation. Although the exact pathogenesis of AK is unknown, long-term UV radiation is known to produce local and systemic immunosuppression, mutations in the p53 tumor suppressor gene, and DNA pyrimidine covalent dimers, each of which are believed to contribute to the development of AK.

The most common current therapies for AK include cryosurgery, curettage with or without electrosurgery, and topical fluorouracil. Despite the widespread use of these therapies, most have limitations such as inconvenience, pain, and scarring. Furthermore, none of the current therapies target a critical component underlying the disease pathogenesis: the suppression of the immune response.

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The only treatment for AK that works by enhancing the immune response against dysplastic cells is 5% imiquimod cream (Aldara; 3M Pharmaceuticals, St Paul, Minn). Imiquimod has been shown to induce the production of interferon α, tumor necrosis factor α, and interleukin (IL) 12 (IL-12), with a resulting cytokine cascade that may induce and/or support a cytotoxic T-lymphocyte immune response.

See also pages 447 and 507

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quimod may also act through Toll-like receptor 7 to stimulate rapid synthesis and release of cytokines from monocytes, macrophages, and dendritic cells. Toll-like receptors are receptors that recognize special patterns on immune cell surfaces and are considered essential components of the human innate immune response.6

Since imiquimod works through an immunological mechanism, regimens with infrequent dosing for an extended duration have been evaluated to minimize potentially intolerable adverse effects. To date, 5 large randomized, double-blind, parallel-group, vehicle-controlled studies have been conducted to evaluate the efficacy and safety of topically applied 5% imiquimod cream vs vehicle cream for the treatment of AK lesions on the face and balding scalp. Two of these studies evaluated once-daily dosing 2 times per week for 16 weeks; the other 3 studies evaluated once-daily dosing 3 times per week for 16 weeks. The complete and partial clearance rates for both studies that evaluated dosing 2 times per week and for one of those that evaluated dosing 3 times per week have been reported.7,8 The efficacy endpoint in the previously reported study of dosing 3 times per week included histological confirmation and clinical lesion assessments. The results of the remaining 2 studies that evaluated the regimen of dosing 3 times per week are presented herein.

METHODS

STUDY POPULATION

The study population consisted of otherwise healthy men and women 18 years or older with a clinical diagnosis of 4 to 8 AK lesions within a contiguous 25-cm² treatment area on the face or the balding scalp as previously described.7

STUDY DESIGN

Two independent, randomized, double-blind, parallel-group, vehicle-controlled studies collectively enrolled patients from 26 US study centers (13 centers per study). The primary and secondary objectives of these studies were to evaluate the efficacy and safety of 5% imiquimod cream, respectively, compared with vehicle cream in the treatment of AK lesions on the face or the balding scalp when the cream was applied once daily 3 times per week for 16 weeks.

The studies consisted of a prestudy (≤2 weeks), treatment (16 weeks), and posttreatment (8 weeks) periods. Patients underwent assessment during treatment weeks 1, 2, 4, 6, 8, 10, 12, 14, and 16 and posttreatment weeks 4 and 8. At the treatment initiation visit, enrolled patients were assigned to the next sequential patient study number and the corresponding study cream, which was randomized and labeled, on the basis of a computer-generated randomization schedule (stratified by study center). Patients were randomized to imiquimod or to vehicle cream in a 1:1 ratio. At the treatment initiation visit, the treatment area and the location of the 4 to 8 baseline AK lesions were recorded and mapped.

Patients were instructed to apply the study cream (imiquimod or vehicle) to the entire treatment area at the same time of day (just before normal sleeping hours), and the cream was to remain in place for approximately 8 hours. Rest periods from study cream were allowed at the discretion of the investigator, but did not alter the length of the 16-week treatment period. Patients who discontinued treatment were asked to return for an assessment of their AK lesions at the 8-week posttreatment visit.

All study procedures and informed consent documents received approval from the respective institutional review boards, and all enrolled patients signed informed consent forms.

Efficacy Measurements

Actinic keratosis lesions were counted at the 4-, 8-, and 16-week treatment visits and the 8-week posttreatment visit. No differentiation was made between the baseline and new AK lesions.

The primary variable was the complete clearance rate, defined as the proportion of patients at the 8-week posttreatment visit with no clinically visible AK lesions in the treatment area. The secondary efficacy variable was the partial clearance rate, defined as the proportion of patients at the 8-week posttreatment visit with at least a 75% reduction in the number of baseline AK lesions in the treatment area. An additional measurement of clearance was the median percentage of reduction of baseline AK lesions at the 8-week posttreatment visit.

Safety Measurements

Safety was monitored by reviewing concomitant medication use and assessing the incidence and severity of adverse events and local skin reactions. For the purposes of these studies, local skin reactions were differentiated and prospectively collected independently from adverse events (spontaneously reported). Local skin reactions in the treatment and surrounding areas were clinically categorized as erythema, edema, erosion/ulceration, scabbing/crusting, weeping/exudation, vesicles, and flaking/scaling/dryness. The intensity of an investigator-assessed local skin reaction was rated, with 0 indicating none; 1, mild; 2, moderate; and 3, severe. Reactions within the treatment area that were not assessed as local skin reactions were reported as adverse events. At the treatment initiation and 8-week posttreatment visits, investigators performed skin quality assessments of the treatment area. Characteristics assessed included skin surface (roughness/dryness/scaliness), hyperpigmentation, hypopigmentation, mottled or irregular pigmentation (hyperpigmentation and hypopigmentation), degree of scarring, and degree of atrophy. After visual, clinical, and tactile examinations of the treatment area, the investigator coded the intensity of each characteristic (with 0 indicating none; 1, mild; 2, moderate; and 3, severe).

Statistical Analysis

The primary dataset analyzed was the intent-to-treat dataset, which consisted of combined data from the 2 studies and included all randomized patients. For each study, 94 patients per treatment group were required to have at least 90% power to detect a difference in complete clearance rates of 35% for the imiquimod group vs 14% for the vehicle group, with a type I error rate of 0.05. Assuming a 20% dropout rate, 120 patients per treatment group were required, giving a total of 240 patients per study. There were no interim analyses or stopping rules.

The Cochran-Mantel-Haenszel test was used to compare the treatment groups (imiquimod vs vehicle) with respect to complete clearance rate; the test was performed at the .05 level of significance. The difference in complete clearance rates (imiquimod minus vehicle) with an associated 95% confidence interval (CI) was calculated. The same analyses were performed on partial clearance as described for complete clearance. The Cochran-Armitage test for trend in proportions (2 sided) examined relationships between complete clearance and the most intense local skin reaction experienced by patients.
Adverse events were compared between treatment groups using the Fisher exact test. Wilcoxon rank sum tests were used to compare treatment groups with respect to local skin reaction assessments. For skin quality assessments, Wilcoxon signed rank tests were used to assess the significance of within-treatment changes from baseline, and Wilcoxon rank sum tests were used to assess the significance of between-treatment changes from baseline.

RESULTS

The combined studies enrolled 492 patients; 242 patients were randomized to 5% imiquimod cream and 250 patients were randomized to vehicle cream (Figure 1). Enrollment for both studies began in August 2001, and all study procedures were completed by August 2002.

DEMOGRAPHICS

The median age of the patients was 67 years. All were white; 61 (12.4%) were female, and 431 (87.6%) were male. The sex distribution observed in this study was consistent with previous epidemiological data. There were no distribution differences for sex, age, race, or skin type between treatment groups (Table 1).

EFFICACY

Complete clearance occurred in 117 (48.3%) of 242 patients in the imiquimod group and 18 (7.2%) of 250 patients in the vehicle group ($P<.001$). The difference in complete clearance rates was 41.1% (95% CI, 34.1%-48.2%). Partial clearance occurred in 155 (64.0%) of imiquimod-treated patients and 34 (13.6%) of vehicle-treated patients ($P<.001$).

Differences for the complete and partial clearance rates in the imiquimod groups were observed between the 2 studies; complete clearance rates were 56.4% vs 40.8% and partial clearance rates were 71.8% vs 56.8%. No differences in baseline characteristics or demographics of the patients were noted between the 2 studies (data not shown).

For the imiquimod group, there was a statistically significant observed association between complete and partial clearance rates and the intensity of local skin reactions. Specifically, clearance rates tended to increase as the intensity of erythema increased (Figure 2).

The number of patients who had an increase in AK lesion count at any point in the treatment period was higher in the imiquimod group (103/242 [42.6%]) compared with the vehicle group (55/250 [22.0%]). The complete clearance rate was slightly higher for imiquimod-treated patients who had an increase in lesion count over baseline (56/103 [54.4%]) compared with imiquimod-treated patients who did not have an increase in lesion count (61/139 [43.9%]).

At the 8-week posttreatment visit, the median percentage of reduction in AK lesion count was 86.6% for the imiquimod group and 14.3% for the vehicle group. This means that half of the patients in the imiquimod group had at least an 86.6% reduction in the number of baseline AK lesions.

**Table 1. Summary of Patient Demographics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>5% Imiquimod Cream (n = 242)</th>
<th>Vehicle Cream (n = 250)</th>
<th>$P$ Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female 32 (13.2)</td>
<td>29 (11.6)</td>
<td>.59</td>
</tr>
<tr>
<td></td>
<td>Male 210 (86.6)</td>
<td>221 (88.4)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>Mean ± SD 66.7 ± 10.6</td>
<td>65.9 ± 9.9</td>
<td>.82</td>
</tr>
<tr>
<td></td>
<td>Range 41-87</td>
<td>41-93</td>
<td></td>
</tr>
<tr>
<td>White race</td>
<td>242 (100)</td>
<td>250 (100)</td>
<td></td>
</tr>
<tr>
<td>Skin type (Fitzpatrick)</td>
<td>I-II 157 (64.9)</td>
<td>149 (59.6)</td>
<td>.26</td>
</tr>
<tr>
<td></td>
<td>III-VI 85 (35.1)</td>
<td>101 (40.4)</td>
<td></td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are expressed as number (percentage) of patients.
†$P$ values for sex and skin type are calculated by means of the Fisher exact test; for age, by means of analysis of variance.
Flaking/Scaling/Dryness, and for 2 vehicle-treated patients for Scabbing/Crusting.

...surrounding the treatment area and beyond.

...the denominator for the imiquimod group is 241 rather than 242. Baseline data were missing (not collected) for 1 vehicle-treated patient for imiquimod cream–treated subjects. Cochran-Armitage test for trend intensity of erythema increased.

‡Calculated by means of the Fisher exact test.

Table 2. Application Site Reactions Possibly or Probably Related to Study Drug Reported by at Least 1% of Patients

<table>
<thead>
<tr>
<th>Application Site Reaction†</th>
<th>Treatment Group, No. (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5% Imiquimod Cream (n = 242)</td>
</tr>
<tr>
<td>Itching at target site</td>
<td>70 (28.9)</td>
</tr>
<tr>
<td>Burning at target site</td>
<td>18 (7.4)</td>
</tr>
<tr>
<td>Itching at remote site</td>
<td>17 (7.0)</td>
</tr>
<tr>
<td>Pain at target site</td>
<td>9 (3.7)</td>
</tr>
<tr>
<td>Tenderness at target site</td>
<td>5 (2.1)</td>
</tr>
<tr>
<td>Infection at target site</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>Burning at remote site</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>Sizzling at target site</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>Swollen at remote site</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>Tenderness at remote site</td>
<td>3 (1.2)</td>
</tr>
</tbody>
</table>

*Both study treatments were applied 3 times per week.
†Target site refers to the treatment area; remote site refers to the area surrounding the treatment area and beyond.
‡Calculated by means of the Fisher exact test.

Table 3. Three Most Frequent Investigator-Assessed Local Skin Reactions

<table>
<thead>
<tr>
<th>Summary by Intensity</th>
<th>Skin Reactions, No. (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Erythema</td>
</tr>
<tr>
<td></td>
<td>Imiquimod</td>
</tr>
<tr>
<td>Most intense during the study</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>4/241 (1.7)</td>
</tr>
<tr>
<td>Mild</td>
<td>36/241 (14.9)</td>
</tr>
<tr>
<td>Moderate</td>
<td>121/241 (50.2)</td>
</tr>
<tr>
<td>Severe</td>
<td>80/241 (33.2)</td>
</tr>
<tr>
<td>Any during study (mild, moderate, or severe)</td>
<td>237/241 (98.3)</td>
</tr>
<tr>
<td>Baseline score (none)</td>
<td>73/242 (30.2)</td>
</tr>
<tr>
<td>8-wk Posttreatment visit score (none)</td>
<td>130/226 (57.5)</td>
</tr>
</tbody>
</table>

*Imiquimod administered as 5% imiquimod cream. One imiquimod-treated patient did not undergo an assessment of local skin reactions after treatment initiation, so the denominator for the imiquimod group is 241 rather than 242. Baseline data were missing (not collected) for 1 vehicle-treated patient for flaking/scaling/dryness, and for 2 vehicle-treated patients for scabbing/crusting.

SAFETY

Adverse Events

Adverse events occurred in both the imiquimod (176/242 [72.7%]) and vehicle (149/250 [59.6%]) treatment groups. At least 1 adverse event considered by the investigator as possibly or probably related to the study drug was reported by 104 (43.0%) of imiquimod-treated patients and 22 (8.8%) of vehicle-treated patients (P < .001). The most frequently reported adverse event was application site reaction, with “itching at target site” reported most often. Application site reactions were reported by 94 (38.8%) of imiquimod-treated patients and 18 (7.2%) of vehicle-treated patients (P < .001). The most frequently reported application site reactions that were considered possibly or probably related to study cream are listed by type in Table 2.

Other adverse events showing statistically significant differences between the imiquimod and vehicle groups were fever (7 patients [2.9%] vs 1 patient [0.4%]; P = .04) and postoperative pain (9 patients [3.7%] vs 2 patients [0.8%]; P = .03). The adverse events of postoperative pain reported by patients included references to dental procedures (5 patients), unspecified operation (2 subjects), and squamous cell carcinoma removal from the ear of a subject randomized to the treatment of the scalp, hammer toe surgery, arthroscopic knee surgery, and kidney surgery (1 patient each). None of the adverse events of postoperative pain were considered by the investigator to be related to study drug.

Forty-two serious adverse events were reported by 20 patients (12 imiquimod- and 8 vehicle-treated patients); none of the serious adverse events were considered by the investigator to be related to study drug. No deaths occurred in these studies.

Local Skin Reactions

Local skin reactions were common and occurred in both treatment groups. Both imiquimod- and vehicle-treated patients experienced severe local skin reactions; the rate of severe local skin reactions was higher in the imiquimod group. Table 3 includes the most intense...
investigator-assessed local skin reactions in the treatment area during the course of the study (excluding the treatment initiation visit), the percentage of patients with any reaction at any time after treatment initiation, the number of patients with no reaction at treatment initiation, and the number of patients with no reaction at the 8-week posttreatment visit. Overall, local skin reactions were well tolerated and generally resolved or diminished in intensity after cessation of treatment (Figure 3).

Discontinuations From Study

Patients could have discontinued (withdrawn) from the treatment period, the posttreatment period, or both. Patients who withdrew from the treatment period did not restart treatment, but were asked to return for posttreatment procedures. During the treatment period, 32 (13.2%) of 242 imiquimod-treated patients and 13 (5.2%) of 250 vehicle-treated patients discontinued from the study. Fifteen imiquimod-treated patients and 15 vehicle-treated patients discontinued during the posttreatment period. Table 4 summarizes the patients who discontinued during the treatment and posttreatment periods, stratified by reason for the discontinuation.

Rest Periods

Rest periods were taken by 99 (40.9%) of 242 imiquimod-treated patients and 2 (0.8%) of 250 vehicle-treated patients. Of the patients taking rest periods, 86 (86.9%) of the 99 imiquimod-treated patients and 2 (100%) of the 2 vehicle-treated patients resumed treatment after their last rest period.

Skin Quality Assessment

In general, the 8-week posttreatment assessments for each skin quality category indicated more patients with less intense scores than those with more intense scores after treatment with imiquimod.

Scores for scarring and skin surface categories showed statistically significant within-treatment shifts from baseline to 8 weeks after treatment for the imiquimod group. Statistical significance was also found when scores for skin surface were compared between imiquimod and vehicle groups. Each significant shift was due to imiquimod-treated patients having less intense scores at 8 weeks after treatment than at baseline. Of the 226 imiquimod-treated patients with both initiation and 8-week posttreatment skin surface assessments, 9 (4.0%) had an increase and 115 (50.9%) had a decrease in intensity at the 8-week posttreatment assessment compared with baseline. Because of inconsistencies in the investigators’ interpretation of hyperpigmentation, hypopigmentation, and mottled pigmentation, these data are not presented.

COMMENT

The results from these large clinical studies and previously published studies confirm that 5% imiquimod cream is a safe and effective treatment option for AK. Unlike other treatments for AK, imiquimod is an immune-based therapy. Imiquimod has been shown to stimulate the immune system by activating antigen-presenting cells such as monocytes/macrophages and dendritic cells to produce interferon and other cytokines and chemokines. Imiquimod appears to mediate these cellular effects through a Toll-like receptor, leading to the activation of transcription factor nuclear factor κB, which then culminates in the transcription of a number of cytokines including tumor necrosis factor α, IL-1, IL-6, IL-8, and IL-12. These cytokines stimulate several other aspects of the innate immune response and are important for directing the adaptive immune response. The enhancement of the immune response is an ideal therapeu-
The end point of complete clearance was a rigorous study end point that underestimated the clinical effectiveness of this treatment. For example, patients who experienced resolution of 7 of 8 lesions were still considered treatment failures because they did not achieve complete clearance. A more clinically useful measurement of the benefit is the median percentage of reduction in the number of lesions counted at baseline for each patient. The median percentage of reduction in baseline lesions was greater than 86% for imiquimod-treated patients were 48.3% and 64.0%, respectively. The clinical response with imiquimod dosing 3 times per week was higher than the response seen with dosing 2 times per week; however, the magnitude of the increase was not as large as expected for a dosing regimen that was 50% higher. The modest difference in the clinical response between the 2 dosing regimens may be partly related to the low complete clearance seen in one of the studies evaluating dosing 3 times per week (40.8% vs 56.4%).

An additional benefit from imiquimod treatment appears to be improved skin quality compared with vehicle treatment. Although this phenomenon has been observed with nonspecific treatments that induce inflammation, the cytokines observed after imiquimod treatment have been reported to mediate wound healing and tissue remodeling. Therefore, an improved cosmetic outcome may be another potential benefit of imiquimod treatment.

Because imiquimod works by enhancing the innate and adaptive immune responses, individual patient responses will vary depending on many intrinsic and extrinsic factors, such as the number and responsiveness of Langerhans cells and extent of solar damage. Although it is not known which factors will predict a patient’s response to imiquimod, it is reassuring to clinicians that many different dosing regimens appear to be safe and effective.

Table 4. Patients Discontinued From the Treatment and Posttreatment Periods for Any Reason*

<table>
<thead>
<tr>
<th>Primary Reason for Discontinuation</th>
<th>Treatment Period</th>
<th>Posttreatment Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Imiquimod (n = 242)</td>
<td>Vehicle (n = 250)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>10 (4.1)</td>
<td>6 (2.4)</td>
</tr>
<tr>
<td>Lost to follow-up†</td>
<td>2 (0.8)</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>Decreased</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Personal</td>
<td>8 (3.3)</td>
<td>4 (1.6)</td>
</tr>
<tr>
<td>Noncompliance</td>
<td>1 (0.4)</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1 (0.4)§</td>
</tr>
<tr>
<td>Local skin reaction</td>
<td>10 (4.1)</td>
<td>0</td>
</tr>
<tr>
<td>Entry criteria violated</td>
<td>1 (0.4)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>32 (13.2)</td>
<td>13 (5.2)</td>
</tr>
</tbody>
</table>

*Patients could have been discontinued from the treatment period, the posttreatment period, or both.
†Imiquimod administered as 5% imiquimod cream.
§Of the 6 patients lost to follow-up, 1 moved out of state, 4 did not respond after repeated telephone calls and letters, and 1 was coded as unknown reason.
‡Other was specified for 1 imiquimod-treated patient for use of exclusionary drugs and treatment with liquid nitrogen and for 1 vehicle-treated patient for treatment of actinic keratosis during the posttreatment period.

Dosing with 5% imiquimod cream 3 times per week for 16 weeks was a safe and effective regimen for the treat-
ment of AK. The overall efficacy was higher for dosing 3 times per week than for 2 times per week; however, the rate of local skin reactions was also higher. These results, in addition to results from previously published studies, suggest that many different dosing regimens are effective and that dosing could be tailored to minimize drug exposure and adverse effects.

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REFERENCES