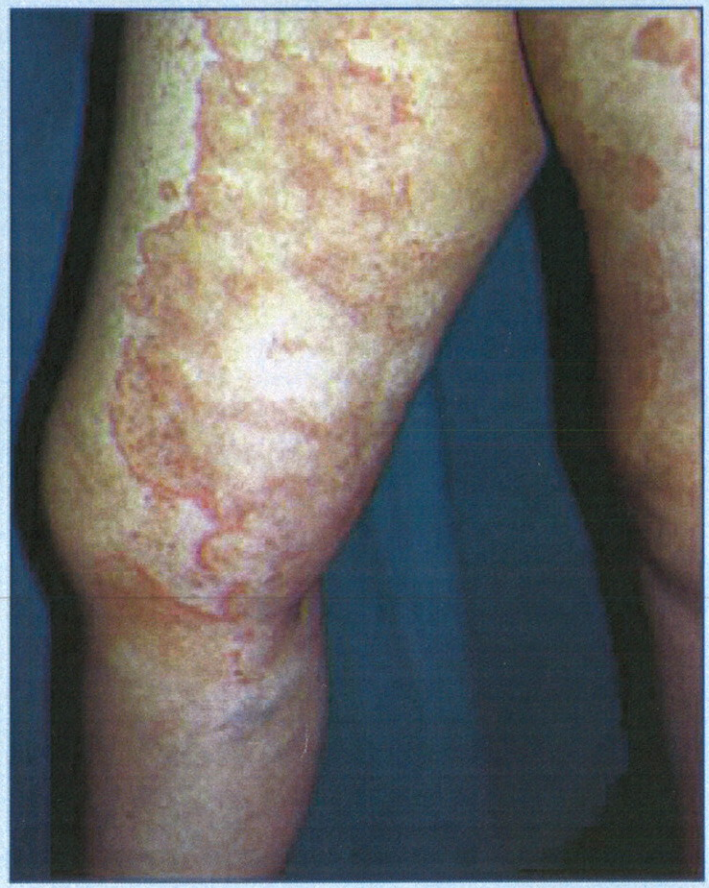
JAAD

Journal of the American Academy of Dermatology

April 2010
Volume 62 • Number 4

www.eblue.org



CME Urticarial lesions: If not urticaria, what else? The differential diagnosis of urticaria

Anna Peroni, MD, Chiara Colato, MD, Donatella Schena, MD, and Giampiero Girolomoni, MD

Verona, Italy

Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: Results of two placebo-controlled studies of daily application to the face and balding scalp for two 3-week cycles

C. William Hanke, MD,[a] Kenneth R. Beer, MD,[b] Eggert Stockfleth, MD,[c] Jason Wu, MD,[d] Theodore Rosen, MD,[e] and Sharon Levy, MD[d]

Carmel, Indiana; West Palm Beach, Florida; Berlin, Germany; Exton, Pennsylvania; and Houston, Texas

Background: Imiquimod 5% cream is approved as a 16-week regimen for the treatment of actinic keratoses involving a 25-cm^2 area of skin.

Objective: We sought to evaluate imiquimod 2.5% and 3.75% creams for short-course treatment of the entire face and scalp.

Methods: In two identical studies, adults with 5 to 20 lesions were randomized to placebo, or imiquimod 2.5% or 3.75% cream (1:1:1). Up to two packets (250 mg each) were applied per dose once daily for two 3-week treatment cycles, with a 3-week, no-treatment interval. Efficacy was assessed at 8 weeks posttreatment.

Results: In all, 490 subjects were randomized to placebo, or imiquimod 2.5% or 3.75% cream. Median baseline lesion counts for the treatment groups were 9 to 10. Complete and partial clearance rates were 5.5% and 12.8% for placebo, 25.0% and 42.7% for imiquimod 2.5%, and 34.0% and 53.7% for imiquimod 3.75% ($P < .001$, each imiquimod vs placebo; $P = .034$, 3.75% vs 2.5% for partial clearance). Median reductions from baseline in lesion count were 23.6%, 66.7%, and 80.0% for the placebo, imiquimod 2.5%, and imiquimod 3.75% groups, respectively ($P < .001$ each imiquimod vs placebo). There were few treatment-related discontinuations. Temporary treatment interruption (rest) rates were 0%, 17.1%, and 27.2% for the placebo, imiquimod 2.5%, and imiquimod 3.75%, respectively.

Limitations: Local effects of imiquimod, including erythema, may have led to investigator and subject bias.

Conclusions: Both imiquimod 2.5% and 3.75% creams were more effective than placebo and had an acceptable safety profile when administered daily as a 3-week on/off/on regimen. (J Am Acad Dermatol 2010;62:573-81.)

Key words: actinic keratosis; clinical trial; dose optimization; imiquimod.

Previously considered premalignant precursors to squamous cell carcinomas, actinic keratoses (AKs) are now regarded by some as early squamous cell carcinomas in situ because they have the same histologic and genetic alterations.[1] Although treatment of AKs in the general population has not yet been shown definitively to decrease the subsequent risk of squamous cell

From the Laser and Skin Surgery Center of Indiana[a]; Palm Beach Esthetic Dermatology and Laser Center[b]; Department of Dermatology, Charité University Hospital, Berlin[c]; Clinical Development, Graceway Pharmaceuticals LLC, Exton[d]; and Department of Dermatology, Baylor College of Medicine, Houston.[e]

Supported by Graceway Pharmaceuticals LLC.

Disclosure: Drs Hanke and Beer were investigators and consultants for Graceway and received compensation for services. Drs Stockfleth and Rosen were consultants for Graceway and received compensation for services. Drs Wu and Levy are employees of Graceway.

Accepted for publication June 3, 2009.

Reprint requests: C. William Hanke, MD, Laser and Skin Surgery Center of Indiana, 13400 N Meridian St, Suite 290, Carmel IN 46032. E-mail: cwmhanke@thelassi.com.

Published online February 4, 2010.

0190-9622/$36.00

doi:10.1016/j.jaad.2009.06.020

carcinoma, it is accepted standard of care to treat AKs.[2,3] Because of the prevalence of AKs and the propensity in patients to develop new lesions over time, the treatment of AKs represents a significant burden to the health care system. In the United States, it is estimated that there are 5.2 million patient visits to treat AK at an annual cost of $900 million.[4] The dominant method of treating AKs in the United States is cryotherapy, which is provider administered and directed at individual lesions.[4,5] Other provider-administered treatments include curettage with electrosurgery, chemical peels, and photodynamic therapy.[6] Topical treatments such as imiquimod cream (5%), 5-fluorouracil solution or cream (2% or 5%), and diclofenac gel (3%) provide physicians and patients with field-based treatments that can be patient administered.[7]

CAPSULE SUMMARY

- Imiquimod 2.5% and 3.75% creams were both more efficacious than placebo in clearing actinic keratoses.
- Daily application of these imiquimod creams to the full face or scalp was adequately tolerated using a cycle regimen of two 3-week cycles with a 3-week, no-treatment interval.
- Transient increases in lesion counts during treatment was consistent with presence of subclinical lesions in the field and correlated with pharmacologic effects of imiquimod.

Imiquimod activates innate immune cells such as plasmacytoid dendritic cells through the Toll-like receptor 7 pathway, resulting in endogenous production of cytokines.[8] Treatment of AKs with imiquimod increases expression of genes associated with dendritic cell, macrophage, T-cell, and natural killer cell activation[9]; down-regulates antiapoptotic genes[10]; and reverses aberrant expression of some genes observed in AKs.[11] In addition to treating clinically apparent lesions, topical treatment with imiquimod can reveal and clear subclinical lesions. Imiquimod 5% cream is approved to treat AKs of the face or balding scalp using dosing regimens of 2×/wk for a single 16-week course in the United States[12,13] and 3×/wk for two sequential 4-week cycles separated by a 4-week, no-treatment interval in Europe.[14-16] Although these regimens have been demonstrated to be safe and effective, the dosing frequencies may be nonintuitive and the total treatment durations too long to ensure compliance. Once-daily application may be a more patient-friendly dosing frequency and might allow for an overall shorter total dosing duration; however, imiquimod 5% cream applied 5 or 7×/wk (daily) for AKs was associated with a high discontinuation rate and a high incidence of severe skin reaction.[17] In evaluating a formulation of imiquimod that could be applied daily and could shorten overall AK treatment duration, we conducted two randomized, placebo-controlled studies. These studies assessed the safety and efficacy of two new formulations of imiquimod cream (2.5% and 3.75%) applied to the entire face or balding scalp for two 3-week treatment cycles, separated by a 3-week, no-treatment interval. The results of two companion studies, evaluating two 2-week treatment cycles, are reported in an accompanying article.[18]

METHODS

Study population

Adults in general good health with 5 to 20 visible or palpable AKs in an area greater than 25 cm^2 in size on either the face or the balding scalp, but not both, were eligible for participation in the studies. A study subject could not have any significant condition in the treatment area that might impair evaluation, have atypical AKs (eg, AK >1 cm^2 in size), be pregnant or lactating, have a chemical or alcohol dependency, or have a known allergy to imiquimod or study cream excipients. Prior therapy exclusions included: within 1 year before treatment initiation—imiquimod 5% cream on the head; within 90 days—interferon, interferon inducers, cytotoxic drugs, immunomodulators, immunosuppressants, oral or parenteral corticosteroids, topical corticosteroids more than 2 g/d, investigational drug or device use outside of the treatment area, dermatologic procedures or surgeries in the treatment area, and any AK therapy in the target treatment area; and within 30 days—imiquimod outside of the head, and topical prescription drugs and investigational drug or device within treatment area. Use of any of the aforementioned treatments was also excluded throughout the study.

The studies were conducted in compliance with the Code of Federal Regulations of the US Food and Drug Administration (21 CFR parts 50 and 56), and International Conference on Harmonization Guideline E6 (Good Clinical Practice). The study protocols and informed consents were reviewed and approved by a central institutional review board. All subjects provided written informed consent before any study procedures. Enrollment for both studies began in January 2008, and all study procedures were completed by July 2008. The studies were registered on Clinicaltrials.gov on January 16, 2008, registration identifier NCT00603798.

Abbreviations used:

AE: adverse event
AK: actinic keratosis
EOS: end of study
IGIP: Investigator Global Integrated Photodamage
LSR: local skin reaction

Study design and study cream dosing

Subjects were enrolled at 26 study centers in the United States in two identically designed studies conducted in parallel. Both studies included a screening phase, a treatment period (two 3-week treatment cycles separated by a 3-week, no-treatment interval; 3-week on/off/on), and a follow-up period (Fig 1). Eligible subjects were randomized to placebo, imiquimod 2.5%, or imiquimod 3.75% cream in a 1:1:1 treatment allocation. Each study cream was identical in appearance to the others and contained the same excipients. The investigator selected the treatment area for each subject, either the entire face or the entire balding scalp, but not both. During each treatment cycle, subjects applied up to two packets (250 mg of cream/packet) of study cream once daily to the treatment area. Sufficient cream was applied as a thin layer to cover the entire treatment area, avoiding the periocular areas, lips, and nares, before normal sleeping hours and removed approximately 8 hours later with mild soap and water. Temporary dosing interruptions (rest periods) could be instituted by the investigator as needed to manage local skin reactions (LSRs) or adverse events (AEs). Treatment was resumed upon adequate resolution as determined by the investigator; however, doses missed as a result of rest periods or for other reasons were not made up and the duration of each dosing cycle remained at 3 weeks. After the baseline visit, subjects were assessed at weeks 1, 2, 3 (end of cycle 1), 6 (beginning of cycle 2), 7, 8, 9 (end of cycle 2), 13, and 17 (end of study [EOS]) (Fig 1). Subjects who discontinued the study prematurely were requested to return for the EOS visit.

Efficacy evaluation

The primary efficacy parameter was the number of all visible or palpable AKs, baseline or new, in the treatment area as enumerated at each visit by the investigator. The primary efficacy end point was the complete clearance rate, defined as the proportion of subjects at the EOS visit with a count of zero lesions in the treatment area. Secondary efficacy end points were the partial clearance rates, defined as the proportion of subjects with 75% or greater reduction in AK count in the treatment area at the EOS visit as compared with baseline, and the percent change in AK number at the EOS visit as compared with baseline. In addition, an Investigator Global Integrated Photodamage (IGIP) score was assessed at the EOS visit. The IGIP score was an overall assessment of the subject's photodamage change from baseline in the treatment area (including an integrated assessment of fine wrinkling, coarse wrinkling, mottled pigmentation, roughness, sallowness, skin laxity, and telangiectasias).

Efficacy analyses were conducted on the combined intent-to-treat population comprised of all enrolled subjects from the two studies. For each of the studies, the sample sizes for each treatment group were selected to have 90% power to detect a difference in complete clearance rates of 30% for the active groups versus 5% for the placebo group. For the primary efficacy parameter, imputations were made for missing data points using last observation carried forward. All data from interim visits before the EOS or last visit (if lost to follow-up) were analyzed at their nominal time points. Complete clearance rates, partial clearance rates, and percent change in AK counts from baseline were analyzed using Cochran-Mantel-Haenszel statistics, stratifying by center. Confidence intervals were calculated using exact binomial statistics. For secondary efficacy variables of partial clearance and percent change in lesion number, each of the active arms and placebo were compared using Hochberg modified Bonferroni procedure.[19]

Safety evaluations

Safety was evaluated at each visit by measurement of vital signs, recording of AEs, and investigator assessment of LSRs. The LSRs were a defined set of local AEs (erythema, edema, weeping/exudate, flaking/scaling/dryness, scabbing/crusting, and erosion/ulceration) assessed independently of other AEs. At each visit, each LSR was graded as none, mild, moderate, or severe. At the prestudy visit and EOS visit, hematology, serum chemistry, and urinalyses were performed. For women of childbearing capacity, urine pregnancy tests were performed at prestudy, baseline, and EOS visits.

Treatment-emergent AEs were summarized for each treatment group by preferred term, intensity, and investigator assessment of relationship to study cream. Serious AEs and discontinuations as a result of AEs were summarized. The LSRs were summarized by the most intense score for each LSR and by the sum score at each visit and over the course of the study. All statistical analyses were performed using

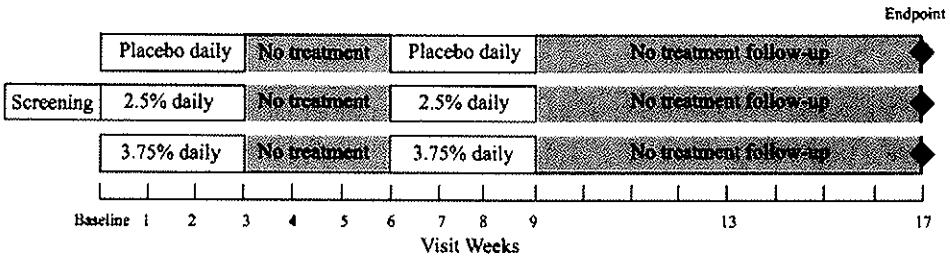


Fig 1. Study design. Each study was identical in design. Primary end point was assessed at end-of-study visit (week 17).

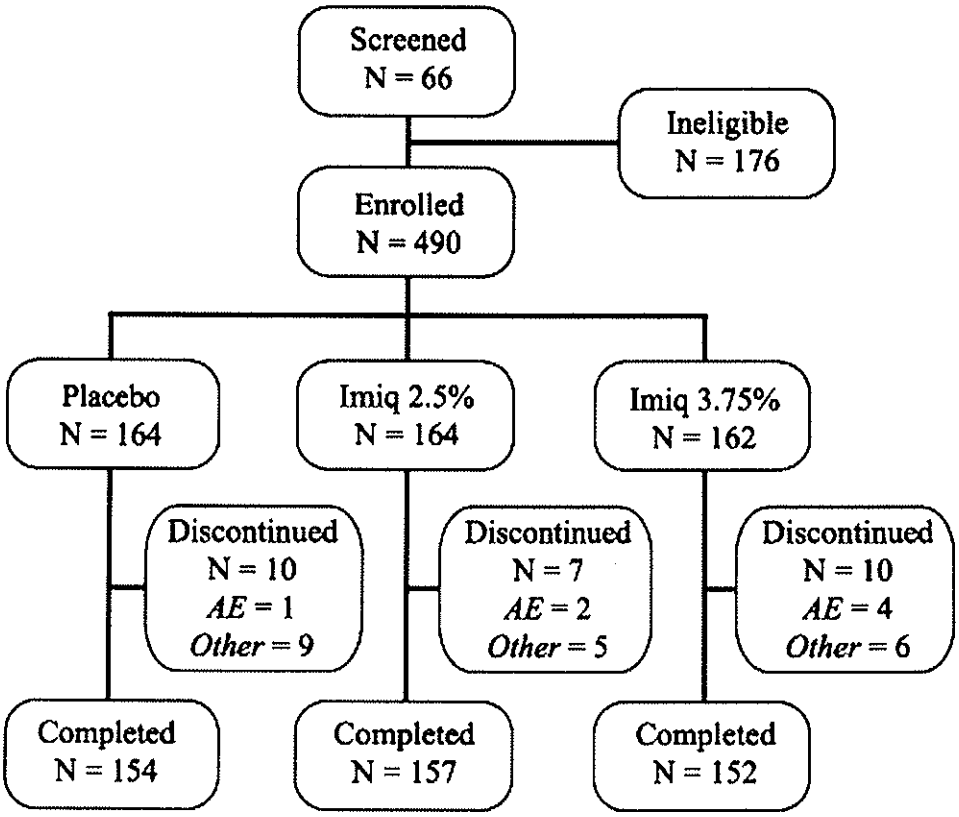


Fig 2. Subject disposition. *AE*, Adverse event; *Imiq*, imiquimod.

software (PC/SAS, Version 9.1.3, SAS Institute Inc, Cary, NC).

RESULTS

Subject population

In the combined studies, 490 male and female patients (Fig 2) were enrolled and 463 completed the studies. The most frequent reason for discontinuation was for personal reasons (11 subjects), followed by AEs (7 subjects). The majority of subjects were male (79%), white (99%), and treated the face (72%); their mean age was 65 years (Table I). The treatment groups were considered comparable with respect to demographic characteristics within and across the two studies. Overall, 96% of subjects were compliant with dosing per the study protocol, with greater than 95% compliance in each of the treatment groups.

Efficacy

The median number of baseline AK lesions per subject across the treatment groups was 9 to 10 (Table I). Complete clearance rates, partial clearance rates, and percent reduction in AK lesions from baseline were all statistically significant for both imiquimod 2.5% and 3.75% compared with placebo (Fig 3). Efficacy for imiquimod 3.75% was numerically greater than that of imiquimod 2.5% for all of these outcomes, and statistically different at the EOS

Table I. Subject characteristics by treatment group

	Placebo	Imiquimod 2.5%	Imiquimod 3.75%
Subjects	164	164	162
Age, y			
Mean (SD)	63.7 (10.9)	66.0 (10.2)	64.3 (10.2)
Median (range)	63.9 (38-87)	66.3 (33-87)	63.8 (40-91)
Sex, n (%)			
Male	135 (82.3)	128 (78.0)	123 (75.9)
Female	29 (17.7)	36 (22.0)	39 (24.1)
Race, n (%)			
White	163 (99.4)	164 (100)	160 (98.8)
Non-white	1 (0.6)	0	2 (1.2)
Ethnicity, n (%)			
Hispanic	6 (3.7)	8 (4.9)	7 (4.3)
Non-Hispanic	158 (96.3)	156 (95.1)	155 (95.7)
Fitzpatrick skin type, n (%)			
I or II	90 (54.9)	83 (50.6)	100 (61.7)
III or IV	68 (41.5)	78 (47.6)	61 (37.7)
V	6 (3.7)	3 (1.8)	1 (0.6)
Treatment location, n (%)			
Face	122 (74.4)	115 (70.1)	115 (71.0)
Balding scalp	42 (25.6)	49 (29.9)	47 (29.0)
Baseline AK, lesions			
Mean (SD)	10.3 (4.3)	10.6 (4.2)	11.1 (4.9)
Median (range)	9 (5-20)	10 (5-20)	9 (5-23)

AK, Actinic keratosis.

visit for partial clearance (P = .034) (Fig 3). The median lesion counts increased from baseline during treatment cycle 1 and again during treatment cycle 2, and then decreased during the follow-up period, for both of the imiquimod groups (Fig 4).

Within each study, both imiquimod 2.5% and 3.75% were superior to placebo with respect to complete clearance rates, partial clearance rates, and percent reduction in AK lesions from baseline. For the primary end point of complete clearance in each of the two studies, the intent-to-treat rates were 5.1% (95% confidence interval 1.4%-12.6%) and 5.8% (1.9%-13.0%) for placebo, 23.2% (14.6%-33.8%) and 26.8% (17.6%-37.8%) for imiquimod 2.5%, and 32.5% (22.4%-43.9%) and 35.4% (25.1%-46.7%) for imiquimod 3.75%, with P less than .001 for all pairwise active to placebo comparisons.

For the imiquimod 2.5% and 3.75% groups, the mean IGIP scores were higher (2.0 ± 1.1 and 1.8 ± 1.1) and more subjects were considered significantly or much improved (62.3% and 70.9%) than in the placebo group (0.7 ± 1.1, 23.4%), respectively. The IGIP results were consistent with the clearance rate and lesion number results.

Safety

In the combined studies, no subjects died and there were 18 serious AEs reported in 13 subjects (two placebo, 4 imiquimod 2.5%, 7 imiquimod 3.75%). Only one serious AE, pancytopenia in the imiquimod 3.75% group, was considered by the investigator to be probably related to study cream. The subject had a history of intermittent thrombocytopenia and pancytopenia, and was given a diagnosis of non-Hodgkin lymphoma with bone-marrow involvement (considered by the investigator not to be related to study cream) while on study.

No unexpected safety issues were observed. Seven subjects (one placebo, two imiquimod 2.5%, 4 imiquimod 3.75%) reported 13 AEs that led to discontinuation from the study. Three subjects discontinued as a result of AEs considered by the investigator to be probably related or related to study cream: two imiquimod 3.75% subjects, one with pancytopenia and the other with application site irritation, and one imiquimod 2.5% subject with application site pain, application site bleeding, and erythematous rash. There was a greater incidence of subjects in the imiquimod groups having any AEs and any treatment-related AEs than in the placebo group (Table II). The AE terms reported by the most subjects included "application site pruritus," "application site pain," and "influenza-like illness." As a group, application site reactions were the treatment-related AEs reported by the most subjects (Table II). Influenza-like illness was the most common non-application site AE, and along with fatigue, headache, pyrexia, and lymphadenopathy, appeared to increase in a dose-dependent fashion. There were also greater incidences of subjects in the imiquimod groups requiring rest periods than in the placebo group (Table II). Clinical laboratory values were generally within normal limits for all parameters. Vital sign measurements and physical examinations did not reveal any significant safety concerns in any treatment group across both studies.

LSRs were observed in almost all of the subjects during treatment. With increasing imiquimod concentration, there was a greater incidence of LSRs and severe LSRs (Table III). Erythema and scabbing/crusting were the LSRs observed by the most subjects. The mean erythema scores over time (not shown) increased from baseline during each treatment cycle for the imiquimod groups and essentially returned to baseline by the end of the no-treatment interval and by week-4 posttreatment.

DISCUSSION

In two multicenter studies conducted in parallel, both imiquimod 2.5% cream and imiquimod 3.75%

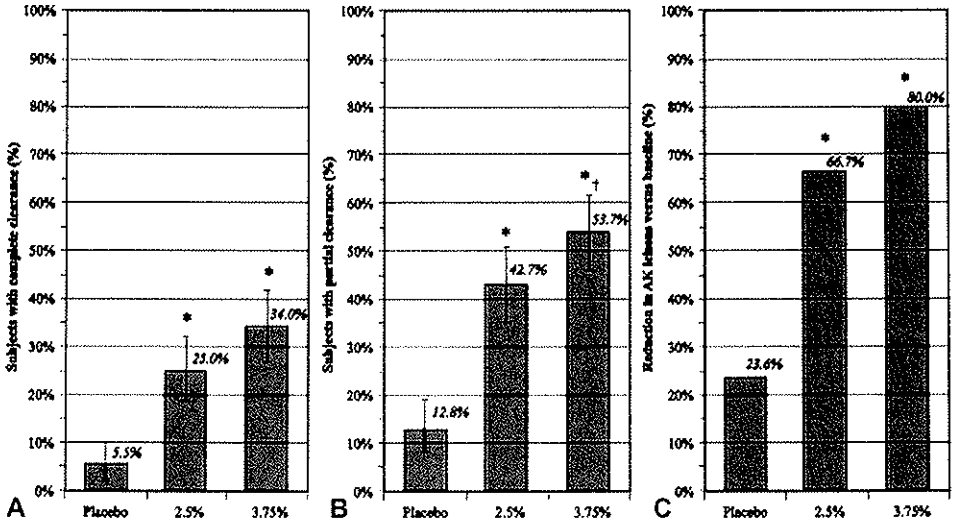


Fig 3. **A**, Complete clearance rates, with 95% confidence intervals (CI), by treatment groups for combined studies. *$P < .001$ for pairwise comparison versus placebo. **B**, Partial ($\geq$ 75% reduction in actinic keratosis [*AK*] lesions compared with baseline) rates, with 95% CI, by treatment groups for combined studies. *$P < .001$ for pairwise comparison versus placebo. †$P = .034$ for pairwise comparison 3.75% versus 2.5%. **C**, Median percent reduction in AK lesions in treatment area compared with baseline by treatment group for combined studies. *$P < .001$ for pairwise comparison versus placebo.

cream were safe and effective in treating AKs on the full face or balding scalp when applied as a 3-week on/off/on treatment regimen. Each of the imiquimod creams was superior to placebo cream with respect to complete clearance rates, partial clearance rates, and median percent lesion reductions. These efficacy outcomes were greater in the imiquimod 3.75% group compared with the 2.5% group, although only the difference in partial clearance rates was statistically significant. Similarly, an increase in the incidence of side effects was observed with increasing imiquimod concentration; however, few subjects discontinued the study for reasons related to AEs.

Complete clearance was achieved by 34% and 25% of subjects in the imiquimod 3.75% and 2.5% treatment groups, respectively. This end point may understate the potential clinical benefit. For example, a subject who had 10 AKs at baseline and only one at EOS would be considered a treatment failure with respect to complete clearance criteria. The reduction in lesion count may be a more clinically relevant end point to clinicians and patients. At least half of the subjects had an 80% reduction in lesion count in the imiquimod 3.75% group and a 67% reduction in the 2.5% group. In placing these results in context, it should be noted that all lesions in the treatment field, baseline or new, were counted in assessing efficacy. Compared with prior phase III studies of imiquimod 5% cream, it should be noted that the current subjects had more baseline AKs

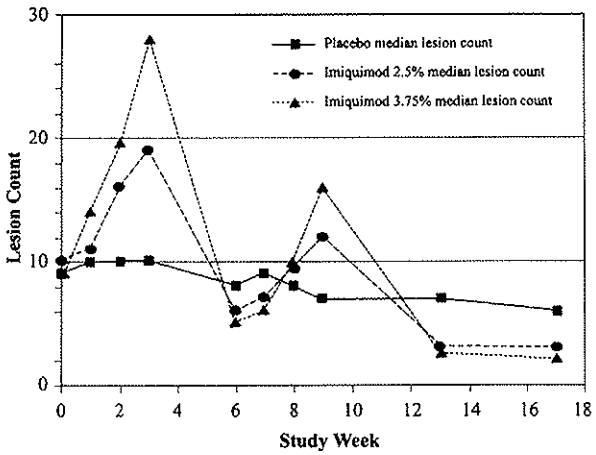


Fig 4. Median lesion count over time for placebo, imiquimod 2.5%, and imiquimod 3.75% groups. For visits where lesion count was indeterminable, count for subject was set at above median for this analysis. Mean erythema scores (not shown) had similar pattern for each treatment group.

treated, and a larger treatment area in which new lesions might develop during the course of the study.

During dosing for both treatment cycles, there was a transient increase in the median lesion counts for the imiquimod groups. This increase in lesion counts is consistent with observations in prior AK studies of imiquimod, and may be a result of activation of immune cells surrounding foci of dysplastic keratinocytes that are not clinically apparent, ie,

Table II. Summary of safety parameters by treatment group

Subjects	Placebo 164	Imiquimod 2.5% 164	Imiquimod 3.75% 162
AE, n (%)			
Any AE	53 (32.3)	82 (50.0)	97 (59.9)
Any treatment-related AE	4 (2.4)	44 (26.8)	60 (37.0)
Any severe grade AE	0	6 (3.7)	9 (5.6)
AEs other than ASRs >2% any group			
Influenza-like illness	0	6 (3.7)	13 (8.0)
Headache	1 (0.6)	6 (3.7)	8 (4.9)
Sinusitis	5 (3.0)	3 (1.8)	7 (4.3)
Fatigue	1 (0.6)	5 (3.0)	8 (4.9)
Lymphadenopathy	0	4 (2.4)	7 (4.3)
Upper respiratory tract infection	4 (2.5)	4 (2.4)	1 (0.6)
Pyrexia	0	1 (0.6)	6 (3.7)
Urinary tract infection	1 (0.6)	4 (2.4)	2 (1.2)
Cough	2 (1.2)	0	4 (2.5)
Myalgia	0	0	5 (3.1)
ASRs, n (%)			
Any ASR	5 (3.0%)	28 (17.1%)	39 (24.1%)
ASR >2% any group			
Application site pruritus	1 (0.6)	12 (7.3)	15 (9.3)
Application site pain	0	11 (6.7)	15 (9.3)
Application site irritation	1 (0.6)	6 (3.7)	9 (5.6)
Application site bleeding	1 (0.6)	2 (1.2)	5 (3.1)
Rest periods, n (%)			
At least 1 rest period	0	28 (17.1)	44 (27.2)

AE, Adverse event; *ASR*, application site reaction.

subclinical lesions. It has been suggested that this may explain the sustained lesion clearance that has been observed after treatment with imiquimod 5%.[20,21] In the current studies, the peak increase in lesion counts (cycle 1) was noted to be greater in the imiquimod 3.75% group than in the 2.5% group. Although this might be a result of an imbalance in baseline severity of subclinical disease, it may also be that greater immune activation results in unmasking of smaller foci of abnormal cells. Histologic assessments of skin biopsy specimens were not performed as part of the study, so this remains speculative. The peak increase for each cycle was at the end of treatment for both of the cycles, with decreases to below baseline 3 to 4 weeks after treatment. However, the median AK counts were lowest at the last visit, suggesting that evaluation of clearance should be performed at least 4 weeks, and preferably 8 weeks, after completion of therapy. The lower peak lesion count during the second treatment cycle might be a result of clearance of some clinically apparent and subclinical lesions from the prior cycle. The clinical relevance of these observations is unknown, ie, whether fewer de novo AKs may develop in the treated area over longer-term follow-up.

Table III. Incidence of local skin reaction of severe intensity by treatment group

Subjects	Placebo 164	Imiquimod 2.5% 164	Imiquimod 3.75% 162
Severe intensity			
Any LSR	0	68 (41.5)	89 (54.9)
Erythema, n (%)	0 (0.0)	46 (28.2)	72 (44.7)
Edema, n (%)	0 (0.0)	12 (7.4)	21 (13.0)
Weeping/exudate, n (%)	0 (0.0)	12 (7.4)	16 (9.9)
Flaking/scaling/dryness, n (%)	0 (0.0)	18 (11.0)	21 (13.0)
Scabbing/crusting, n (%)	0 (0.0)	37 (22.7)	56 (34.8)
Erosion/ulceration, n (%)	0 (0.0)	39 (23.9)	49 (30.4)

LSR, Local skin reaction.

Both imiquimod 2.5% and 3.75% creams were tolerated when administered using repeated 3-week cycles. The incidences of subjects with AEs (treatment-related, severe AEs), application site reactions, and severe grade application site reactions appeared to be related to imiquimod concentration. This dose relationship was also observed with respect to the proportion of subjects requiring a rest period. Imiquimod concentration has previously been shown to affect both safety and efficacy in studies of external genital warts,[22] but has not been previously evaluated with respect to treatment of AKs. Qualitatively, the AEs were mostly consistent with those reported previously with treatment of AKs and other cutaneous conditions with imiquimod 5% cream. Although transient decreases in hematologic parameters have been reported in treating AKs with imiquimod,[12,14,17] the AE of pancytopenia reported as probably related was more likely related to a preexisting non-Hodgkin lymphoma given the natural history of the malignancy, the bone-marrow involvement, and the episodes of pancytopenia before the study. Although not all of the events were considered treatment related by the investigator, it was noted in these studies that there was an increase in the incidence of subjects with influenza-like illness in the imiquimod 3.75% group (8%) compared with the placebo group (0%). Adverse events of influenza-like illness have also been previously reported with imiquimod treatment, and have been proposed to be

possibly related to release into the circulation of cytokines induced locally at the application site. After topical administration, serum concentrations of imiquimod typically do not reach high-enough levels to activate immune cells in the blood to produce cytokines.[23]

In spite of these dose-related side effects, there were few discontinuations overall related to these events. This contrasts with the at least 30% subject discontinuation rate observed with application of imiquimod 5% cream 5×/wk or daily to AKs for 8 weeks.[17] Other studies of imiquimod 5% cream have shown that when concentration and dosing duration are fixed, variations in dosing frequency can have marked effects on safety and efficacy.[24,25] Therefore, lowering the imiquimod concentration, using short cycle durations, and incorporating the no-treatment interval likely significantly improved the tolerability of daily dosing as evidenced by these studies. Although tolerability appears sensitive to concentration, as a discernable difference was still observable between the imiquimod 2.5% and 3.5% creams, it also appears sensitive to cycle duration. Although not evaluated within these same studies, in a pair of similar studies conducted in parallel using a 2-week on/off/on regimen, both the imiquimod 2.5% and 3.5% creams appeared better tolerated than in these studies.[18] Surprisingly, efficacy did not appear to be increased in these studies using 3-week cycles as compared with the efficacy observed in the studies using 2-week cycles.

The mechanism of action of imiquimod contributed to one of the study limitations. By stimulating the immune response, imiquimod treatment can lead to visible effects in the treatment field in many of the subjects, eg, erythema, which correlate with the dosing cycles. This pharmacologic response may have biased investigator assessments and subject reporting during the study. Although the studies were designed to limit bias using a double-blind study design with a placebo cream, this type of bias is inherent in studies with an obvious pharmacodynamic response. However, the conclusions drawn between the two imiquimod arms were less likely to be affected by this limitation.

In conclusion, imiquimod 2.5% and 3.75% creams were both superior to placebo cream in clearing AK lesions of the full face and balding scalp. Although imiquimod 3.75% cream yielded slightly greater efficacy along with a greater incidence of side effects than imiquimod 2.5%, both creams were adequately tolerated when applied daily using a 3-week on/off/on treatment regimen.

The authors would like to acknowledge the contribution of the other investigators in this study: Melanie Appell, Birmingham, AL; Amir Bajoghli, Woodbridge, VA; Michael Bukhalo, Arlington Heights, IL; Steven A. Davis, San Antonio, TX; Lester Fahrner, Champaign, IL; Joseph Fowler, Louisville, KY; Caron Meg Grin, New Britain, CT; Holly Harris, South Bend, IN; David Horowitz, Nashville, TN; Robert T. Matheson, Portland, OR; David Pariser, Norfolk, VA; Andrew Pollack, Philadelphia, PA; Tooraj Joseph Raoof, Encino, CA; David Rodriguez, Coral Gables, FL; Joseph Samady, Vista, CA; Ronald Savin, New Haven, CT; Joel Schlessinger, Omaha, NE; Daniel Smith, Little Rock, AR; Franz Stadler, Reno, NV; Naji Tawfik, Evansville, IN; Eduardo Tschen, Albuquerque, NM; Stephen Tyring, Houston, TX; and David Whiting, Dallas, TX. We also thank the staff and patients at each of the study centers for their participation, Richard D. Gilbert for biostatistical analyses, Valyn Bahm for management of the studies, and Tze-Chiang Meng and John Furst for assistance with the manuscript.

REFERENCES

1. Röwert-Huber J, Patel MJ, Forschner T, Ulrich C, Eberle J, Kerl H, et al. Actinic keratosis is an early in situ squamous cell carcinoma: a proposal for reclassification. Br J Dermatol 2007; 156(Suppl):8-12.
2. Drake LA, Ceilly RI, Cornelison RL, Dobes WL, Dorner W, Goltz RW, et al. Guidelines of care for actinic keratoses. J Am Acad Dermatol 1995;32:95-8.
3. Stockfleth E, Kerl H. Guideline subcommittee of the European dermatology forum: guidelines for the management of actinic keratoses. Eur J Dermatol 2006;16:599-606.
4. Warino L, Tusa M, Camacho F, Teuschler H, Fleischer AB Jr, Feldman SR. Frequency and cost of actinic keratosis treatment. Dermatol Surg 2006;32:1045-9.
5. Balkrishnan R, Cayce KA, Kulkarni AS, Orsagh T, Gallagher JR, Richmond D, et al. Predictors of treatment choices and associated outcomes in actinic keratoses: results from a national physician survey study. J Dermatol Treat 2006;17:162-6.
6. Mcintyre WJ, Downs MR, Bedwell SA. Treatment options for actinic keratoses. Am Fam Physician 2007;76:667-71.
7. Weinberg JM. Topical therapy for actinic keratoses: current and evolving therapies. Rev Recent Clin Trials 2006;1:53-60.
8. Gaspari AA. Mechanism of action and other potential roles of an immune response modifier. Cutis 2007;79(Suppl):S36-45.
9. Torres A, Storey L, Anders M, Miller RL, Bulbulian BJ, Jin J, et al. Immune-mediated changes in actinic keratosis following topical treatment with imiquimod 5% cream. J Transl Med 2007;5:7.
10. Lysa B, Tartler U, Wolf R, Arenberger P, Benninghoff B, Ruzicka T, et al. Gene expression in actinic keratoses: pharmacological modulation by imiquimod. Br J Dermatol 2004; 151:1150-9.
11. Torres A, Storey L, Anders M, Miller RL, Bulbulian BJ, Jin J, et al. Microarray analysis of aberrant gene expression in actinic keratosis: effect of the Toll-like receptor-7 agonist imiquimod. Br J Dermatol 2007;157:1132-47.
12. Lebwohl M, Dinehart S, Whiting D, Lee PK, Tawfik N, Jorizzo J, et al. Imiquimod 5% cream for the treatment of actinic keratosis: results from two phase III, randomized, double-blind, parallel group, vehicle-controlled trials. J Am Acad Dermatol 2004;50:714-21.
13. Aldara (imiquimod cream, 5%) [package insert]. Bristol, TN: Graceway Pharmaceuticals; 2007.
14. Jorizzo J, Dinehart S, Matheson R, Moore JK, Ling M, Fox TL, et al. Vehicle-controlled, double-blind, randomized study of