

The Use of Topical Imiquimod for the Treatment of Actinic Keratosis: A Status Report

James Q. Del Rosso, DO

Topical imiquimod 5% cream is approved for the treatment of actinic keratosis (AK), superficial basal cell carcinoma, and external genital warts. The drug's mechanism of action is via stimulation of innate and acquired immune responses, which ultimately leads to inflammatory cell infiltration within the field of drug application followed by apoptosis of diseased tissue. This article reviews available data on the use of topical imiquimod for AK. Topical imiquimod is an effective and safe treatment option for AK that produces complete eradication or marked reduction in the number of lesions in most patients. Subclinical lesions also emerge during treatment of the affected skin region ("field treatment"). In addition, there is evidence that topical imiquimod at least partially reverses some of the cellular, molecular, and genetic photocarcinogenic changes that develop in skin damaged by UV light. Recent evidence suggests that many patients who effectively are cleared of AK lesions after topical imiquimod use remain free of lesions for several months to 2 years or develop a minimal number of new AK lesions.

Cutis. 2005;76:241-248.

Actinic keratosis (AK) is a common dermatologic disease. Its reported incidence in white individuals older than 40 years who live in the northern hemisphere ranges from 11%

to 25%; what's more, 40% to 60% of people living in Australia are affected by the disorder.^{1,2} Multiple therapeutic modalities are available for treatment of AK, including ablative, physical/surgical, and pharmacologic approaches. Three topical agents currently are approved by the US Food and Drug Administration (FDA) for the treatment of AK: 5-fluorouracil (Efudex[®], Carac[®]), diclofenac (Solaraze[®]), and imiquimod (Aldara[™]). These agents have demonstrated efficacy and safety based on clinical trials and widespread community experience.^{3,4}

Topical 5-fluorouracil, diclofenac, and imiquimod induce their therapeutic effects through different mechanisms of action.^{3,5} At present, there are no published blinded, controlled, randomized, adequately powered studies comparing the relative efficacy and safety of these 3 agents. Importantly, adverse events observed in association with the use of topical 5-fluorouracil, diclofenac, and imiquimod have been local application site reactions, with no major systemic side effects reported.^{3,5}

Imiquimod 5% cream, the most recent topical agent approved for AK, also is approved by the FDA for the treatment of superficial basal cell carcinoma (BCC) and external genital warts, though recommended treatment regimens differ among these indications.^{4,6}

Topical imiquimod, an imidazoquinolone immune response modifier, has been studied extensively for the treatment of AK and superficial BCC; additionally, clinical trials and multiple case reports have demonstrated the drug's efficacy for the treatment of squamous cell carcinoma (SCC) in situ.⁵⁻¹⁵ Suggested treatment regimens with topical imiquimod based on a thorough literature review of AK, superficial BCC, and SCC in situ are shown in Table 1.³⁻¹⁵

Accepted for publication August 8, 2005.

From the Department of Dermatology, University of Nevada School of Medicine, Las Vegas.

Dr. Del Rosso is a consultant and speaker for 3M Pharmaceuticals, and a speaker for Dermik Laboratories and Doak Dermatologics, a subsidiary of Bradley Pharmaceuticals, Inc.

Reprints not available from the author.

The following discussion is a status report on the use of topical imiquimod 5% cream for AK.

What is the proposed mechanism of action of topical imiquimod?

Based on in vitro and in vivo studies, topical imiquimod is classified as an immune response modifier; the mechanism of action of imiquimod is reviewed in detail elsewhere.^{7,16-23} Study models evaluating the use of imiquimod for human papillomavirus infection and BCC demonstrate upregulation of both innate and acquired immune response within the drug's application field.^{16-19,21-23} Imiquimod functions as a sur-reptitious ligand for toll-like receptor 7, a surface receptor found on cutaneous plasmacytoid dendritic cells involved in immune surveillance and antigen recognition.^{16,19,22} Stimulation of a local innate response through production of specific cytokines upregulates an adaptive immune response characterized by a helper T cell 1 (T_H1) lymphocytic response (Figure).^{5,7,16-23} An admixture of various cell types, which is based on identification using immunohistochemical techniques, comprises the inflammatory infiltrate that develops within the treatment field where topical imiquimod has been applied. The imiquimod-induced inflammatory response is composed predominantly of CD4⁺ cells (helper T cells), natural killer cells, and some CD8⁺ cells, which reflects an augmentation and amplification of immune response directed at an underlying antigenic target (eg, tumor, virus).^{7,10,18-21} The final common pathway involved in disease eradication is interferon- α and interferon- γ production with apoptosis of cells infected with a tumor or virus (eg, human papillomavirus).^{7,16,17,19,23}

Although the complete mechanism of action of topical imiquimod in the treatment of AK has not been fully defined and the specific tissue antigen has not been identified, the mechanism described is believed to be operative. This immune response mechanism has been suggested in patients receiving topical imiquimod therapy for SCC in situ on the lower extremities based on evaluation of infiltrate cell types.¹⁰

Table 1.

Suggested Regimens of Topical Imiquimod 5% Cream

Diagnosis	Frequency, times/wk	Duration*
Actinic keratosis	2	16 wk ^{†‡}
	3	4–8 wk [‡]
	3	Cycle therapy ^{‡§}
Superficial basal cell carcinoma	5	6 wk ^{†‡}
Squamous cell carcinoma in situ	3	6–8 wk [‡] (≤ 16 wk)

*Based on available data. May be adjusted based on response.

[†]US Food and Drug Administration–approved indication with on-label regimen.

[‡]May extend or repeat therapy.

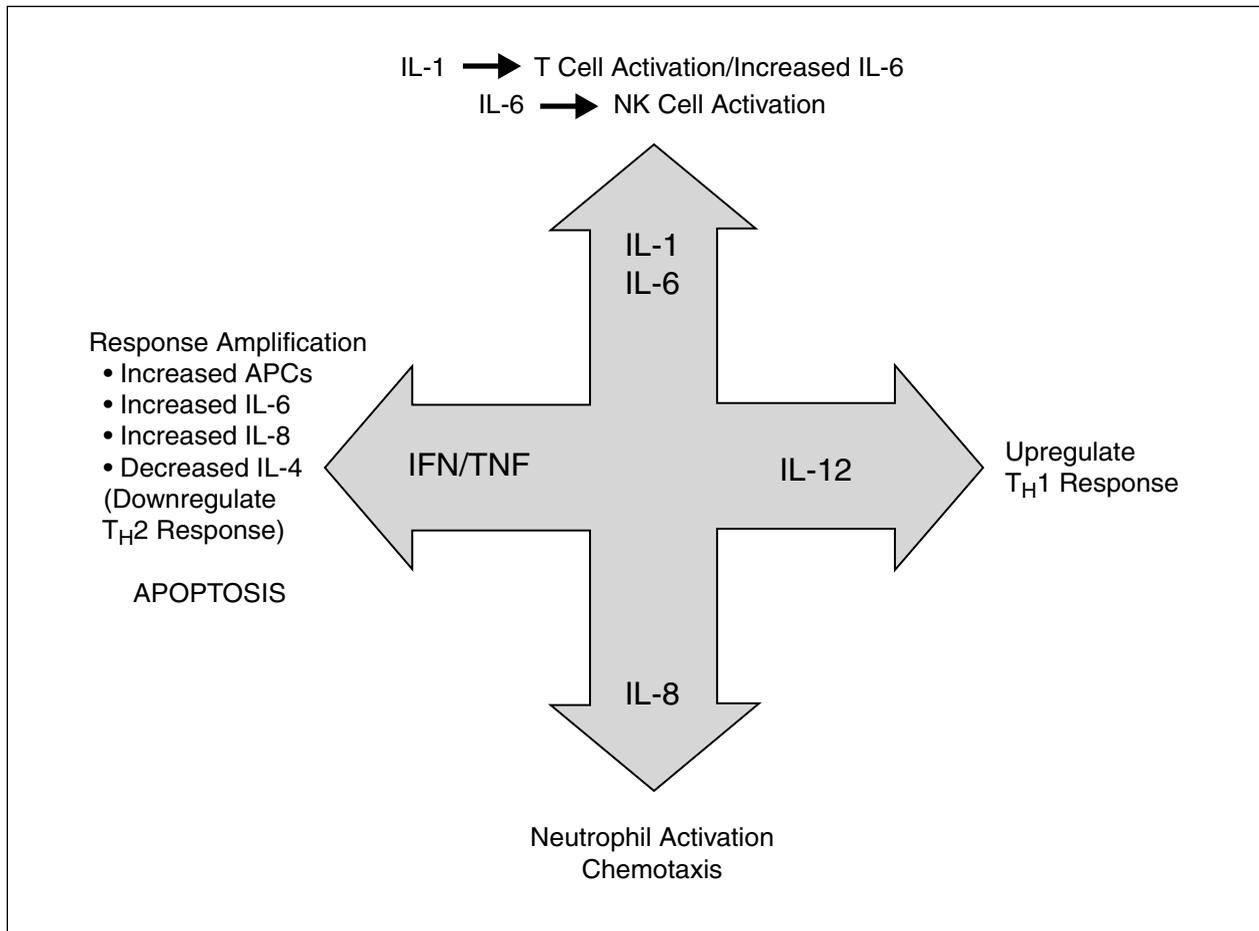
[§]Each cycle=4 weeks on drug followed by 4 weeks off drug. One or 2 cycles used based on clinical response.

^{||}Further study underway to evaluate regimens/durations of therapy.

How is topical imiquimod applied for the treatment of AK?

Photocarcinogenesis occurs through “field cancerization” as epithelial genetic and cellular changes develop progressively over time.²⁴ Essentially, long-term UV-light exposure genetically reprograms regions of exposed skin and is associated with cutaneous immunosuppression.^{24,25} Multiple key genetic mutations are found on *ras* oncogene and both *p53* and *PTCH* suppressor genes, with such changes identified in both clinically diseased and surrounding regions of skin.²⁵ As a result, topical therapies are more likely to be effective if they can eradicate or significantly reduce the number of both clinically evident and subclinical AK lesions.^{3-5,26-28} In addition, topical application of imiquimod 5% cream 3 times weekly for 4 weeks has been shown to at least partially reverse the expression of genes associated with tumor proliferation and to at least partially upregulate the expression of tumor suppressor genes that have been downregulated within scalp skin affected by previously untreated AK.²⁹ These preliminary data suggest that the therapeutic field effect produced by topical imiquimod includes treatment of visible and subclinical AK lesions and at least partial reversal of adverse genetic changes in skin damaged by UV light that are associated with the promotion of carcinogenesis.

In both of the phase 3, randomized, double-blind, vehicle-controlled trials of patients with AK



Topical imiquimod immune response upregulation and amplification.^{5,7,16-23} IL indicates interleukin; NK, natural killer; APCs, antigen presenting cells; IFN, interferon; TNF, tumor necrosis factor. The author acknowledges Neal Bhatia, MD, for his assistance in the figure's content development.

on which FDA approval of topical imiquimod was based, the target treatment area for each patient measured 25 cm² on the face or scalp, but not on both.²⁸ As a result, the manufacturer is required to state in the FDA-approved full prescribing information that the application area is 25 cm².³⁰

In clinical studies and “real-world” practice, topical imiquimod is applied to larger surface areas of application.³⁶ Most clinical trials and case reports of patients treated for AK have used topical imiquimod applied to the entire cosmetic unit, including regions such as the scalp, dorsum of hand, forehead, or cheeks to achieve field treatment in conjunction with therapy for clinically evident lesions.^{3-6,26,27,30-32} A study evaluating coverage area with the application of a single sachet of imiquimod 5% cream (250 mg) using a fluorescein skin fluorescence technique demonstrated the average area of coverage on pig skin was 196 cm² and 386 cm² on human arm skin.³³

What dosing regimen is recommended for topical imiquimod in the treatment of AK?

As noted earlier, the FDA-approved product labeling indicates twice weekly application of topical imiquimod for 16 weeks. In many studies and published case reports, 3 times weekly dosing over durations ranging from 4 to 12 weeks have been used effectively.^{4,6,26,27,31,32,34} The results of the application of topical imiquimod 3 times weekly for AK suggest that many patients respond with complete or marked clearance of lesions with a treatment duration of 4 to 8 weeks.^{3,5,26}

What should be anticipated during treatment with topical imiquimod for AK?

Imiquimod upregulates both innate and adaptive immunity; thus, an inflammatory response is anticipated within the application field that is typically characterized by varying degrees of focal and diffuse erythema and lesion crusting.^{3-6,26-28,31,32,34} This

inflammatory response, sometimes referred to as cytokine dermatitis, is reflective of therapeutic activity due to infiltration of inflammatory cells within the field of imiquimod application.^{3,5}

Brisk inflammatory response is not uncommon within the treatment field; thus, the use of imiquimod was temporarily discontinued in approximately 50% of patients for periods of 1 to 2 weeks (rest period) in some trials and case reports.^{5,6,26,27,32,34} In most cases, treatment was resumed using a dosing frequency of 1 less day per week. The reported clearance rates in these studies include patients who used rest periods. Importantly, the symptomatology associated with the inflammatory response induced by imiquimod is usually mild or absent, even in cases presenting with a brisk response.^{3,5,28,34}

The concept of “cycle therapy” with topical imiquimod was reported in an open-label pilot evaluation of patients treated for AK involving a variety of “cosmetic units” (scalp, cheeks, forehead, and/or temples); the cycle therapy approach automatically built in a rest period to allow for monitoring of therapeutic response.²⁶ In this study, 33 cosmetic units were treated in 25 patients. Based on this approach, a single cycle is defined as the application of imiquimod to the entire treatment region (cosmetic unit) 3 times weekly over 4 weeks followed by a 4-week rest period. It was observed in this trial that a 4-week rest period better allows for evaluation of lesion clearance because many AK lesions that are still present after 1 to 2 weeks off imiquimod therapy are cleared by the end of the 4-week rest period.²⁶ At this point, a second cycle may be initiated if residual AK lesions are noted. Beyond 2 treatment cycles, additional therapeutic benefit was absent or minimal. Therefore, the cycle therapy approach used active imiquimod application for a total of 4 or 8 weeks, depending on the extent of lesion clearance observed in each patient.

What is the efficacy of topical imiquimod therapy for AK?

In both of the phase 3 vehicle-controlled trials undertaken to achieve FDA approval, application of topical imiquimod twice weekly evaluated clearance of AK lesions at 8 weeks posttherapy (week 24).²⁸ In the actively treated arms (n=215), 45.1% and 59.1% of patients achieved complete clearance (100% lesion clearance) or partial clearance (≥75% lesion clearance), respectively. The corresponding clearance rates in vehicle-treated study subjects (n=221)

were 3.2% for complete clearance and 11.8% for partial clearance.

Investigations of imiquimod therapy applied 3 times weekly for AK have included case reports and vehicle-controlled trials.^{3,5,27,32,34} In a published case report collection of refractory scalp AK, application of imiquimod 3 times weekly was continued for 6 to 8 weeks, with complete clearance observed in all cases by clinical and histologic examinations over a follow-up range of 2 to 12 months.³² In a double-blind, randomized, vehicle-controlled study, patients continued therapy for a maximum duration of 12 weeks until they achieved complete clearance of AK lesions.²⁷ Complete clinical and histologic resolution was observed in 84% of imiquimod-treated patients. None of the study subjects in the vehicle-treated arm achieved complete clearance of AK lesions.²⁷

Response to treatment with cycle therapy was based on complete clearance of treated cosmetic units.²⁶ A single cycle evaluated at the end of the 4-week rest period produced complete clearance of 46% of treated cosmetic units. An additional 36% of cosmetic units were completely cleared after a second cycle of topical imiquimod. In summary, 1 cycle of topical imiquimod completely cleared AK lesions, including subclinical lesions that emerged during therapy, in nearly half of the anatomic regions that were treated; 2 cycles completely cleared 82% of treated anatomic regions.

How is response to treatment monitored during use of topical imiquimod, and how is duration of therapy determined?

As reviewed earlier, response to topical imiquimod treatment is monitored by evaluating the intensity of inflammatory response observed within the treatment field, the extent of clearance of AK lesions present prior to therapy, the emergence and extent of clearance of subclinical AK lesions noted during therapy, and the tolerability of the treatment course by the patient. Due to interpatient variability in the intensity of the inflammatory response, it is difficult to use a stringent “cookbook approach” with imiquimod therapy.⁵

In the treatment of AK and other disorders, such as superficial BCC and SCC in situ, the intensity of the inflammatory response to imiquimod application appears to be as important as, or possibly more important than, completion of a designated duration of therapy.^{3,6} For the use of topical imiquimod 3 times weekly, the range of duration that has typically demonstrated effective clearance or marked AK lesion reduction is 4 to

8 weeks.^{3,6,26,27,32,34} The duration of use in each patient may be adjusted based on clinical response, and treatment may be repeated if warranted.⁵ As noted earlier, cycle therapy uses either 4 or 8 weeks of active imiquimod application, 3 times weekly, depending on the observed clinical response.²⁶

The duration of active therapy needed to consistently provide long-term clearance of AK within the treatment field after imiquimod therapy is discontinued warrants additional study. Although data are limited, some authors have advocated maintenance therapy with topical imiquimod in selected patients treated for AK.³¹ Individual cases of long-term AK treatment with topical imiquimod applied twice weekly to the hands and forehead over 9 months have noted continued improvement and maintenance of lesion clearance.³¹ Further data on maintenance therapy with topical imiquimod are needed before widespread use of this approach can be recommended as a routine practice.

What is the longevity of therapeutic benefit after treatment of AK with currently available therapies?

Overall, long-term clearance rates related to use of ablative therapies (eg, cryotherapy) or topical therapies for AK are limited. Available data suggest that response to cryotherapy is based on freeze time, with clearance rates for treated AK at 3 months reported to be 39%, 75%, 80%, 69%, and 83% with freeze times of 1 to 5 seconds, 5 to 10 seconds, 10 to 15 seconds, 15 to 20 seconds, and longer than 20 seconds, respectively.³⁵ Development of hypopigmentation at sites treated with cryotherapy usually correlated with a more prolonged freeze time.³⁵

In patients treated for AK with 5-fluorouracil 0.5% microsphere cream or vehicle cream once daily for 1 week followed by cryotherapy of visible lesions at week 4, the mean percentage lesion reduction and complete clearance rates at 6 months were 67% and 30%, respectively, for the group treated with topical 5-fluorouracil and cryotherapy, and 45.6% and 7.7%, respectively, for the study arm treated with vehicle cream and cryotherapy.³⁶

Does topical imiquimod provide prolonged remission and a low relapse rate of AK within regions of previous application because of augmentation of host immune response?

Because of the augmentation of immune response by imiquimod and conversion of naive

nodal T lymphocytes to an activated clone of circulating T cells directed against an antigenic target, it has been postulated that imiquimod use may produce “immunologic memory” that results in prolonged disease remission and lower relapse rates.^{5,37} Retrospective analysis of treatment data compiled from one study center in patients treated for anogenital warts suggests that imiquimod application may afford more sustained remission.³⁷ The data evaluation demonstrated a 65% recurrence rate of anogenital warts within an average period of 5 months in patients treated with surgical removal alone versus a 20% recurrence rate within an average period of 19 months for patients treated with 16 weeks of topical imiquimod followed by surgical removal of residual lesions.³⁷

Long-term follow-up data of patients treated with topical imiquimod for AK suggest prolonged therapeutic benefit. A follow-up report from a previously published study²⁷ indicated that at 2 years posttherapy, 80% of patients treated with topical imiquimod 3 times weekly for 12 weeks remained completely clear of AK development in the treatment field (n=25) compared with 10% of vehicle-treated patients (n=10).³⁸ None of the imiquimod-treated patients (0%) developed SCC within the treatment field during 2 years of follow-up compared with one patient (10%) in the vehicle-treated group.

Additional data evaluating multiple studies demonstrate that after complete clearance of AK in patients treated with topical imiquimod (n=131), 75% (58/77) of subjects in study groups treated 3 times weekly and 57% (31/54) of subjects in study arms treated 2 times weekly remained clear of AK in the treatment field at a median follow-up of 16 months.³⁹ These data suggest that topical imiquimod may impart prolonged clearance of AK and reduce development of new lesions through a variety of effects that reduce photocarcinogenic changes in skin damaged by long-term UV-light exposure.^{7,18-25,29,38}

What is the safety profile of topical imiquimod?

The therapeutic inflammatory response that develops within imiquimod’s application field correlates with local skin reactions reported during clinical trials. The intensity of the response influences the incidence of reported visible reactions such as edema, exudation, erosion, crusting, and to a lesser extent, the nature and severity of associated symptomatology.⁵ In the phase 3 trials, erythema was reported by 97.2% of subjects treated with

Table 2.

Suggestions for the Use of Topical Imiquimod for Actinic Keratosis*⁵

- When selecting therapy for AK, consider all available Tx options and Pt-related factors.
- If any lesion is clinically suggestive of an invasive malignancy, biopsy is indicated.
- Initiate therapy with once-daily application 3 d/wk.
- Apply drug to affected lesions and surrounding skin of entire anatomic unit (eg, scalp, forehead, cheek, dorsum of hand), preferably at bedtime; occlusion is not suggested.
- Educate Pt regarding expected development of visible inflammatory response to maximize expectations and enhance compliance.
- Inform Pts that local skin response may be low grade or brisk. Most Pts, including those who exhibit a brisk inflammatory response, experience no or only minor local symptoms of irritation (eg, itching, stinging).
- Follow-up with Pt 4 wk after initiation of therapy to evaluate clinical Tx response.
- Educate Pts to follow-up earlier if they experience a brisk inflammatory response, especially if associated with significant discomfort.
- Continue application regimen if only minimal or moderate inflammation is noted. Monitor for resolution of AK at approximately 4-wk intervals over an average total Tx duration of 16 wk; adjust duration based on clinical response; alternatively, frequency may be increased by 1 weekly application and continue to monitor at approximately 4-wk intervals.
- Allow a 4-wk rest period if a brisk inflammatory response is noted; reexamine at end of rest period. If complete clearance is observed, no further active Tx is needed other than periodic follow-up to monitor for development of new lesions; if residual lesions are noted, Tx may be reinitiated 3 times/wk for another 4 wk, followed by a 4-wk rest period.
- If AK lesions have resolved completely after completion of 2 cycles of topical imiquimod therapy, periodic clinical follow-up is recommended.
- If a partial response is noted (ie, some lesions have resolved, with scattered lesions still present in the Tx field), an ablative measure such as cryotherapy may be used and another 4-wk course of topical imiquimod application may be considered. If any persistent lesion is clinically suggestive of an invasive malignancy, biopsy is indicated.
- If limited response to imiquimod therapy is noted, another form of therapy may be warranted or a trial of topical imiquimod using an augmented frequency of application, such as daily or every other day may be tried.
- Regular periodic long-term follow-up is indicated in Pts with AK, regardless of what forms of therapy are used.
- Instruct Pts to examine their skin and educate them on practical photoprotection guidelines, which are both vital components of the Pt management plan.

*AK indicates actinic keratosis; Tx, treatment; Pt, patient.

imiquimod and 93.6% of vehicle-treated subjects, with severe erythema more commonly observed in actively treated subjects (17.7% vs 2.3%, respectively).²⁸ Localized pruritus occurring within the target application area was reported in 20.5% of subjects treated with imiquimod and 6.8% of those treated with the vehicle cream. All other application site reactions, such as stinging, burning, tenderness, and pain, were reported to occur

in 1.4% to 5.6% of imiquimod-treated subjects and in 0% to 1.8% of vehicle-treated subjects. Among imiquimod-treated patients, 5.6% reported burning and 2.3% reported pain at the local application site compared with 1.8% and 0.9%, respectively, noted in vehicle-treated subjects.²⁸

Overall, based on available data, severe systemic reactions have not been attributed to topical imiquimod therapy.^{4,5,8,28,34} Occasional patients

may experience mild, transient, flulike symptoms related to interferon production induced by imiquimod use.

What treatment tips or additional suggestions are provided based on the experience of the author?

Based on the author's clinical experience and understanding of the literature, because of the likelihood of repeated development of AK over the years in patients with actinically damaged skin, management of AK requires selection of therapy based on individual patient considerations and continued long-term follow-up. Over time, effective therapy in most patients, especially for treatment of the field of disease, warrants the use of both ablative and topical therapies.

Topical imiquimod offers a viable therapeutic alternative that is well suited for treatment of actively present AK and subclinical lesions and also may at least partially reverse some of the photocarcinogenic cellular and molecular changes induced by long-term UV-light exposure. Importantly, to optimize therapeutic benefit, imiquimod should be applied to the treatment field and not to individual lesions (spot application). Although a visible inflammatory response is apparent, symptomatology is usually minimal, especially compared with the use of topical 5-fluorouracil.^{4,5}

Additionally, improved skin quality and texture commonly are noted after use of topical imiquimod for AK. These clinical observations are supported by results from more than 200 patients actively treated in phase 3 vehicle-controlled trials.²⁸ From the imiquimod-treated study arm, 56% of subjects demonstrated improved skin quality posttherapy (characterized by reduction in roughness, dryness, and scaliness) compared with 22% of vehicle-treated subjects. Improved skin quality also may be observed after AK treatment with other topical therapies or with photodynamic therapy.

The author's preference when using topical imiquimod for AK is the cycle therapy approach.²⁶ A suggested stepwise approach to the use of topical imiquimod is outlined in Table 2.⁵ In some cases, especially in those treated twice weekly with imiquimod, patients exhibit minimal or low-grade inflammation and demonstrate a slower, smoldering resolution of AK. In such cases, treatment is continued for 16 weeks or longer if necessary. In this subset of patients, based on a lesser intensity of inflammatory response, treatment duration is longer than the 4 to 8 weeks that is usually adequate in most patients, especially those treated

with a frequency of 3 times per week. In cases exhibiting no inflammatory response and little to no resolution of AK within 4 to 8 weeks, the dose-response characteristics of topical imiquimod allow for an increase in application frequency to every night or every other night.⁵ If no response is observed after an additional 4 weeks, imiquimod therapy may be discontinued and other options considered. In such cases exhibiting little to no response after an adequate trial of topical imiquimod, insufficient expression of toll-like receptor 7 expression on cutaneous dendritic cells or insufficient presence of plasmacytoid dendritic cells may be contributory factors.

Because AK is associated with the potential to progress to invasive SCC and SCC in situ, it is important to recognize that many published reports demonstrate the effective use of topical imiquimod for SCC in situ.^{5,10-15} A variety of anatomic sites have been treated effectively, including lesions of both smaller and larger clinical size involving the legs, face, and genitalia. Recommended regimens are similar to those for AK, using an initial application frequency of at least 3 times weekly and a usual duration range of 6 to 17 weeks. Some reports have indicated no evidence of recurrence over a follow-up range of 12 to 15 months.^{12,13}

REFERENCES

1. Frost CA, Green AC. Epidemiology of solar keratosis. *Br J Dermatol.* 1994;131:455-464.
2. Heaphy MR Jr, Ackerman AB. The nature of solar keratosis: a critical review in historical perspective. *J Am Acad Dermatol.* 2000;43:138-150.
3. Del Rosso JQ. New and emerging topical approaches for actinic keratosis. *Cutis.* 2003;72:273-276, 279.
4. Ceilley RI, Del Rosso JQ. Topical chemotherapy for the treatment of skin cancer. In: Rigel DS, Friedman RJ, Dzubow LM, et al, eds. *Cancer of the Skin.* Philadelphia, Pa: Elsevier Saunders; 2004:619-630.
5. Del Rosso JQ. Therapy for cutaneous epithelial malignancy: a review of research, development, current status and practical use of topical imiquimod. *Skin & Aging.* 2003;11:44-54.
6. Tran H, Chen K, Shumack S. Summary of actinic keratosis studies with imiquimod 5% cream. *Br J Dermatol.* 2003;149(suppl 66):37-39.
7. Sullivan TP, Dearaujo T, Vincek V, et al. Evaluation of superficial basal cell carcinomas after treatment with imiquimod 5% cream or vehicle for apoptosis and lymphocyte phenotyping. *Dermatol Surg.* 2003;29:1181-1186.
8. Tyring S, Conant M, Marini M, et al. Imiquimod: an international update on therapeutic uses in dermatology. *Int J Dermatol.* 2002;41:810-816.

9. Marks R, Gebauer K, Shumack S, et al. Imiquimod 5% cream in the treatment of superficial basal cell carcinoma: results of a multi-center 6-week dose-response trial. *J Am Acad Dermatol.* 2001;44:807-813.
10. Mackenzie-Wood A, Kossard S, De Launey J, et al. Imiquimod 5% cream in the treatment of Bowen's disease. *J Am Acad Dermatol.* 2001;44:462-470.
11. Cook-Bolden F, Weinberg JM. Topical imiquimod 5% cream in the treatment of Bowen's disease of the penis. *J Am Acad Dermatol.* 2002;46:146-147.
12. Hengee UR, Stark R. Topical imiquimod to treat intraepidermal carcinoma. *Arch Dermatol.* 2001;137:709-711.
13. Orengo I, Rosen T, Guill CK. Treatment of squamous cell carcinoma in situ of the penis with 5% imiquimod cream: a case report. *J Am Acad Dermatol.* 2002;47(suppl 4):S225-S228.
14. Nouri K, O'Connell C, Rivas MP. Imiquimod for the treatment of Bowen's disease and invasive squamous cell carcinoma. *J Drugs Dermatol.* 2003;2:669-673.
15. Arlette JP. Treatment of Bowen's disease and erythroplasia of Queyrat. *Br J Dermatol.* 2003;149(suppl 66):43-47.
16. Miller R. Imiquimod stimulates innate and cell mediated immunity which controls virus infections and tumors. *Int J Dermatol.* 2002;41(suppl 1):3-6.
17. Stanley MA. Imiquimod and the imidazoquinolones: mechanism of action and therapeutic potential. *Clin Exp Dermatol.* 2002;27:571-577.
18. Sauder DN. Imiquimod: modes of action. *Br J Dermatol.* 2003;149(suppl 66):5-8.
19. Hurwitz DJ, Pincus L, Kupper TS, et al. Imiquimod: a topically applied link between innate and acquired immunity. *Arch Dermatol.* 2003;139:1347-1350.
20. Berman B, Sullivan T, De Araujo T, et al. Expression of Fas-receptor on basal cell carcinomas after treatment with imiquimod 5% or vehicle. *Br J Dermatol.* 2003;149(suppl 66):59-61.
21. Dahl MV. Imiquimod: a cytokine inducer. *J Am Acad Dermatol.* 2002;47(suppl 4):S205-S208.
22. Gibson S, Lindh J, Riter T, et al. Plasmacytoid dendritic cells produce cytokines and mature in response to the TLR7 agonists, imiquimod and resiquimod. *Cell Immunol.* 2002;218:74-86.
23. Gaspari AA, Sauder DN. Immunotherapy of basal cell carcinoma: evolving approaches. *Dermatol Surg.* 2003;29:1027-1034.
24. Kraemer KH. Sunlight and skin cancer: another link revealed. *Proc Natl Acad Sci U S A.* 1997;94:11-14.
25. Sarasin A. The molecular pathways of ultraviolet-induced carcinogenesis. *Mutat Res.* 1999;428:5-10.
26. Salasche S, Levine N, Morrison L. Cycle therapy of actinic keratoses of the face and scalp with 5% topical imiquimod: an open label trial. *J Am Acad Dermatol.* 2002;47:571-577.
27. Stockfleth E, Meyer T, Benninghoff B, et al. A randomized, double-blind, vehicle-controlled study to assess 5% imiquimod cream for the treatment of multiple actinic keratoses. *Arch Dermatol.* 2002;138:1498-1502.
28. Lebwohl M, Dinehart S, Whiting D. 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;50:714-721.
29. Torres A, Storey L, Miller RL, et al. Induction of cellular and molecular changes in actinic keratoses with imiquimod 5% cream (1467-IMI). Poster presented at: 10th World Congress of Cancers of the Skin; May 13-17, 2005; Vienna, Austria.
30. Aldara [package insert]. St. Paul, Minn: 3M Pharmaceuticals; 2004.
31. Persaud A, Lebwohl M. Imiquimod in the treatment of actinic keratoses. *J Am Acad Dermatol.* 2002;47(suppl 4):S236-S239.
32. Stockfleth E, Meyer T, Benninghoff B, et al. Successful treatment of actinic keratosis with imiquimod cream 5%: a report of six cases. *Br J Dermatol.* 2001;144:1050-1053.
33. Berman B, Ricotti CA Jr, Cazzaniga A, et al. Determination of the area of skin capable of being covered by 250 mg of 5% imiquimod cream. *Dermatol Surg.* 2004;30:784-786.
34. Flowers F. Imiquimod in the treatment of actinic keratoses and other intraepithelial neoplasms. *Int J Dermatol.* 2002;41(suppl 1):12-15.
35. Thai KE, Fergin P, Freeman M, et al. A prospective study of the use of cryosurgery for the treatment of actinic keratosis. *Int J Dermatol.* 2004;43:687-692.
36. Jorizzo J, Weiss J, Furst K, et al. Effect of a 1-week treatment with 0.5% topical fluorouracil on occurrence of actinic keratosis after cryosurgery: a randomized, vehicle-controlled clinical trial. *Arch Dermatol.* 2004;140:813-816.
37. Carrasco D, Vander Straten M, Tying SK. Treatment of anogenital warts with imiquimod 5% cream followed by surgical excision of residual lesions. *J Am Acad Dermatol.* 2002;47(suppl 4):S212-S216.
38. Stockfleth E, Christophers E, Benninghoff B, et al. Low incidence of new actinic keratoses after topical 5% imiquimod cream treatment: a long-term follow-up study [letter]. *Arch Dermatol.* 2004;140:1542.
39. Lee PK, Harwell WB, Loven KH, et al. Long-term clinical outcomes following treatment of actinic keratosis with imiquimod 5% cream. *Dermatol Surg.* 2005;31:659-663.