The Long-term Management of Actinic Keratosis: Treatment Options and Their Implications

Proceedings from a Clinical Dermatology Roundtable
Actinic keratosis (AK) is one of the most common skin conditions seen by dermatologists in clinical practice. AK most often results from chronic ultraviolet (UV) light exposure, usually from the sun. However, sunlamps and tanning lamps may also contribute to the development of AKs. AKs develop after the affected skin region becomes genetically altered and the natural immune surveillance of the skin is unable to contain all of the potential altered epidermal foci, which can progress to visible AK and possibly to squamous cell carcinoma (SCC). The process of genetically altering the epidermis occurs over several years and affects the skin diffusely in chronically exposed regions. Therefore, once the process begins, AK development is a progressive and chronic process, and visible AK lesions represent only the tip of the iceberg. Due to the chronic nature of AK, patients will often require multiple courses of therapy and long-term management. While individual, well-defined AK lesions may be treated in the office with an ablative modality, such as cryotherapy, it is often necessary to address a treatment field that is affected diffusely by both visible and subclinical AK lesions with a topical therapy. Available topical agents vary in terms of their mechanisms of action, extent of visible inflammation in the treatment field, and application schedules. Efficacy, tolerability, extent and duration of visible inflammation, and compliance are important factors when selecting a topical therapeutic option for patients.

Irritation and inflammation were once considered prerequisites for an effective topical treatment of AK. Clinical data from trials of diclofenac sodium 3% gel (Solaraze®, PharmaDerm, a division of Nycomed US Inc., Florham Park, New Jersey), however, suggest that AK can be effectively treated with a topical agent without much of the erythema and irritation associated with some other topical options. For some patients, such tolerability may outweigh the convenience of more rapid treatment, especially when AKs are located in more visible areas, which is very common.

In October 2008, a panel of leading dermatologists participated in a roundtable to discuss the best practices for long-term management of AK. The discussion included a brief review of AK epidemiology and pathogenesis and then concentrated on treatment issues. After a review of commonly used treatment modalities and a discussion of current treatment algorithms, the participants focused on the available clinical data for diclofenac sodium 3% gel. Finally, the clinicians discussed the implications of long-term management, especially regarding the importance of efficacy, tolerability, compliance, and patient satisfaction.
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Actinic Keratosis Prevalence is on the Rise

AK represents the second most common skin diagnosis seen by dermatologists, accounting for more than five million office visits annually and more than $900 million in healthcare costs each year in the United States. Lesions can often be diagnosed by their gritty, rough, or sandpaper-like texture. Visibly, they appear as skin-colored, pink, or red macules, often with superficial scaling or as thin or thick keratotic papules. Given their association with UV light exposure, AKs are most commonly noted on sun-exposed areas of the body, including the scalp, face, neck, dorsum of the hands, upper chest, shoulders, and forearms. AK lesions can also occur on both the cutaneous and mucosal surfaces of the lip.

It is recommended that AKs be treated because they exhibit the potential to progress to SCC. Histologically, AK lies on one end of a spectrum of epidermal cellular abnormalities whose range extends to SCC in situ and invasive SCC. Microscopically, AK is characterized by atypical keratinocytic proliferation in the epidermis, and while some lesions may regress without treatment, the risk of an individual lesion progressing to SCC is believed to be as high as 10 percent. Conversely, approximately 82 percent of SCC lesions were found to arise from, or be in close proximity to, an AK lesion. Equally concerning is the fact that the incidence of AK appears to be on the rise. It is important to recognize that in a given patient, an AK lesion serves as both a marker for the propensity of the individual to develop SCC in photodamaged skin and as a precursor lesion that may itself progress to SCC.

Medical and Ablative Therapeutic Options for Actinic Keratosis

A number of treatment options are available for the management of AK, and they can be classified as ablative or medical. Each treatment option has distinct advantages and disadvantages. Therefore, the option best suited for a patient is dependent on individual patient preferences, the lesion characteristics, and the clinical expertise of the treating physician. As will be discussed, in some cases treatment regimens can be used in tandem to increase efficacy while improving safety and tolerability profiles.

Ablative therapeutic options. Curettage (which may be followed by electrodessication) is sometimes used to treat isolated lesions, especially hyperkeratotic or refractory AKs. Additionally, a tissue sample of the removed lesion allows for histologic confirmation, especially in cases where the clinical diagnosis is unclear. In practice, however, liquid nitrogen cryotherapy (LN2) is the mainstay of ablative treatment options for AK. The efficacy and
safety of LN2 is generally regarded as being dependent on the amount of time the cryogen is applied to the skin. As there is no standardized approach to how LN2 is used to treat AK other than common utilization of the spray technique, application time varies among practitioners and is generally dependent on the size and thickness of the lesion.10

LN2 is a well-established treatment modality for AK, yet there is a relative dearth of prospective studies designed to evaluate both the efficacy and safety of the procedure. In a study by Thai et al,11 67.2 percent of lesions treated with LN2 demonstrated a complete response three months after treatment.11 The rates of response were dependent on the duration of freeze times with shorter freeze times associated with lower response rates. Of the lesions that demonstrated a complete response at three months, 29 percent were associated with hypopigmentation. Hyperpigmentation was documented in six percent of lesions and scar formation occurred in two percent of lesions. A majority (52%) of the cryosurgery procedures were associated with pain, stinging, or a burning sensation. Less common adverse events included erythema, edema, blistering, and infection.

LN2 is considered a lesion-directed therapy as opposed to a field-directed therapy. It is well suited for patients with a relatively few number of AK lesions (Table 1). Because treatment with cryotherapy targets individual lesions, use of LN2 does not address subclinical AK lesions in the treatment field and has no apparent impact on the development of new AKs over time. A study by Jorizzo et al12 demonstrated that more than 92 percent of patients treated with LN2 alone developed AK lesions within six months, suggesting a need for consistent follow up.12

Photodynamic therapy (PDT) is another nonsurgical, ablative therapy for treatment of AKs. PDT is applicable to treatment of individual lesions and, like other medical options, can also be used as a field-directed treatment covering a large number of lesions over a wide area of skin. PDT combines the use of a topical drug that induces the formation of photoactive porphyrins (PAPs) in the target cells. After time for the PAPs to partition into the desired subcellular structures, the treatment area is illuminated with light in a wavelength that reacts with the PAPs to cause tissue destruction. Two PDT systems are approved by the Food and Drug Administration (FDA) for treatment of AKs in the United States, one using 5-aminolevulinic acid (ALA) and blue light and one using methylaminolevulinate and red light. The efficacy of these two systems for treating AKs is similar and compares well to other medical options.13–15

Medical options. For the treatment of multiple AKs, a few topical therapies are available in the therapeutic armamentarium of clinicians. These field-directed treatments target a large number of lesions over a wide area of skin. Currently, three distinct topical therapies are approved for the treatment of AK-imiquimod, 5-fluorouracil (5-FU), and diclofenac sodium (Table 2). Their mechanisms of action suggest that at least two of these agents, diclofenac and imiquimod, rather than being purely destructive, actually address components of the underlying pathogenesis of AK.2 While each modality differs in its mechanism of action, safety profile, and tolerability, they share several common traits. Each drug regimen requires patient compliance entailing a regular application schedule. All of the topical therapies, as they are applied to an entire field of involvement (e.g., scalp, cheek, forehead, hand, dorsum), treat both currently visible lesions and also subclinical lesions, referred to as field-directed therapy. Although, each topical treatment has been associated with some degree of inflammation and may cause erythema, burning, and irritation in some patients, the predictability of visible inflammation and the degree of tolerability varies among the available topical agents.

The antineoplastic agent 5-FU has been used as a topical treatment for AK for decades and treats AK lesions by interfering with DNA and RNA synthesis.16,17,20 Topical 5-FU is available in a 5% cream and a 0.5% cream. Whereas
it is recommended that 5-FU 5% be applied twice a day based on FDA-approved labeling, 5-FU 0.5% cream was studied as a once-daily therapy for up to four-weeks duration in clinical studies and is FDA approved using this application frequency.\textsuperscript{16,17} Additionally, the 5-FU 0.5% is formulated using the microsphere (Microsponge\textsuperscript{®,} AMCOL Health & Beauty Solutions, Inc., Hoffman Estates, Illinois) cream vehicle.\textsuperscript{16} The 5-FU 0.5% is currently approved for the treatment of AK lesions on the face and anterior scalp.\textsuperscript{18} As its mechanism as a chemotherapeutic agent is via cytodestruction, topical 5-FU is associated with an anticipated, highly predictable, markedly visible, inflammatory reaction within the region of application. Associated signs and symptoms include frequent pain, erythema, erosions, and crusting. Changes in pigmentation and scarring have also been reported in some cases.\textsuperscript{17,20} Topical 5-FU is not indicated for use on mucosal areas.\textsuperscript{16,17} Patients should be advised that treatment with 5-FU results in an unsightly reaction both during treatment and for at least a few weeks following treatment.\textsuperscript{16,17}

Imiquimod 5% cream is approved for the treatment of AKs on the face and scalp.\textsuperscript{16} Imiquimod is an immune response modulator and functions by activating antigen-presenting cells, leading to stimulation of both the innate and acquired immune response of the host against the disease.\textsuperscript{16,21} Currently, the drug is indicated for application to the affected area twice a week for 16 weeks. A pair of Phase 3 clinical trials demonstrated that a 16-week course of imiquimod resulted in complete clearance of lesions in 45.1 percent of subjects.\textsuperscript{18} Treatment with imiquimod resulted in partial clearance (i.e., more than 75% of baseline lesions cleared) in approximately 59 percent of patients.\textsuperscript{18} The use of imiquimod on the lips and nostrils is not recommended in the FDA-approved product labeling.\textsuperscript{16} Local skin reactions during treatment with imiquimod are common and may include erythema, flaking, scaling, dryness, and scabbing/crusting.\textsuperscript{16,21} As with 5-FU, patients should be educated that they will likely experience some amount of visible inflammation at the application site, although the intensity of the inflammatory response is more variable and typically less uncomfortable as compared to what occurs with use of 5-FU.\textsuperscript{18} While the efficacy of imiquimod has been demonstrated, it can take up to 16 weeks for maximum efficacy to be seen with use of the FDA-approved application regimen. Topical imiquimod has also been studied for treatment of AK using a variety of regimens, which vary in application frequency and duration.

The third topical agent approved for the treatment of AK is diclofenac sodium 3% gel. While the mechanism of action of diclofenac sodium has not been fully elucidated, its efficacy for AKs is believed to relate to its ability to inhibit the cyclooxygenase-2 (COX-2) pathway, a cascade that appears to correlate with the presence of AK and SCC.\textsuperscript{22–24} Phase 3 clinical trials have demonstrated that diclofenac sodium is associated with a complete clearance rate of target lesions in 50 percent of patients and a complete clearance rate of cumulative lesions in 47 percent of patients.\textsuperscript{25} Diclofenac sodium is typically applied twice daily for 60 to 90 days.\textsuperscript{19} A Phase 4 trial demonstrated a 90-percent mean decrease in the number of AKs 30 days after completion of a 90-day course of

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<th>Table 2. Summary of Approved Topical Treatments for Actinic Keratosis\textsuperscript{16–18}</th>
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<td><strong>Imiquimod</strong> 5% cream</td>
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<td><strong>Treatment indication</strong></td>
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<td><strong>Application schedule</strong></td>
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<td><strong>Indicated for mucosal use</strong></td>
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<td><strong>Most common adverse events reported in pivotal trials (%)</strong></td>
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<tr>
<td><strong>Imiquimod</strong> 5% cream</td>
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<tr>
<td>Erythema (93%)</td>
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<tr>
<td>Dryness (83%)</td>
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<td>Burning (75%)</td>
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<td>Erosion (44%)</td>
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<td>Edema (35%)</td>
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* = Adverse-event data for 60-day use. † = Approved for use in 1970. Detailed safety data from pivotal trials unavailable.
treatment. Diclofenac sodium has no limitations on body area treated and appears well suited for treatment of mucosal and cutaneous lip lesions. In a recent study, 95 percent of patients treated with diclofenac sodium for AKs on their lips reported they would recommend the treatment to others with similar lesions.

While the recommended duration of treatment with diclofenac sodium can be up to 90 days, improvement in the number of lesions is seen throughout treatment, and in fact, has been shown to continue to improve through 30-days post-treatment. In clinical trials, diclofenac sodium gel has been well tolerated by patients. After 60 days of treatment, pain and pruritus at the application site were more frequent in vehicle-treated subjects than in those using diclofenac sodium. Interestingly, dermatologists report that some patients, and even some clinicians, misconstrue a lack of visible inflammation and/or absence of local side effects as an indication of decreased efficacy. Both clinicians and patients have come to adopt the “no pain, no gain” mentality based on experience over the years primarily with LN2 and/or 5-FU. Importantly, due to different mechanisms of action, it is possible to achieve efficacy for AKs without the presence of visible inflammation or side effects, as evidenced by outcomes with diclofenac sodium in clinical studies.

Differences in Mechanism of Action Among Topical Therapies for AK

The available FDA-approved topical agents for AK—5-FU, imiquimod, diclofenac—differ in the purported mechanisms of action that are believed to be operative for treatment of AK. With all three agents, available data demonstrate that the mechanisms of action allow for treatment of currently visible and subclinical lesions. These differences in mechanism of action appear to correlate with the anticipated type and intensity of visible inflammation and symptomatology and potential to induce high long-term clearance rates of AK. Topical 5-FU reduces AKs through a chemotherapeutic mechanism that is cytodestructive, accounting for its rapid onset of effect, relatively short duration of therapy (up to 4 weeks), predictable visible inflammatory reaction, and high rate of associated symptomatic discomfort. Topical imiquimod amplifies both innate and acquired immune response, explaining the variable intensity of visible inflammation among patients, which reflects therapeutic activity. The mechanism of action of imiquimod explains the variations in treatment regimens that have been suggested and the presence of a visible inflammatory response, which is typically associated with symptomatology that is not as severe as topical 5-FU. Topical diclofenac appears to reduce the presence and development of AKs by inhibiting the COX-2 pathway. This pathway has been shown to be up-regulated in AK and SCC lesions and is believed to correlate with the development and progression of these lesions. By inhibiting the COX-2 pathway, topical diclofenac blunts a signal that is believed to be a component of the drive to form AKs and potentially progress to SCC. The mechanism of action of topical diclofenac appears to explain its association with a longer duration of therapy and a significantly lower tendency to produce visible cutaneous inflammation and associated symptoms, especially as compared to other topical therapies for AK such as 5-FU.

Topical Diclofenac Sodium for the Treatment of Actinic Keratosis

Diclofenac sodium 3% gel (Solaraze®) has been approved for the treatment of AK since 2000. Diclofenac is believed to preferentially inhibit the COX-2 pathway, and appears to play a role in promoting apoptosis, modifying cell proliferation, and inhibiting angiogenesis. Previous studies have demonstrated that diclofenac sodium 3% gel is effective and well tolerated in the treatment of AK. Since other treatment options are more consistently associated with visible inflammation and local side effects, the initial studies with topical diclofenac sodium were encouraging and led to its evaluation for the treatment of AK.

Phase 3 trials of diclofenac sodium gel. Randomized, double-blind, pivotal trials were conducted to evaluate the efficacy and safety of diclofenac sodium 3% gel for treating AK with a total of 427 patients participating—213 receiving diclofenac sodium and 214 receiving a gel vehicle. In two studies, patients were treated with study med-
ication for 90 days and followed for 30 days post-treatment. In Study 1, Wolf et al. demonstrated that 50 percent of patients achieved 100 percent clearance of target lesions. More than three-quarters (77%) of patients demonstrated complete or significant lesion improvement. In the second Phase 3 trial, 80 percent of patients achieved cumulative clearance of AK lesions on their face and 63 percent of patients achieved cumulative clearance of AK lesions on their arms/forearms. A third pivotal trial differed in that subjects were randomized to 1 of 4 treatment groups (i.e., either vehicle or diclofenac sodium for either 30 or 60 days). After 60 days of treatment with topical diclofenac, 53 percent of patients experienced complete clearance of lesions on their faces. In the same study, while patients receiving diclofenac sodium 3% gel demonstrated higher rates of clearance (versus vehicle) in most anatomic areas evaluated, the results did not reach statistical significance. When all three trials were pooled, treatment with diclofenac sodium 3% gel was associated with higher rates of complete clearance than treatment with vehicle in all anatomic areas tested (Figure 1).

**Phase 4 trial with diclofenac sodium gel.** A Phase 4, multicenter, single-arm, open-label trial of diclofenac sodium 3% gel was conducted to further quantify efficacy. Subjects received a 90-day treatment with diclofenac sodium 3% gel and were evaluated at 30, 60, and 90 days as well as at a post-treatment follow-up visit at Day 120 (30 days post-treatment). Efficacy assessments included the Target Lesion Number Score (TLNS), the Cumulative Lesion Number Score (CLNS), and a qualitative efficacy measure, the Investigator’s Global Improvement Index (IGII).

Of the 76 patients entering the study, 67 completed the trial. Subjects demonstrated a steady decrease in mean TLNS and CLNS (a measure of target and new lesions in an area) starting at Day 30 and continuing through end of treatment (Day 90) and through 30 days post-treatment (Day 120). A 90 percent mean decrease in target lesions (i.e., TLNS) was recorded at Day 120 (Figure 2). As early as Day 30, a marked decrease in TLNS was observed. At Day 120, 85 percent of patients demonstrated a 75 percent clearance of target lesions while 58 percent demonstrated complete clearance of target lesions. The most common adverse events were dry skin, rash, and exfoliation, reported by 30 percent, 14 percent, and nine percent of subjects, respectively.

When following patients with AK, dermatologists are often faced with the challenge of trying to determine if a lesion that is evident several months/years after prior treatment is a new lesion or a previously “treated” lesion that has re-emerged. Given the postulated mechanism of action of topical diclofenac, clinicians have hypothesized that it may be effective at preventing new/recurring AK lesions long after a course of treatment has ended. As such, a Phase 4 extension study was conducted to evaluate the long-term therapeutic effects of diclofenac sodium gel 3% for AK at approximately one year after completion of
The results were presented at the 2009 Winter Clinical Dermatology Conference (January 16–21, 2009, Kohala Coast, Hawaii), and preparation of a manuscript for publication is forthcoming.

**Treating AK lesions on the lip.** The treatment of AK lesions on the lip can present a challenge to dermatologists. The lip is generally regarded as susceptible to inflammation and edema, and given its high visibility, scarring is considered a highly unacceptable outcome. As such, surgical treatments of AK on the lip are approached with marked caution and are often avoided. Topical treatment with imiquimod or 5-FU, while less invasive than cryosurgery, curettage, or laser ablation, are not FDA approved for mucosal surfaces, though they have been used anecdotally in selected cases. When applied to the vermilion area of the lip (visible mucosal area), the degree of inflammation may be very marked with topical imiquimod or 5-FU. This poses a potentially greater risk of scarring that is dependent on the intensity of the response, which is unfortunately unpredictable in each patient. Diclofenac sodium 3% gel has shown proven safety and efficacy for use on the lip and vermilion. A recent study by Nelson et al evaluated the efficacy of diclofenac sodium 3% gel on AK lesions of the upper and lower cutaneous and mucosal lip. In this open-label trial, subjects were treated with diclofenac sodium 3% gel twice daily for 90 days and followed up at Day 120 (30 days post-treatment). As with the Phase 4 study discussed above, efficacy was evaluated by TLNS, CLNS, and IGII scores. A total of 22 patients entered the study and 19 completed the study. Statistically significant mean percent decreases of target lesions were seen at Day 90 (67%) and Day 120 (85%). The percentage of subjects experiencing at least a 75-percent reduction in the number of target lesions increased from Day 30 through Day 120. Similarly, the percentage of patients experiencing complete clearance as assessed by both CLNS and TLNS increased at each post-baseline visit. By Day 120, all patients (20/20) were assessed as significantly improved or completely cleared by clinicians as measured by the IGII (Figure 3). Tolerability was highly favorable with only a mild-to-moderate inflammatory reaction observed in some patients during treatment, which tended to dissipate over time. There were no episodes of scarring or disfigurement observed as treatment sequelae. Patient acceptability of the use of topical diclofenac for AK of the lip was very high.

**Split-face AK trial.** The efficacy of the currently available topical treatments for AK has been demonstrated in multiple vehicle-controlled studies, but there is a conspicuous scarcity of head-to-head trials in which two active treatments are compared. A trial by Smith et al aimed to compare the efficacy and tolerability of 5-FU 5% cream and diclofenac sodium 3% gel utilizing a single-center, bilateral, open-label, evaluator-blinded methodology. The study enrolled 30 subjects, each with at least three AK lesions on each side of his or her face/scalp. Subjects were instructed to apply diclofenac sodium 3% gel to one side of their faces twice daily for 90 days. At Day 63, they were instructed to begin a twice-daily, 28-day regimen of 5-FU on the contralateral side of their faces such that at the end of the trial each patient received four weeks of therapy with 5-FU and 90 days of therapy with topical diclofenac sodium. At Day 120, 93 percent of patients receiving diclofenac and 100 percent of patients receiving 5% 5-FU were found to have at least a 66-percent clearance. Both treatments demonstrated similar lesion clearance rates 30 days post-treatment (5-FU: 98%; diclofenac: 89%). The two treatments, however, demonstrated marked differences in terms of tolerability (see figures on page 11). As will be discussed in more detail, topical diclofenac was associated with much lower rates of erythema, scaling, oozing/crusting, and edema and markedly higher rates of patient satisfaction when compared to 5-FU.

The safety and efficacy of diclofenac sodium 3% gel for the treatment of AK has been demonstrated in multiple
trials. Clearance rates appear to increase over time with available data supporting a 90-day course in many patients. As previously stated, further data regarding the long-term efficacy of topical diclofenac for AK were presented at the 2009 Winter Clinical Dermatology Conference (January 16–21, 2009, Kohala Coast, Hawaii) and preparation of a manuscript for publication is forthcoming.

**Current Guidelines/Algorithms for Long-Term Management of Actinic Keratosis**

It is only over the last decade that AK treatment options available to clinicians and patients have extended beyond topical 5-FU and surgical procedures. These treatment options come at a time when the prevalence of AK is on the rise. However, with the advent of new treatment options also comes the potential for confusion among clinicians regarding selection of therapy. With an increasing availability of data from prospective, randomized, clinical trials, several treatment guidelines and algorithms have emerged to assist physicians in choosing an appropriate treatment regimen for their patients. At this time it is impossible to develop one set of guidelines or recommendations for all patients with AK, although treatment guidelines attempt to assist clinicians in making rational therapeutic decisions. The roundtable discussion of these guidelines as well as the presentation of new clinical data resulted in a number of excellent treatment suggestions by the leading dermatologists attending the meeting.

**British Association of Dermatologist Guidelines.** In 2007, the British Association of Dermatologists published guidelines for the management of patients with AK. The authors evaluated available data on all of the available therapies for AK. They concluded that 5-FU is an effective treatment although they noted that the consistency of anticipated application site side effects often require that less aggressive application schedules be used. The authors observed that topical imiquimod, while having demonstrated efficacy, also commonly induces a marked inflammatory response with side effects similar to that reported with 5-FU, although the severity of associated symptoms is less. Diclofenac sodium 3% gel was found to offer efficacy combined with a higher degree of tolerability than other topical therapy options. LN2 was judged to be superior to PDT for the treatment of thick AK lesions, although it carries risks of hypopigmentation and scarring. The cost implications of PDT treatment, inclusive of physician, staff, drug, equipment, and time-related expenses, may prove prohibitive. Finally, while controlled studies of curettage or excisional surgery are lacking, these approaches were found to be of value when histological evaluation is warranted (e.g., refractory lesions, hypertrophic AK).

**Current treatment practices.** When analyzing the current state of AK treatment, Warino et al observed that despite the proven efficacy and safety of newer topical therapies, LN2 remains the standard of care for the management of AK. However, the British Association of Dermatologists supports the use of topical medications...
in cases where multiple superficial AK lesions are present and medical providers support that these cases represent the most common use of topical medications.\textsuperscript{2,30} Medical providers advise that in some cases therapy with 5-FU can be “temporarily disfiguring” and are associated with application site reactions that can persist for weeks.\textsuperscript{30}

During the roundtable discussion at the 2008 27th Anniversary Fall Clinical Dermatology Conference™, dermatologists related that their experiences mirrored much of the available data and treatment recommendations. They reported that PDT, while effective, is often reserved for use in immunosuppressed patients or those patients with multiple hyperkeratotic lesions on the extremities, although efficacy for hypertrophic AK has not been proven to be greater with PDT. In addition to an elevated cost, clinicians expressed concern that the treatment protocol for AK with PDT has not been standardized. Similarly, concern about the standardization of LN2 technique exists. The panelists agreed that there has been no reliable formal study regarding the length of time the cryogen should be applied to the skin, and that there is wide variability among clinicians in techniques used to apply LN2 for AK. In fact, each clinician may randomly vary their own technique from lesion to lesion or patient to patient.

Of the topical therapies available for AK, the roundtable panel expressed that diclofenac sodium 3% gel is the least irritating, the best tolerated, and associated with the fewest number of patient concerns during treatment. The panel also stressed the importance of setting appropriate patient expectations before beginning any topical therapy treatment. These expectations should include efficacy, the magnitude of possible side effects, and the timing of both inflammation and resolution of the lesions. Attendees suggested that even after seemingly comprehensive patient education, some patients are invariably surprised by the extent of inflammation experienced with topical 5-FU and imiquimod.

In cases where the side effects of treatment become visibly and/or symptomatically intolerable, clinicians reported that they sometimes lessen the frequency of application of topical therapies, but that such modifications may prolong the necessary duration of therapy and may potentially reduce efficacy. The roundtable panel also stressed that due to the long history of experience with 5-FU and its associated side effects, many clinicians and patients inherently believe that visible inflammation is a necessary component of effective treatment of AK. However, the predictability and intensity of visible inflammation that develops is largely related to the mechanism of action of the individual drug. Importantly, the body of evidence that demonstrates topical diclofenac is able to effectively treat AK without associated intense visible inflammation dispels this contention and offers, in certain situations, a more “user friendly” option for the treatment of patients with AK.

There is relatively little data available regarding the
long-term efficacy of treatments for AK. Data from short-term trials indicate that all approved treatments for AK will result in significant reduction in lesions a month or so after treatment, leaving tolerability as the differentiating factor. It is interesting to note that in a recent trial by Krawtchenko et al, 31 subjects were screened one year after treatment with 5% 5-FU cream, cryosurgery, or imiquimod 5% cream. Of patients demonstrating clinical clearance shortly after therapy ended, only six percent of patients treated with LN2 and 35 percent of the patients treated with 5-FU sustained clearance one year after therapy ended. Long-term results with topical imiquimod were superior to 5-FU. The results of the study clearly indicate that patients with AK, even those that respond well to therapy initially, will often need additional treatment in the future. This is especially true when patients are initially treated with options that are more ablative in nature. It is therefore important that clinicians consider the tolerability of the therapies they prescribe for the treatment of AK. Another very important consideration is that topical therapies allow for “field treatment” and therefore address therapy for both currently visible and subclinical AKs. Ablative therapies, such as LN2 and curettage, only address the individual lesions and do not suppress the emergence of AK from subclinical lesions present in the surrounding area.

**Sequential therapy.** Treatment of AKs need not rely only on monotherapy. Patients with multiple lesions are candidates for sequential therapy in which both LN2 and topical therapies are used consecutively on the same patient. Sequential therapy allows clinicians to treat well-demarcated lesions with LN2 and subsequently treat a field of diffuse lesions using topical therapy. The consensus of the panel was that sequential therapy is a useful option when a patient presents with multiple lesions and some of those lesions are particularly amenable to LN2 (e.g., thick lesions).

In a trial conducted by Berlin and Rigel, subjects had all AK lesions contained within a given target area treated with LN2. Half of the study population had no further treatment while half received diclofenac sodium 3% gel for 90 days (beginning 15 days after LN2; when patients had healed). A considerably greater percentage of subjects receiving sequential therapy achieved 100-percent cumulative clearance at the end of the study (Day 135) compared to patients receiving LN2 alone (46% versus 21%) (Figure 4). Additionally, the rate of complete target clearance was twice as high (64%) in the sequential treatment group when compared to the group receiving LN2 alone (32%) (Figure 4). These data, in addition to other measures, suggest that sequential therapy with LN2 and topical diclofenac is more efficacious than LN2 alone (Table 3). Sequential therapy of LN2 followed by diclofenac sodium 3% gel appears to lead to an additive effect that results in more effective treatment of clinical and subclinical lesions than LN2 alone.
Actinic keratosis (AK) is a chronic disorder. It is important that patients are educated that optimal treatment requires periodic, long-term followup and that intermittent courses of treatment may be needed as new AK lesions emerge over time. The goal is prevention of invasive SCC, and early detection should progression to SCC occur.

As AKs are present predominantly in visible areas, the extent and intensity of visible treatment reactions, such as edema and blistering with cryotherapy (LN2) or erythema and crusting with topical 5-fluorouracil (5-FU) or imiquimod, are very important considerations with regard to ultimate treatment selection for each patient. Patients need to be aware up front of the likely visible reactions to treatment and associated symptomatology before consenting to whatever treatment is chosen.

Sequential treatment of AKs is commonly used in clinical practice. This approach, which typically combines use of LN2 with a topical agent, provides the advantages of additive therapeutic benefit, more immediate treatment of currently visible AKs with ablative therapy, and “field treatment” of both visible and subclinical AKs.

Patients with AK usually present with multiple lesions and frequently return with additional AKs months to years later. Patients are more likely to repeat a treatment if they find it to be both effective and well tolerated.

In the past, 5-FU was the only available topical treatment for AK. The extended duration of topical 5-FU or imiquimod are very important considerations with regard to ultimate treatment selection for each patient. Patients need to be aware up front of the likely visible reactions to treatment and associated symptomatology before consenting to whatever therapy is chosen.

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Considerations in Long-Term Management of Actinic Keratosis

The management of AK is rarely limited to a single office visit. Long-term treatment and management of the condition is usually necessary. In practice, patient satisfaction with a given treatment may be based on a number of factors including efficacy and tolerability of the treatment as well as how closely the drug meets patient expectations.

Patient expectations and education can help increase compliance. Patient adherence to a treatment regimen can be influenced by their understanding of the disorder being treated as well as their expectations regarding the treatment. It is important that patients understand that the presence of AK is a marker of diffuse photodamage, which contributes to future development of skin cancers as well as photoaging.

Patients should be advised that the emergence of new lesions does not indicate a failure of previous treatment. Rather, emergence of new AKs over time represents progression of the underlying disease process occurring within their skin. The genetics of their skin have been fundamentally altered over time due to years of cumulative UV light exposure. Furthermore, patients should be counseled that subclinical lesions may become visible when treatment with topical therapies is initiated.

**Tolerability and compliance.** The consensus of the roundtable panel was that, of the three topical therapies approved for use in treating AK, topical diclofenac exhibits a more favorable tolerability profile compared with other topical pharmacological agents for AK. High compliance rates have been demonstrated in clinical trials with topical diclofenac for AK. After 90 days of twice-daily treatment in a Phase 4 study, 75 percent of subjects reported missing six or less applications of the drug.

In a recent clinical trial, 100 percent of the 244 patients randomized to receive treatment with topical diclofenac for 90 days that completed the 135-day trial had compliance rates of at least 85 percent as assessed by patient diaries.

In addition to demonstrated efficacy and safety, diclofenac sodium 3% gel is also associated with high rates of patient satisfaction. In one clinical trial, 84 percent of patients were satisfied with topical diclofenac use overall after 90 days of twice-daily application for lip lesions. Similarly, 95 percent of patients reported they
would recommend topical diclofenac to others with the same type of lip lesions. When patients were treated with diclofenac sodium 3% gel and 5-FU 5% cream in a split-face study, both demonstrated substantial efficacy, but patients reported higher levels of satisfaction with topical diclofenac. In the same study, there was a marked difference in tolerability between the two treatments. On the side of the face treated with diclofenac sodium 3% gel, only 27 percent of patients were observed to have moderate or severe erythema compared to more than 80 percent of patients found to have moderate or severe erythema on the facial side treated with 5-FU (Figure 5). Similarly, treatment with diclofenac sodium 3% gel was associated with lower rates of moderate or severe edema than 5-FU (Figure 6). Diclofenac sodium 3% gel caused far less visible inflammation and associated symptomatology than 5-FU 5% cream despite a longer duration of therapy (Figures 7a and 7b).

Conclusion and Consensus of the Roundtable Panel

AK is a chronic condition that requires long-term management. Compliance is a very compelling issue when treating AK. Efficacy and tolerability must be taken into consideration when recommending treatment. Patients should not only be educated about the nature of the disease and the need for treatment, but should also be made aware of the visible reaction and associated symptoms that they are likely to encounter during treatment, especially those which are more predictable, as with topical 5-FU.

Several topical treatments have demonstrated efficacy at reducing AK lesions, but they differ markedly in their side effect and tolerability profiles and application schedules. Diclofenac sodium 3% gel has far greater tolerability than other topical agents and provides comparable efficacy rates based on available studies. The differences in tolerability among topical therapies for AK can impact patient satisfaction and long-term patient compliance with current and future treatment regimens. Additionally, topical therapies, such as diclofenac, 5-FU, and imiquimod, may be combined with ablative treatment, such as LN2, to achieve additive benefit. This combination approach allows for more immediate treatment of currently visible lesions and addresses management of subclinical AK lesions in the surrounding field of involvement.

References


A photocarcinogenicity study with up to 0.035% diclofenac in the Solaraze® vehicle gel was sodium and 2.5% hyaluronate sodium in albino mice. Applications of diclofenac sodium gel for 2 years at concentrations up to 0.035% diclofenac did not appear to be any increase in drug-related neoplasms following daily topical administration. Application of dermatologic products such as sunscreens, cosmetics, and other drug products was not permitted. Patients were instructed to apply a small amount of Solaraze® Gel (approximately 0.5 g) onto the affected skin, using their fingers, and gently smoothing the gel over the lesion. In addition, all patients were instructed to avoid sun exposure. Complete clearing of the AK lesions 30 days after completion of treatment was the primary efficacy variable. No long-term patient follow-ups, after the 30-day assessments, were performed for the detection of recurrence.

| Complete Clearance of Actinic Keratosis Lesions 30 Days Post-Treatment (all locations) |
|---------------------------------|-----------------|------------------|
| Solaraze® Gel                  | Vehicle         | p-value          |
| Study 1 90 days treatment      | 27/58 (47%)     | 11/59 (19%)      | <0.001 |
| Study 2 90 days treatment      | 18/53 (34%)     | 10/55 (18%)      | 0.061  |
| Study 3 60 days treatment      | 15/48 (31%)     | 5/49 (10%)       | 0.021  |
| Study 3 30 days treatment      | 7/49 (14%)      | 2/49 (4%)        | 0.221  |

**CONTRAINDICATIONS** Solaraze® (diclofenac sodium) Gel is contraindicated in patients with a known hypersensitivity to diclofenac, benzyl alcohol, polyethylene glycol monomethyl ether 350 and/or hyaluronate sodium.

**WARNINGS** As with other NSAIDs, anaphylactoid reactions may occur in patients without prior exposure to diclofenac. Solaraze® diclofenac sodium gel should be given with caution to patients with the aspirin triad. The triad typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs.

**PRECAUTIONS** General Solaraze® (diclofenac sodium) Gel should be used with caution in patients with active gastrointestinal ulceration or bleeding and severe renal or hepatic impairments. Solaraze® should not be applied to open skin wounds, infections, or exfoliative dermatitis. It should not be allowed to come in contact with the eyes.

**Information for Patients** In clinical studies, localized dermal side effects such as contact dermatitis, exfoliation, dry skin and rash were found in patients treated with Solaraze® at a higher incidence than in those with placebo. If severe dermal reactions occur, treatment with Solaraze® may be interrupted until the condition subsides. Exposure to sunlight and the use of sunlamps should be avoided. Safety and efficacy of the use of Solaraze® together with other dermal products, including cosmetics, sunscreens, and other topical medications on the area being treated, have not been studied.

**Drug Interactions** Although the systemic absorption of Solaraze® is low, concomitant oral administration of other NSAIDs such as aspirin at anti-inflammatory/analgesic doses should be minimized.

**Carcinogenesis, Mutagenesis, Impairment of Fertility** There did not appear to be any increase in drug-related neoplasms following daily topical applications of diclofenac sodium gel for 2 years at concentrations up to 0.035% diclofenac sodium and 2.5% hyaluronate sodium in albino mice. A photocarcinogenicity study with up to 0.035% diclofenac in the Solaraze® vehicle gel was conducted in hairless mice at topical doses up to 2.8 mg/kg/day. Median tumor onset was earlier in the 0.035% group (Solaraze® contains 3% diclofenac sodium).

Diclofenac was not genotoxic in in vitro point mutation assays in mammalian mouse lymphoma cells and Ames microbial test systems, or when tested in mammalian in vivo assays including dominant lethal and male germinal epithelial chromosomal studies in mice, and nucleus anomaly and chromosomal aberration studies in Chinese hamsters. It was also negative in the transformation assay utilizing BALB/3T3 mouse embryo cells.
In the treatment of multiple actinic keratosis (AK) lesions

Prescribe a Powerful Force
and watch AKs disappear

SOLARAZE® Gel starts strong and stays strong with continuous improvement

★ Significant improvement in the first 30 days of a phase 4, multicenter study1
★ 90% mean decrease in target lesions at Day 120 (follow-up 30 days posttreatment) vs baseline1
★ Well-tolerated therapy—most related adverse events were mild to moderate in severity1

SOLARAZE® GEL
diclofenac sodium-3%

Starts strong. Stays strong.

SOLARAZE® Gel is indicated for the topical treatment of actinic keratoses (AK).

Selected Safety Information

SUN AVOIDANCE IS INDICATED DURING SOLARAZE® GEL THERAPY. As with other NSAIDs, anaphylactoid reactions may occur in patients without prior exposure to diclofenac. Diclofenac sodium should be given with caution to patients with the aspirin triad. The triad typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs. In clinical trials, the most common adverse reactions involved the skin and included contact dermatitis, rash, dry skin and exfoliation. The majority of these reactions were mild to moderate in severity, and resolved upon discontinuation of therapy. SOLARAZE® Gel should be used with caution in patients with active gastrointestinal ulceration or bleeding and severe renal or hepatic impairments. SOLARAZE® Gel should not be applied to open skin wounds, infections, or exfoliative dermatitis. It should not be allowed to come in contact with the eyes. The safety of concomitant use of sunscreens, cosmetics or other topical medications and SOLARAZE® is unknown.

Please see adjacent page for Brief Summary of full Prescribing Information.


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