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Current Regimens and Guideline Implications for the Treatment of Actinic Keratosis: Proceedings of a Clinical Roundtable at the 2011 Winter Clinical Dermatology Conference

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United States guidelines for the treatment of actinic keratosis (AK) are out of date. A consensus roundtable of 5 thought leaders in dermatology was held in January 2011 to review US and European guidelines and glean from them what seems current and clinically applicable in the management of AK, and subsequently recommend what therapies may need to be added. Current AK treatments, including sequential therapy of various treatment options, and any new agents in development were also taken into consideration.

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The American Academy of Dermatology (AAD) guidelines for the treatment of actinic keratosis (AK) were published in 1995 to create a fundamental reference that could be applied to clinical practice.[1] Other AK guidelines from Europe and Australia subsequently have been published and include current treatment options as well as more relevant thoughts on treatment algorithms. Recently, the AAD proposed adoption of the 2007 British Association of Dermatologists (BAD) guidelines along with a companion document that was to include 6 qualifications. After input from AAD members, including a letter of objection signed by 17 dermatologists who are well-recognized leaders in the field of nonmelanoma skin cancer (NMSC), the AAD decided to abandon this idea. Members of the AAD raised concerns of the following aspects of the BAD guidelines[2]: (1) exclusion of imiquimod cream 3.75%; (2) exclusion of aminolevulinic acid (ALA) with photodynamic therapy (PDT); (3) treatment of AK by primary care clinicians

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(often recommended by the United Kingdom healthcare system); and (4) retention of language that suggests "no treatment" of AKs is sometimes appropriate.

At the Winter Clinical Dermatology Conference in Hawaii in January 2011, 5 thought leaders in dermatology convened for a roundtable to discuss current regimens and guideline implications for the treatment of AK. The roundtable panelists included:

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  Valley Hospital Medical Center
  Las Vegas, Nevada
- Roger I. Ceilley, MD (Panelist)
  Clinical Professor of Dermatology
  University of Iowa Department of Dermatology
  Iowa City
- Mark G. Lebwohl, MD (Panelist)
  Professor and Chairman, Department of Dermatology
  Mount Sinai School of Medicine
  New York, New York
- Stephen K. Tyring, MD, PhD, MBA (Panelist)
  Clinical Professor, Departments of Dermatology, Microbiology/Molecular Genetics, and Internal Medicine
  University of Texas Medical School at Houston
- John E. Wolf Jr, MD, MA (Panelist)
  Professor and Chairman, Department of Dermatology
  Baylor College of Medicine
  Houston

The roundtable panel reviewed various global AK treatment guidelines, the relevance of the guidelines in the US market, and the impact of the guidelines on clinical decisions. This article is a synopsis of the roundtable proceedings.

Actinic Keratosis Guidelines: Pros and Cons

Given the increasing incidence of AKs worldwide and the possibility of progression to squamous cell carcinoma (SCC), it is important for clinicians to be aware of and consider suitable treatment algorithms for AKs. The most recent AK treatment guidelines from the AAD were published in 1995.[1] These guidelines were written prior to the development of topical therapies such as imiquimod cream and diclofenac gel and therefore focused largely on ablative therapies and 5-fluorouracil (5-FU).

Conspicuously absent from the published guidelines is the issue of adherence to treatment. Some of the available treatments of AK are associated with physical discomforts such as burning, pruritus, and visible inflammation. Also absent from the guidelines is the important issue of duration of remission after medical procedures and topical treatments. Additionally, the 1995 guidelines lack the distinction and relationship between lesion-directed and field-directed treatments.

The dermatologists' armamentarium of options for the treatment of AK has expanded since the AAD guidelines of 1995. For instance, imiquimod cream 5% did not receive the indication for the treatment of AK until January 2005, the role of PDT was recognized in 2004, 5-FU cream 0.5% was approved in 2000, and diclofenac gel 3% was approved for AK treatment in 2000.[3] Also excluded from the AAD guidelines was further analysis of prospective data examining cryosurgery, which demonstrated that only 67.2% of treated AKs exhibited complete response.[4] Previously, cure rates were assumed to approach 99.0%, despite the lack of data substantiating this perception. In addition, although the AAD guidelines of 1995 recognized that immunosuppression was a risk factor for the development of AK, they did not specify management recommendations for immunocompromised patients such as organ transplant recipients.

In 2007, Krawtchenko and colleagues[5] compared cryosurgery to topical AK therapy. An important outcome of the study was that many lesions either did not clear or recurred after treatment with cryosurgery. The clinical clearance rate at 6 weeks after cryosurgery was 68%. This outcome, which is lower than many would predict, also seemed to be predictive of the low long-term clearance rate evaluated 1 year later, with only 28% of AKs that initially were responsive to cryosurgery remaining clear. In addition to lesion clearance, it is important to consider the cosmetic outcome of cryosurgery, as dyspigmentation, usually presenting as hypopigmentation, is a common sequela.[5]

The 2006 European Dermatology Forum guidelines explored the more recent concept of field cancerization, which addresses newer topical therapies as well as approaches to PDT.[6] The role of human papillomavirus (HPV) also was reviewed; the consensus of most virologists and dermatologists was that HPV may play a prominent role in AK development in certain immunocompromised patients and organ transplant patients. Additionally, in patients with the hereditary disorder epidermodysplasia verruciformis, the association between special cutaneous HPV types and the development of NMSC is well-established.[7] These findings demonstrate that, along with UV, there is a putative

role of HPV infection as a cocarcinogen in the pathogenesis of SCC including AK, at least in certain population subsets.[8]

Although the BAD guidelines for the management of AK were published in 2007, they were based on pre-2005 data. The BAD guidelines make minimal reference to sequential therapy and its potential role in the management of AK. They also suggest that when faced with a patient with mild thin AKs, it is appropriate to consider not treating the lesions, an approach that is controversial.[9]

The specifics of the 2008 treatment algorithm of the European Skin Academy bring the guidelines to a more current state and take into consideration lesion-directed versus field-directed treatment regimens (Figure 1).[10] For patients with solitary or few lesions, initial therapy is lesion directed. For patients with multiple AKs or suspected subclinical lesions, field-directed therapy is recommended. The order of topical therapy shown in Figure 1 is the order that is recommended. The algorithm specifically mentions that field-directed therapies can be used sequentially with lesion-directed therapies. Stockfleth and colleagues[10] presented recommendations for the treatment of AKs in "special situations" (eg, AK of the lower lip), at high risk for progression to SCC, or occurring in immunocompromised patients, all of which were lacking in prior guidelines. When discussing immunosuppressed patients, the authors referred to organ transplant recipients and patients with human immunodeficiency virus.[10]

Absent from the European guidelines is compliance and duration of remission. Cryosurgery and 5-FU may not be as effective long-term as some of the other treatments because of the relatively low remission rates that have been noted.[5] Finally, the guidelines discourage the role of observation, stressing that all AK lesions should be treated.[10] Immunocompromised patients, such as organ transplant recipients, are at particular risk for the development of AKs and invasive SCC. Recommendations in the 2008 treatment algorithm suggest that topical therapy with diclofenac gel 3% is safe and effective for the treatment of AK in this population.[10]

The Australian guidelines for the management of NMSC also were published in 2008.[11] Discussion of sequential therapy is minimal with specific mention of the role of 5-FU to highlight subclinical AKs prior to cryosurgery as well as the sequential use of diclofenac and cryosurgery for the treatment of hypertrophic or treatment-resistant lesions. The guidelines include a complete discussion of topical treatments of NMSC and a large section in which the treatment of NMSC in immunosuppressed patients is reviewed.[11]

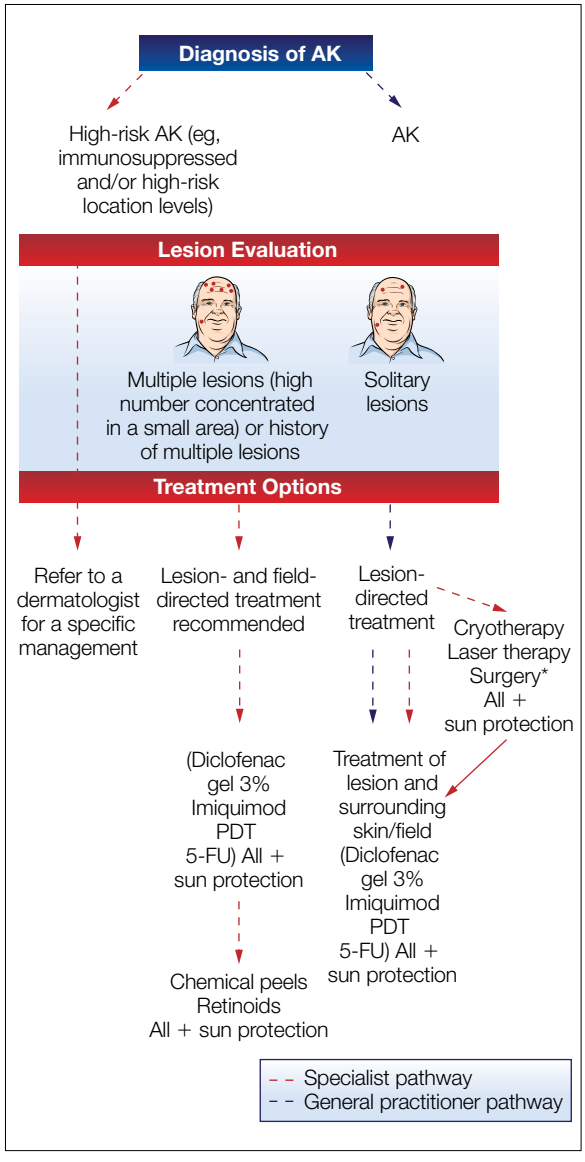

Figure 1. Actinic keratosis (AK) treatment algorithm (2008) of the European Skin Academy. PDT indicates photodynamic therapy; 5-FU, 5-fluorouracil. Asterisk indicates histologic investigation is recommended before surgery. Adapted with permission from Stockfleth et al.[10]

Most recently, at the end of 2009, the Italian guidelines were published.[12] These treatment recommendations were based on published data as well as the clinical experience of the authors. In the discussion of the pathogenesis of AK, the role of cyclooxygenase 2 is highlighted. The Italian guidelines stress the potential benefits of field-directed therapy. They point out that sequential therapy may assist in optimizing the outcome depending on

the clinical scenario. It is worth noting the absence of suggested treatment with topical 5-FU 5%, as it is not available in Italy. The Italian guidelines recommend cryosurgery as first-line treatment of lesion-directed AKs that are hyperkeratotic. For field-directed AKs that are not hyperkeratotic, the Italian guidelines recommend diclofenac gel 3% first line. The algorithm differentiates between pigmented lesions and nonpigmented lesions. A prime difference between the treatments of these 2 types of lesions is the avoidance of PDT when treating pigmented lesions.[12]

Current clinical practices in the United States mirror recent European treatment recommendations. When applicable, most dermatologists in the United States use cryosurgery for lesion-specific treatment. For field-directed therapy, dermatologists rely on topical agents. However, the prevailing opinion suggests that existing European guidelines cannot be adopted en bloc.

The thought leaders present at the Winter Clinical Dermatology Conference AK roundtable all agreed that new US guidelines are needed. In the short-term, a possible compromise would be to bring clinicians up-to-date on AK pathogenesis and to develop formal recommendations for sequential therapy (Figure 2).

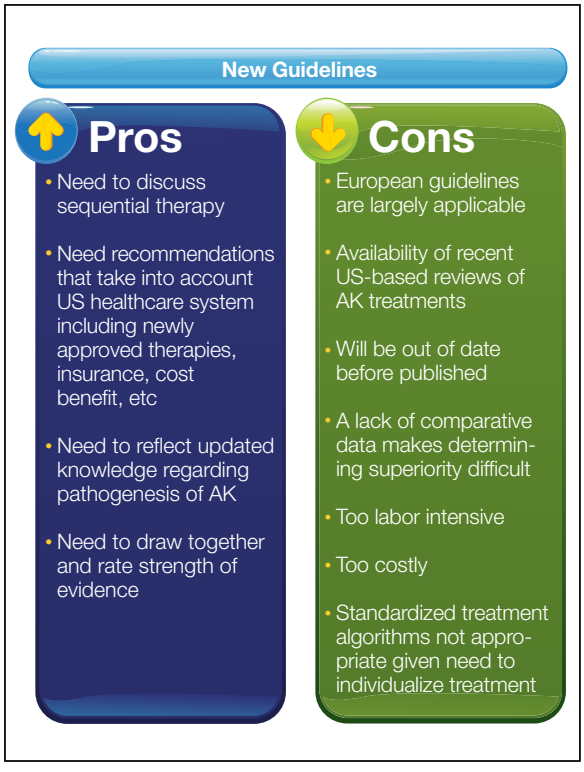

Figure 2. The pros and cons of new US guidelines for the treatment of actinic keratosis (AK).

Sequential Therapy and Its Role in Clinical Practice

The available treatment guidelines, particularly older published guidelines, tend to stress the role of monotherapy for the management of AK. Target lesion–directed procedures often were recommended for solitary AKs, while field-directed therapy was reserved for the treatment of multiple AKs. In clinical practice, however, sequential therapy often is employed.[13] A large part of the therapeutic decision deals with compliance and tolerability. It recently has been proposed that sequential therapy become the standard of care for patients at risk for multiple AKs and SCC.[14] Field-directed therapy offers a number of potential benefits over lesion-directed therapy, particularly the potential to treat subclinical lesions. Lesion-directed therapies are inappropriate for large areas, while topical therapy may be less effective for hyperkeratotic AKs. The use of sequential therapy provides for modifications of the treatment regimen (Figure 3).

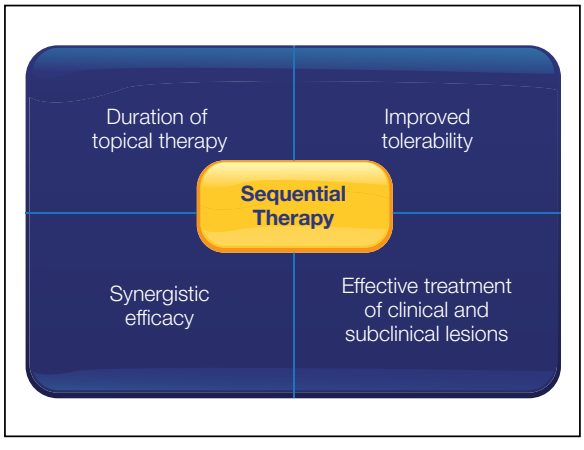

Figure 3. Theoretical benefits of sequential therapy for actinic keratoses. Synergistic means that the efficacy of the sequential treatment exceeds either therapy alone, which may be an incremental or additive increase regarding actinic keratosis lesion reduction.

Sequential therapy for AK can be divided into 2 broad groups. Target lesion–directed therapy, which is performed before field-directed therapy, theoretically reduces the AK burden prior to field-directed application, potentially reducing the severity of local skin reactions. Field-directed therapy also may catch any subclinical AKs missed by lesion-directed therapy. Conversely, topical field-directed therapy prior to lesion-directed therapy may allow for visual identification of those lesions, enabling the clinician to use a lesion-directed

modality as needed.[15,16] For particular patients, sequential therapy may be done in 3 stages. The first stage is cryosurgery for the hypertrophic lesions followed by topical field-directed therapy. After an appropriate period, the patient returns for additional cryosurgery, as needed. This practice, known as triple F (freeze, field therapy, freeze), is widely used based on anecdotal reports from dermatologists. Because AKs are more difficult to eliminate than most clinicians realize, many clinicians may be fooled when they freeze lesions and then need to freeze another collection of lesions when the patient returns for follow-up 6 months to 1 year later.

Many studies have investigated the safety and efficacy of sequential therapy. The concept of using 5-FU to identify subclinical lesions and then treat them with cryosurgery is not new. A major study examined the efficacy of cryosurgery with and without 1 week of pretreatment with 5-FU cream 0.5%.[17] In both treatment groups, cryosurgery and either vehicle or 5-FU resulted in significant reductions in facial AKs ($P<.001$). However, most participants developed new lesions in the treatment area after 6 and 12 months of follow-up. Application-site reactions were more common among participants receiving 5-FU.[17]

Two AK treatment regimens combining cryosurgery and diclofenac gel have been described.[18,19] In the first, lesion-directed therapy with cryosurgery was performed prior to a course of diclofenac gel.[18] Participants with at least 5 AKs in target areas on the forehead, scalp, hands, or face were randomized to receive treatment of all lesions by cryosurgery followed by either no additional therapy (n=277) or a 90-day course of diclofenac gel 3% twice daily (n=244). Diclofenac gel was started 15 days postcryosurgery. At day 135, approximately two-thirds of participants who received both cryosurgery and diclofenac gel demonstrated 100% target lesion clearance compared with only one-third of participants treated with cryosurgery alone. The mean reduction in target AKs was 68% in the cryosurgery-only treatment group and 89% in the sequentially treated group. Substantial improvements in cumulative lesion reduction also were observed, suggesting that diclofenac gel effectively treated subclinical AKs. Despite a 90-day course of topical therapy with diclofenac gel, compliance did not appear adversely impacted, with all participants reporting greater than 85% compliance and most reporting 100% compliance.[18]

A 2009 study looked at the benefits of therapy with diclofenac gel 3% prior to cryosurgery.[19] Participants with a history of recurrent AKs following cryosurgery and 5 or more AKs on their scalp, face, and/or arms were instructed to apply diclofenac gel 3% twice daily for 12 weeks. All residual lesions were treated using cryosurgery. Prior to cryosurgery, complete clearance was exhibited by 71% (21/29) of participants. The remaining participants were treated with cryosurgery to treat residual lesions. Following therapy, participants demonstrated a mean lesion-free period of 10 months (range, 6–20 months). Adverse events were mild and did not result in treatment discontinuation. The findings support a potential role of sequential treatment of diclofenac gel 3% followed by cryosurgery in the management of patients with multiple and recurrent AKs.[19]

The role of sequential therapy with cryosurgery and imiquimod also has been evaluated. Enrolled participants with 4 or more AKs on the face or balding scalp in an area 50 cm^2 or less were treated with cryosurgery.[20] Participants were randomized to receive imiquimod cream 5% or vehicle twice weekly for 8 weeks in a double-blind fashion. At week 22, participants could opt for treatment with cryosurgery or imiquimod following cryosurgery of target AKs, or to receive no further treatment. As assessed by rates of complete clearance at week 22, imiquimod therapy was associated with a numerically greater clearance of total, new, and target AKs, but these differences did not reach statistical significance. At week 22, cryosurgery followed by imiquimod resulted in a mean 79.3% reduction in target lesions compared with 76.0% among participants treated with cryosurgery and vehicle.[20]

To examine the safety and efficacy of cryosurgery followed by imiquimod cream 3.75%, a recent randomized, double-blind, placebo-controlled trial was conducted among adults with 10 or more facial AKs.[21] At least 5 AKs were treated with cryosurgery (mean AKs treated, 7) while at least 5 were left untreated (mean AKs untreated, 9). Participants were allowed a 1- to 2-week healing period before returning to the study site where they were randomized to topical treatment with either imiquimod cream 3.75% (n=126) or placebo (n=121). Topical therapy was applied once daily for 2 weeks followed by a 2-week no treatment period and then a second 2-week treatment cycle. The sequential use of cryosurgery and imiquimod cream 3.75% was associated with an 86.5% median reduction in total AK count compared with 50% in the cryosurgery and placebo treatment group at week 26 ($P<.0001$). At week 26, 30.2% of participants who received imiquimod exhibited complete clearance of all AKs compared with 3.3% of placebo-treated participants. Local-site reactions, particularly severe reactions, were

considerably more common among participants treated with imiquimod cream 3.75%.[21]

Photodynamic therapy also can be used in sequential therapy with topical field-directed AK treatments. A split-face study was used to examine the efficacy of PDT plus imiquimod cream 5% for the treatment of extensive facial AKs.[22] A total of 25 adults were enrolled in the trial, each with 10 or more facial AKs. All participants received 2 PDT sessions 1 month apart. The procedure was standardized for the study and included application of ALA 20% followed by a 1-hour incubation period. Participants subsequently were exposed to blue light for 8 minutes. At month 2, participants began to apply imiquimod cream 5% or vehicle to half of their face twice weekly for 16 weeks in a double-blind fashion. At month 12, significantly superior reductions were observed on the imiquimod-treated side of the face (P=.0023). Significant differences were not observed earlier. Complete clearance was rare. No participant discontinued the trial secondary to adverse events. Local skin reactions were common during topical therapy on the imiquimod-treated side. Pretreatment with PDT did not reduce the incidence of severe local skin reactions associated with imiquimod.[22]

The effectiveness of pretreatment with 5-FU prior to PDT was evaluated in a small open-label trial.[23] All participants applied 5-FU cream 5% to the affected area nightly for 5 days. On day 6, participants underwent ALA-PDT that included a 30- to 45-minute incubation period followed by a single pass of 560- to 1200-nm intense pulsed light. All participants demonstrated erythema and scaling at days 3 to 4, some more severe than others, which was largely resolved by days 7 to 10. At 13 months posttreatment, 90% of treated AKs had resolved in all but 1 participant (N=15). The investigator hypothesized that pretreatment with 5-FU may enhance ALA absorption, resulting in augmented efficacy.[23]

The final study evaluating the safety and efficacy of sequential therapy with PDT was a placebo-controlled, randomized, double-blind study that examined if pretreatment with diclofenac gel 3% improved the efficacy of PDT.[24] Rather than investigating facial AKs, the study enrolled adults with extensive AKs on the dorsal aspect of both hands. Participants were instructed to apply diclofenac gel to one hand and vehicle to the other (in a double-blind manner) twice daily for 4 weeks. Two weeks after topical therapy was completed, participants received ALA-PDT. The incubation time was 4 hours followed by 16 minutes of exposure to a red light source of 633 nm. In both treatment groups, there was a significant decrease in the total lesion number score from baseline at 6 weeks (P=.012), 6 months (P=.001), and 12 months (P=.001) after PDT. One year after PDT, hands treated with diclofenac gel were found to have significantly fewer AKs than those treated with vehicle prior to PDT (P=.001). As assessed by patient- and physician-rated global improvement scores, no significant tolerability differences were noted between the vehicle and diclofenac gel treatment groups. The investigators concluded that pretreatment with diclofenac gel 3% prior to PDT resulted in better long-term results than pretreatment with vehicle.[24]

The Role of New Topical Treatment Options to Be Considered for AK

In March 2010, a 3.75% formulation of imiquimod cream was approved by the US Food and Drug Administration (FDA) for the treatment of clinically typical, visible, or palpable AKs of the full face or balding scalp in immunocompetent adults.[25] Participants were asked to apply imiquimod cream 3.75% once daily to the face or scalp for two 2-week treatment cycles separated by a 2-week no treatment period. The cream was to be washed off after 8 hours, similar to imiquimod cream 5%. When comparing partial and complete clearance rates at 8 weeks posttreatment, treatment with imiquimod was superior to vehicle. Both application-site and local skin reactions were more common among participants treated with imiquimod compared with vehicle.[25] Severe local skin reactions were observed in 33.8% (54/160) of imiquimod-treated participants and 1.3% (2/159) of vehicle-treated participants.[26]

Ingenol mebutate is a topical agent currently in development for the treatment of AK. The active ingredient appears to exert antitumor effects via 2 main mechanisms: (1) shortly after application, primary tumor necrosis commences as a result of disrupting plasma and mitochondrial membranes; and (2) approximately 1 day after topical application to skin tumors, ingenol mebutate induces an acute inflammatory response.[27]

A gel formulation of ingenol mebutate appears to require a treatment regimen of only 2 or 3 days. It is believed that regulatory approval for ingenol mebutate will be pursued in 2011.[27-29] In phase 2 studies reported to date (N=116), 27% of participants exhibited complete clearance of all AKs in the treated area at day 57 compared with 5% in the vehicle group (P<.0001). Overall, treatment with ingenol mebutate resulted in a median reduction in

baseline AKs of 69.1%. Among participants treated with ingenol mebutate gel, the most common local skin reactions were erythema (92.0%) and flaking/scaling (90.4%). Other tolerability issues included crusting, swelling, vesiculation/pustulation, and erosion/ulceration.[30] Among all groups receiving ingenol mebutate at any concentration for 2 or 3 days, irritation and pruritus were the most common treatment-related adverse events reported by participants.[31] The investigator also indicated that periorbital swelling was noted in some participants when applied in this area. Changes in pigmentation occurred in 25% (63/250) of participants. Local skin reactions were common and increased with the concentration of ingenol mebutate and duration of therapy.[31]

There are several questions to consider for ingenol mebutate. Because of its rapid brisk reaction, will ingenol mebutate be approved for at-home or in-office application? Studies to date have been performed on target lesions. What will happen with more widespread application when ingenol mebutate is used for field-directed application? Additionally, what is the long-term response rate of the gel?

Conclusion

The dermatologists present at the Winter Clinical Dermatology Conference AK roundtable believe that new US guidelines for the treatment of AK are necessary. They agreed that the new guidelines should offer information regarding the present trends and appropriate use of sequential therapy for AK, reflect the present understanding of the pathogenesis of AK and formal recommendation that all AKs be treated in some manner, and take into account the US healthcare system including insurance and cost benefit as well as recurrence data and tolerability for both lesion-directed and field-directed treatments.

In addition, the dermatologists stressed that in clinical practice, sequential therapy for AK treatment often is employed and should be encouraged. Field-directed therapy used sequentially with cryosurgery is widely used. Although tolerability issues vary from patient to patient, the roundtable panel believed that the newer 3.75% formulation of imiquimod cream is a welcome addition to field-directed therapy for AK. Diclofenac gel 3% offers good efficacy and a low risk for skin inflammation.[7]

Regarding ingenol mebutate, if FDA approved, the topical gel will be judged by its efficacy, including long-term AK clearance rates; tolerability in terms of visible appearance and symptomatology after treatment; and whether or not its use will be only lesion directed or applicable and effective as a field therapy. Because of the rapid tissue reaction after only one or a few applications, some members of the panel questioned if ingenol mebutate is best administered in the office rather than by the patient at home.

Although AKs are treated on a patient-by-patient basis, up-to-date guidelines are beneficial to clinicians to guide treatment selection. Updated guidelines should help clinicians consider sequential therapy options for AKs when data suggest better treatment outcomes, including field efficacy (both target and subclinical AKs), tolerability, and long-term clearance. As new treatments of AK are FDA approved or as new regimens emerge, guidelines are best amended with evidence-based data from clinical studies and/or consistent observations from clinical experience that are reproducible and documented.

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