

# Actinic Keratoses: Sequelae and Treatments

RECOMMENDATIONS FROM  
 A CONSENSUS PANEL

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**A**ctinic, or solar, keratoses (AKs) are commonly encountered intraepidermal, sun-induced skin lesions.<sup>1,2</sup> AKs are markers of cumulative ultraviolet (UV) skin exposure and should be considered the precursors of at least 60% of invasive squamous cell carcinoma (SCC) of the skin<sup>3-6</sup>; up to 40% of SCC are estimated to rise de novo. As part of a disease continuum, it is not surprising that AK and SCC share the same genetic alterations, morphology, and are frequently contiguous (**FIGURE 1**).

A growing body of histologic evidence suggests that AK should be regarded as early SCC in situ,<sup>7-9</sup> since AK is frequently the initial lesion in the sequence of tumor progression leading to SCC.<sup>8</sup> Biopsy sampling of sun-damaged skin, AK lesions, and SCC provides evidence of histologic similarities and shows the cellular progression of AK to SCC.<sup>9</sup> One study used step-wise biopsy sections to determine the presence of cutaneous

## Key points and recommendations

- Accumulating evidence indicates that actinic keratosis (AK) should be regarded as early squamous cell carcinoma (SCC) confined to the epidermis (SCC in situ). (SOR: C)
- Predictable risk factors for AK and SCC include ultraviolet exposure, age, male sex, and immunosuppression. (SOR: A)
- Two main approaches to treating AK are lesion-directed therapy, typically surgical or ablative methods targeted to one lesion, and field-directed therapy, typically topical drugs applied to multiple lesions or an entire area at risk. (SOR: A)
- Cryotherapy, the most common lesion-directed therapy, is very effective and reasonably well tolerated. (SOR: A)
- Imiquimod and 5-fluorouracil are the most effective field-directed therapies. (SOR: A)
- If there is evidence of extensive photodamage, field-directed therapy should be considered given the likelihood of additional subclinical AKs. (SOR: C)

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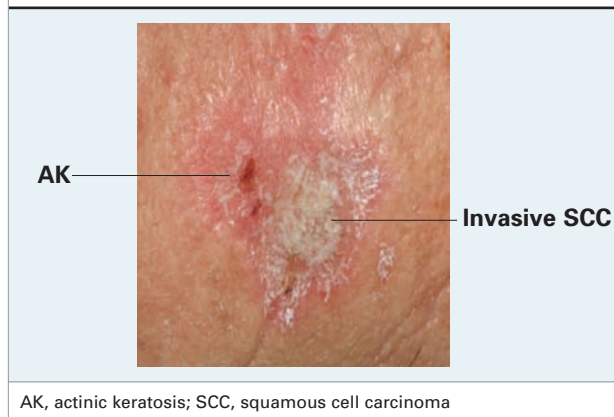


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Dr Berman reports that he has received grant or research support from, serves as a consultant to, and is on the speakers' bureau of 3M Pharmaceuticals. Ms Bienstock reports that she is on the speakers' bureau of Amgen Pharmaceuticals. Dr Kuritzky reports that he is on the speakers' bureau of 3M Pharmaceuticals. Dr Mayeaux reports that he serves as a consultant to and is on the speakers' bureau of 3M Pharmaceuticals, Merck & Co, Inc, and GlaxoSmithKline. Dr Tyring reports that he has received grant or research support from, serves as a consultant to, and is on the speakers' bureau of 3M Pharmaceuticals.

This supplement to *The Journal of Family Practice* is supported by a grant from 3M Pharmaceuticals. It was submitted by the Primary Care Education Consortium and the Texas Academy of Family Physicians and was edited and peer-reviewed by *The Journal of Family Practice*.

**FIGURE 1****AK: Frequent Proximity to SCC Lesions**

AK, actinic keratosis; SCC, squamous cell carcinoma

malignant tumors in patients who were initially diagnosed by biopsy sampling as having AK.<sup>8</sup> On further analysis, histologic findings of deeper sections showed that 20% of patients were found to have malignant lesions (SCC or basal cell carcinoma [BCC]). BCC and SCC, both nonmelanoma skin cancers (NMSCs), are the most common skin cancers in the world.<sup>10</sup>

It is impossible to determine which AK lesions may progress to SCC,<sup>11</sup> and predictions on the progression vary considerably. Two well designed, prospective longitudinal studies suggest that the yearly rate of progression of an AK lesion to invasive SCC in an average-risk person in Australia is between 8 and 24 per 10,000,<sup>3,12</sup> while a study with data from Arizona found a rate of progression of 12% over 5 years.<sup>13</sup> Additionally, about 25% of AK lesions spontaneously recede without treatment, and some SCC arise de novo.

## ■ EPIDEMIOLOGY

Actinic keratosis is likely underdiagnosed and underreported, partially because separating AK from SCC is a challenge and partially because it is difficult to track, since reports of AK diagnosis are not included in cancer registries. In northern hemisphere populations, 11% to 25% of adults have at least one AK, compared with 40% to 60% of adult Australians, who live closer to the equator.<sup>10</sup> Epidemiologic studies from Australia, Wales, Sweden, and the northern United States demonstrate that the incidence of AK and NMSC is increasing in both men and women, with an average increase of 3% to 8% since the 1960s.<sup>14-16</sup> Perhaps more alarming is that the incidence is increasing in persons younger than 40 years of age.<sup>16</sup>

## ■ RISK FACTORS

Risk factors for NMSC are also risk factors for AK because of the direct relationship of AK to SCC. The majority of all skin cancers are thought to be caused by

high intensity or cumulative exposure to UV radiation.<sup>10,15</sup> There are no “safe” UV rays: UV-B is the primary carcinogen, while UV-A is synergistic.<sup>14</sup>

## General risk factors

A culture that promotes tanning, as well as clothing styles that expose skin, increased outdoor activities, and increased longevity, contribute to UV radiation exposure.<sup>14</sup> More than 80% of NMSCs occur on areas of the body that are frequently exposed to sunlight, such as the face, balding scalp, the posterior aspect of the neck, ears, and dorsal side of the arms and hands.<sup>10,15</sup> Therefore, people who work outdoors or who live closer to the equator are at greater risk.<sup>15</sup> However, because of the use of tanning beds, AK is increasingly seen in “unexposed areas.”<sup>14</sup>

Advancing age is another strongly related risk factor for increased prevalence of AK, partially because age is a proxy for total UV exposure.<sup>15</sup> Skin phenotype is a variable for increased risk, as fair-skinned individuals who tan poorly are more frequently affected by NMSC than individuals with darker skin types. Men are at greater risk for AK than women.

## Immunosuppression

Immunosuppression by iatrogenic means, such as transplant or other uses of immunosuppressive drugs, or inherent means, such as chronic lymphocytic leukemia or human immunodeficiency virus infection, is more strongly linked to SCC than to AK. Skin cancer is the most common malignancy facing immunosuppressed patients, particularly those in the post-organ-transplant setting.<sup>17,18</sup> It is estimated that skin cancer affects 30% to 40% of transplant recipients within 20 years posttransplant.<sup>17,18</sup>

## ■ PRIMARY CARE APPROACH TO AK: PREVENTION AND SCREENING

The most important aspect of AK and skin cancer management is prevention.<sup>19</sup> Primary care providers should encourage patients to wear clothing and hats that offer sun protection, to use sunscreens with a sun protection factor of 30 that are effective against UV-A and UV-B, and to avoid sun during its most intense hours (between 11:00 AM and 2:00 PM). A small, controlled trial found that daily application of sunscreen decreased the number of AKs by 51% over 2 years.<sup>20</sup>

A 5-minute skin exam can be used to screen for sun-induced damage. This can be done casually as part of a typical routine. When greeting a patient with a handshake, use the opportunity to palpate the dorsa of the patient’s hand with your left hand. At this close proximity, inspect the face or neck for any lesions. If any are spotted, palpation of the lesion and further examination for others are warranted. When one AK is seen, it should be assumed that other, perhaps invisible, AKs exist.

## ■ DIAGNOSIS

Triaging skin lesions is a complex and difficult task. The size, shape, color, texture, location, and growth pattern of skin lesions must be considered along with patient history.<sup>21</sup> Diagnosis of AK is made even more difficult because there are many clinical variants (**FIGURE 2**). Differentiation of these types has important implications, since the treatment varies somewhat by type.

The differential diagnosis of unpigmented AK includes warts and seborrheic keratoses, while pigmented AK includes BCC and malignant melanoma. Referral to a dermatologist should be considered for those with AK of the lip (actinic cheilitis) since metastasis occurs commonly if SCC arises in this area.

One of the main challenges in the differential diagnosis of AK is the separation of early SCC from AK, since SCC has the potential to metastasize. Therefore, identifying invasive SCC is critical, because misdiagnosing a lesion as AK might allow SCC to progress. However, even among dermatologists, there is a high intraobserver variation in the diagnosis of AK.<sup>1,22</sup>

A pilot study was designed to determine if a software triaging system would help primary care providers more accurately diagnose and stage skin cancer.<sup>21</sup> When diagnoses were made without the use of the software, physicians incorrectly triaged 36.7% of lesions, while use of the software reduced the frequency of incorrect triage to 13.3%. However, in this computer simulation, physicians were not able to feel the lesion, which is one important aspect in skin diagnoses.

### Visual inspection of a lesion

The initial appearance of an AK lesion may be skin colored to pink, red, or brown; lesions on darker skin may be pigmented.<sup>23</sup> The lesion may progress to a white scale or rough macula. AK lesions may cause itching and often are poorly demarcated, ranging in size from 1 to 3 mm to several centimeters.

### Palpation of a lesion

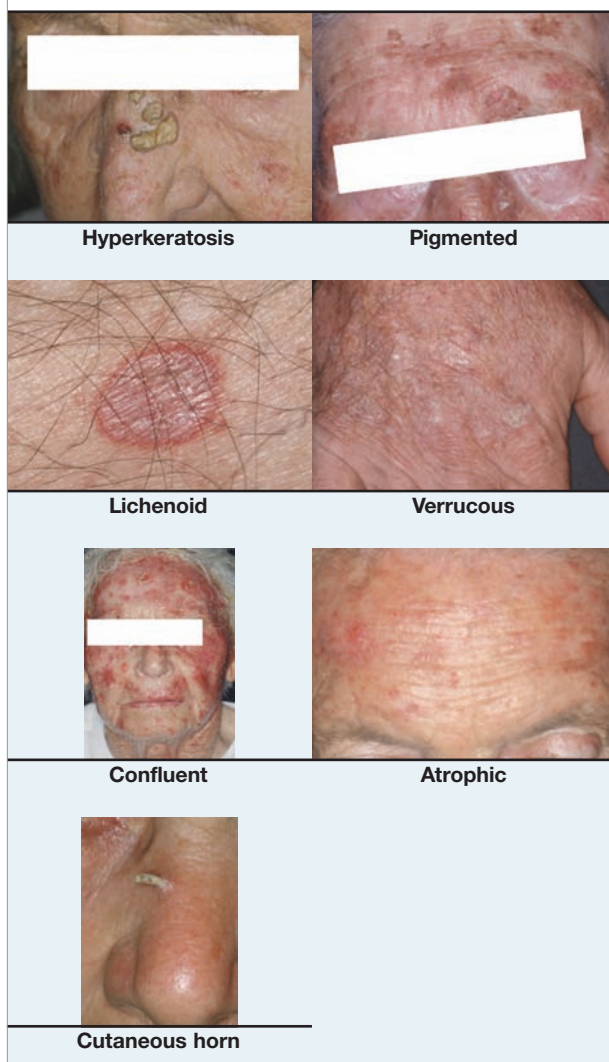
The importance of skin palpation cannot be overemphasized and, in fact, may be more important than visual inspection in making the diagnosis. Characteristically, AKs are easily palpated and have a different feel, often described as soft, rough, or “gritty,”<sup>7,23</sup> from healthy skin. AKs eventually progress to scaly, thick lesions.<sup>10</sup> Usually, there are multiple AK lesions in an area, and they may be surrounded by other solar skin damage.

## ■ HISTOPATHOLOGY

Skin biopsy specimens taken from sites with long-term exposure to the sun commonly have histologic features of AK, which may appear alone or may be associated

**FIGURE 2**

### Clinical variants of actinic keratosis



with various benign and malignant lesions.<sup>8</sup> Sun-damaged skin may exhibit dermal solar elastosis and nuclear crowding but only minor nuclear abnormalities or epidermal thickening.<sup>9</sup> As sun damage progresses to AK, scaly erythematous plaques appear with histologic features including epidermal thickening, dysplastic nuclei, and superficial parakeratosis. Dysplasia involving all layers of the epidermis defines carcinoma in situ, which may be followed by tumor cell invasion of the basement membrane, the hallmark of SCC.<sup>9</sup>

## ■ TREATMENTS

After appropriate diagnosis, treatment choice depends somewhat on lesion size, morphology, location, and likelihood of patient compliance.<sup>20</sup> There are 2 main approaches to treating AK lesions: lesion-directed therapy or field-directed therapy.

TABLE 1

## Lesion-directed therapy: Physical treatments for actinic keratoses

	Cryotherapy	Curettage and Electrodesiccation	Dermabrasion/Chemical Peel	Photodynamic Therapy
<b>Description</b>	Destroys solar keratosis which resides in the epithelium  Use requires experience  Freeze times determine AK response: 39% for <5 sec 83% for >20 sec  BCC: 60-120 sec	Based on the difference in feel between tumor (friable, easily scraped away) and healthy dermal tissue. Proceeds until healthy dermis is reached on all perimeters.  Requires experience  Electrodesiccation involves tissue destruction at margins, which helps eliminate residual tumor	Superficial peel with dermabrasion or chemical peel (ie, trichloroacetic acid chemexfoliation)  Requires prospective studies	Photosensitization of skin using aminolevulinic acid which is converted to heme precursor (requires 14–18 h)  Treatment with blue light induces cytotoxic reaction
<b>Place in therapy</b>	Standard treatment for isolated AK lesions  Most appropriate for small lesions with well-demarcated borders  Thin lesions may respond better than thick lesions	Often used for a single AK  Best applied to well-demarcated, noninvasive tumors	Useful in treating large areas with multiple keratoses  Low recurrence first years postprocedure  Gradually diminishes with time, 54% clear at 5 y	Indicated for mild-to-moderate AK on face and/or scalp  Not widely used for AK  Complete clearance of AK lesions in 73% of patients (30% required 2nd treatment)
<b>Adverse events/ Cautions</b>	AEs include postoperative pain, blistering, hypopigmentation, numbness/peripheral nerve injury for several months posttreatment  Healed cryolesions prone to sunburn and require sunscreen  Nonspecific tissue destruction; can be difficult to control	AEs are rare with well-performed C&E. Preservation of healthy tissue is excellent substrate for healing, minimizing scarring  Contraindications: recurrent tumor, punch-biopsied tumor, invasive SCC, hair-bearing sites, tumors that reach subcutaneous fat because fat cannot be distinguished on the basis of feel	Associated complications are rare and tend to be mild with an experienced and skilled operator	Pain may be significant  Stinging/burning during treatment  Erythema and edema for 1 to 4 wk posttreatment  Photosensitivity

AE, adverse events; AK, actinic keratoses; BCC, basal cell carcinoma; C&E, curettage and electrodesiccation

Stulberg DL, et al. *Am Fam Physician*. 2004;70:1481-1488; Stengel RM, Stone S. *Common Skin Diseases*. 2003;19-23; Nguyen TH, Ho DQ. *Curr Treat Options Oncol*. 2002;3:193-203; Coleman WP, et al. *Dermatol Surg*. 1996;22:17-21; Piacquadro DJ, et al. *Arch Dermatol*. 2004;140:41-46.

## Lesion-directed therapy

Lesion-directed therapy typically involves a physical treatment, such as surgical or ablative methods, targeted to one lesion<sup>19,23-26</sup> (TABLE 1). Physical treatments generally produce lesion resolution in one patient encounter, but some follow-up may be needed to monitor postprocedure healing. Of the physical treatments available, cryotherapy is considered the standard treatment for removal of individual or isolated AK lesions.<sup>11</sup> This therapy is very effective for superficial lesions, but less so for thick lesions or those on the dorsum of the hand.<sup>27</sup> Two recent clinical trials involving liquid nitrogen spray observed lesion response rates at 3 months of 68% (complete and noncomplete)<sup>28</sup> and 75% (complete).<sup>29</sup>

Cryotherapy is easy to learn; the key is to apply the cryotherapy agent for a sufficient period of time. Liquid nitrogen, for example, must be applied to the lesion to cause basement membrane separation; application of liquid nitrogen for up to 20 seconds is often needed for less superficial lesions. Cryotherapy results in erythema, edema, and

blister formation. Possible side effects include burning pain, hypopigmentation or hyperpigmentation, and scarring. Cryotherapy is contraindicated if the diagnosis is uncertain.

Curettage and electrodesiccation is another physical therapy often used for a single AK lesion. This approach is less commonly done in primary care than in other settings and is best for small, well-demarcated lesions.<sup>24</sup>

## Field-directed therapy

The other general approach to AK is field-directed therapy, in which a topical agent is applied to multiple lesions or to an entire area at risk<sup>23,30-35</sup> (TABLE 2). Topical treatments are advantageous from a primary care perspective because of their broader applicability for field-directed therapy and because some of the agents (imiquimod and 5-fluorouracil [5-FU]) reveal and treat subclinical lesions.<sup>23</sup> All of the topical therapies must be used for several weeks for lesion resolution, and they typically cause notable erythema, burning, and ulceration at the application site.<sup>30-33</sup>

**TABLE 2**

**Field-directed therapy: Topical drugs for actinic keratoses**

	<b>5-fluorouracil (Efudex<sup>®</sup>, Fluoroplex<sup>®</sup>, Carac<sup>®</sup>)</b>	<b>Diclofenac (Solaraze<sup>®</sup> Gel)</b>	<b>Imiquimod (Aldara<sup>™</sup>)</b>
<b>Mechanism</b>	Interferes with DNA and RNA synthesis	Inhibits cyclooxygenase and up-regulation of the arachidonic acid cascade	Up-regulates cell-mediated immune response in the skin
<b>Dosing regimen and application</b>	Twice daily until ulceration occurs (about 2-4 wk) Apply with nonmetal applicator and gloves	Twice daily for 60–90 days	AK: 2X per wk for 16 wk BCC: 5X per wk for 6 wk Wash off after 8 h One sachet is expected to cover 386 cm <sup>2</sup>
<b>Expected clearing</b>	Complete clearance in ~50% of patients Minimal scarring	Complete clearance in 30%–50% of patients	Complete clearance in about 45% of patients Minimal scarring
<b>Medication benefits</b>	Treats clinically undetectable AK	May be less irritating than 5-FU	Treats clinically undetectable AK Continued clearing during rest Reduced recurrence
<b>Other notes</b>	Efficacy reduced by incomplete dosing due to intolerable adverse events	Use with caution in patients with the aspirin triad	Cycle therapy with rest periods if irritation becomes unbearable  Excellent compliance and 82% complete clearance were demonstrated in a pilot study (25 patients) of application: 3X/wk for 4 wk followed by a 4-wk rest period – repeat for any remaining AK (up to 3 cycles). <sup>34</sup>
<b>Cost*</b>	Fluoroplex 1% cream, 30 g: \$120.01 Carac 0.5% cream, 30 g: \$126.06	Solaraze 3% gel, 50 g: \$138.32	Aldara 5% cream, 12 packets: \$169.99

There are no head-to-head comparison trials of the drugs for actinic keratoses.

5-FU, 5-fluorouracil; BCC, basal cell carcinoma

\*<http://www.drugstore.com>, Accessed 4/14/2006.

Stengel RM, Stone S. *Common Skin Diseases*. 2003;19-23; Aldara [prescribing information]. St. Paul, Minn: 3M Pharmaceuticals; 2004; Solaraze Gel [prescribing information]. Fairfield, NJ: Doak Dermatologics; 2006; Efudex [prescribing information]. Costa Mesa, Calif: Valeant Pharmaceuticals North America; 2005; Carac [prescribing information]. Berwyn, Pa: Dermik Laboratories; 2003; Salasche SJ, et al. *J Am Acad Dermatol*. 2002;47:571-577; Berman B, et al. *Dermatol Surg*. 2004;30:784-786.

The intensity of the site reaction indicates the likelihood of clearance, that is, the more severe the erythema and ulceration, the more efficacious the treatment is expected to be. However, if the local effects become too burdensome, a prescriber may offer a “drug holiday” or cycle the application to allow more time between applications. Using a topical steroid or moisturizer between applications may offer some benefit, but this approach has not been studied thoroughly. Some tips to improve compliance are shown in **TABLE 3**.

**Imiquimod**

Imiquimod 5% cream (Aldara<sup>™</sup>) is an immune response modifier currently indicated for the treatment of AK and superficial BCC lesions of 2 cm or less. Imiquimod is also indicated for the treatment of genital and perianal warts. Its proposed pharmacologic mechanism is up-regulation of cell-mediated immune response in the skin leading to apoptosis of the tumor cells.<sup>36</sup> Sequential biopsies of superficial BCCs, followed by gene expression analysis, have

documented changes in expression for about 1300 different genes following treatment with imiquimod.<sup>37</sup>

The most important consequence of these actions appears to be activation of the innate immune system. Increased innate immune system activity demonstrated by imiquimod is characterized histologically by epidermal invasion by macrophages (mostly neutrophils), and clinically by epidermal erosion.<sup>36,37</sup> T-cell activation also has been documented following imiquimod treatment. This occurs later in the course of treatment (after innate immune system activation) and may not be a major factor in the elimination of tumor cells. T-cell activation may play a subsequent role in immunosurveillance.<sup>36,37</sup>

**Imiquimod efficacy data**

The clinical data from imiquimod studies is compelling and interesting for its pharmacologic mechanism, as well as its clinical benefits. Data suggest that imiquimod induces an “immune memory” that serves to minimize recurrence of AK lesions. A 12- to 18-month follow-up

TABLE 3

### Tips to improve compliance with topical field-directed therapy

- Explain side effects before patient begins therapy
- Show pictures of expected side effects and expected outcomes
- Give the patient a sense of control
- Keep treatment options simple
- Inform the patient that there is minimal or no scarring

study of patients who had demonstrated complete clearance of AK lesions showed that imiquimod treatment prevented AK recurrence in 75.3% of patients treated 3 times per week and 57.4% of patients treated 2 times per week.<sup>38</sup> Even in patients who demonstrated AK recurrence, the number of recurrent lesions was small.

Data also indicate that imiquimod treats subclinical as well as clinically apparent lesions. Two phase 3, double-blind studies evaluated the efficacy of imiquimod 5% cream compared with vehicle cream in the treatment of AK lesions on the face and balding scalp.<sup>39</sup> A total of 436 participants were randomized to either imiquimod 5% or vehicle cream applied once a day, 2 days per week for 16 weeks. At 8 weeks, the complete clearance rate was 45.1% for the imiquimod group and 3.2% for the vehicle group (**FIGURE 3**). The partial (at least 75% clearance) clearance rate was 59.1% for the imiquimod group and 11.8% for the vehicle group.

It also appears that the greater the erythematous response with imiquimod, the larger the number of AK lesions that are being attacked (**FIGURE 4**). A study by Salasche and colleagues evaluated the use of imiquimod in AK treatment using a cycle-therapy regimen in which 4-week treatment periods (once-daily application 3 times/week) alternated with 4-week rest periods.<sup>34</sup> In this

open-label study, 25 patients with between 5 and 20 AK lesions on the forehead, scalp, and/or cheek were treated with up to 3 full cycles (treatment plus rest period). Serial AK lesion counts were obtained at 2-week intervals during the study. During the first treatment cycle, imiquimod treatment “revealed” subclinical lesions (eg, increased number of lesions at weeks 2 and 4). However, lesions continued to clear (ie, reduction in AK lesion count) during the 4-week rest period. Continued clearance during the rest period may be the result of immune memory or immunosurveillance established by prior imiquimod treatment.<sup>34</sup>

### 5-fluorouracil

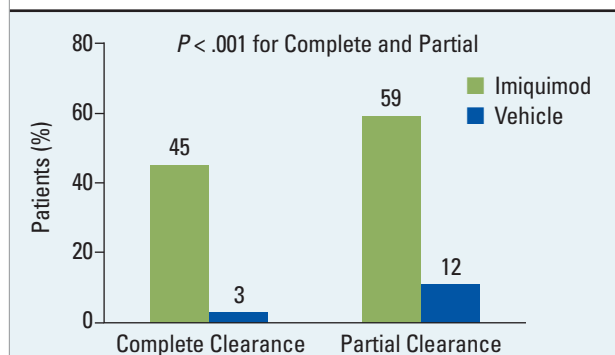
5-Fluorouracil (Efudex<sup>®</sup>, Fluoroplex<sup>®</sup>, Carac<sup>®</sup>) is an anti-neoplastic drug that has been used with good success for multiple AK lesions. Available in various strengths and formulations, 5-FU 5% is indicated for AK, although the prescribing information also states it “may be useful” for superficial BCC.<sup>32</sup> A 10-fold less concentrated formulation, 0.5%, is indicated only for solar AK.<sup>33</sup> 5-FU is especially recommended for patients with multiple lesions or for those with tumors in sites not appropriate for cryotherapy or surgical excision.<sup>32</sup> Contraindications to 5-FU include pregnancy and high-risk or invasive tumors.<sup>24</sup>

For AK lesions, 5-FU (1% or 2% on the face and 5% elsewhere) is applied twice daily until superficial ulceration occurs (usual duration is 2 to 4 weeks).<sup>32,33</sup> Topical 5-FU is generally effective in more than 90% of patients who can tolerate it and has the advantage of treating clinically undetectable AK with minimal scarring. The anticipated skin reaction with 5-FU follows a 4- to 6-week pattern of initial inflammation and erythema, progressing into vesiculation and erosion, and finally reepithelialization<sup>32</sup> (**FIGURE 5**). To reduce inflammation until complete healing occurs, administration of the 5-FU can be followed in 15 minutes by a low-potency topical corticosteroid cream. However, the discomfort, pruritus, ulceration, and soreness related to the expected skin reaction are the most common adverse events. The pain and unsightliness from these reactions can be severe enough to impact patient tolerability and compliance.<sup>23</sup> Various approaches have been tried to reduce the severe adverse events. At least one study provides evidence that a reduction in dosing frequency produces less irritation and similar efficacy, but time to healing was increased.<sup>40</sup>

Patient preference for 5-FU has been clinically evaluated. One study showed that patients preferred the 0.5% concentration compared with a 5% formulation, primarily because of tolerability.<sup>41</sup> Another study demonstrated that patients preferred a chemical peel using Jessner’s solution and 35% trichloroacetic acid to 5-FU, because the chemical peel required only a single application and caused less skin reaction.<sup>42</sup>

FIGURE 3

### Complete and partial response to imiquimod



Lebwohl M, et al. *J Am Acad Dermatol.* 2004;50:714-721.

**FIGURE 4**

**Clinical Response to Imiquimod**



The combination of 5-FU 0.5% and cryosurgery has been investigated in 144 patients with 5 or more visible or palpable AK lesions on the face.<sup>43</sup> Patients were randomized to receive 5-FU 0.5% or vehicle cream once daily for 7 days. At the 4-week follow-up, residual lesions were treated with cryosurgery. At week 4, the lesion count was reduced by 62% in the 5-FU group compared with 29% in the vehicle group. The addition of cryosurgery increased the reduction in lesion count at 6 months to 67% and 46%, respectively. Significantly more patients in the 5-FU group than in the vehicle group achieved total lesion clearance at 4 weeks (17% vs 0%) and 6 months (30% vs 8%) (**FIGURE 6**).

**Diclofenac**

Diclofenac (Solaraze® Gel) is a nonsteroidal anti-inflammatory drug (NSAID) that inhibits the conversion of arachidonic acid (AA) to prostaglandins (the mechanism believed to underlie the analgesic properties of NSAIDs). Activation of the AA cascade may be involved in the promotion of NMSCs.<sup>44</sup> Topical diclofenac is currently indicated only for treatment of AK and is applied as a 3% gel twice daily over 12 weeks of treatment.<sup>31</sup> The recommended duration of therapy is 60 to 90 days, although complete healing of the lesion may not be evident for up to 30 days following the cessation of therapy.<sup>31</sup> In several studies, diclofenac produced complete clearance of AK lesions in 30% to 50% of patients.<sup>31,45</sup> Adverse events include application-site reactions and pruritus, which are rarely severe enough to cause treatment discontinuation. Contact sensitization is common with diclofenac, and patients are advised to avoid sun exposure.<sup>31</sup>

**■ CONSENSUS RECOMMENDATION**

A main treatment goal in primary care is to ensure that the patient has a good outcome by minimizing the risk of progression of AK to invasive SCC. Therefore, patient follow-up is important, particularly when treating AK as it can

**FIGURE 5**

**Clinical Response to 5-FU**



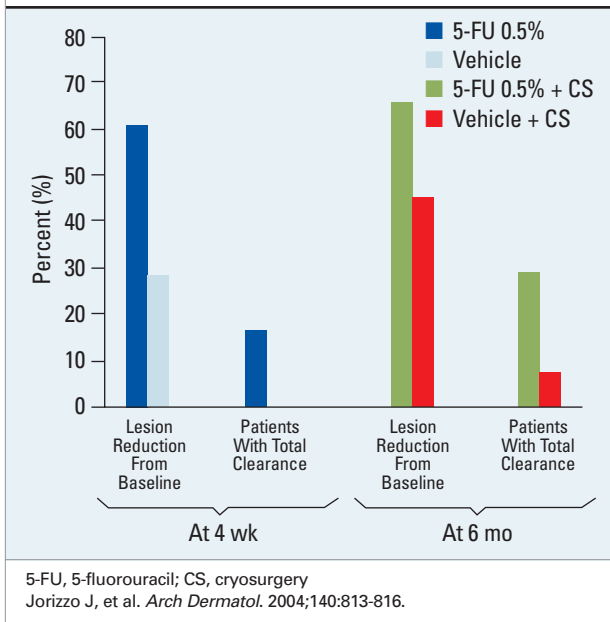
recur or progress to SCC. The primary decision point in AK diagnosis is the appearance of a single lesion versus multiple lesions. Lesion-directed treatment may be considered for a single lesion, but when there is evidence of extensive photodamage additional subclinical AK lesions are likely, and field therapy also should be considered.

In patients with multiple lesions, field therapy should be a strong consideration as an adjunct to lesion-directed ablation since field therapy is the only modality capable of addressing these foci. Finally, in an area harboring a significant number of AK lesions, regional topical therapy is warranted.

It is not fully understood whether an existing AK transforms/progresses to invasive SCC or if a particularly aggressive clone of mutated cells is predestined to evolve directly into invasive SCC. It is not possible to predict which AK will progress into SCC; therefore, treating all AK lesions makes sense. Considerations for treatment

FIGURE 6

### Efficacy of 5-fluorouracil in actinic keratoses



choice are the size and location of the lesions and likelihood of patient compliance with a topical medication.

Patients who should be considered for referral include those with actinic cheilitis, as well as those with AK lesions following treatment since biopsy is recommended. ■

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