



Managing Actinic Keratoses: A Review of Recent Advances

Today's View of Actinic Keratosis: A Snapshot

The Scientific Basis of Skin Cancer

Management of Actinic Keratoses:
Current Options and Patient Selection

When and Why Should Actinic Keratoses Be Treated?

Imiquimod in AKs: A Study of Cosmetic Outcomes

FACULTY

CHAIRMAN

James M. Spencer, MD, MS
Mount Sinai School of Medicine
New York, N.Y.

Mark H. Goldgeier, MD, FAAD, FABIM, FACP
University of Rochester Medical Center
Rochester, N.Y.

Arielle N.B. Kauvar, MD
NYU School of Medicine
New York, N.Y.

Albert M. Kligman, MD, PHD
University of Pennsylvania
School of Medicine
Philadelphia

Daniel M. Siegel, MD, MS
SUNY Downstate Medical Center
Brooklyn, N.Y.



CME
CONTINUING MEDICAL EDUCATION

Jointly sponsored by the
Elsevier Office of Continuing
Medical Education and
SKIN & ALLERGY NEWS

President, Elsevier/IMNG
Alan J. Imhoff

Vice President, Medical Education
& Business Development
Sylvia H. Reitman, MBA

Program Manager,
Medical Education
Sara M. Hagan

Clinical Editor
Joanne M. Still

National Account Manager
Cheryl J. Gromann

Graphic Design
Lehner & Whyte, Inc.

Production Manager
Judi Sheffer

The articles in this supplement are based on presentations made at a continuing medical education program held September 17, 2005, in New York, N.Y.

This supplement was supported by an educational grant from

3M Pharmaceuticals

The supplement was produced by the medical education department of International Medical News Group. Neither the Editor of SKIN AND ALLERGY NEWS, the Editorial Advisory Board, nor the reporting staff contributed to its content. The opinions expressed in this supplement are those of the faculty and do not necessarily reflect the views of the supporter or of the Publisher.

Copyright ©2005 Elsevier Inc. All rights reserved. No part of this publication may be reproduced or transmitted in any form, by any means, without prior written permission of the Publisher. Elsevier Inc. will not assume responsibility for damages, loss, or claims of any kind arising from or related to the information contained in this publication, including any claims related to the products, drugs, or services mentioned herein.



**INTERNATIONAL
MEDICAL NEWS
GROUP**

Introduction	4
Today's View of Actinic Keratosis: A Snapshot	4
The Scientific Basis of Skin Cancer	7
Management of Actinic Keratoses: Current Options and Patient Selection	9
When and Why Should Actinic Keratoses Be Treated?	12
Imiquimod in AKs: A Study of Cosmetic Outcomes	14
CME Post-Test and Evaluation	16

Faculty

CHAIRMAN

James M. Spencer, MD, MS

Professor of Clinical Dermatology
Mount Sinai School of Medicine
New York, N.Y.
Private Practice
St. Petersburg, Fla.

Albert M. Kligman, MD, PhD

Professor of Dermatology
University of Pennsylvania
School of Medicine
Philadelphia

**Mark H. Goldgeier, MD, FAAD, FABIM,
FACP**

Clinical Assistant Professor
of Medicine
University of Rochester
Medical Center
Private Practice
Rochester, N.Y.

Daniel M. Siegel, MD, MS

Clinical Professor of Dermatology
SUNY Downstate Medical Center
Brooklyn, N.Y.
Private Practice
Smithtown, N.Y.

Arielle N.B. Kauvar, MD

Director
New York Laser and Skin Care Center
Clinical Associate
Professor of Dermatology
NYU School of Medicine
New York, N.Y.
Co-Director of
Procedural Dermatology
SUNY Downstate Medical Center
Brooklyn, N.Y.

Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Elsevier Office of Continuing Medical Education (EOCME) and SKIN & ALLERGY NEWS. The EOCME is accredited by the ACCME to provide continuing medical education (CME) for physicians.

CME Credit Statement

The EOCME designates this educational activity for a maximum of 2 AMA/PRA category 1 credits toward the American Medical Association (AMA) Physician's Recognition Award (PRA). Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

Term of Approval: December 2005–December 31, 2006

Special Needs

We encourage participation by all individuals. If you have any special needs, please contact mededinfo@elsevier.com for assistance.

Target Audience

This activity has been developed for dermatologists and other healthcare professionals involved in the diagnosis and treatment of actinic keratoses (AKs).

Educational Needs

Actinic keratosis lesions are an extremely common consequence of long-term exposure to ultraviolet light. In recent years, research has demonstrated the nature of AK lesions: they represent a proliferation of neoplastic keratinocytes and are characterized at the molecular level by a mutation in the p53 gene, leading to perturbation of apoptosis and, thus, the potential for the development of skin carcinomas (squamous cell carcinoma [SCC], in particular). Because it cannot be predicted which particular lesions will remain unchanged, regress, or progress to carcinoma, the consensus among

researchers and clinicians alike is that all AKs should be treated. This activity provides clinicians with the most current information regarding the nature, diagnosis, and management of AKs. The faculty addresses both lesion-targeted and field treatments. The discussion also includes the results of several recently completed studies involving the topical immune response modifier imiquimod.

Educational Objectives

By reading and studying this supplement, participants should be able to:

- Discuss the epidemiology of actinic keratoses, the geographic differences in incidence, and the prevalence of these lesions in individuals with various Fitzpatrick skin types.
- Explain what is currently known about the etiopathogenesis and carcinogenic potential of AKs.
- Describe the clinical presentation of AKs and the characteristic histologic features that distinguish AKs from invasive SCC.
- Discuss the rationale for treating AKs.
- List and describe the options now available for treating AKs, and discuss patient selection issues.

Faculty and Unapproved Use Disclosures

As sponsors accredited by the ACCME, it is the policy of the EOCME to require the disclosure of the existence of any significant financial interest or any other relationship a faculty member has with the manufacturer(s) of any commercial product discussed during his/her presentation. The faculty of this CME activity discloses the following:

Dr Goldgeier is an attending physician to patients with the diseases to be discussed. Dr Goldgeier is a participant in 3M Pharmaceuticals-sponsored phase IIIB and IV imiquimod trials for AKs, and has received grant/research support from 3M. He discusses the unlabeled use of imiquimod. **Dr Kauvar**

has nothing to disclose. **Dr Kligman** has nothing to disclose. He discusses the unlabeled use of imiquimod. **Dr Siegel** is a consultant to, on the Speaker's Bureau at, and is a stock shareholder of 3M. He is also on the Speaker's Bureau at Dermik Laboratories. Dr Siegel discusses the unlabeled uses of—that is, alternative dosing schedules for—diclofenac, imiquimod, and 5-fluorouracil, in the treatment of AKs. **Dr Spencer** is a consultant to Connetics Corporation and PhotoMedex, Inc. He is also on the Speaker's Bureau at 3M and Doak Dermatologics.

Conflict of Interest Acknowledgement

In accordance with the ACCME Standards and the policy of the EOCME, some of the faculty have indicated that they have a relationship which, in the context of their presentations, could be perceived as a real or apparent conflict of interest, but do not consider that it will influence their presentation. The nature of the conflict is listed above.

Unapproved/Off-Label Use Disclosure

The EOCME requires CME faculty (presenters) to disclose to the attendees:

- 1) When products or procedures being discussed are off-label, unlabeled, experimental, and/or investigational (not US Food and Drug Administration [FDA] approved); and
- 2) Any limitations on the information that is presented, such as data that are preliminary or that represent ongoing research, interim analyses, and/or unsupported opinion.

Faculty may discuss information about pharmaceutical agents that are outside of FDA-approved labeling. This information is intended solely for CME and is not intended to promote off-label use of these medications. If you have questions, contact the medical affairs department of the manufacturer for the most recent prescribing information.

Introduction

Actinic keratosis (AK) is one of the most common reasons for patient visits to a dermatologist, second only to acne. Specialty profiles compiled by Verispan indicate that AKs account for nearly 4 million patient visits each year to dermatology practices.¹

AKs are an extremely common consequence of long-term exposure to ultraviolet light. In recent years, research has demonstrated that AKs represent a proliferation of neoplastic keratinocytes and are characterized by molecular and genetic changes including mutations in the p53 tumor suppressor gene. These p53 mutations lead to a perturbation of apoptosis and, in turn, have the potential to result in the development of skin cancers, especially squamous cell carcinoma.

Currently, it is not possible to predict which particular lesions will remain unchanged, regress, or progress to carcinoma. Therefore, the consensus among both researchers and clinicians is that all AKs should be treated. Important advances continue to be made in understanding the nature and treatment of AKs, including the role of traditional, lesion-targeted modalities and topical field therapies such as topical 5-fluorouracil, diclofenac, and the immune response modifier imiquimod.

This expert roundtable provides clinicians with the most current information regarding the nature, diagnosis, and management of AKs. The faculty participating in this program are **Mark H. Goldgeier, MD, FAAD, FABIM, FACP**, Clinical Assistant Professor of Medicine, University of Rochester Medical Center, Rochester, New York; **Arielle N.B. Kauvar, MD**, Director of the New York Laser and Skin Care Center, Clinical Associate Professor of Dermatology, New York University School of Medicine, and Co-Director of Procedural Dermatology, State University of New York (SUNY) Downstate Medical Center, Brooklyn, New York; **Daniel M. Siegel, MD, MS**, Clinical Professor of Dermatology, SUNY Downstate Medical Center; and **Albert M. Kligman, MD, PhD**, Professor of Dermatology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

— James M. Spencer, MD, MS, Chairman
Professor of Clinical Dermatology, Mount Sinai School of Medicine

Reference 1. Verispan, Physician Drug and Diagnosis Audit, 2004.

Today's View of Actinic Keratosis: A Snapshot

JAMES M. SPENCER, MD, MS

Actinic keratoses (AKs) occur in 14% of patients who consult dermatologists, representing a significant proportion of dermatology practices.¹ These lesions are most common in men over 50 years of age and both men and women with blue eyes, freckling, and sun-sensitive skin.² Some authors have suggested that a high-fat diet increases susceptibility to AKs.³ The risk for AK progression to squamous cell carcinoma (SCC) justifies treatment of all AKs. Early identification of AKs and prompt treatment of these lesions are of particular importance in several populations of patients who are at an increased risk for SCC. These include patients with diseases such as epidermodysplasia verruciformis⁴ and xeroderma pigmentosum,⁵ individuals who are medically immunosuppressed following organ transplanta-

tion,⁶ and those who are immunosuppressed secondary to human immunodeficiency virus infection.⁷

Characteristics of AK Lesions

Clinically, AKs begin as small, scaly, red or brown spots arising in chronically sun-exposed areas—most commonly, the face, scalp, neck, forearms, and the dorsum of the hands. In the early stages of development, AKs may not be visible but may be detected by the feeling of sandpaper when the fingers are run across the skin. Over time, minute lesions may enlarge to several centimeters in diameter and may become raised and hyperkeratotic. Multiple lesions can arise within a single field; in some cases, these lesions become quite large and the affected site can appear as one or more areas of confluent AKs (**Figure** on next page).⁸⁻¹⁰

Historically, AKs have been considered to be premalignant, implying that an AK lesion is not yet cancerous but could become an invasive SCC. Recently, the argument has been made that an AK may be SCC in situ, based on the observation that AK and SCC share histologic and molecular features. AK is characterized by disordered keratinocytes in the epidermis, pleomorphism, loss of polarity, and alternating parakeratosis. All of these features also describe SCC, but AK is a partial-thickness dysplasia limited to the epidermis, whereas SCC lesions extend into the dermis.

In terms of natural history, AKs may remain unchanged, may clear spontaneously, or may progress to SCC. The actual rate of progression of any particular AK is impossible to predict, but it has

been estimated that as many as 10% of these lesions do progress to SCC within 10 years.¹¹ Because the risk for progression is uncertain and the treatments available for eliminating AKs are effective and well tolerated, it is generally agreed that treatment for all AK lesions is warranted. In addition to clearing AKs, any treatment strategy should include prevention involving sun protection¹² and, perhaps, a low-fat diet, which may enhance resolution of existing lesions and help prevent new AKs.³

Rationale for Choosing Therapy

Much of our information regarding many of the currently available treatments for AK is anecdotal. In the quest for applying principles of evidence-based medicine, scientific evaluation has been done on a number of modalities. However, the manner in which these evaluations were done presents problems in interpreting the reported data.

In the past, efficacy of a therapy was determined by the percentage of lesions that resolved; however, newer standards from the US Food and Drug Administration (FDA) require that efficacy be reported in terms of the percentage of patients who experienced complete clearance of their AKs. This has important implications for analyzing the literature—for example, the results of a study can show a 90% improvement rate (ie, 9 out of 10 lesions cleared), but because 1 out of 10 lesions remained, the complete clearance rate is 0%. When reading the literature, therefore, it is

important to keep this distinction in mind.

Categories of Therapy

Destructive Modalities

Destructive therapies—those that eliminate AKs by applying a physical technique to produce cell death within the lesion—currently are the most popular. These are cryotherapy, curettage (with or without electrodesiccation), shave excision, and surgical excision.

Of these, the most commonly used is cryotherapy, although this modality had never been studied in an evidence-based manner until recently. In a study published in 2004, Thai and colleagues¹³ conducted a prospective study of 89 patients with 421 AKs treated with cryotherapy for various freeze times. The end points in this study were lesion count and subjective evaluation of the cosmetic outcome. The overall response rate was 67.2%, but an analysis of subgroups showed a resolution rate of only 39% when the freeze time was 5 seconds or less, 69% when freeze times were between 6 and 20 seconds, and 83% for freeze times longer than 20 seconds. Overall, hypopigmentation was seen in 29% of sites where lesions were eradicated.

Curettage and shave excision are destructive techniques that have not been subjected to controlled efficacy studies, but clinical experience demonstrates that these modalities are effective in eliminating specific, visible lesions. The addition of electrodesiccation to curettage results in a slightly wider extent of tissue destruction, but its main utility is to control bleeding. These techniques are indicated if SCC is suspected and a tissue sample is needed for histologic analysis.

To summarize, among the destructive therapies, cryosurgery is moderately painful and, more importantly, often leads to hypopigmentation due to the melanocyte sensitivity to cold. Curettage and shave excision are procedures that require anesthesia and are very likely to result in scarring. All of the destructive modalities produce a wound, so only a limited area can be treated at any given time. In addition, these techniques allow treatment of only discrete, visible lesions because subclinical lesions are, by definition, undetectable on visual inspection. Finally, destructive techniques are not recommended to treat multiple AKs

within a single anatomic area, particularly cosmetically sensitive areas such as the face, forehead, or scalp.

Field Treatments:

Field-Destructive Modalities

Two categories of field therapies are available for managing AKs: field destruction and medical treatment. Field-destructive techniques are cosmetic procedures that safely destroy the entire epidermis. This can be accomplished with a medium-depth chemical peel (trichloroacetic acid), a deep chemical peel (phenol), dermabrasion, or laser resurfacing. All of these procedures require downtime for healing, and all pose the risk for infection and scarring. In addition, these are cosmetic procedures for which patients will not be reimbursed and which require specialized skill and experience to perform. Considering all these factors, cosmetic field destruction techniques are best reserved for cases in which cosmetic treatment is the primary goal and destruction of AKs is a secondary benefit.

Field Treatments: Medical Therapies

Medical therapies are not mechanically destructive to targeted, specific lesions but eliminate AKs by a chemical effect on a field of sun-damaged skin. The desirable characteristics for such modalities are treatment of both visible and subclinical lesions in a large area, high degree of efficacy, good tolerability, and a pleasing cosmetic outcome. The medical therapies currently available are 5-fluorouracil (5-FU), diclofenac, photodynamic therapy/aminolevulinic acid (PDT/ALA), and imiquimod. (Tretinoin and colchicine, in topical preparations, have been studied for the treatment of AKs, but tretinoin is not approved for this indication and topical colchicine is not available for clinical use.)

5-FU. Various formulations of topical 5-FU currently are marketed: 5% cream, 1% cream and solution, and 0.5% micronized cream. The 5% cream preparation has been available longer than the others, having become available in the early 1960s. At that time, phase III trials were not required by the FDA, and such studies have not been done.

Although the efficacy of 5-FU 5% cream has not been established in phase III clinical trials, most dermatologists

Figure. Multiple, Large Actinic Keratoses



Application of topical field therapy typically results in erythema of both visible AKs and subclinical lesions. This patient was treated with diclofenac.

Photo courtesy of James M. Spencer, MD, MS

who have treated AKs with this agent undoubtedly have found it effective. Anecdotal evidence suggests that this medication probably has an efficacy of about 75%. An early, 1-month, split-face study in 16 patients compared 5% and 1% concentrations; the results suggested that these formulations are clinically equivalent, at least in the short term.¹⁴

The disadvantage of 5-FU is that it causes significant discomfort and temporary disfigurement. The most recent addition to the roster of 5-FU formulations is 0.5% micronized cream, which was developed not to improve efficacy but to improve tolerability. In a split-face study, Loven and colleagues¹⁵ compared the micronized formulation with 5% cream. The rate of clearance—that is, the percentage of patients in whom treatment resulted in 100% clearance of AKs—was the same for both formulations (50%), as was investigators' assessment of adverse events such as erythema, crusting, and scabbing. The patients preferred the micronized cream because it requires only once-daily application.

Diclofenac. This is a topical non-steroidal antiinflammatory agent that is suspended in a hyaluronic acid gel. This medication works by blocking the enzyme cyclooxygenase, preventing the production of prostaglandins and prostacyclins, which have been implicated in the carcinogenic pathway. In the 3-month pivotal clinical trial that led to FDA approval of this drug, Nelson and colleagues¹⁶ compared diclofenac to a placebo gel in 120 patients. After 3 months of twice-daily applications, 50% of patients in the active treatment group had 100% clearance. The investigators reported that efficacy was substantially lower at 1 and 2 months, so a 3-month course of treatment is required to achieve this rate of complete clearance. Therapy was generally well tolerated, with only mild cutaneous effects; vesicles and ulcerations were seen but were rare.

PDT/ALA. This technique involves the use of ALA combined with exposure to a blue light source. ALA preferentially accumulates in dysplastic and malignant cells, where it is converted enzymatically to the potent photosensitizer protoporphyrin IX. In response to visible light, reactive oxygen species are generated, resulting in oxidative cell damage and cell death.

In the pivotal study of this modality,¹⁷ investigators recruited patients with flat AKs. The lesions were graded from 1 to 3, with grade 1 indicating flat AKs and grade 3 denoting hyperkeratotic AKs, and grade 3 lesions were excluded from the study. Only patients with grade 1 and 2 AKs were included; the researchers reported that 88% of patients had 100% clearance of these lesions. In a head-to-head comparison of PDT/ALA and 5-FU 5% cream, Kurwa et al¹⁸ treated one hand in each of 17 patients with PDT/ALA and had these patients apply 5-FU twice daily to the other hand for 3 weeks. In the 14 patients who completed the study, the treatments were equally effective, but the patients also reported the same subjective complaints of erythema and pain. Studies are currently under way to improve this modality by shortening the time between ALA application and light exposure to less than 1 hour and exploring the effects of the use of higher doses of blue light and the use of ALA with either pulsed-dye laser or intense pulsed light.

Imiquimod. Imiquimod, an immune response modifier, represents a unique approach to the treatment of AKs. This medication is FDA approved for the treatment of genital warts, AK, and superficial basal cell carcinoma. Imiquimod works by binding to a molecule known as toll-like receptor-7, inducing a variety of cytokines including interferon- α and - γ and interleukin-12. This stimulates a nonspecific immune response via interferons and natural killer cells, as well as a specific immune response, involving stimulation of cytotoxic T cells that have the potential for memory.

In an early study of the use of imiquimod for AKs, Stockfleth and colleagues¹⁹ used imiquimod to treat facial lesions in 25 patients; 11 patients served as controls. The patients applied either imiquimod or placebo cream to the area three times a week for 12 weeks. Lesion counts were done before and after therapy, and some of the patients underwent biopsies before and after treatment. The researchers found that 21 patients in the active treatment group had complete clearance of AKs, confirmed by biopsy. Two of the patients in the group had partial clearance. In 13 patients, the treatment regimen yielded a vigorous

response that caused discomfort. As a result, 12 of these had their medication dosage reduced to twice weekly, and one had the dosage reduced to once weekly. Those who used imiquimod twice weekly had the best clearance rates. The results of this study suggest that imiquimod can be titrated to tolerability and still be effective.

The phase III pivotal study of imiquimod for AKs was a multicenter, randomized, placebo-controlled trial involving 436 patients.²⁰ Patients applied the active medication or placebo cream twice weekly for 16 weeks. Eight weeks after stopping these applications, the patients were assessed for complete clearance of lesions. The overall rate of complete clearance was 45.1%, with severe erythema reported in 17%. The median rate of clearance was 83%.

Finally, Salasche and colleagues²¹ tested a concept of cycle therapy with imiquimod, having 25 patients apply the medication for 1 month to a discrete cosmetic unit (eg, forehead, cheek, scalp). After 1 month of twice-weekly applications, the patients stopped imiquimod for 1 month, then used the medication for another month. This cycle was repeated if a patient had residual lesions. After one cycle, 15 of 30 treated areas—50%—completely cleared; an additional 12 treated areas were completely clear after a second cycle. The overall clearance rate was 90%.

Conclusion

By every indication, the incidence of skin cancer and AKs will continue to rise. Therefore, the therapy of AKs will continue to be an ever larger part of dermatologic practice. Although the exact risk of any one AK progressing to an invasive SCC is impossible to determine, the fact that there is risk justifies treating all AKs when possible. Simple destructive techniques are the most popular choice for treating AKs. However, when confronted with many AKs over a large area or in a cosmetically sensitive patient in whom blistering and hypopigmentation is unacceptable, medical field therapies are the treatment of choice. ■

References

1. Gupta AK, Cooper EA, Feldman SR, Fleischer AB. A survey of office visits for actinic keratosis as reported by NAMCS,

Continued on page 11

The Scientific Basis of Skin Cancer

MARK H. GOLDGEIER, MD, FAAD, FABIM, FACP

Research into the physical, molecular, and immunologic nature of actinic keratosis (AK) is revolutionizing our approach to the diagnosis and treatment of sun-related skin conditions. AKs are scaling lesions on sun-exposed skin that display partial-thickness keratinocytic atypia and at least some molecular changes typical of cutaneous squamous cell carcinoma (SCC). AKs are the major antecedent lesions to SCC. Given the nature of biologic systems and our current level of understanding, it may not yet be possible to provide a universal answer to the question of whether AKs are precancerous or cancerous. Nevertheless, the question has important scientific and practical implications.

Current Understanding of Carcinogenesis in Skin Cancer

The precancerous state shares characteristics with cancer; however, at a conceptual and observational level it may be distinguished from cancer. When the precancer becomes indistinguishable from a cancer—whether clinically, behaviorally, or on laboratory testing—at that moment the lesion is, in fact, a cancer.

Multistep carcinogenesis has been the conceptual framework of cancer development for many decades. In this framework, precancers progress along the path to cancer by the accumulation of multiple cellular insults. Ultraviolet (UV)-induced DNA damage is felt to be the most important and is the most studied factor in cutaneous carcinogenesis. UV light causes signature damage to DNA, causing mutations (usually, a C to T or a CC to TT mutation), as well as alterations in the p53 gene, that result in diminished apoptosis and, consequently, a threat to homeostasis. In addition, p16, *ras*, and a host of other oncogenes may be affected by UV exposure.¹ UV-induced genetic damage is common in Caucasian adults.

Photoinduced DNA damage, as well as protein damage and inflammation, are localized consequences of UV insult—that is, they are events that occur only at the sites of UV exposure.

Immunosuppression is a systemic consequence of UV exposure. As a result, distant harm is caused even by localized UV exposure. Both genetic mutations and immune compromise contribute to the development of cancer.^{2,3} Genetic defects and signature mutations are markers of photoinduced carcinogenesis. Reduced antigen-presenting cell function, a decrease in the number of Langerhans' cells, and reduced cell-mediated immunity define photoinduced immunosuppression. Immunosuppression leads to a loss of the normal mechanisms of immunosurveillance and provides the opportunity for DNA-damaged keratinocytes to escape destruction. The combination of genetic damage and immunosuppression results in the development of AK and SCC alike.^{2,3}

Association Between Photodamage, AK, and SCC

Clinically, what is recognized as aging skin is more accurately defined as photoaging, manifested by solar elastosis, dyschromias, and telangiectasias. UV light is, by common definition, the cause of photoaging, and is recognized as the most important cause of both AK and SCC.⁴ UVB is more damaging than is UVA, but UVA is less filtered by chemical sunscreens and is more deeply penetrating.

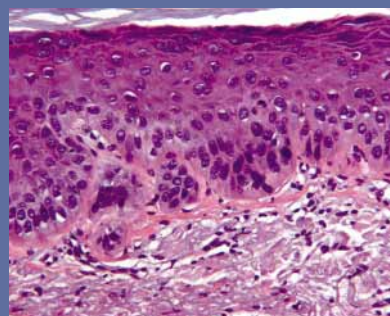
The clinical definition of AK as a scaling, variably pigmented papule or plaque is well described throughout the derma-

tology literature. The histologic definition is partial-thickness keratinocytic squamous atypia (**Figure 1**). The cellular biologic definition is skin with a so-called oncogenic molecular profile and diminished immune response. Histologically, SCC is characterized by full-thickness keratinocytic squamous atypia (**Figure 2**) along with progressive oncogenic molecular abnormalities. In both AK and SCC, histologic examination demonstrates adjacent areas of photodamage.⁵

Three major arguments support the contention that AKs are cancer. First, other conditions that were previously considered to be “precancers”—including Bowen's disease and melanoma in situ—now are recognized as true cancers, albeit at early stages of development and with only partial-thickness atypia. Second, AK may be indistinguishable from SCC in terms of clinical and molecular biological features. Third, the path from AK to SCC, although unpredictable, is common enough to make AK the major antecedent lesion to SCC. Semantically, the term “actinic keratosis” may be a historical inaccuracy because AKs already may be SCC. At least some AKs will develop full-thickness atypia, invade the dermis, and metastasize.

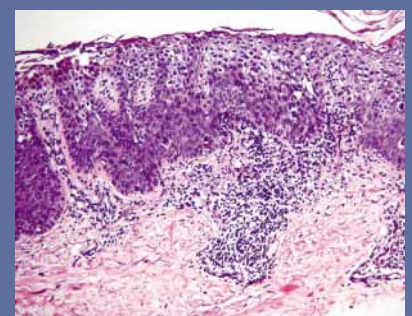
On the other hand, there are three major arguments against the redefinition of AK as an early cancerous condition. First, although there may be overlap lesions, there is a recognized histologic demarcation between AK and SCC. AKs

Figure 1. Actinic Keratosis (AK)



This biopsy specimen of an AK lesion shows partial-thickness keratinocytic atypia and adjacent photo-damage.

Figure 2. Squamous Cell Carcinoma (SCC)



In contrast to what is seen with AK, SCC is characterized by full-thickness keratinocytic atypia. Note also that, as with AK, photodamage is evident adjacent to the cancerous area.

have partial-thickness keratinocytic atypia, whereas SCCs display full thickness keratinocytic atypia throughout the epidermis.

Second, the majority of AKs fail to progress to SCC, and the path from AK to SCC is not unidirectional. The development of SCC from AK is neither necessarily progressive, predictable, nor common.⁶ The risk for any single AK progressing to SCC in a given patient is variable and unless other factors such as immunocompromise intervene, almost certainly is less than 10% per year.

Third, it has not yet been established which factors predict progression of AK to SCC. Should clinical, histologic, or molecular markers be used to quantify the risk of progression of lesions and, indeed, to ultimately differentiate AK from SCC?

Nevertheless, by any manner of investigation to date, AKs appear to be on a continuum with SCCs and are predecessors of the majority of SCCs. One study showed that 97.2% of SCCs have histologic evidence of adjacent AK.⁵ Photodamaged skin is a precursor to both AK and SCC; it has been clearly established that photodamaged skin adjacent to clinically recognizable AK lesions share histologic and biologic markers with both AK and SCC.⁵ It may well be the case that the precursor lesion to SCC is not AK, but rather photodamaged skin.

Implications for Clinical Management

An understanding of the natural history of AK is necessary for three basic reasons: (1) to recognize the preventable factors that lead to photodamage, to AK, and, eventually, to SCC; (2) to identify high-risk SCC precursors and eradicate them; and (3) to target SCCs early in their genesis.

Considering the current level of understanding—and the knowledge gaps that remain to be filled—what are the implications for day-to-day clinical practice? Currently, the answer is that universal treatment should be applied to eradicate AK lesions which, if untreated, will become cancerous and metastasize in a certain number of cases. Because prevention is a fundamental tenet of medical care, the goal of management is restora-

tion of the skin to a clinically less photodamaged, genetically native, immunologically competent state and, ultimately, the prevention of SCC in situ, as well as invasive and metastatic disease.

While an important target, DNA is not the exclusive target of UV light. Photodamage may occur in any layer of the epidermis or dermis, as well as in cells trafficking through the dermis. Thus, of paramount importance in the primary prevention of cutaneous disease is the delivery of the broadest-spectrum photoprotection to all layers of skin. The specific steps in the prevention of SCC in a patient with AKs include avoidance of further direct damage to DNA and other integumentary structures, suppression of harmful inflammation, the reversal of immunosuppression, and eradication of precursor lesions.

Patients with one actinic keratosis lesion are likely to develop other lesions; global [ultraviolet light] insults are likely to require global therapy. Thus, treatment of the entire field—field therapy—is becoming increasingly accepted as the preferred management strategy.

Field Therapy: Science-Based Approach to AK Management

Lesion-targeted therapy, also known as focused or ablative therapy, is a practical, time-honored, and effective approach for treating AK lesions. However, with lesion-targeted therapy, only the AKs that are visible are treatable, and any subclinical lesions that may be present in the same area are left untreated. Not surprisingly, recurrence rates in treated areas can be high.

Because photodamage is not focal, patients with one AK lesion are likely to develop other lesions; global insults may require global therapies. Thus, treatment of the entire field in which visible AK lesions occur—known as field therapy—is becoming increasingly accepted as the preferred management strategy.

Field therapy is an approach that utilizes the latest cancer biology concepts.

The field therapies currently approved by the US Food and Drug Administration (FDA) and in common use for the treatment of AK are three topical agents: 5-fluorouracil (5-FU), the nonsteroidal antiinflammatory drug diclofenac, and the immune response modifier (IRM) imiquimod. 5-FU works mainly by inhibiting thymidylate synthetase, interfering with the process of DNA synthesis and causing cell death. Diclofenac's mechanism of action has not been firmly established, but it is likely to involve inhibition of cyclooxygenase-2. The mechanism of action of imiquimod is described in the next section.

Field therapy is particularly important in patients who have undergone solid organ transplantation because immunosuppression dramatically increases the risk for cutaneous neoplasias, including malignant melanoma, basal cell carcinoma (BCC), and SCC. The incidence of SCC is between 65-fold and 100-fold greater than that in immunocompetent individuals.⁷

IRMs: A Brief Overview

Imiquimod, the first agent in the class of IRMs, stimulates toll-like receptors (TLRs) on dendritic cells, subsequently inducing a variety of cytokines and activating dendritic cells and effector cell responses. TLRs, which are present in many types of animals, recognize highly conserved, species-specific molecules, including bacterial lipoproteins, lipopolysaccharides, peptidoglycans, and DNA. TLRs also recognize RNA, viral components, and IRMs. TLR-7 and TLR-8, specifically, are stimulated by IRMs.⁸

Activation of the innate and the acquired immune system is thought to be the mechanism of action in imiquimod, the FDA-approved treatment for genital warts, AK, and superficial BCC. The innate system is nonspecific and has no memory—it is immediately available, requires no education, and provides rapidly responding physical, chemical, and biological barriers to thwart invasion. The acquired system is activated via cytokine cascades that stimulate the T-helper cell type 1 (T_H1) response (cellular immunity) while suppressing the T_H2 response (humoral

Continued on page 13

Management of Actinic Keratoses: Current Options and Patient Selection

DANIEL M. SIEGEL, MD, MS

Two main approaches to treatment of actinic keratoses (AKs) may be considered: physician-controlled, office-based modalities and at-home, patient-applied treatments. A major advantage of the former is that patient compliance is not involved—once the treatment is performed, the patient leaves the office and the intervention is complete. In contrast, with patient-applied therapies, efficacy depends on a patient's ability and motivation to comply with the prescribed regimen.

The most commonly used physician-applied treatments are cryotherapy, curettage, shave excision, electrocautery, photodynamic therapy (PDT), chemical peels, dermabrasion, and various combinations of these. The patient-applied therapies that currently are approved are the pharmacologic mainstays of our armamentarium for the treatment of AKs: the topical agents 5-fluorouracil (5-FU), diclofenac, and imiquimod.

Cryotherapy

Cryotherapy is the most commonly used treatment for AKs. Many cryogens are available, but clinicians seem to prefer liquid nitrogen, with a temperature of -196°C . Keratinocytes die when frozen to temperatures between -40° and -50°C ; a fast freeze with direct application of liquid nitrogen using a cryotherapy gun can give greater cell death. An alternative is indirect application, by dipping a cotton swab in the liquid nitrogen and touching the swab to the lesion. This is less painful than direct application, but it produces a slower freeze and is not as destructive, perhaps reducing the efficacy of the treatment.

Cryotherapy works by a physical phenomenon: ice crystals develop within cells that are frozen, resulting in cell death. The various structures in the skin have different sensitivities to cold temperatures. Keratinocytes are more sensitive to destruction by cryogens, whereas collagen, blood vessels, and nerves are more cold-resistant, so this modality preserves these important dermal structures. However, melanocytes in the epidermis

are destroyed even before keratinocytes, so hypopigmentation is a common consequence of cryotherapy.

The advantages of this modality are that it is performed quickly and easily, and anesthesia is optional. The disadvantages are that cryotherapy may be painful, and only the targeted lesions are treated, meaning that any subclinical lesions are not eradicated and may later emerge as new, clinical AKs. The treated area heals in 7 to 10 days. The cosmetic outcome tends to be fair to excellent, although hypopigmentation is common.

My Preference: I use a cryotherapy gun, and for small lesions, I administer two cycles to each lesion. For broad AKs, I use a back-and-forth motion to cover the surface of the lesions. However, I avoid producing a deep ice ball; the appropriate depth is indicated by an immediate whealing by the end of the second cycle, and bullae should occur the next day.

When more than a few lesions are to be treated in a large anatomic area (such as the forehead, scalp, cheeks, or arms), anesthesia during treatment and analgesics following therapy are necessary. Premedication with aspirin with oxycodone, acetaminophen with hydrocodone, or another analgesic also may be considered.

Curettage and Shave Excision

Curettage allows the clinician to experience a "feel" for the depth of a lesion. If the curette descends through the dermis, a biopsy is indicated to rule out squamous cell carcinoma (SCC). Curettage shares a disadvantage with cryotherapy: only targeted lesions are treated. Unlike cryotherapy, curettage is almost always painful and anesthesia usually is necessary. Electrocautery is a helpful adjunct to control bleeding.

Curettage results in physical destruction of lesions, and, with the addition of thermal destruction from electrocautery, most of an AK lesion is eradicated. The inflammation that results as part of the healing process may eliminate any residual lesion at the site of treatment. Healing takes 7 to 10 days. The cosmet-

ic outcome is fair to excellent, but hypopigmentation is common; scarring can occur, particularly if the electrocautery technique is aggressive.

My Preference: If the curette dips when I remove what appears to be an AK, my index of suspicion for invasive SCC increases and I have the specimen biopsied. If my initial clinical examination leads me to suspect that an AK may have progressed to SCC, I perform a shave excision prior to curettage so the pathologist will have a specimen that can be cut vertically.

I prefer cryotherapy to curettage in most cases. I use curettage when SCC seems possible, if a patient requests it, or, if I am performing a Mohs' procedure and another lesion is in the operative field, I remove the AK with a curette conveniently at hand on the instrument tray.

Electrosurgery

Electrosurgery as monotherapy is not desirable. It is a blind approach, requires anesthesia, and only targeted lesions are treated. The mechanism of action is thermal destruction of a lesion; healing occurs in 10 to 21 days. The cosmetic results are fair to good, but scarring and hypopigmentation are not uncommon.

Photodynamic Therapy/ Aminolevulinic Acid

The protocol for PDT/aminolevulinic acid (ALA) approved by the US Food and Drug Administration (FDA) calls for application of a 20% solution of ALA to the skin at the first office visit and a waiting period of 14 to 18 hours, during which this agent is converted enzymatically to protoporphyrin IX. (Therapy has evolved over the past few years to the point where an overnight incubation period is used infrequently; incubation periods of as little as 1 to 3 hours are more commonly employed.) After incubation, the treated area is exposed to a blue light source for 1,000 seconds—approximately 16 minutes.

A benefit of PDT/ALA is that it can be used for spot treatment or for a large

anatomic area, such as the entire scalp. A problem with this therapy is that during the ALA conversion period, the treated area must be protected from light exposure to prevent premature activation of ALA. This means that a patient must remain in the dermatologist's office for the duration of ALA conversion, resulting in a long period of downtime for the patient.

The healing time is 10 to 20 days, and patients have substantial edema for 1 to 6 days. The cosmetic outcome tends to be excellent, and an incidental benefit is a good rejuvenation effect.

My Preference: To ensure good penetration of ALA, I prepare the lesions with an acetone scrub followed by a scrub with Jessner's solution, using gauze pads. For the same reason, I remove the top layers of hyperkeratotic lesions by sanding with sandpaper or drywall sanding screen. I use a soap-and-water wash to remove any residual Jessner's solution. If the patient tolerates it, I prefer a longer incubation period after ALA application, but a minimum of 2 to 3 hours, in any case.

To control discomfort, pretreatment with an analgesic is a reasonable step, and using an electric fan to cool the treated skin often helps as well.

Medium-Depth Chemical Peels

Medium-depth chemical peels have the important benefit that the entire face can be treated at one time. Unfortunately, the epithelium on appendages does not respond to medium-depth peels; for these areas, a deeper peel with phenol is required, but this can result in the appearance of porcelain-white skin and is associated with the risk for cardio- and nephrotoxicity.

The medium-depth peels work by physical destruction via protein coagulation, inflammation resulting from this coagulation, and some thermal damage from an exothermic reaction. The healing period is 5 to 10 days, and the cosmetic outcome is very good to excellent.

My Preference: As with PDT/ALA, I perform acetone and Jessner's solution scrubs before doing the procedure. Using a proctoscopy swab, I apply 35% trichloroacetic acid to the forehead, into the hairline, and on the cheeks, chin, nose, and lips. I treat the eyelids with a large-head standard swab. I continue with the application until frosting is visi-

ble and the entire treated area appears white. Following this, fanning the area and applications of very cold, saline-soaked gauze help ease discomfort. When the discomfort is under control, the patient is released from the treatment room and sent home.

Dermabrasion

Dermabrasion is a time-consuming procedure, but it can be used both to spot-treat and to manage large fields of AKs. As with medium-depth peels, dermabrasion is not effective for treating appendages. This technique works on the principle of physical destruction. Healing occurs in 5 to 10 days, and the cosmetic outcome is very good to excellent.

My Preference: Dermabrasion is not commonly done in my practice, and I limit these procedures to treating the scalp in patients who have undergone organ transplantation. These patients often have large areas of AKs, and dermabrasion is well tolerated and is a fast, efficient way to clear these fields. When I do use this modality, I use tumescent anesthesia and abrade the area using drywall sanding sheets rather than the standard electrical dermabrasion device.

Combining Procedures

According to each patient's unique clinical picture, these techniques can be mixed and matched. Any of the benefits of each modality will be seen. However, combination therapy also can result in overtreatment, and all of the risks of each modality may occur. Depending on individual patient responses, the cosmetic outcomes can range from poor to excellent.

5-Fluorouracil

5-FU has been the long-term mainstay of patient-applied therapies for AKs. Although 5-FU has a long track record of efficacy, noncompliance is a common problem because the side effects of treatment are unpleasant. 5-FU causes itching, burning, and crusting beginning at about the eighth day of treatment and persisting through the end of the treatment period plus an additional week.

To minimize the duration of these effects—and, perhaps, enhance compliance—some clinicians have tried using shorter courses of therapy, but, in my opinion, these strategies adversely affect efficacy, resulting in much of the disease

being untreated. The full course of therapy provides the best therapeutic outcome.

5-FU's mechanism of action is twofold: (1) the inhibition of thymidylate synthetase, which affects DNA synthesis, resulting in cell death, and (2) inflammation.

Healing usually occurs within 7 to 10 days after the course of therapy has been completed. The cosmetic outcome is very good to excellent, leaving the skin smooth and clear. However, the beginning of the healing process also is characterized by erythema, which can persist for months.

My Preference: My approach with 5-FU is "no pain, no gain" because I think that inflammation is a very important component of this drug's mechanism of action. I prescribe either 0.5% micronized cream applied once daily or the 5% cream formulation applied twice daily. I have tried a once-daily regimen, and my experience is that this can be as effective as the twice-daily regimen; I believe the frequency of daily applications is less important than the duration of the treatment period.

I use a course of 30 days when treating the face and 45 days to 60 days when treating the scalp, arms, or trunk. When increased penetration of the arms or scalp is needed, I have the patient occlude the treated area with plastic wrap.

To control itching, I prescribe antihistamines, and I control pain with nonsteroidal antiinflammatory drugs (NSAIDs) or, if necessary, with narcotics. I avoid both topical and systemic corticosteroids. In the past, I treated some patients with corticosteroids during 5-FU therapy, but I found that this combination results in a lower response rate than when 5-FU is used alone.

Diclofenac

The topical NSAID diclofenac represents an intriguing new approach to the treatment of AKs. This drug is thought to work by inhibiting cyclooxygenase-2. Diclofenac does not appear to cause much inflammation or irritation, and patients are not distressed by this treatment. Further, because the surface effects on the skin are limited, no healing time is involved following cessation of therapy. The cosmetic outcome of treatment is excellent.

The disadvantages of diclofenac ther-

apy are the long duration of treatment (6 months or more of daily applications) and, in my experience, an efficacy below that of other therapies.

Imiquimod

Imiquimod is a topical immune response modifier that works by stimulating the local immune system. (For further details on imiquimod's mechanism of action, see Dr Goldgeier's article on page 7.) This agent is nontoxic, has no effect on normal skin, and may have some long-lasting beneficial effects on immune surveillance. The main disadvantage of imiquimod treatment is that not all health plans accept this drug as first-line therapy.

Healing with imiquimod is an interesting process. Many lesions heal during the course of therapy. Others may heal within 2 to 3 weeks after cessation of a course of therapy involving applications two or three times a week for 16 weeks.

The cosmetic result of imiquimod treatment is very good to excellent. In addition, therapy results in a rejuvenation effect, similar to what is seen with 5-FU, medium-depth chemical peels, and dermabrasion.

Alternatives to the FDA-approved

regimen of twice-weekly applications for 16 weeks have been used with comparable success. If a patient can tolerate more frequent applications—three times a week—a shorter duration (12 weeks) can be considered. Some clinicians prefer to use a pulsed regimen in selected patients, treating on a schedule of 7 days on and 21 days off, or 5 days on and 10 days off. These schedules offer the advantage of less inflammation, often resulting in little or no downtime.

My Preference: I prefer to use the FDA-approved dosing schedule of twice-weekly applications for 16 weeks.

Patient Selection: Some General Considerations

The number, character, and location of AKs should strongly influence the choice of therapy. For example, a few lesions on otherwise normal skin may be treated with lesion-targeted modalities; multiple lesions on severely sun-damaged areas are best managed with field therapies. Other issues that should be factored into this decision include travel distance to the clinician's office or transportation barriers, time constraints (taking time off during a work day is problematic for

many patients), ability to use a patient-applied therapy (limited mobility can affect which sites the patient can reach), and patient preference.

A major concern for patients is whether a treatment is covered by their health insurance provider. Some patients have prescription plans that permit the clinician to choose the treatment, with few or no restrictions, whereas other plans require strict adherence to a set formulary. When asked to choose between a drug that must be paid for out-of-pocket and discretionary purchases, patients almost always will choose the latter.

Conclusion

The ideal treatment for AKs would be affordable, easy to use, associated with minimal cosmetic concerns, and not associated with discomfort, inconvenience, or downtime for the patient. No single therapy currently available fulfills all of these criteria, but careful matching of therapy to patient—considering both medical and practical needs—allows the clinician to provide effective and safe treatment that is acceptable and suited to each patient. ■

Today's View of Actinic Keratosis: A Snapshot *Continued from page 6*

- 1990-1999: National Ambulatory Medical Care Survey. *Cutis*. 2002;70(2 Suppl):8-13.
2. Salasche SJ. Epidemiology of actinic keratoses and squamous cell carcinoma. *J Am Acad Dermatol*. 2000;42(1 Pt 2):4-7.
3. Black HS, Herd JA, Goldberg LH, et al. Effect of a low-fat diet on the incidence of actinic keratosis. *N Engl J Med*. 1994;330:1272-1275.
4. Harwood CA, Suretheran T, Sasieni P, et al. Increased risk of skin cancer associated with the presence of epidermodysplasia verruciformis human papillomavirus types in normal skin. *Br J Dermatol*. 2004;150:949-957.
5. Chang LC, Sheu HM, Huang YS, Kuo KW. Quantitative determination of the expression of xeroderma pigmentosum F gene in human nonmelanoma skin cancers. *Biochem Biophys Res Commun*. 2000;273:454-458.
6. Ulrich C, Schmook T, Nindl I, Meyer T, Sterry W, Stockfleth E. Cutaneous precancers in organ transplant recipients: An old enemy in a new surrounding. *Br J Dermatol*. 2003;149(Suppl 66):40-42.
7. Nguyen P, Vin-Christian K, Ming ME, Berger T. Aggressive squamous cell carcinomas in persons infected with the human immunodeficiency virus. *Arch Dermatol*. 2002;138:758-763.
8. Stulberg DL, Crandell B, Fawcett RS. Diagnosis and treatment of basal cell and squamous cell carcinomas. *Am Fam Physician*. 2004;70:1481-1488.
9. Nguyen TH, Ho DQ. Nonmelanoma skin cancer. *Curr Treat Options Oncol*. 2002;3:193-203.
10. McGovern TW, Leffell DJ. Actinic Keratoses and Non-Melanoma Skin Cancer. American Academy of Dermatology. <http://www.aad.org/professionals/Residents/MedStudCoreCurr/DCActinicKer-NoMelCancer.htm>. Accessed October 31, 2005.
11. Glogau RG. The risk of progression to invasive disease. *J Am Acad Dermatol*. 2000;42(1 Pt 2):23-24.
12. Thompson DC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. *N Engl J Med*. 1993;329:1147-1151.
13. Thai KE, Fergin P, Freeman M, et al. A prospective study of the use of cryosurgery for the treatment of actinic keratoses. *Int J Dermatol*. 2004;43:687-692.
14. Simmonds WL. Management of actinic keratoses with topical 5-fluorouracil. *Cutis*. 1976;18:298-300.
15. Loven K, Stein L, Furst K, Levy S. Evaluation of the efficacy and tolerability of 0.5% fluorouracil cream and 5% fluorouracil cream applied to each side of the face in patients with actinic keratosis. *Clin Ther*. 2002;24:990-1000.
16. Nelson C, Rigel D, Smith S, Swanson N, Wolf J. Phase IV, open-label assessment of the treatment of actinic keratosis with 3.0% diclofenac sodium topical gel (Solaraze). *J Drugs Dermatol*. 2004;3:401-407.
17. Jeffes EW, McCullough JL, Weinstein GD, Kaplan R, Glazer SD, Taylor JR. Photodynamic therapy of actinic keratoses with topical aminolevulinic acid hydrochloride and fluorescent blue light. *J Am Acad Dermatol*. 2001;45:96-104.
18. Kurwa HA, Yong-Gee SA, Seed PT, Markey AC, Barlow. A randomized comparison of photodynamic therapy and topical 5-fluorouracil in the treatment of actinic keratoses. *J Am Acad Dermatol*. 1999;41:414-418.
19. Stockfleth E, Meyer T, Benninghoff B, et al. A randomized, double-blind, vehicle-controlled study to assess 5% imiquimod cream for the treatment of multiple actinic keratoses. *Arch Dermatol*. 2002;138:1498-1502.
20. Lebowitz M, Dinehart S, Whiting D, et al. Imiquimod 5% cream for the treatment of actinic keratosis: Results from two phase III, randomized, double-blind, parallel group, vehicle-controlled trials. *J Am Acad Dermatol*. 2004;50:714-721.
21. Salasche SJ, Levine N, Morrison L. Cycle therapy of actinic keratoses of the face and scalp with 5% topical imiquimod cream: An open-label trial. *J Am Acad Dermatol*. 2002;47:571-577.

When and Why Should Actinic Keratoses Be Treated?

ARIELLE N.B. KAUVAR, MD

Actinic keratoses (AKs) historically have been regarded as premalignant lesions. Although these lesions are present only in the epidermis and, as such, have no metastatic potential, it is now believed that AKs represent the earliest form of squamous cell carcinoma (SCC).

AKs and SCCs share many features. The same individuals who are at risk for AKs also are at risk for SCC—most commonly, these are fair-skinned Caucasian individuals who have a history of excessive sun exposure. Risk also is related to geography: individuals who live in regions close to the equator have a greater risk than do those who live in northern climates. In populations in the northern hemisphere, 11% to 25% of adults have at least one AK;¹ in Australia, AKs are seen in 40% to 60% of adults.²

Progression From AK to SCC

The exact number of AKs that progress to SCC is unknown, but one study estimates the risk as 0.075% to 0.096% per lesion per year.³ An individual with AK has an average of 7.7 lesions, so the risk for developing an SCC is 10.2% over the course of 10 years.⁴ Another study estimates the rates of progression from AK to SCC to be 13% to 20% over 10 years.⁵

These estimated rates for progression of AK lesions to SCC are similar to the rates seen in other forms of intraepithelial neoplasia. For example, 15% of low- to moderate-grade lesions of cervical intraepithelial neoplasia (CIN) that are classified as CIN I or II will progress to carcinoma in situ—CIN III—or more advanced carcinoma.⁶ New terminology for AKs has been proposed—keratinocytic intraepithelial neoplasia (KIN)—that reflects the similarities between the AK-SCC and CIN-cervical carcinoma.⁷

For a detailed discussion of the histologic, histochemical, and molecular characteristics of AKs and SCCs, see Dr Goldgeier's article on page 7.

Risk for AK Progression to SCC

Virtually all SCCs arising on sun-damaged skin are associated histological-

ly with AKs. In addition, the cytologic features of individual altered keratinocytes that comprise AKs and SCCs are indistinguishable. The atypical keratinocytes characteristic of both AKs and SCCs show a loss of polarity, nuclear pleomorphism, disordered maturation, and increased mitotic figures, but with AKs, these features are confined to the epidermis and, with invasive SCCs, they are observed in the dermis.

Virtually all SCCs arising on sun-damaged skin are associated histologically with AKs. In addition, the cytologic features of individual altered keratinocytes that comprise AKs and SCCs are indistinguishable.

The risk for SCC increases with increased sun exposure and the length of time that the AKs are present, as well as the number of baseline AKs that are present (Table). In an Australian population, Green and Battistutta⁸ showed that individuals who had five or fewer AKs had a relative risk of developing SCC of 1.0; those who had between 6 and 20 lesions had a relative risk increased to 4.0, and individuals with more than 20 AKs had a relative risk of 20.0.

It is now known that AKs on photo-damaged skin are a visible manifestation of the presence of expanded clones of dysplastic cells at a subclinical, cellular level—that is, it is unlikely that visible AKs exist alone in a photodamaged region of the skin. This concept, known as field cancerization, describes the presence of developing clones that may remain stable, may spontaneously regress, or may progress to AKs. Support for this concept comes from observations of topical therapies in areas of visible AKs: applications of these agents reveal the presence and location of subclinical

lesions within the treated field. Subclinical lesions light up—that is, they become erythematous—when exposed to topical AK therapies. This reinforces the advisability of treating an entire anatomic unit when multiple AKs are present.

Conclusion

In 2003, an estimated 900,000 to 1.2 million cases of nonmelanoma skin cancer (NMSC) occurred in the United States; 20%, or approximately 200,000, were cases of SCC. NMSCs account for \$650 million annually in medical care costs in the United States. Each year, approximately 2,200 Americans die from NMSC, and most of these are metastatic SCC.^{9,10}

AKs now are recognized to be the earliest manifestation on the continuum of SCC and are more aptly classified as KIN rather than precancerous lesions. The number, location, and type of lesions and patient tolerability of a modality should determine the choice of therapeutic intervention.

AKs have the potential to progress to invasive and metastatic SCC and, therefore, should be treated promptly. ■

References

1. Gupta AK, Cooper EA, Feldman SR, Fleischer AB Jr. A survey of office visits for actinic keratosis as reported by NAMCS, 1990-1999. *Cutis*. 2002;70:8-13.
2. Frost CA, Green AC, Williams GM. The prevalence and determinants of solar keratosis at a subtropical latitude (Queensland, Australia). *Br J Dermatol*. 1998;139:1033-1039.

Table. Skin Cancer Risk Stratified According to Number of AKs at Baseline

No. of AKs	Relative Risk
5 or less	1.0
6 to 20	4.0
>20	20.0

Source: Green A, Battistutta D. *Int J Cancer*. 1990;15:356-361.

3. Marks R, Rennie G, Selwood TS. Malignant transformation of solar keratosis to squamous cell carcinoma. *Lancet*. 1998;1:795-797.
4. Dodson JM, DeSpain J, Hewett JE, et al. Malignant transformation of actinic keratosis and the controversy over treatment: A patient oriented perspective. *Arch Dermatol*. 1991;127:1029-1031.
5. Montgomery H, Dorffel J. Verruca senilis und keratoma senile. *Arch f Dermat u Syphil*. (Berlin). 1939;39:387-408.
6. Oster AG. Natural history of cervical intraepithelial neoplasia: A critical review. *Int J Gynecol Patbol*. 1993;12:186-192.
7. Cockerell C, Wharton JR. New histopathological classification of actinic keratosis. *J Drugs Dermatol*. 2005;4:462-467.
8. Green A, Battistutta D. Incidence and determinants of skin cancer in a high-risk Australian population. *Int J Cancer*. 1990;15:356-361.
9. Gloster HM Jr, Brodland DG. The epidemiology of skin cancer. *Dermatol Surg*. 1998;22:217-226.
10. Weinstock MA. Death from skin cancer among the elderly: Epidemiologic patterns. *Arch Dermatol*. 1997;133:1207-1209.

The Scientific Basis of Skin Cancer Continued from page 8

immunity). Imiquimod also has been shown to induce apoptosis in cell culture, albeit at concentrations several orders of magnitude higher than those used in clinical practice.⁹

Conclusion

Photodamage is a precancerous condition that results from exposure to UV light. AKs represent a relatively late stage in the development of UV-induced lesions. Although only a percentage of AKs become SCC, AKs remain the major precursor to SCC. AK and SCC may be indistinguishable clinically, histologically, and/or molecular biologically. These lesions now are commonly felt to exist on a spectrum of disease with identical causation, mutation, and progressive morphology.

Instead of progressing to SCC, some AKs may remain stable, in an arrested atypical state, or can regress to a clinically less aggressive state. Currently, it is

impossible to predict which particular AKs will progress to SCC. For this reason, it is appropriate to treat all AKs.

As diagnostic abilities become more refined, the distinction between AK and SCC will blur further. Evolving concepts of cutaneous carcinogenesis provide the conceptual framework for treatment of cancer at increasingly earlier stages in its development. State-of-the-art biomedical research provides elegant tools for the dermatologist to prevent photodamage and to utilize field therapies in the treatment of cutaneous neoplasia. ■

References

1. Callen JP, Bickers DR, Moy RL. Actinic keratoses. *J Am Acad Dermatol*. 1997;36:650-653.
2. Grossman D, Leffell DJ. The molecular basis of non-melanoma skin cancer: A new understanding. *Arch Dermatol*. 1997;133:1263-1270.
3. Kripke ML. Ultraviolet radiation and immunology: Something new under the sun—Presidential address. *Cancer Res*. 1994;54:6102-6105.
4. Yantsos VA, Conrad N, Zabawski E, Cockerell CJ. Incipient intraepidermal cutaneous squamous cell carcinoma: A proposal for reclassifying and grading solar (actinic) keratoses. *Semin Cutan Med Surg*. 1999;18:3-14.
5. Guenther ST, Hurwitz RM, Buckel LJ, et al. Cutaneous squamous cell carcinomas consistently show histologic evidence of in situ changes: A clinicopathologic correlation. *J Am Acad Dermatol*. 1999;41:443-448.
6. Marks R, Foley P, Goodman G, et al. Spontaneous remission of solar keratosis: The case for conservative management. *Br J Dermatol*. 1986;115:649-655.
7. Berg D, Otley CC. Epidemiology of skin cancer in organ transplant recipients. *J Am Acad Dermatol*. 2002;47:1-17.
8. Data on file, 3M, Minneapolis, Minn.
9. Schon M, Bong B, Drewniak C, et al. Tumor-selective induction of apoptosis and the small-molecule immune response modifier imiquimod. *J Natl Cancer Inst*. 2003;95:1138-1149.

Imiquimod in AKs: A Study of Cosmetic Outcomes

ALBERT M. KLIGMAN, MD, PhD

A number of treatments for actinic keratosis (AK) have been well described in other articles in this supplement. A recent study by our group has proposed a new approach, based on the concept of field cancerization and field therapy. Our purpose was to determine whether subclinical AKs can be eradicated before they become clinically visible, a preventive rather than a treatment strategy.

Our initial hypothesis was that, as occurs with topical 5-fluorouracil, treatment with imiquimod would show the presence of subclinical AKs in the form of red “flares.” However, we unexpectedly found that imiquimod yielded important cosmetic improvements. The purpose of this presentation is to document the clinical benefits and to describe the histologic changes which underlie the cosmetic improvements.

Design and Methods

We enrolled 10 healthy women between 45 and 55 years of age with no clinically visible AKs. Each showed early signs of photodamage, including fine periorbital wrinkles, dyspigmentation (mottling), roughness, and poor texture. They also had prominent widened follicular orifices, often called clogged pores, which are horn-filled sebaceous follicles

analogous to microcomedones in acne vulgaris (Figure 1).

Photodamage at baseline was assessed by several methods. Global assessment of appearance was made by a dermatologist experienced in studies of the photoaged face. Pre- and posttreatment biopsies were taken for histochem-

The posttreatment histochemical examination showed complete correction of atrophy and atypia, with a greatly enhanced granular layer, and restoration of differentiation and polarity.

ical analysis. Two imaging methods, digital photography and videomicroscopy, were used to document improvement. Finally, three bioengineering techniques—Minolta colorimetry, Silflo replicas, and fringe projection—were used to provide objective measurements of improvement.

The patients were treated with imiquimod 5 days a week for 4 weeks.

This dosage differs from what is approved by the US Food and Drug Administration for the treatment of AKs, which is thrice-weekly applications for 16 weeks.

Study Findings*

By the end of the study, patients’ fine wrinkles were no longer visible (Figure 2). Clogged pores were no longer in evidence (Figure 3 on next page). Surface irregularities and poor texture were substantially reduced. The skin looked and felt smoother to the touch.

The most revealing aspect of this study relates to the histologic changes. Pretreatment histochemical examination demonstrated epidermal atrophy, atypia, diffuse dysplasia with poor differentiation, lack of polarity, and hyperchromatic nuclei. Marked differences in staining, sizes, and shapes of keratinocytes were evident. These features are characteristic of the photodamaged epidermis in which AKs develop, traditionally called premalignant changes. The posttreatment specimens showed complete correction of atrophy and atypia, with a greatly enhanced granular layer, and restoration of differentiation and polarity.

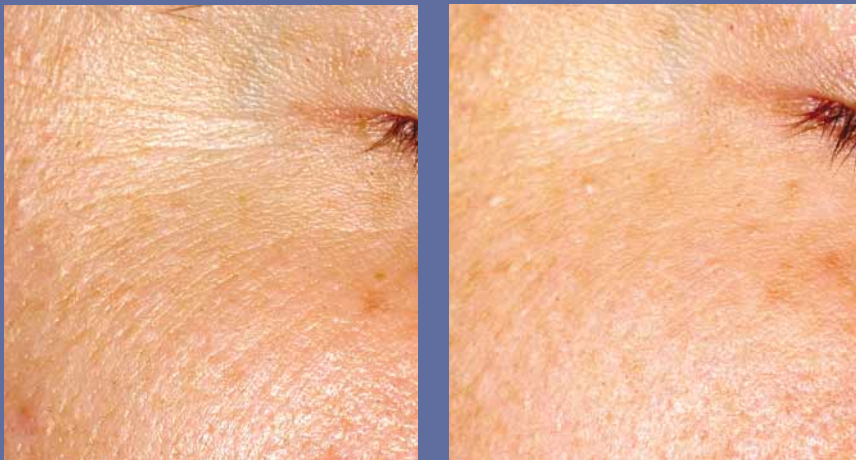
In the pretreatment Fontana-stained specimens, dense aggregates of melanosomes were concentrated over the

Figure 1. Hyperkeratotic Follicle



One early sign of photodamage is horn-filled sebaceous follicles. A characteristic prominent widened follicular orifice is shown on this histologic specimen.

Figure 2. Digital Photography



Digital photographs taken before (left) and after (right) treatment with imiquimod demonstrate the resolution of many of the fine periorbital wrinkles that are characteristic early signs of photodamage.

basal keratinocytes. In normal skin, melanosomes are incorporated into phagolysosomes of the keratinocytes, which enzymatically degrade them so that no pigmented granules are found in the upper epidermis or in the stratum corneum. By contrast, in photodamaged skin, melanosomes are not phagolysed and can be seen not only in the upper epidermis but also within corneocytes of the stratum corneum. After imiquimod treatment, there were far fewer melanosome aggregates in the basal keratinocytes and none could be seen in the horny layer. The clinical consequence is that mottling and irregular pigmentation faded, providing a more uniform color, a result that was highly valued by patients.

The effect of imiquimod was confined to the epidermis. The three main components of the dermal matrix—collagen bundles, abnormal elastic fibers, and glycosaminoglycans—were not altered.

The photoaged stratum corneum has a number of deficiencies; prominent among them is increased transepidermal water loss. The horny layer is leaky and, as a consequence, loses too much water to the environment. It has long been recognized that failure of the horny layer to maintain a level of hydration greater than 10% results in brittleness, cracking, scaling, and roughness.¹ Bioengineering techniques were performed to assess the hydration state (including hygroscopicity and hydrophilicity) of the horny layer before and after imiquimod treatment. In every case, 1 month of therapy with imiquimod resulted in improved hydration of the stratum corneum. This, in turn, softens the stratum corneum's horny layer, makes it more



elastic, smoothes its surface, and eliminates rough scaling, promoting an even texture.

The global improvement ratings by the subjects and the dermatology expert indicated substantial improvement in appearance.

Conclusion

Studies in which imiquimod was used to treat AKs with thrice-weekly applications for 16 weeks show that this regimen often produces erosions, crusting, exudation, and discomfort, often accompanied by pain and stinging.² In our study, none of the patients showed visible side effects, and none reported any adverse sensory reactions such as stinging/burning. The cosmetic attributes of the 5% formulation were rated highly, with good slip and rub-in, leaving no residue, and without greasiness.

In the published studies of imiquimod-treated AKs, the authors noted that in addition to clearance of the AKs, there were substantial cosmetic

improvements which they briefly described as improvement in “skin quality.” As studies of this agent in AKs and other conditions demonstrate, the therapeutic benefits of imiquimod can be explained by activation of the innate and acquired immune system, but this agent also possesses other effects that are just beginning to be understood.^{3,4}

In sum, we demonstrated a new benefit of imiquimod treatment, in a 1-month schedule, a kind of added value to its ability to correct epidermal dysplasia. These findings justify further longer-term treatment of photodamage. ■

References

1. Vender RB, Goldberg O. Innovative uses of imiquimod. *J Drugs Dermatol.* 2005;4:58.
2. Korman W, Moy R, Ling M, et al. Dosing with 5% imiquimod cream three times weekly for the treatment of actinic keratoses. *Arch Dermatol.* 2005;141:467.
3. Leffel AJ. The scientific basis of skin cancer. *J Am Acad Dermatol.* 2000;42:518.
4. Sauder DW. Imiquimod: Modes of action. *Br J Dermatol.* 2003;149:5.

* An overview of the study results is presented here. Detailed findings including statistical results, will be submitted at a later date.

Release Date: December 2005 **Expiration Date for AMA/PRA credit:** December 31, 2006 **Estimated Time to Complete This Activity:** 2 hours
CME INSTRUCTIONS: This issue of SKIN & ALLERGY NEWS provides 2 free AMA/PRA Category 1 credits. To receive FREE CME credit, forward the Test Answer Sheet and Evaluation Form to the address or FAX number shown below. A photocopy of this form is acceptable. Please return via FAX (908-547-2201) or mail to: The Elsevier Office of Continuing Education (EOCME), Department 290049-c • 685 Route 202/206, Bridgewater, NJ 08807
Responses for AMA/PRA credit must be submitted by December 31, 2006.

Please circle the most appropriate response. Seven correct responses are required for credit.

1. Cryotherapy's mechanism of action in the treatment of actinic keratoses is physical destruction of _____.
 - a. Atypical keratinocytes
 - b. Melanocytes
 - c. Subclinical lesions
 - d. Both keratinocytes and melanocytes
2. Which one of the following statements about imiquimod is true?
 - a. Imiquimod is approved for the treatment of dysplastic nevi.
 - b. Imiquimod may be toxic in immunocompromised patients.
 - c. Imiquimod use may have some long-lasting beneficial effects on immune surveillance.
 - d. Imiquimod's mechanism of action has not been described, but is thought to be related to inhibition of cyclooxygenase-2.
3. The most studied target of the multistep carcinogenesis concept of cancer development has been:
 - a. DNA
 - b. Langerhans' cells
 - c. RNA
 - d. p53 tumor suppressor gene
4. Partial-thickness keratinocytic squamous atypia is characteristic of:
 - a. Actinic keratosis
 - b. A definitive sign that an actinic keratosis lesion is in the process of progressing to invasive squamous cell carcinoma
 - c. In situ squamous cell carcinoma (Bowen's disease)
 - d. Invasive squamous cell carcinoma
5. Which of the following statements concerning ultraviolet light insult is *not* true?
 - a. Any layer of the epidermis or dermis may be affected.
 - b. Cells trafficking through the dermis may be affected.
 - c. DNA is affected.
 - d. Only DNA and the epidermal layer of skin are affected.
6. In terms of natural history, actinic keratoses:
 - a. May progress to squamous cell carcinoma
 - b. May progress to basal cell carcinoma
 - c. Will progress to squamous cell carcinoma
 - d. Both a and b
7. Newer standards for efficacy of actinic keratosis therapy from the US Food and Drug Administration require that:
 - a. Efficacy may be established on the basis of percentage of lesions cleared in the study population.
 - b. Efficacy may be established on the basis of number of lesions cleared in the study population.
 - c. Efficacy must be reported in terms of number of lesions cleared per patient.
 - d. Efficacy must be reported in terms of the percentage of patients who experience complete clearance of their actinic keratoses.
8. In populations in the northern hemisphere, the percentage of adults who have at least one actinic keratosis lesion ranges from:
 - a. 1% to 15%
 - b. 11% to 25%
 - c. 21% to 35%
 - d. 31% to 45%
9. Which one of the following statements concerning the risk for squamous cell carcinoma is *not* true?
 - a. Risk increases with increased sun exposure.
 - b. Risk increases with the length of time that actinic keratoses are present.
 - c. Risk increases in a particular region of skin when actinic keratosis lesions are hyperkeratotic in that area.
 - d. Studies of actinic keratoses and squamous cell carcinoma show that squamous cell carcinoma risk increases according to the number of actinic keratoses that are present at baseline.
10. The early signs of photodamage include mild wrinkling, dyspigmentation, and _____.
 - a. Cornflake-like scaling
 - b. Solar elastosis
 - c. Telangiectasias
 - d. Rough surface features

Course Evaluation: Please evaluate the effectiveness of this activity by circling your choice on a scale of 1 to 5, with 1 the lowest and 5 the highest.

Please indicate if the following objectives were met.

Objective #1 1 2 3 4 5
Discuss the epidemiology of actinic keratoses (AKs), the geographic differences in incidence, and the prevalence of these lesions in individuals with various Fitzpatrick skin types.

Objective #2 1 2 3 4 5
Explain what is currently known about the etiopathogenesis and carcinogenic potential of AKs.

Objective #3 1 2 3 4 5
Describe the clinical presentation of AKs and the characteristic histologic features that distinguish AKs from invasive squamous cell carcinoma.

Objective #4 1 2 3 4 5
Discuss the rationale for treating AKs.

Objective #5 1 2 3 4 5
List and describe the options now available for treating AKs, and discuss patient selection issues.

How do you rate the overall quality of the activity? 1 2 3 4 5

How do you rate the educational content of the activity? 1 2 3 4 5

Was the information presented to be fair, objective, balanced, and free of bias in the discussion of any commercial product or service?
____Yes ____No

If not, please describe:

Suggested topics for future activities:

Suggested authors for future activities:

After participation in this activity, have you decided to change one or more aspects in the treatment of your patients?
____Yes ____No

If yes, what changes will you make:
If no, why?

Would you be willing to participate in follow-up evaluations? ____Yes ____No

The EOCME thanks you for participation in this CME activity. All information provided improves the scope and purpose of our programs and your patient's care.

CME Credit Verification

I verify that I have spent ____hours/____minutes of actual time working on this CME activity. No more than 2 CME credits will be issued for this activity.

Please Print

Name: _____

Specialty: _____

Degree: _____

Affiliation: _____

Street: _____

City: _____

State: _____ ZIP: _____

Telephone: _____

FAX: _____

E-mail: _____

Signature: _____

(All information is confidential)