

Current World Views on Actinic Keratoses: Natural History and Recent Treatments

TOPIC AREAS

Epidemiology of AK: A World View

Characterizing AKs: Carcinoma in Situ?

Issues in Treatment: US and International

Treatment of Special Populations:

The Immunocompromised Patient and Others

Immune Response Modifiers:

Additional Discussion

Reimbursement Issues



Proceedings of A Clinical Roundtable

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Natural History and Recent Treatments

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Dr. Camacho-Martinez has nothing to disclose.

Dr. Gaspari discusses the unlabeled and investigational use of imiquimod for the treatment of nonmelanoma skin cancer and actinic keratosis (AK).

Dr. Johnson has received clinical grants from 3M Pharmaceuticals, Inc. He discusses the unlabeled use of imiquimod for treating AK, squamous cell carcinoma in situ (SSCIS), and basal cell carcinoma (BCC).

Dr. Maibach has nothing to disclose.

Dr. Shumack has received research grants from 3M. He discusses the unlabeled and investigational use of imiquimod for the treatment of AK, BCC, and Bowen's disease.

Dr. Spencer has received research grants from 3M. He discusses the unlabeled use of imiquimod as topical therapy for AK.

Dr. Stockfleth has received clinical grants from 3M. He discusses the unlabeled and investigational use of imiquimod.

ACCREDITATION

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TARGET AUDIENCE

This activity has been developed for dermatologists and other health care professionals who are involved in the treatment of patients with actinic keratosis (AK) and non-melanoma skin cancer.

EDUCATIONAL NEEDS

Actinic keratosis (AK), a proliferation of neoplastic keratinocytes, are treated because of their potential to progress to squamous cell carcinoma. Immunocompromised patients, such as individuals infected with human immunodeficiency virus (HIV) and those who have undergone organ transplantation, have an especially high rate of malignant transformation. Because of the long-term potential sequelae that may be associated with AKs, clinicians must have available the most current information from around the world regarding both research and clinical experience with the natural history and treatment advances in the treatment of these lesions.

LEARNING OBJECTIVES

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

- Discuss the epidemiology of actinic keratoses (AKs), including the data from the United States, Australia, and the European Union.
- Explain what is currently known about the etiopathogenesis of AK, as well as the potential for natural progression of AK to squamous cell carcinoma (SCC) and other nonmelanoma skin cancers.
- List and describe the major issues in treatment that clinicians face today throughout the world.
- Describe the research advances in the past decade that have helped clinicians understand and prevent AK progression to nonmelanoma skin cancer in immunocompromised and other high-risk populations.
- Discuss the current treatment options for AK, including the newer modalities such as photodynamic therapy and immune response modulation with imiquimod, and how reimbursement issues have affected therapeutic choices in various countries.

Current World Views on Actinic Keratoses: Natural History and Recent Treatments

Actinic keratoses (AKs) are skin lesions characterized by a proliferation of neoplastic keratinocytes. In the past, AKs were considered a cosmetic problem rather than a medical concern. Thus, treatment was once considered optional and was recommended for cosmetic improvement. However, data accumulated recently have demonstrated that AKs are biologically related to and may progress to squamous cell carcinoma (SCC), so that AKs warrant medical attention.

Recently, a panel of experts from the European Union, the United States, and Australia were convened in Paris, France, to share their clinical and research experience and views on the nature and treatment of AK.

Epidemiology of AK: A World View

Dr. Maibach: This discussion provides an update on the current evidence and opinions regarding actinic keratosis (AK) from a worldwide perspective. Dr. Camacho, would you begin the discussion of the epidemiology of AKs?

Dr. Camacho: Worldwide, among non-Latin individuals who work outdoors—in construction, for example—the prevalence of AK is 90%. In the United States, AKs affect about 4.5 million persons, and AK lesions are responsible for about 1 million physician visits per year.¹ In Australia, among Caucasians who have lived in that country for more than 40 years, its prevalence is 11%² to 50%.¹

Dr. Maibach: Dr. Shumack, you have a particularly severe problem with AKs in Australia.

Dr. Shumack: Most individuals over the age of 40 who have grown up in Australia have at least one AK lesion. Not surprisingly, we also have the highest incidence of nonmelanoma skin cancer in the world in Australia. There are basically three reasons for this: our largely Anglo-Celtic population, the low latitudes of our geography, and our outdoor lifestyle. About 40% of Australians with an Anglo-Celtic background develop basal cell carcinoma (BCC) before 70 years of age. Photodamage is a significant problem in our country.

Characterizing AKs: Carcinoma in Situ?

Dr. Maibach: Dr. Gaspari, what is important to note about the clinical presentation of AKs?

... it can be extremely difficult to distinguish clinically between AKs, seborrheic keratoses, squamous cell carcinomas, and other lesions, even when the dermatologist is highly experienced in dealing with these lesions.

—DR. ANTHONY A. GASPARI

Dr. Gaspari: The clinical description of AKs, summarized in Table 1, is well known to dermatologists: it can be extremely difficult to distinguish clinically between AKs, seborrheic keratoses, squamous cell carcinomas (SCCs), and other lesions,

even when the dermatologist is highly experienced in dealing with these lesions.³ This fact makes clinical studies of AKs problematic, because lesion counts are the logical parameter to measure to establish a baseline and evaluate efficacy of a therapy.

Dr. Maibach: The scientific literature is replete with studies in epidemiology, histopathology, and molecular science that support the association between AKs and nonmelanoma skin cancer. What evidence and clinical experience should be highlighted?

Dr. Gaspari: Two issues are important to emphasize in our discussion here. The first concerns what we now know about the chromosomal abnormalities found in AKs, and the other issue is related to that, namely, the current debate on whether AKs are actually early SCCs.

Dr. Camacho: We know from studies in etiopathogenesis that ultraviolet (UV) radiation produces a

Table 1. Clinical Features of AKs

Size:	Range from papules of 1–2 mm to lesions of 1 cm in diameter
Color:	Flesh-colored, slightly red, or deeply pigmented
Surface texture:	Usually hyperkeratotic
Number:	May occur singly, but also may be grouped or confluent

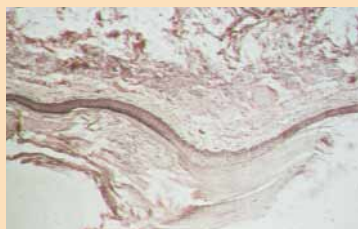
Table 2. AK to SCC: A Spectrum of Clinical and Histologic Features

Keratinocytic intraepidermal neoplasia (KIN) is a term proposed for the lesions that range from AKs to SCCs. Three grades of KIN have been described.

KIN I (Low Grade)



Clinical description: Flat pink macule; or patch on solar-damaged skin.



Histologic features: Focal atypia of basal keratinocytes of the lower one third of the epidermis.

KIN II (Intermediate Grade)



Clinical description: Pink to red papule or plaque with rough, hyperkeratotic surface.

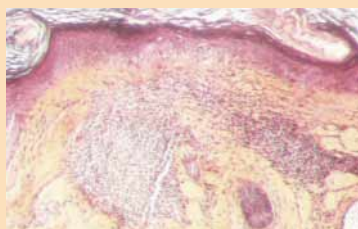


Histologic features: Focal atypical keratinocytes in at least the lower two thirds of the epidermis; overlying parakeratosis; nuclear hyperchromaticity; presence of mitotic structures; solar elastosis.

KIN III (High Grade)



Clinical description: Red, scaly, indurated plaques on sun-damaged skin; may be pigmented.



Histologic features: Diffuse atypical keratinocytic proliferation involving the full thickness of the epidermis; close apposition of hyperchromatic and pleomorphic nuclei; scattered mitotic structures; parakeratosis, acanthosis, papillomatosis.

Source: Yantsos V. Continuous spectrum between actinic keratoses and SCC, analogous to CIN (cervical intraepithelial neoplasia). *Semin Cutan Med Surg.* 1999;18:3-14.

mutation in the p53 gene and produces AKs.^{4,6} However, it has also been suggested that if a mutation also occurs in p16, it is more likely that the lesion will progress to invasive SCC.⁷ Another important factor for the development of UV-induced skin cancer is the dysregulation of the CD95L-CD95 interaction (Fas-L-Fas). The normal interaction of Fas-L-Fas eliminates “sunburn cells” by apoptosis,⁸ thus preventing UV-induced p53 mutations.⁶

Dr. Gaspari: I agree with those points and will amplify your comments on the effect on the skin immune system of UV radiation. In addition to the p53 and p16 mutations, there is another permissive factor related to UV radiation. The skin immune system is perturbed and damaged by UV light. Specifically, the epidermal Langerhans’ cells are damaged, do not mature normally, and do not present antigens to the skin immune system. The signature UV light damage—namely, genomic damage—has been detected in Langerhans’ cells, and these cells, of course, are critical to communicating the message to the immune system that tumor or viral antigens are present. This is definitely a permissive factor that probably allows AKs to progress to SCC and BCC.⁹

Further, to underscore a point that often is made regarding the benefits of photoprotection with sunscreens, cutaneous immunosuppression has been demonstrated in both mouse^{10,11} and human models.^{12,13} There also is evidence that, to some extent, sunscreens can mitigate UV damage to cutaneous immunosuppression.^{14,15}

Dr. Maibach: Are AKs and SCCs the same thing?

Dr. Camacho: Some have stated clearly and emphatically their belief that AKs are carcinoma in situ, whereas others have proposed that

Multiple Facial AKs



Dermabrasion is a treatment option for facial AKs that provides good cosmetic results.

AKs are on a continuum and may or may not become malignant. In the second camp are those who propose a change in nomenclature, to refer to AKs as keratinocytic intraepidermal neoplasia (KIN).¹⁶ Three grades of KIN have been proposed for the lesions that range from AKs to SCCs; these are shown and described in Table 2 on page 5.

Dr. Shumack: This issue is controversial; it would be extremely difficult at this point to achieve worldwide consensus on whether AKs are premalignant or represent malignancy in situ. There are many reasons why this debate will not likely be resolved soon. For example, in Australia, physicians receive Medicare reimbursement for the treatment of AKs only if we treat more than 10 premalignant lesions with destructive measures. Thus, we have the government referring to AK as a premalignant condition, and basing payment for therapy on that designation.

Furthermore, if AKs were to be referred to as cancer in situ, we are faced with the problem of what to tell patients. Patients are far less worried when they are told they have a premalignant or precancerous condition but become very alarmed if they hear that they have cancer. These are just a few problems that we in the dermatologic community

will have to work through if serious consideration is given to a change in nomenclature for AKs.

Widespread adoption of the KIN designation would be very useful because we all recognize there are

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—DR. FRANCISCO CAMACHO-MARTINEZ

certain AK lesions that do progress. There are some AKs that will spontaneously resolve: studies from Australia have shown spontaneous resolution in approximately 25% of AKs, and longer-term follow-up shows that some of those will recur.¹⁷ So AK is clearly a condition that encompasses both benign and malignant aspects, and the KIN terminology addresses that.

Dr. Gaspari: I agree—and I think most dermatologists would concur—with the concept of a spectrum of

disease, which this KIN classification system accommodates. It has been demonstrated that AK and SCC are related biologically, from the low-grade KIN I to high-grade KIN III, and beyond that, to full-blown SCC that has the potential to metastasize.

Dr. Shumack: However, it may be difficult in some localities to convince physicians to accept the KIN classification system. This is because these lesions are not necessarily treated by dermatologists, who appreciate the clinical and histologic subtleties between low- and high-grade neoplasia in the skin. In Australia, for example, the vast majority of AKs—and, for that matter, BCCs—are treated by primary care physicians or surgeons, who seem to prefer dealing with a clear demarcation between benign and malignant and are not so comfortable with the concept of a spectrum.

Dr. Spencer: For us as dermatologists, debating whether we should call AKs precancers or actual cancers is an interesting intellectual exercise—certainly the molecular changes that have been identified are important in AKs. The other side of the coin is the practical side, and I agree with Dr. Shumack, that in the real world of clinical practice, saying the word “cancer” can be very alarming to patients, who may demand, for example, Mohs’ surgery for their AKs.

Issues in Treatment: US and International

Dr. Maibach: Why are AKs treated—or not treated?

Dr. Shumack: Cosmetic improvement is one issue, but the most important reason to treat is the potential for transformation of AKs to SCC. The original reports from Germany in the 1930s cited rates of progression of 20%,¹⁸ and the more recent literature reports rates rang-

ing from 0.25% to about 15% or 20%.^{17,19} In Australia, it is the impression of dermatologists that the rate of progression is around 1% to 2% per year per AK. In fact, about 50% of dermatologists' work in Australia entails the treatment of nonmelanoma skin cancers and AKs.

Dr. Spencer: I don't think any dermatologist, regardless of location, would disagree that whether AK lesions are called by another name or whether they are considered premalignant or cancer in situ, it is wise to treat them.

Dr. Maibach: What specific techniques do you use?

Dr. Camacho: Currently, in Europe, we have available three categories of therapy for AKs: surgical treatment, medical treatment, and photoprotection (Table 3). The most frequently used surgical treatments are radiosurgery, with or without curettage, and cryosurgery. Laser—especially CO₂ laser—yields a good cosmetic outcome.

Dermabrasion is another option that produces good cosmetic results. The final surgical option, excision,

usually is not necessary, but when it is performed, direct suture is the best technique. When a large quantity of tissue is removed, flaps rather than grafts are preferable.

In the category of medical treatment are 5-fluorouracil (5-FU), medium-depth chemical peel, photodynamic therapy, and the immune

response modifier imiquimod. For extensive AKs, I normally use a medium-depth peel with trichloroacetic acid (TCA). Photodynamic therapy with topical 5-aminolevulinic acid and, in

Europe, the methyl ester of aminolevulinic acid, combined with light exposure, is our newest option. Finally, imiquimod in the treatment of AKs is excellent.

Dr. Spencer: I categorize those treatments a bit differently, dividing the physician interventions into destructive and nondestructive modalities. Cryosurgery is the destructive modality most often used in the United States, followed by curettage, with or without electro-surgery. In cases in which a tissue sample is desirable to rule out invasive tumor by histologic examination, excision is the method of choice.

Generally, the destructive techniques are not cosmetically elegant and usually leave some kind of mark. Cryosurgery tends to be toxic to melanocytes and therefore can leave a white spot. Curettage, with and without electro-surgery, is likely to leave a scar. Thus, the destructive techniques are usually reserved for treating isolated, discrete lesions on areas that are not cosmetically sensitive.

When more than a few isolated, discrete lesions must be eliminated, medical treatment, as Dr. Camacho discussed, is preferred. We have many medical approaches in the form of topical medications. In the past, the problem with medical modalities has been tolerability. The most commonly used, 5-FU, is very poorly tolerated by patients, and those who have an intense response are likely to reject any recommendation of retreatment should AKs recur—which they often do.

Fortunately, we now have the option of imiquimod, which is effective, safe, and tolerable, and is associated with good patient compliance. The most common protocol is applications three times weekly at night, but in my own practice, I have found that this schedule can be titrated to patient tolerability. If the response is

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—DR. STEPHEN P. SHUMACK

Table 3. Recommended Treatments for AKs

SURGICAL	MEDICAL
Cryosurgery	5-fluorouracil
Dermabrasion	Imiquimod
Excision	Medium-depth chemical peel
Laser (CO ₂)	Oral retinoids
Radiosurgery	Photodynamic therapy
	Salicylic acid
PHOTOPROTECTION	
Sunscreen	
– UVB filters: PABA, salicylates, cinnamates	
– UVA filters: oxybenzone, sulisobenzene, metil anthranilate, avobenzone	
Physical barriers	
– Zinc oxide, titanium dioxide, iron oxide, caolin, magnesium oxide, calamine and talcum (SiO ₂ Mg)	
– Wear hat, long sleeves, long pants; seek shade	

too intense, I have patients reduce the frequency of application to twice weekly or even once weekly, which is still quite effective.

Also, based on anecdotal experience, I believe that the duration of therapy usually recommended (up to 4 months) actually may be too long. The reason we treat for up to 4 months is that this is the recommendation derived from the clinical

trials with this drug. Of course, the length of clinical trials must be sufficient to detect both beneficial and adverse effects, but in the case of imiquimod, I think that as we gain more experience we will find that it works in 4 weeks or less.

Dr. Maibach: Does the notion of the so-called field effect influence your choice of therapy?

Dr. Spencer: Obviously, damage from UV radiation affects more than just a single keratinocyte, so it is not unreasonable to assume that where a clinically apparent AK has developed, other AKs may be present that are subclinical. Destructive modalities can only eliminate the visible lesions, whereas field treatment with the chemotherapeutic agent 5-FU or the immune response

Case Presentation: Richard Allen Johnson, MD

The natural history of actinic keratoses (AKs) and the relationship of these lesions to squamous cell carcinoma (SCC) in situ and invasive SCC is illustrated by a patient I first saw in 1992.

The patient was a 70-year-old man of Celtic heritage who had a history of a lifetime of excess sun exposure. In addition, the patient had undergone treatment for lung cancer, which was successful. At the time of his first visit, multiple AKs were noted on the patient's face and scalp and the dorsa of the hands. These were treated with cryosurgery.

At a follow-up visit in 1995, confluent AKs were identified on the forehead and scalp. These were treated with 5% 5-fluorouracil cream (*left*), with an excellent result. By June 1999, numerous in situ as well as invasive SCC lesions had developed on the scalp (*center*). These were treated with Mohs' micrographic surgery. In addition, acitretin, 25 mg b.i.d. was prescribed, which resulted in resolution of the rest of the lesions on the scalp and dorsa of the hands. When xerosis developed, the drug was gradually tapered to 25 mg twice weekly.

New malignant lesions—both in situ and invasive SCCs—quickly developed on the scalp. In January 2002, the patient consulted his primary care physician complaining of a lump on the upper left chest. The enlarged supraclavicular lymph node was assumed to be a site of metastasis from his prior lung cancer. I saw him again in June of 2002, at which time a new invasive SCC was noted on the left scalp (*right*). This lesion, not lung cancer metastasis, is the probable primary site for the supraclavicular node malignancy.

The clinical course of this patient's malignant disease exemplifies the natural history of AKs in an otherwise healthy individual, and suggests the presence of an underlying compromise of the immune system.



In 1995, confluent AKs on the forehead and scalp were treated with 5% 5-FU cream; therapy yielded excellent results.



By 1999, numerous in situ and invasive SCCs had developed on the scalp.



Numerous AKs on the ear, neck, and face surround the invasive SCC on the left scalp. Note the supraclavicular scar at the site of the excision of the nodal metastasis.

modifier imiquimod eliminates both clinically apparent and subclinical lesions. The difference between these two field therapies is that 5-FU is cytotoxic and to be effective, therefore, must penetrate every cell, whereas imiquimod causes an immune response that seems to extend beyond the area and level of the medication's penetration.

Dr. Shumack: Another consideration in choosing therapy is the age of the patient. In some of the elderly patients I have treated, compliance can be a problem, particularly if they have to do something for many weeks. I often find in my practice that those patients would actually prefer destructive measures, such as cryotherapy, in spite of the potential for cosmetic problems such as hypopigmented spots.

Conversely, I find that younger patients tend to place much more emphasis on cosmetic outcome. These individuals tend to be highly compliant and are likely to follow a regimen with a topical therapy like imiquimod.

Treatment of Special Populations: The Immunocompromised Patient and Others

Dr. Maibach: The populations in whom treatment of AKs must be given special consideration include patients who are immunocompromised, either because of a disease—particularly, human immunodeficiency virus (HIV) infection—or because they must use immunosuppressant therapy subsequent to an organ transplantation. We have two colleagues with us today with special expertise in these areas. Dr. Johnson, please begin.

Dr. Johnson: In the United States, HIV-infected individuals constitute the largest group of immunocompromised patients, about 900,000 currently.²⁰ These individuals probably have more aggressive SCCs than are

Table 4. Cytokines Induced by Imiquimod

Imiquimod stimulates the innate immune response through induction, synthesis, and release of cytokines:

β-Interferon

Interleukins 1, 5, 6, 8, 10, and 12

Tumor necrosis factor

Interleukin-1 receptor antagonist

Granulocyte colony-stimulating factor

Granulocyte-macrophage/colony-stimulating factor

Macrophage inflammatory protein 1α and 1β

Macrophage chemotactic protein

Source: Sauder DN. Immunomodulatory and pharmacologic properties of imiquimod. *J Am Acad Dermatol.* 2000;43:S6-S11. Used with permission.

seen in immunocompetent individuals, according to a recent report.²¹

About 100,000 individuals in the United States with transplants are systemically immunosuppressed as well.²² Those of northern European

(approximately 250-fold higher than normal) as well as SCCs (an estimated 200 to 250 times higher than normal).²³ Complicating the problem, the clinical presentation of lesions in these patients—which we and others have named “wartlike lesions”—is confusing. It often is impossible to determine whether a lesion is a simple wart, an AK, an early SCC, or invasive SCC. In up to 35% of cases, the SCCs metastasize.²⁴ In heart, liver, and kidney transplant recipients in Germany, the mortality risk from skin cancer is almost as great as it is from complications associated with the transplant itself.

Dr. Maibach: What are the risk factors in those patients?

Dr. Stockfleth: First, of course, immunosuppressive treatment is lifelong for transplant recipients. In addition, because 80% of tumors occur on sun-exposed areas, it is obvious that sun exposure is a risk factor. Finally, it has been established that in cervical cancer, the oncogenic types of human papillomavirus (HPV) (namely, types 16, 18, 31, and 33) are integrated in those host cell genomes and are responsible for the development of malignancy, so it is also possible

In the United States, HIV-infected individuals constitute the largest group of immunocompromised patients, about 900,000 currently.

—DR. RICHARD ALLEN JOHNSON

heritage probably have more aggressive SCCs than do other individuals. In studies from Australia and New Zealand, the incidence of death from metastatic SCC 4 to 5 years after transplantation is 25%.²³

Dr. Stockfleth: Throughout the world, there are more than 1 million patients who have received organ transplants. In Germany, we have 100,000 such patients. It has been documented that transplant recipients are at an extremely increased risk for developing both AKs

that an oncogenic virus—such as HPV, herpesvirus 8, or Epstein-Barr virus—may have an influence on the development of tumors in transplant recipients. Skin tumors are the most common tumors in transplant recipients, followed by non-Hodgkin's lymphoma, Kaposi's sarcoma, and anogenital cancer.

In a study from our group of the prevalence of HPV in skin lesions of transplant recipients versus non-transplanted and versus non-immunosuppressed patients (and using patients with verruca vulgaris as a control group), we found a higher prevalence of HPV DNA in patients with transplants.

Dr. Maibach: What other avenues of research with AKs and nonmelanoma skin cancer are you pursuing?

Dr. Stockfleth: One is the development of a method to follow patients in a systematic way so that we gather reliable epidemiologic information on AKs and other skin lesions. We developed the Skin Care in Organ-Transplanted Patients (SCOP) network system, at first just to handle the 6,000 transplant patients we see twice a year as outpatients. Later, we invited colleagues from other dermatology centers with a transplant center nearby to join the system. Its great advantage is that it standardizes the data as the information is entered,

so that it will be valid for epidemiologic analysis.

A second main avenue concerns the identification of early detection markers such as p53 and p16. For example, we know that the expression of p16 is strongly correlated to the dysplasia grade in cervical intraepithelial neoplasia, and we are trying to discover whether it may work the same way in AK.

In heart, liver, and kidney transplant recipients in Germany, the mortality risk from skin cancer is almost as great as it is from complications associated with the transplant itself.

—DR. MED. EGGERT STOCKFLETH

Finally, we are conducting research in therapy of AKs in immunocompromised patients. One of the main problems in transplant recipients is that all medical treatments, with the exception of cyclosporine, are off-label because they have not been studied in this population. Surgical treatments are problematic because of issues such as wound healing.

Cellular immunity is important in virus-infected and tumor cells, and it

involves mainly the type 1 helper T cell response (Table 4 on page 9). Therefore, we are involved in two areas of treatment research. Firstly, we have developed a vaccination system. As I mentioned, HPV is one of the biggest problems for these patients. It is not only a medical problem but also a psychological problem, because many have multiple HPV warts that create a disfiguring appearance. Working with the German Cancer Center in Heidelberg, we identified the most prevalent HPV types in organ transplant patients and developed virus-like particles. We are now using them in a vaccination system against those virus types.

The second area of treatment research involves the extensive use of imiquimod. We began to use imiquimod in 1995 in transplant recipients with multiple warts and multiple AKs as a possible alternative to surgery or to decreasing the dosage of immunosuppressive agents.²⁴ We reasoned that this may be a good treatment option for these patients because imiquimod works on the cellular immune system only in that area where it is topically applied. Because the main problems in these patients occurred in the skin, we believed that this would be a safe treatment that would not affect the systemic immune system. We have found it to be effective against warts, AKs, Bowen's disease, and BCC. The use of imiquimod has decreased tumor development, and this has resulted in fewer surgeries for our organ transplant patients. It seems that imiquimod has the ability to induce apoptosis—or cell death—in tumor cells.

Further, we have found imiquimod to be safe. We have not seen any flulike symptoms, such as what occurs with the use of interferon. In July 2002, we began enrolling patients in a multicenter European study using imiquimod in organ-transplanted patients for the indication of AKs.

Excision of AK



When excision of an AK is necessary (left), direct suture is usually the best technique (right).

Facial Basal Cell Carcinoma



A 48-year-old woman presented with a biopsy-proven nodular basal cell carcinoma (BCC) on her left cheek (left). She was instructed to apply topical imiquimod 5% five times weekly (center photo was taken 2 weeks after initiation of therapy). After 2 months of treatment, the lesion resolved (right). This patient will be monitored every 2 to 3 months so that any recurrence of BCC or development of any new lesions will be detected early.

Dr. Gaspari: Dr. Stockfleth, I wanted to amplify some comments you made related to the mechanism of action study that you did in AKs in terms of the cytokine profiles and the cellular infiltrates. There have been other studies in different disease states that have given parallel results, and I think it would be instructive to briefly describe these studies.

First, when imiquimod was developed, the application for approval was for the indication of treating external genital warts. The mechanism-of-action study by Tyring and associates²⁵ involving the cellular infiltrate in external genital warts described helper T-cell infiltrates that were activated, β -interferon production, and loss of HPV DNA in external genital warts that were being treated with imiquimod and were regressing. These kinds of molecular changes are the same as those that occur when any type of HPV lesion undergoes spontaneous regression.

A second study, as yet unpublished (G. Halliday, personal communication, June 2002), involving the use of topical imiquimod in the treatment of BCC documented the in situ changes that occurred as the tumors regressed in response to treatment. These changes occurred early in the course of treatment—within the first week—and showed the same kind of early helper T-cell infiltrates, β -interferon

production, and a local delayed-type hypersensitivity reaction. Later, these investigators noted an influx of cytotoxic T cells. Again, if you compare these changes induced by imiquimod to those that have been documented

We reasoned that [imiquimod] may be a good treatment option for [transplant] patients because imiquimod works on the cellular immune system only in that area where it is topically applied.

—DR. MED. EGGERT STOCKFLETH

in studies in which BCCs have spontaneously regressed,^{26,27} it seems that imiquimod actually mimics the natural phenomenon that occurs when the host immune system successfully fights off a virus like HPV or a skin cancer like BCC.

Dr. Johnson: I have a question for Dr. Stockfleth on the frequency of application of imiquimod in patients who have undergone organ transplantation. How often do you rec-

ommend that such patients with severe AKs of the face or scalp apply imiquimod?

Dr. Stockfleth: Normally patients start with three times per week for 8 to 10 hours, usually applying it at night and washing it off in the morning. When they start to develop erythema—that is, when they get an up-regulation of subclinical lesions—applications can be reduced to two times per week. This regimen works well.

In our first study, we used imiquimod for 12 weeks, and I think maybe this is too long. Seven or 8 weeks of treatment seems to be enough. From our data with BCC, it seems to be sufficient to treat only until an induction of the immune system occurs. However, these are just speculations at this point.

Immune Response Modifiers: Additional Discussion

Dr. Maibach: In addition to imiquimod's approved use in the United States for genital warts as well as the experience that is accumulating concerning its use for managing AKs, what other experience can we share about immune response modifiers that could help explain how this new class of drugs

works and what applications it might have in the future?

Dr. Spencer: We are finding more uses for imiquimod, which is the first in this new class of agents known as immune response modifiers. I have dedicated my career to treating skin cancers, and unfortunately I occasionally see extramammary Paget's disease, an extremely difficult cancer to treat; even with wide excision, the recurrence rate is 40%. To date, I have successfully used imiquimod to treat two patients with recurrent extramammary Paget's disease of the genital region. Of course, this is only anecdotal and only in two patients. Nevertheless, it is my impression that imiquimod will, over time, prove to have many uses in oncology, in general.

Dr. Gaspari: I agree. Another area of potential utility is skin cancer chemoprophylaxis. I was involved with a recently completed study using a mouse model of cutaneous immunosuppression.²⁸ The experiments involved UVB irradiation for 4 days, after which the mice were sensitized with 2,4-dinitrofluorobenzene (DNFB). We expected, from previous work in this area,²⁹ that these animals would lose cutaneous

delayed hypersensitivity, which is a measure of a number of events, but most likely mediated by T cells. Thus, this loss of delayed hypersensitivity is thought to be acute immunosuppression, an acute effect of UV light exposure.

I find that many patients with hypertrophic AKs also have a large number of ordinary AKs (KIN I and II). I often treat them in a field fashion with imiquimod,...
—DR. STEPHEN P. SHUMACK

In our model, when we applied imiquimod to mouse skin before the UV radiation, we showed a prevention of loss of contact hypersensitivity—actually, preventing this cutaneous immunosuppression. We also determined that the timing of the dose of the imiquimod is important. If imiquimod is applied after UV irradiation, loss of contact hypersen-

sitivity still occurs. However, if imiquimod is applied before exposure to UV radiation, the immunosuppression effect is prevented. This implies, of course, that if this model is applicable to humans, we may be able to use it prophylactically, in low and infrequent doses, to attempt to prevent UV immunosuppression over the long run.

Dr. Johnson: As far as its use in prophylaxis of dysplastic lesions, a similar model exists with HPV-induced dysplasia, in which the range is from benign neoplasm (with a wart, for instance), to dysplastic lesion or squamous intraepithelial lesion (SIL), to SCC in situ, to invasive cancer. I have experience in using imiquimod for HPV-induced SIL in anogenital skin, with response in the majority of the patients. Because some patients do not develop cytokine dermatitis, imiquimod is not effective in all cases.

Nevertheless, I think imiquimod is a good agent that should be looked into for treatment of cutaneous dysplastic lesions in external genital skin. It might be an agent to be used in the anus or cervix also, but it is difficult to apply to the anus and it causes erosions when applied to the vagina.

Squamous Cell Carcinoma and AKs, Scalp



This patient was referred for Mohs' surgery to remove a squamous cell carcinoma (SCC) of the scalp, but confluent actinic keratoses (AKs) made localization of the tumor impossible (left). The patient was instructed to apply topical imiquimod 5% nightly for 2 weeks, which caused the expected erythematous reaction, seen here (center), in both clinical and previously subclinical lesions. After imiquimod therapy, the AKs resolved completely, the location of the SCC was revealed, and the tumor was excised (right).

Furthermore, I have one patient with lentigo maligna who is 85 years of age and had recurrence of his disease, a widespread lesion on the face. He used imiquimod for about 7 months, once or twice a week, with resolution of the lesion clinically and also on rebiopsy of the lesion. Therefore, imiquimod also may have potential use in some patients with lentigo maligna.

Dr. Shumack: I have used imiquimod to treat patients with recurrent superficial and nodular BCCs or BCCs around scarred areas, with excellent results. I think for the majority of physicians, this is an area in which imiquimod will have a place.

We know that the failures with BCC treatment tend to be superficial failures, because we know that the inflammatory action is coming from underneath to attack the skin cancer. We are fortunate in Australia that we tend to see patients on a regular basis—I see many of my patients every 2 to 3 months—so there is an opportunity to follow them on an ongoing basis. This is important if we are going to treat recurrences, particularly when we know that the failures with BCC treatments are not necessarily leaving remnants of the BCC deep in tissue. I think that imiquimod will have a place in these recurrent BCCs, especially in patients who are followed up on a regular basis.

I find that many patients with hypertrophic AKs also have a large number of ordinary AKs (KIN I and II). I often treat them in a field fashion with imiquimod, then when they return for follow-up, I treat the two or three remaining hypertrophic AKs with cryotherapy.

Does anyone have any comments regarding the areas on which imiquimod does not work so well? In my experience, imiquimod does not work well on the backs of the hands.

Dr. Johnson: I have found that patients with severe solar skin damage and hypertrophic AKs have difficulty responding on the face.

Dr. Gaspari: I have noticed the same thing with hypertrophic AKs. I believe this is a penetration issue. Some of the approaches I have used to try to enhance the penetration of imiquimod include concomitant use of a keratolytic agent or, depending on the location on the body, using imiquimod with occlusion or pre-treating the skin with a topical retinoid to temporarily impair the barrier function.

A consensus panel convened by the American Academy of Dermatology advised the [United States] federal government that whether AKs are precancerous or cancerous, they are worth treating.

—DR. JAMES M. SPENCER

Reimbursement Issues

Dr. Maibach: There was a recent change in the Medicare coverage policy in the United States. Dr. Spencer, please provide an overview of the rationale for those changes and the outcome of the decision.

Dr. Spencer: In the past few years in the United States, we have had a challenge from our government on AKs for our senior citizens—that is, individuals older than 65 years of age. The health care for these older persons is provided by the federal government under a program called Medicare. Although Medicare is a national program, it is administered in each of the 50 states by a state

administrative agency. A few years ago, in response to what was perceived as too much money billed for the destruction of AKs, the state of Florida decided that, except for a few isolated situations, a medical approach must be taken first before the government would pay for destructive techniques.

This was an extraordinary policy change, not just for dermatologists but for physicians in general, because it was the first time that an insurance company—particularly a national one—dictated that a physician's judgment is not relevant, that there is a treatment they must do. Of course, this caused great concern among all physicians, not just dermatologists.

The American Academy of Dermatology (AAD) vigorously and successfully fought this policy. The first issue that was decided was whether it was wise to treat AKs and whether they were worth treating. A consensus panel convened by the AAD advised the federal government that whether AKs are precancerous or cancerous, they are worth treating. In addition, all of the literature on AK treatment was reviewed and analyzed. There is now a national policy that the physician is free to choose the appropriate treatment, be it a destructive or a medical one, based on the clinical situation.

Dr. Maibach: What is the situation with the private insurance companies, the insurance programs not administered by the government?

Dr. Spencer: In a perfect world, the physician would work with the patient and make decisions based on the patient's best interest. In the United States these days, we have a great deal of intervention from the insurance companies. They are almost our partners in the office, whether we like it or not,

and this represents a practical issue that we must deal with. I will be interested to hear from our European colleagues about how the insurance industry works in their countries, but in the United States, physicians are not rewarded much for thinking. If you think about a problem and provide a prescription, that is not economically rewarded very well, but if you physically do something, such as a cryosurgery, that is rewarded relatively well.

Dr. Shumack: In Australia, there are large companies, such as our major telecommunications provider, which will now cover their outdoor workers. If the linesmen or other employees develop AKs or nonmelanoma skin cancers, the cost of their treatment is paid for by the company rather than by our national health service.

Dr. Camacho: In Spain, we recognize that it is much more reasonable to treat AKs than to wait until SCC develops. Furthermore, we absolutely believe that the treatment of AKs should be covered by public funds, and we do that in Spain.

Dr. Johnson: The billing that we do for destructive procedures is really high, and I think that the use of

imiquimod will markedly reduce the cost of treating AK. I have used imiquimod for several years. I tend to prescribe it for application once a week for a year, and have patients come back for cryosurgery for persistent lesions. Usually they have nothing to freeze on the return visit. Although patients who do not have prescription drug coverage may be concerned about the cost, imiquimod is very inexpensive compared with destructive methods of therapy.

Concluding Remarks

Dr. Shumack: One of the issues that requires attention on an international level is the end point for treatment of AKs. In many cases, regulatory studies require total cure—in other words, if a patient has 10 AKs at baseline, a cure is defined as 0 AKs at the conclusion of the study period. However, in clinical practice—and certainly in Australia—a 70% to 80% improvement is considered satisfactory. We know patients will develop more AKs and possibly an SCC or a BCC over time. We must reconcile to the fact that solar damage requires long-term, continuing management.

Dr. Gaspari: The relationship between the dermatologist and the

patient with AKs is one that should be ongoing and long term. These lesions are markers for advanced sun damage and definitely represent a major risk factor for skin cancer. It is important to have patients under surveillance so that we can intervene at defined intervals when we feel it is appropriate.

Dr. Camacho: Prevention of UV-induced precancerous lesions and skin cancer certainly is a superior strategy compared to any type of treatment, and it is less expensive. If UV damage has occurred, the treatment of AK is the best treatment for SCC.

Dr. Maibach: The changes that have occurred in the treatment of AKs in Australia, the European Union, and the United States reflect the growing knowledge and understanding about the natural history and pathogenesis of these lesions. Although worldwide consensus still is lacking about the nature of AKs—whether they can be called SCC in situ or represent, instead, the potential for malignancy—there is little debate that AKs are an indication of actinic damage and that a patient with AKs deserves careful monitoring so that potentially precancerous or cancerous lesions are identified and treated early.

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**Current World Views On Actinic Keratoses: Natural History and Recent Treatments
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INSTRUCTIONS: For each question or incomplete statement, one answer or completion is correct. Seven out of 10 correct responses are required for credit. Circle the most appropriate response.

1. Among non-Latin individuals who work outdoors, the worldwide prevalence of actinic keratosis is:
 - a. 30%
 - b. 50%
 - c. 70%
 - d. 90%
2. Histologically, keratinocytic intraepidermal neoplasia (KIN) grade II, or intermediate KIN, is associated with all of the following features except:
 - a. focal atypical keratinocytes in the lower one third of the epidermis
 - b. nuclear hyperchromaticity
 - c. parakeratosis
 - d. presence of mitotic structures
3. For a large field of AKs, such as the scalp in a bald male, the modality least likely to result in hypopigmentation or scarring is:
 - a. cryosurgery
 - b. curettage
 - c. excision
 - d. topical treatment with 5-fluorouracil or imiquimod
4. In organ transplant recipients receiving immunosuppressive therapy, squamous cell carcinoma metastasizes in up to ___ of cases.
 - a. 25%
 - b. 35%
 - c. 45%
 - d. 55%
5. Cellular immunity, which is important against virus-infected and tumor cells, involves mainly a:
 - a. p16 mutation
 - b. p53 mutation
 - c. T_H1 response
 - d. T_H2 response
6. In immunocompromised patients, topical use of the immune response modifier imiquimod has been studied and found to be effective for the treatment of all of the following except:
 - a. actinic keratosis
 - b. basal cell carcinoma
 - c. Bowen's disease
 - d. fungal infections
7. Which of the following countries has the highest incidence of non-melanoma skin cancer in the world?
 - a. Australia
 - b. Germany
 - c. Spain
 - d. United States
8. Which one of the following statements about actinic keratosis is not true?
 - a. Actinic keratosis is related biologically to squamous cell carcinoma.
 - b. Clinical studies in AKs are problematic because these lesions are difficult to count.
 - c. It has been demonstrated in vitro that if a mutation occurs in the p53 gene, the AK is likely to progress to squamous cell carcinoma.
 - d. Photoprotection is a valid therapeutic option for AK.
9. As a result of ultraviolet light exposure, _____ cells are damaged, do not mature normally, and do not present antigens to the skin immune system.
 - a. basal
 - b. Langerhans'
 - c. mast
 - d. squamous
10. In studies involving a mouse model of immunosuppression, researchers showed that prevention of loss of contact hypersensitivity can be prevented (i.e., prevention of cutaneous immunosuppression can be prevented) with:
 - a. applications of imiquimod after ultraviolet B irradiation
 - b. applications of imiquimod prior to ultraviolet B irradiation
 - c. applications of 2,4-dinitrofluorobenzene prior to ultraviolet B irradiation
 - d. applications of 2,4-dinitrofluorobenzene after ultraviolet B irradiation

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