A SUPPLEMENT TO
Skin & Allergy News®

Immune Response Modifier Therapy: Advances in the Management of AK and BCC

Introduction: The Role of Immune Response Modifier Therapy in Actinic Keratosis and Basal Cell Carcinoma

Treatment of Actinic Keratosis and Basal Cell Carcinoma: Today and Tomorrow

Immunomodulation: An Update on Proposed Mechanisms of Action in Basal Cell Carcinoma

Immune Response Modifier Therapy in Superficial Basal Cell Carcinoma: Clinical Studies and Experience

Actinic Keratosis: Newer Concepts for a Comprehensive Management Approach

New Horizons in the Treatment of Basal Cell Carcinoma: Noninvasive Treatment and Monitoring

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Immune Response Modifier Therapy:

4 Introduction: The Role of Immune Response Modifier Therapy in Actinic Keratosis and Basal Cell Carcinoma
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4 Treatment of Actinic Keratosis and Basal Cell Carcinoma: Today and Tomorrow
Stuart J. Salasche, MD, (Co-Chair)
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6 Immunomodulation: An Update on Proposed Mechanisms of Action in Basal Cell Carcinoma
David Vidal, MD, and Prof. Agustín Alomar
Staff Physicians, Department of Dermatology
Hospital de Sant Pau
Barcelona, Spain

8 Immune Response Modifier Therapy in Superficial Basal Cell Carcinoma: Clinical Studies and Experience
Amit G. Pandya, MD
Associate Professor, Dermatology
University of Texas Southwestern Medical Center, Dallas

10 Actinic Keratosis: Newer Concepts for a Comprehensive Management Approach
Joseph L. Jorizzo, MD
Professor and Chairman
Department of Dermatology
Wake Forest University, Winston-Salem, N.C.

12 New Horizons in the Treatment of Basal Cell Carcinoma: Noninvasive Treatment and Monitoring
Abel Torres, MD, JD
Associate Professor of Dermatology
Chair, Division of Dermatology
Loma Linda University, Loma Linda, Calif.

15 CME Post-Test and Evaluation
Advances in the Management of AK and BCC

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 and basal cell carcinoma.

Educational Needs
The incidence of nonmelanoma skin cancers is high and is increasing. Heretofore, the treatments for these lesions have been primarily limited to surgical modalities, which have the common side effect of scarring and which are associated with recurrences, that require lifelong monitoring of patients and, commonly, repeated surgical intervention. The development of the immune response modifier imiquimod seems to offer a topical, noninvasive approach to the treatment of basal cell carcinoma and actinic keratosis, the latter newly recognized as a lesion on a continuum that may lead to invasive squamous cell carcinoma. This activity provides dermatologists with current information regarding imiquimod's mechanism of action, efficacy, and safety, and introduces conjugated focal plane (confocal) microscopy, a new method for noninvasive monitoring of patients with basal cell carcinoma.

Learning Objectives
By reading and studying this supplement, participants should be able to discuss:
• Current and emerging therapies in the treatment of actinic keratosis and basal cell carcinoma.
• Five clinical studies that have been published to date on the use of immune response modifier therapy in patients with basal cell carcinoma.
• The proposed mechanism of action of immune response modifier therapy in basal cell carcinoma.
• The benefits and experience to date with conjugated focal plane (confocal) microscopy for monitoring basal cell carcinoma.
• Actinic keratosis and the potential for development of invasive squamous cell carcinoma.
• Current evidence for the efficacy of immune response modifier therapy in the treatment of actinic keratosis.

Faculty Disclosure
Faculty/authors must disclose any significant financial interest or relationship with proprietary entities that may have a direct relationship to the subject matter. They must also disclose any discussion of investigational or unlabeled uses of products. This supplement discusses the off-label/unapproved use of imiquimod in the treatment of actinic keratoses and basal cell carcinoma.

Dr. Camacho-Martinez has nothing to disclose. Dr. Jorizzo has received funding for clinical grants from 3M Pharmaceuticals and Dermik Laboratories. He discusses the unlabeled use of imiquimod for the treatment of actinic keratoses. Dr. Pandya has performed funded clinical research for 3M. He discusses the unlabeled use of imiquimod for basal cell carcinoma. Dr. Salasche is a consultant to 3M. He discusses the unlabeled use of imiquimod in the treatment of actinic keratoses and basal cell carcinoma. Dr. Vidal has no conflicts of interest to report. He discusses the unlabeled use of imiquimod in the treatment of basal cell carcinoma. Dr. Torres is a consultant to 3M and has received clinical grants from 3M and Lucid, Inc. He discusses the unlabeled use of imiquimod for the treatment of actinic keratoses and basal cell carcinoma.
Introduction: The Role of Immune Response Modifier Therapy in Actinic Keratosis and Basal Cell Carcinoma

Many treatments have been used for actinic keratoses (AKs) and basal cell carcinoma (BCC). For AKs, the surgical treatments have included radiosurgery, cryosurgery, dermabrasion, laser therapy, and surgical extirpation. Medical treatments began several decades ago with 5-fluorouracil, and have included, over the years, medium-depth chemical peels with trichloroacetic acid, oral retinoids, and, more recently, photodynamic therapy (topical 5-aminolevulinic acid plus laser light) and the immune response modifier imiquimod. As discussed in the article by Joseph L. Jorizzo, MD, imiquimod is proving to be a useful topical treatment for AKs.

In superficial BCC, surgery has been the traditional method of treatment. However, studies of imiquimod have shown that topical therapy is both effective and safe and offers an alternative to surgery. In this supplement, the articles by David Vidal, MD, and Prof. Agustín Alomar, by Amit G. Pandya, MD, and by Abel Torres, MD, JD, provide valuable information on this important topic.
and addressing persistent lesions with cryotherapy, or, if SCC is suspected, performing a biopsy.

The previous standard topical treatment for AKs was 5-fluorouracil (5-FU), an agent with proven efficacy. However, 5-FU treatment also is associated with an inflammatory response that is typically unsightly and that is at least uncomfortable and may be painful for many patients. A certain percentage of individuals treated with 5-FU also develop an eczematous, pruritic contact hypersensitivity within the treatment area. As a result of these side effects, compliance with the initial course of treatment or agreement to re-treat with a standard 5-FU regimen may meet with patient resistance.

More recent approaches in topical therapy have included the introduction of a cyclooxygenase inhibitor as well as new formulations of 5-FU with modern delivery systems and in lower concentrations, which reduces the intensity of the inflammatory response. To date, experience with these medications has shown that there has indeed been a pent-up need for an effective topical medication for AKs that offered an easier course of treatment.

A unique topical approach to AK therapy in relation to the concept of ‘field cancerization’ is IRM treatment with imiquimod. Although ultraviolet radiation damage can result in the production of clinically visible AK lesions, research has shown that biopsies of the surrounding photodamaged skin also demonstrate histologic evidence of early preclinical AKs. In addition, a closer look with molecular probes reveals mutated clones of epidermal cells that show the same changes in the DNA apparent in both AKs and SCC. Thus, the topical approach with IRMs has the potential to eliminate not only the visible clinical lesions but also, very likely, the other defects within the sun-damaged area. One manifestation of this phenomenon is that when an area is treated, the AK lesion counts initially rise because the subclinical or incipient AKs also respond to the medication and, like the baseline visible lesions, resolve by the end of treatment.

Current efforts in imiquimod research include the combined goal of finding a dosing regimen that is both efficacious and more “user-friendly.”

Clearly, based on the proposed mechanism of action of cytokine activation, some inflammation is inevitable, but the dosing studies continue to elucidate the optimum schedule that will both eradicate lesions and still keep patients relatively comfortable during treatment.

Finally, it is interesting to note that trends from ongoing follow-up studies with imiquimod indicate that the appearance of new AKs within a treated area seems to be low in number and delayed in onset. It is not yet clear whether this might represent immune memory relating to imiquimod’s mechanism of action or if the field therapy concept—that is, the elimination of subclinical, incipient lesions—may be responsible.

Future studies with imiquimod should continue to elaborate on new methods of dosing. The regimens should identify clinical end points of therapy that will allow reduction or cessation of treatment with assurance that the AKs will subsequently disappear and local inflammatory reactions will be minimized.

Topical Therapy for BCC

The standard of treatment for superficial basal cell carcinoma (BCC) is either destruction with curettage and electrodesiccation or surgical excision. Unfortunately, because superficial BCCs occur commonly on the trunk, chest, and back, the hypopigmentation and thick scarring that often result from such treatment are troublesome for patients. Imiquimod has been studied as a noninvasive treatment for BCC.

The mechanism of action has not yet been determined, but strong indications from well-controlled studies are that imiquimod may reiterate the process that was seen in studies of injected interferon and in patients with spontaneously regressing superficial BCCs—that is, an influx of activated lymphocytes as well as an increase in the apoptosis-signaling pathway, leading to increased cell death. This is consistent with the proposed mechanism of action of the IRMs: the release of interferons and other cytokines from immune-competent cells.

Interesting innovative thoughts on further application for future directions in the treatment of BCCs include using imiquimod in larger regions to reduce the size of the lesion prior to surgical excision or Mohs’ micrographic surgery. In addition, because we know that a certain number of viable malignant basal cells are left after curettage and desiccation, imiquimod may be useful as an after-treatment adjunct to this surgical procedure.

Conclusion

This supplement addresses each of these issues by experts in the field. The excellent basic research elucidated on imiquimod’s mechanism of action on BCC by Dr. Vidal and Prof. Alomar is precise and important as it included all types of BCC, including infiltrative histologic subtypes. Dr. Pandya nicely summarizes the clinical studies done on BCC with topical IRMs, and Dr. Jorizzo not only provides a summary of experience with AKs, but also lends a mature perspective on the place and role of IRMs for this condition. Finally, Dr. Torres presents some interesting and innovative approaches to the treatment of BCCs with combined therapeutic modalities, and he introduces us to new technology (the confocal microscope) that may prove helpful in the study and management of non-melanoma skin cancers.
Immunomodulation: An Update on Proposed Mechanisms of Action in Basal Cell Carcinoma

David Vidal, MD, and Prof. Agustín Alomar

Basal cell carcinoma (BCC) is the most common skin cancer, and its prevalence is increasing worldwide. The treatment of choice is surgery, but many patients cannot undergo surgery and request medical treatment instead.

Basis for BCC Mechanism-of-Action Study

The immune response modifier imiquimod initially was approved by the U.S. Food and Drug Administration for the treatment of external anogenital warts. Subsequently, the compound was identified in clinical studies as beneficial in the topical treatment of BCC. To date, five such randomized trials have been published, and these are addressed in the article by Dr. Pandya (see page 8). This discussion focuses on the mechanism of action of imiquimod in the treatment of BCC.

Chemically, imiquimod is an imidazoquinolinamine derivative with properties that induce local cytokines, including interferon, tumor necrosis factor, and interleukin 12.

Clinical Trial to Determine Mechanism of Action

To determine the exact mechanism of action of imiquimod in BCC, we designed a single-center open trial involving 55 patients, each with a tumor greater than 7 mm. In 78% of cases, the tumor was infiltrative; BCC was nodular in 15% of patients and superficial in 7%. Biopsies were performed prior to and during treatment and 6 weeks after cessation of therapy. The follow-up to date has been 20 months.

All patients in the study received topical imiquimod: 35 patients were treated three times weekly for 8 weeks; the remaining 20 patients were treated five times weekly for 5 weeks. (Photos taken before, during, and after treatment are shown in Figures 1 and 2.) The most common adverse reactions were erythema and erosion, both of which occurred in all patients who used imiquimod five times weekly. Erythema was seen in 91% of patients who used imiquimod three times weekly, and erosion occurred in 77% of these patients. Pustules were seen in less than 10% of patients, regardless of treatment frequency. Systemic reactions were seen in less than 5% of patients overall. Despite the high rate of topical reactions, compliance was extremely high: 100% in the five-times-weekly group and 97% in the group that used imiquimod three times weekly.

Figure 1. Patient with BCC on Temple

This patient had a BCC of the left temple (A). After 2 weeks of treatment three times weekly with imiquimod (B), the lesion was erythematous. Erosion and crusting occurred after 8 weeks of therapy (C). At follow-up 6 weeks after the cessation of therapy, the tumor was completely cleared (D). BCC = basal cell carcinoma
Efficacy also was impressive with superficial and nodular tumors. All superficial tumors showed complete clearance in both groups. Nodular tumors cleared in 83% of patients on the three-times-weekly treatment schedule and in 100% of patients who used imiquimod five times weekly. Infiltrative tumors cleared in 77% of patients on the three-times-weekly schedule and in 56% of patients in the five-times-weekly group.

**Biopsy Results**

On review of the pretreatment biopsies, we noted that there were few peritumoral inflammatory cells, most of which were CD3+. During treatment, there was a rapid increase in the total number of inflammatory cells by the end of the first week, and we observed intense lymphocytic infiltrations around the tumors, which were composed mainly of CD3+ and CD8+ cells. There were also many CD68+ cells (macrophages) and granzyme B+–activated cytotoxic cells, especially around the tumor nests. There also were some CD20+ lymphocytes and S100+ cells (Langerhans’ cells). Surprisingly, there were almost no CD56+ cells, a marker for natural killer cells.

We confirmed these observations with the terminal deoxynucleotidyl transferase technique (commonly known as the TUNEL technique) on frozen samples. Special attention was given to melanin, which, if not carefully handled, could lead to false-positive results.

The apoptotic rate of the BCC cells prior to treatment was 0.6% (6 apoptotic cells out of 1000 cells), and it increased to 1.8% in the biopsies taken during treatment but decreased to 0.9% after treatment.

Apoptosis regulation is rather complex. The main proapoptotic pathways are the death receptors (Fas, TNF), P53, Bax, and the activated cytotoxic cells, through the release of granules of granzyme and perforin. The main antiapoptotic protein is the Bcl-2, which interferes with Bax in the mitochondrion. We studied the expression of the Bcl-2, P53, and Ki-67 proteins in the BCC cells on paraffined sections. Expression of Bcl-2 in the BCC cells decreased in all groups during treatment, whereas expression of P53 decreased only in the five-times-weekly treatment group, and Ki-67 expression showed little modification in all groups.

**Randomized Study Confirms Preliminary Results**

To confirm our preliminary findings, we conducted a randomized, vehicle-controlled trial involving 30 patients with BCC. 12 received imiquimod three times weekly, 12 received the active agent five times weekly, and 6 received vehicle only. Biopsies were performed prior to treatment, on day 8, and on day 15.

Histologically, the tumors from the patients in the active-treatment groups showed a clear increase in total numbers of inflammatory cells, but this did not occur in the vehicle group. In addition, use of 20-MHz sonography showed that infiltration increased around the tumor during treatment in those tumors exposed to imiquimod; this was not observed in patients in the vehicle group.

The apoptotic rate of the BCC cells increased to 1.6% in the imiquimod groups, but not in the vehicle group. Regarding Bcl-2 results, its expression in BCC cells decreased in the imiquimod groups but not in the vehicle group, and these results correlated fairly well with the apoptotic rate. With respect to P53 and Ki-67 expression, there were no statistical differences between the imiquimod and the vehicle groups.

**Summary**

Our clinical studies showed that imiquimod produces infiltration of lymphocytes, macrophages, and activated cytotoxic T cells and induces apoptosis, resulting in destruction of BCC tumors.

**References**

The treatments of basal cell carcinoma (BCC) available to clinicians today may be divided into two categories: ablative and nonablative (Table). Heretofore, the treatments of choice have been the ablative modalities, particularly surgical excision and electrodesiccation-curettage. However, clinical studies published over the last 10 years have demonstrated that nonablative treatments deserve our attention.

Retinoids have been demonstrated to work in patients with nevoid BCC syndrome1 and perhaps in patients who have undergone transplantation of kidneys or other organs.2 In otherwise-healthy patients with BCC, retinoid therapy has not worked well.3 Topical 5-fluorouracil is approved in the United States for the treatment of superficial BCC, but it is not used routinely because the recurrence rate is between 20% and 25%.4,5 Interferons have been demonstrated to be effective in BCC, but have the disadvantage of requiring injections three times a week for 3 weeks. Imiquimod, a topical agent with antitumor properties initially approved for the treatment of external anogenital warts, has been studied in patients with superficial and nodular BCC.6-10

Pilot Study Shows Good Results

Because BCC had been shown to respond to interferon therapy and imiquimod is known to induce cytokines and interferon, Beutner and colleagues6 performed a randomized, double-blind pilot study involving 35 patients with BCC. Twenty-four patients received imiquimod at various dosing schedules for 16 weeks: twice daily (n=7), once daily (n=4), three times weekly (n=4), twice weekly (n=5), and once weekly (n=4). Eleven patients were randomized to groups that received vehicle only, according to this same schedule. Seven patients had nodular BCC; the other 28 patients had superficial BCC.

The adverse reactions reported in this study were application-site reactions, including itching and discharge at the target site and erythema at a remote site. Most of these reactions were of mild or moderate intensity, with some patients requiring a rest period. Subject-reported systemic adverse events included fatigue, headache, fever, and malaise.

Excisional biopsies of the target sites were performed 6 weeks after treatment was completed. On the basis of these histologic examinations, the investigators reported that all patients (100%) in the twice-daily, once-daily, and three-times-weekly treatment groups had complete clearance of their tumors. Tumor clearance was seen in three of the five patients (60%) in the twice-weekly dosing group, and in two of the four patients (50%) on the once-a-week regimen. One of the patients (9%) in the vehicle group had tumor clearance on histologic examination.

Dose-Response Trials for Superficial BCC

Marks and coworkers7 conducted a randomized, dose-frequency, open-label study at 10 sites—9 in Australia and 1 in New Zealand—to determine the optimum imiquimod treatment regimen for superficial BCC. Ninety-nine patients were recruited to receive imiquimod for 6 weeks: twice daily (n=3), once daily (n=33), twice daily three times a week (n=30), or three times weekly (n=33). Tumors ranged in surface size from 0.5 to 2.0 cm². (The twice-daily regimen was discontinued after only three patients had been enrolled because of reports of severe local skin reactions in the twice-daily treatment group in another ongoing study.)

Local skin reactions occurred in all patients, with the four most common being erythema, erosion, excoriation,
and scabbing. These reactions were most severe among patients using the higher-frequency regimens. Nevertheless, 61% of patients (n=60) had 100% compliance and 94% (n=93) had at least 60% compliance.

Clinical clearance, confirmed by histologic examination, was reported in all three patients in the twice-daily treatment group (100%), in 87.9% of those in the once-daily group, in 73.3% of those who used imiquimod twice daily three times a week, and in 69.7% of those who used the medication once daily three times a week. Thus, it appears that use of imiquimod once daily for 6 weeks rather than 12 weeks yields a clearance rate for superficial BCC (87.9%) that compares well to that seen with surgical procedures (90%-95%).

In a double-blind, randomized, vehicle-controlled, 12-week, phase II study, Geisse and colleagues explored various regimens to find the most effective dosing frequency for superficial BCCs with the greatest side effect tolerability. A total of 128 patients were randomly assigned to use imiquimod or vehicle only twice daily, once daily, three times a week, or five times a week, or three times a week. Tumors were primary, noninfected, superficial BCCs between 0.5 and 2.0 cm². Target tumor biopsies were performed to confirm the diagnosis.

After 12 weeks of treatment, the investigators reported that applications of imiquimod once daily or five times a week yielded a complete response of superficial BCCs in 87.1% and 80.8% of patients, respectively, compared with 19% of patients in the vehicle group (P < 0.0001). In this study, it was also found that twice-daily dosing was too irritating and less frequent dosing—that is, three times a week—was significantly less effective (52% clearance, P = 0.008). Erythema, scabbing, erosion, excoriations, and flaking, induration, edema, ulceration, and vesicles occurred in all patients.

A double-blind, vehicle-controlled, randomized phase III dosing study involving 724 patients was recently completed in the United States. Patients were assigned in a 1:1 ratio to receive either imiquimod or vehicle, and to either a 5-day or 7-day dosing schedule—that is, once-daily application of imiquimod or vehicle for 5 consecutive days with 2 days off, or for 7 days/week. Enrollment criteria included the presence of one primary, noninfected BCC with a minimum area of 0.5 cm² and maximum diameter of 2.0 cm² located on the limbs, trunk (but not anogenital area), neck, or head (excluding lesions that were close to the eye, nose, mouth, or ears because of difficulty in treating those areas). The results of that study are expected to be published in the near future.

**Studies With Nodular BCC**

Approximately 60% of BCCs are classified as nodular, with most cases occurring on the head and neck. Shumack and his group conducted both a 6-week and a 12-week randomized, open-label, dose-response study of imiquimod in patients with nodular BCC to establish the optimum dosing regimen for this tumor subtype.

In the 6-week study, 99 patients were randomized to receive imiquimod according to one of four dosing schedules: once or twice daily for 7 days/week or once or twice daily for 3 days/week. The twice-daily 7-day/week regimen was discontinued because of severe local skin reactions. Out of 95 patients who completed the study, 57 (58%) were complete responders to therapy, confirmed by histologic examination. The patients in the once-daily 7-day/week regimen had the highest complete response rate (71%). In addition, in this group the investigators found a statistically significant correlation between the most intense erosion and a complete response rate (P = 0.046).

Ninety-two patients were enrolled in the 12-week study and were randomized to receive imiquimod once or twice daily for 7 days/week, once daily for 5 days/week, or once daily for 3 days/week. (As with the 6-week study, the twice-daily 7-day/week regimen was discontinued.) The highest complete response rate, 76%, was seen in the group using imiquimod once daily for 7 days/week. In this study, investigators found a statistically significant correlation between the most intense erosion and a complete response rate in the once-daily, 5-days/week group (P = 0.003).

Local skin reactions were seen in all groups, and most were of mild to moderate intensity. The frequency of severe local reactions was lower in the 6-week study. Erythema was the most common local skin reaction in all dosing groups, and this was frequently followed by scabbing.

The researchers concluded that imiquimod is a safe and effective alternative option for nodular BCC, with once-daily applications 7 days/week yielding response rates of 71% and 76% for 6-week and 12-week treatment periods, respectively. These response rates are lower than those seen with studies of imiquimod in superficial BCCs. The authors speculate that this difference may be due to the fact that nodular BCCs are more dense tumors and extend deeper into the dermis than superficial BCCs, and thus it may be more difficult for imiquimod, lymphocytes, or local immune cytokines to penetrate central areas of nodular BCCs.

*Continued on top of page 14*
Actinic Keratosis: Newer Concepts for a Comprehensive Management Approach

Joseph L. Jorizzo, MD

The discussion of actinic keratosis (AK) in the United States over the past several years has been particularly passionate. Some nondermatologists still might argue in favor of the concept that AK is a precancerous lesion that does not require treatment. The current prevailing opinion, however, is that this view does not actually do justice to AK. Ultraviolet (UV) light clearly serves as the inducer of these lesions, but, in fact, a continuum exists in which AKs contain cells that have already undergone transformation and have all the markers of malignancy.1 These cells—analogue to what occurs in intraepithelial neoplasia—have not yet organized into a structure that is classifiable as an in situ or an invasive squamous cell carcinoma (SCC).

We know that tumor suppression involves effective cellular immune surveillance. Marks and colleagues2 have noted that in young people, particularly, a small number of AKs regress spontaneously. As individuals age and immune surveillance deteriorates, a much higher percentage of AKs evolve toward the end of the continuum at which invasive SCC is identified. In addition, immunosuppressed patients, particularly those who have undergone organ transplantation— with resultant cellular immune suppression—require constant surveillance because of their high risk for frequent development of invasive SCCs.

Traditional Management of AKs

The traditional mechanisms of management of AKs include sun-awareness education and sunscreens as preventive measures. In contrast to what many clinicians and consumers believe, sunscreen use does not represent only long-term prevention—that is, prevention of the induction phase of AKs. In fact, there is a more immediate role because UV-induced local immunosuppression is decreased when sunscreens are used, and the number of AKs is reduced even in the first year of a rigorous sun-protection program.

Cryosurgery is the standard modality for treating AKs and is effective even for hypertrophic lesions. Other destructive techniques that are commonly used include curettage, laser ablation, photodynamic therapy, and dermabrasion. Topical chemotherapy with 5-fluorouracil is an effective treatment that has been improved recently with the introduction of a formulation that maintains efficacy at one tenth the potency of the previously available products. However, with destructive methods or chemotherapy, the treatment of AKs is an “outside-in” approach. Thus, if a lesion has progressed beyond an AK to SCC in situ (alternatively referred to as a Bowen’s disease lesion) or to invasive SCC, then a deeper follicular or dermal invasive component will be left behind after treatment. For this reason, the newest agents on the list of AK treatment options, immune response modifiers, are intriguing. Immune response modification with agents including interferon and imiquimod offers the opportunity to have the tissue reject the lesion from below. Several studies testing the efficacy of imiquimod are reviewed here.

Evidence for Efficacy of Immune Response Modifier Treatment of AKs

Imiquimod is an immune response modifier currently indicated for the treatment of external anogenital warts. Immune response modifiers act by upregulating the innate and cell-mediated immune response in the skin, stimulating natural-killer-cell activity and augmenting T-cell activity. In addition, imiquimod induces interferon-γ, tumor necrosis factor, and several interleukins.3

Stockfleth and colleagues4 conducted a randomized, double-blind, vehicle-controlled study to assess imiquimod 5% cream for the treatment of multiple AKs. Thirty-six men and women between 45 and 85 years of age were randomized to receive either imiquimod or vehicle. The AK lesions were biopsied at baseline to confirm the diagnosis. The subjects applied the medication or placebo three times a week until the lesions resolved or for a maximum of 12 weeks. Efficacy and safety assessments were made at weeks 2, 3, 6, 9, and 12. At week 14, a final clinical evaluation and biopsy were performed on all subjects, and, at 1 year, the imiquimod-treated patients were evaluated again.

By week 14, 84% (21/25) of the subjects treated with imiquimod had complete clinical clearance of lesions (Figure) and partial clearance was achieved in 8% (2/25). The clinical impression of complete clearance was confirmed histologically. At the 1-year follow-up, only 10% of the imiquimod-treated patients had experienced what the investigators called a recurrence of AKs in the zone of treatment. All of the patients who were in the active-treatment group experienced...
local skin reactions, mostly mild to moderate in severity.

With the goal of decreasing local skin reactions with imiquimod therapy, Salasche and colleagues conducted an open-label pilot study using a "cycle" dosing regimen to treat AKs of the face and scalp. With the cycle concept, imiquimod is applied once daily for 4 weeks, followed by a 4-week rest period, and, after evaluation, a repeat of the cycle, if needed. At baseline, the average lesion count for the group was 368 (mean, 12), which increased to 613 (mean, 19) at week 2. The lesion counts at weeks 4, 6, and 8 were 515 (mean, 16), 228 (mean, 7), and 144 (mean, 5), respectively. Note that effective topical treatment of AKs results in an increase in AK numbers because of the inflammation induced in preclinical lesions. This allows an opportunity for the treated cells to reject these lesions at the preclinical stage.

Complete clearance was seen in 82% (27/33) of anatomic sites in 25 subjects. By the end of the first 4-week cycle, almost half the sites were clear (15/33). The cycle approach achieved high efficacy while minimizing adverse effects, and it may result in better patient acceptance, compliance, and satisfaction. These investigators also noted that, during the rest period, a "therapeutic interval" was identified: Inflammation steadily decreased, but the therapeutic effect—as measured by the diminishing lesion count—continued. This therapeutic interval provides the added benefit of allowing the clinician to assess whether to initiate another cycle of treatment and, if so, which dosing regimen would best suit the patient’s needs.

The issue of safety related to UV light exposure during imiquimod therapy was addressed in a study by Kaidbey and coworkers. These investigators enrolled 185 subjects to test for photocontact dermatitis, phototoxicity, and photodamage. A total of 175 (95%) completed the study; 9 discontinued because of noncompliance or to effects unrelated to the study drug. No subjects had a photocontact allergic reaction following challenge, and no abnormal immediate or delayed phototoxic reactions were seen. Regarding photodamage, there was no significant difference in sunburn cell counts between imiquimod plus UV radiation versus unirradiated control. Further, there was no difference in the number of pyrimidine dimers produced between imiquimod plus UV radiation versus no drug plus UV radiation.

Finally, two phase III, double-blind, randomized, multicenter, vehicle-controlled, parallel-group studies have been completed, and the data will be available soon for review. The subjects in these studies were treated for AKs of the face or scalp, with application of imiquimod or placebo twice a week for 16 weeks.

**Optimal Management of Sun-Damaged Skin**

Five steps should be considered in the optimal management of sun-damaged skin, all of which are best performed by dermatologists who can identify, evaluate, and treat lesions that are associated with high morbidity and/or mortality. Step one is prevention counseling, which includes sunscreen use, sun exposure hours, and other information. Step two is the examination of all sun-exposed skin for melanomas, SCCs, and basal cell carcinomas. Step three is the use of cryosurgery to treat most of the visible AKs, particularly hypertrophic lesions.

Step four is what I call "interval therapy"—that is, the application of a topical agent (for example, imiquimod or 5-FU) twice a week for 1 to 2 weeks at a time to treat residual AKs and AKs that have not yet become clinically apparent, including skin that has the texture of sandpaper. Interval therapy—either cycle therapy or another schedule acceptable to the patient, such as the use of imiquimod five times a week for 2 weeks, or applications of 5-FU once daily for 1 week—was instituted in my practice 3 years ago. In that time, in my anecdotal experience, the number of AKs in each patient that required further cryosurgery has been reduced by half.

The fifth and final step is the discussion of possible cosmetic procedures that are available from our cosmetic dermatology colleagues. This five-step cycle can be repeated at intervals of 2 to 12 months or as appropriate to individual patient needs.

**Summary**

AKs are a major clinical problem in dermatology and represent a key step in the progression to invasive SCC. Recent studies show that imiquimod therapy is an effective topical treatment for AKs. Topical interval therapy for AKs should be explored as an adjunct to cryosurgery in the comprehensive management of patients with sun-damaged skin.

Continued on bottom of page 14

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**Figure. 12-Week Course of Treatment of Actinic Keratoses With Immune Response Modifier Therapy**

This patient participated in a 12-week, double-blind, placebo-controlled study of imiquimod use in actinic keratoses (AKs). Multiple AKs are evident on the right side of the face at baseline (A). By week 6, the local reactions commonly seen with imiquimod therapy are evident (B). This patient experienced complete clearance of lesions, as shown in this photo (C) taken 2 weeks after the end of the 12-week course of therapy.

Photos courtesy of Professor E. Stockfleth.
New Horizons in the Treatment of Basal Cell Carcinoma: Noninvasive Treatment and Monitoring

Abel Torres, MD, JD

The previous discussions in this supplement on the use of imiquimod in basal cell carcinoma (BCC) have addressed the clinical and histologic results of a range of studies. Despite the wealth of accumulated information, a number of questions remain unanswered or are only partially answered. For example:

- What happens when treatment duration and frequency are different from what has been studied and documented—for example, for less than 6 weeks?
- In addition to superficial and nodular BCC, what other types of BCCs can be treated with imiquimod? Infiltrative? Micronodular?
- Can the presence or clearance of tumor be established noninvasively?
- Can presurgical treatment reduce the size of the postsurgical defect, making it possible to use a surgical repair technique that is less complicated and perhaps more cost-effective?

Immune Modifier Therapy As Adjunct to Surgery

Our group at Loma Linda University and investigators at Harvard Medical School conducted a study (as yet unpublished) using imiquimod as an adjunct to Mohs’ surgery in treating BCC. The patients who participated in this randomized, double-blind, vehicle-controlled study had BCCs of all types, including infiltrative, adenoid, and micronodular BCCs. The application regimen was 5 days/week for 2, 4, or 6 weeks, looking for tumor clearance in individual patients. In addition, we evaluated the effectiveness of noninvasive clinical and confocal (conjugated focal planes) microscopy monitoring, as well as the value of imiquimod therapy for tumor reduction prior to excision.

We observed that histologic clearance of BCCs occurred on the 5-day/week regimen. Pooling all types of BCCs, we observed at weeks 4 and 6 a clearance of lesions that was significantly greater than that seen in the vehicle-only group. The tumors that did not clear with imiquimod were reduced in size so that at weeks 4 and 6, Mohs’ surgery defects were significantly smaller than those seen in the vehicle-only group.

The typical skin reaction scenario observed in our study with the 5-day/week regimen was erythema and some minimal crusting at 2 weeks, becoming more intense at 4 to 6 weeks, and then resolving. On occasion, the local skin reactions at 5-day/week applications of imiquimod were severe, with erosion and crusting, and with some patients needing a rest period before continuing therapy. However, these reactions resolved within 2 weeks, with good textural and cosmetic results. Less often, some patients—particularly those with superficial BCCs—had no local skin reactions, yet experienced tumor clearance.

Enhancing Clinical Assessment

The accuracy of determination of tumor clearance by visual inspection was calculated. The negative predictive value of clinical assessment—that is, the rate at which investigators were able to accurately determine the complete clearance of BCCs—was 88.9%. In contrast, the positive predictive value—the rate at which investigators accurately determined by visual inspection that a tumor was still present—was only 69.3%.

<table>
<thead>
<tr>
<th>Table. Confocal Features: Normal Versus Tumor</th>
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<tbody>
<tr>
<td><strong>NORMAL</strong></td>
</tr>
<tr>
<td>Honeycomb arrangement of cells</td>
</tr>
<tr>
<td>Large to small cells from stratum corneum to basal layer</td>
</tr>
<tr>
<td>Normal structures</td>
</tr>
<tr>
<td>Small dermal capillary loops</td>
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<tr>
<td>Reticular collagen</td>
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<td>No white blood cell activity</td>
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We tested the use of the confocal microscope as a method to improve the reliability of noninvasive assessment following imiquimod treatment. This apparatus uses laser light to scan the skin and produce an image, similar to what is done with ultrasonography and sound waves but at a much higher resolution. Confocal imaging provides an axial resolution of 3 to 5 μm and a lateral resolution of 0.5 to 1.0 μm, to maximum depths of 230 μm at 830 nm and 350 μm at 1064 nm. The examination is noninvasive and painless, requires no tissue processing, provides images of cellular activity in real time, and allows inspection of unstained tissue in its native state. Our team has refined a list of features of normal skin versus BCC as seen on confocal microscopic examination (Table).

Confocal microscopy was performed on all patients in the study prior to, during, and after imiquimod treatment. Pretreatment biopsies confirmed the presence of BCC, and post-treatment Mohs’ surgery confirmed the accuracy of confocal microscopy. The Figure shows our typical findings in patients who responded to therapy.

When all of the images were included in our assessment of reliability of confocal microscopy, the negative predictive value was 70% and the positive predictive value was 84.6%. However, some of the images used to calculate the predictive value were of poor quality because of technical difficulty, such as poor contact or other operator error. When only high-quality images were interpreted, the correlation of histology and confocal microscopy was 100%. As we gain more experience with this technique and resolve the technical difficulties, much greater and more consistent predictive reliability can be expected from the use of confocal microscopy.

Table. Confocal Features Seen During BCC Therapy Study

<table>
<thead>
<tr>
<th>Feature</th>
<th>Image</th>
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<tbody>
<tr>
<td>Pleomorphic Actinic Cells</td>
<td>A</td>
</tr>
<tr>
<td>Polarized Elongated Cells</td>
<td>B</td>
</tr>
<tr>
<td>Increased Vascularity</td>
<td></td>
</tr>
<tr>
<td>Marked WBC Adhesion and Rolling</td>
<td></td>
</tr>
<tr>
<td>Honeycomb Pattern of Normal Epidermis</td>
<td>C</td>
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</table>

In our study patients, pretreatment confocal microscopy typically showed pleomorphic surrounding actinic cells and polarized elongated cells (A) in the area of BCC. During treatment with imiquimod, the typical features seen in responders to therapy were signs of inflammation: increased vascularity and marked adhesion and rolling of white blood cells (WBCs) in blood vessels (B). In patients whose tumors completely cleared—as confirmed on specimens taken during Mohs’ micrographic surgery—confocal microscopy showed the honeycomb pattern characteristic of normal epidermis (C).

**BCC** = basal cell carcinoma

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Imiquimod has been studied for the treatment of BCC and is associated with a cure rate in the high-80%-range for superficial BCC and in the low-70%-range for nodular BCC. Imiquimod is not yet approved by the U.S. Food and Drug Administration for this indication.

Our study is not yet published, and, therefore, many of the details concerning our results are not presented here. However, it can be said that our study had too few superficial BCCs to make any assertions in regard to cure rate with imiquimod. However, it included a broad mix of BCCs, indicating that BCC types other than superficial lesions respond to imiquimod at a cure rate similar to what has been reported for nodular BCC. The cure rate we observed, which was lower than that seen in published studies, may reflect the fact that, unlike in these other studies, the lesions in our study were predominantly on the head and neck. Furthermore, 4 weeks of treatment seems to be just as effective as 6 weeks of treatment.

In treating superficial BCC, I have patients apply imiquimod 5 days a week for 6 weeks, titrating this dosing schedule to patient tolerance of local skin reactions (for example, reducing applications to three times a week or stopping treatment after 4 weeks). If the skin looks normal on completion of a course of imiquimod therapy, I feel comfortable following the patient without further treatment or workup. However, if the treated area still shows erythema, swelling, or other changes, I use confocal microscopy to determine whether the tumor has resolved. If confocal microscopy is not available, the patient may be followed clinically to see if erythema resolves, or a biopsy may be done. In patients in whom the tumor does not respond completely, tumor shrinkage appears to result from presurgical treatment with a subsequent smaller surgical defect that allows less complicated surgery.
Immune Response Modifier Therapy

Continued from page 9

Because the higher dosing frequencies have been associated with an increase in local skin reactions and lower dosing frequencies with diminished efficacy, Sterry and colleagues\(^1\) in Europe tested the hypothesis that use of occlusion would enhance imiquimod efficacy at lower dosing frequencies in superficial and nodular BCCs. Patients with BCC underwent biopsies and, according to the histologic determination of the tumor subtype, were assigned to either the superficial or the nodular BCC study. The superficial BCC study had 93 patients; 90 patients were enrolled in the nodular BCC study. Subjects were assigned to one of four 6-week treatment regimens: imiquimod applications twice weekly, with or without occlusion, or three times weekly, with or without occlusion. Assessments were made at weeks 1, 2, 4, and 6; a 6-week posttreatment assessment was made for clinical and histologic clearance.

At the end of the treatment period in the superficial BCC study, the highest complete response rate, 87%, was seen in the group who received treatment three times weekly with occlusion. Those who received treatment three times without occlusion had a response rate of 76%. The complete clearance rates for groups who received twice-weekly treatment were 43% with occlusion and 50% without. The investigators noted that the rates were not significantly different for occlusion versus no occlusion within each dosing frequency group. However, there was a statistically significant difference between the twice-weekly and three-times-weekly groups that used occlusion—43% versus 87%, respectively (\(P = 0.004\)). After 6 weeks of treatment in the nodular BCC study, complete response rates were 50% and 57% in the two twice-weekly treatment groups, with and without occlusion, respectively. In the two three-times-weekly treatment groups, complete response rates were 65% and 50%, with and without occlusion, respectively. There were no statistically significant differences in response rates between any of these groups.

Local skin reactions were reported to be more severe in all groups, with a higher incidence in the three-times-weekly groups. Severe reactions were seen most frequently in the three-times-weekly group that used occlusion.

The 6-week posttreatment assessments showed that the three-times-weekly group that used the highest efficacy rate, 87%. This study demonstrated that although occlusion did not make a significant difference in efficacy in either dosing regimen, imiquimod can be used less frequently and still maintain efficacy in the treatment of superficial and nodular BCCs. The decreased number of applications may increase tolerability, which, in turn, may increase compliance.

**Summary**

Imiquimod has been shown to be safe and effective for the treatment of superficial and nodular BCC. Further studies are ongoing to determine the optimum dosing regimen to achieve the highest efficacy with the lowest incidence of side effects.

**References**

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Immune Response Modifier Therapy: Advances in the Management of AK and BCC

CME Post-Test and Evaluation

Continuing Education Instructions
There is no fee to participate in this activity. Please forward the Test Answer Sheet and Evaluation Form to:
Responses for AMA/Physician's Recognition Award credit must be submitted by September 2004.

INSTRUCTIONS: For each question or incomplete statement, one answer is correct. Check the most appropriate response. Seven of ten correct responses are required for credit.

1. Which one of the following is not a main proapoptotic pathway?
   a. Bax
   b. CD3+ activation
   c. Fas
   d. Tumor necrosis factor

2. All of the following treatments for basal cell carcinoma belong in the same category except:
   a. Cryosurgery
   b. Electrodessication-curettage
   c. Interferons
   d. Surgical excision

3. The most common local skin reaction reported consistently in clinical trials with imiquimod discussed in this supplement is:
   a. edema       c. erythema
   b. erosion      d. excoriation

4. Which one of the following statements regarding imiquimod is not true?
   a. Imiquimod has intrinsic antineoplastic effects.
   b. Imiquimod induces interferon.
   c. Imiquimod induces tumor necrosis factor.
   d. Imiquimod induces interleukin 12.

5. What percentage of basal cell carcinomas are classified as nodular?
   a. 30%       c. 50%
   b. 40%       d. 60%

6. In the randomized, vehicle-controlled trial of imiquimod in patients with basal cell carcinoma, Vidal and Alomar showed an increase of 1.6% in ______ in the imiquimod groups but not in the vehicle group.
   a. apoptotic rate       c. P53 expression
   b. Bcl-2 expression      d. Ki-67 expression

7. In the study of basal cell carcinoma clearance discussed by Torres, the rate at which investigators were able to accurately determine the complete clearance of lesions by visual inspection alone (negative predictive value) was 88.9%. Interpretation of high-quality images obtained on confocal microscopy improved predictive value to ______.
   a. 94%       b. 96%
   c. 98%       d. 100%

8. Which of the following statements concerning actinic keratoses (AKs) is not true?
   a. AKs are of particular concern in patients who are immunosuppressed.
   b. AKs are more likely to evolve into invasive squamous cell carcinomas with increasing age.
   c. AKs do not have markers of malignancy.
   d. AKs may regress spontaneously, particularly in young people.

9. Sunscreen use:
   a. Decreases local immunosuppression induced by ultraviolet light.
   b. Decreases the number of actinic keratoses only if used for at least 2 years.
   c. Is of limited value in preventing actinic keratoses over the long term.
   d. Is of value only for long-term protection against the induction phase of actinic keratoses.

10. Salasche and coworkers’ open-label pilot study of a “cycle dosing” regimen of imiquimod had the goal of:
    a. Completely clearing actinic keratoses.
    b. Decreasing local skin reactions.
    c. Improving response in superficial basal cell carcinomas.
    d. Reducing the amount of medication required to clear actinic keratoses.

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