Topical Therapy for Actinic Keratoses, I: 5-Fluorouracil and Imiquimod

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GOAL

To examine the validity of the topical therapies 5-fluorouracil and imiquimod in the treatment of actinic keratosis (AK)

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the mechanism of action of 5-fluorouracil.
2. Describe the mechanism of action of imiquimod.
3. Explain the efficacy and side-effect profiles of 5-fluorouracil and imiquimod.

CME Test on page 372.

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Mr. Tutrone, Ms. Saini, Ms. Caglar, and Dr. Crespo report no conflict of interest. Dr. Weinberg has been a clinical investigator for 3M Pharmaceuticals. The authors report discussion of off-label use of imiquimod, colchicine, and tretinoin. Dr. Fisher reports no conflict of interest.

Actinic keratoses (AKs) are evolving, malignant cutaneous neoplasms. AKs can be treated with physical or destructive methods and with topical therapies. This article is the first in a 2-part series that will review current topical therapeutic options for AKs. Several topical treatment options offer some significant benefit for the alleviation of these lesions. Therapies include 5-fluorouracil, imiquimod, diclofenac, colchicine, and retinoids. The first part of this review will focus on topical 5-fluorouracil and imiquimod.

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Actinic keratoses (AKs), also known as *solar keratoses*, *senile keratoses*, *squamous cell carcinoma in situ* (solar keratotic type), and *keratinocytic intraepidermal neoplasia*, are the most common neoplastic skin lesions detected in individuals with Fitzpatrick skin type I or II. These lesions are the third most common reason a patient

Table 1.

Topical Formulations for AK Treatment*

Product	Status	Company	Brand Name	Available Strengths, %
5-Fluorouracil	FDA approved	Dermik Laboratories	Carac™ cream	0.5
		ICN Pharmaceuticals	Efudex® cream	5
			Efudex topical solution	2, 5
		Allergan	Fluoroplex® topical cream	1
			Fluoroplex topical solution	1
Imiquimod	Phase 3 trial	3M Pharmaceuticals	Aldara™ cream	5

*FDA indicates US Food and Drug Administration.

visits a dermatologist.[1] AKs were described first in 1898 by Dubreuilh[2] at the Third International Congress of Dermatology. AKs appear as papules in a vast spectrum of sizes, shapes, colors, and other characteristics. Their size and shape can range from a well-circumscribed, single millimeter papule to an irregularly shaped lesion that can span several centimeters. These neoplasms can be flesh colored, red, or pigmented and also can scale or become hyperkeratotic.

AKs can occur anywhere the skin is exposed to chronic sun radiation. The most common sites for these lesions are the face, ears, scalp, neck, forearms, and hands. Chronic, repetitive UV exposure results in repetitive cycles of DNA damage. Eventually, these cycles of damage and repair spawn a significant unrecoverable error. The DNA lesion most likely responsible for these neoplasms is the p53 and/or *ras* proto-oncogene mutation.[3] Multiple studies have shown that the p53 mutation is present in 53% of AKs and in 69% to 90% of squamous cell carcinomas (SCCs).[3,4]

The Australian population has the highest prevalence of AKs (approximately 40%).[5] In the United States, a population study revealed that the relationship between the prevalence of AK and overexposure to the sun ranged from 23.3% to 36.7% in men and 18.6% to 34.1% in women, with low and high UV exposure, respectively.[6] An individual's population of AKs is a dynamic balance between the appearance of new lesions and the spontaneous resolution of a percentage of the existing ones. Annual rates of incidence and resolution are as high as 48% and 26%, respectively.[7] Further, the current literature reflects that 60% to 99% of all SCCs arise from AKs. Subsequently, the overall annual incidence of an AK transforming into SCC is 0.075% to 0.096%.[8] When these data are extrapolated, the 10-year incidence rate for developing SCC in a patient with an average AK burden is 10.2%.[9]

To combat this very common lesion, a host of topical preparations has been investigated. Therapies include 5-fluorouracil, imiquimod, diclofenac, colchicine, and retinoids. This first part of the review will focus on topical 5-fluorouracil and imiquimod (Table 1).

5-Fluorouracil

A mainstay for the treatment of AKs for many years, topical 5-fluorouracil has been the focus of a multitude of studies (Table 2).[10-14] The main mechanism of action is well understood and entails the topical formulation undergoing ribosylation and phosphorylation after entering cells, resembling a natural nucleotide. Fluorouracil then binds to thymidylate synthase, using the cofactor 5,10-methylene tetrahydrofolate. As a result, thymidylate synthase is inhibited and cannot convert deoxyuridine nucleotides to thymidine nucleotides. The depletion of thymidine leads to reduced synthesis of DNA.[15] This agent acts selectively to cause cell death in the actinic lesions but not in the normal skin. It is not clear whether normal cells simply absorb less fluorouracil than AK cells or whether the absorption is the same in both without producing equal effects on both cell types.[16-18]

Among the earlier studies of 5-fluorouracil for the treatment of AKs is a double-blind investigation by Simmonds[10] comparing the 1% and 5% formulations. Sixteen patients applied the 1% cream to one

Table 2.

Summary of Topical 5-Fluorouracil Studies*

Study	No. of Patients	Treatment	Results	Most Common Adverse Events
Simmonds, 1973[10]	16	1% fluorouracil on one side of face and 5% on other side BID for 14–29 days	No difference in treatment time or degree of efficacy for either 1% fluorouracil or 5%	Most patients experienced mild erythema
Levy et al, 2001[11,12]	21	0.5% fluorouracil qd or 5% BID for up to 28 days	Plasma concentrations of fluorouracil were identified in 3 patients treated with the 0.5% cream and in 9 patients treated with the 5% cream	Facial irritation was evident with both formulations but reached a plateau during treatment with 0.5% fluorouracil
Loven et al, 2002[13]	21	0.5% fluorouracil qd and 5% BID to opposite sides of face for 4 weeks	0.5% fluorouracil: lesion reduction from 11.3 to 2.5. 5% fluorouracil: lesion reduction from 10.3 to 4.2. Patients preferred 0.5% fluorouracil (P=.003)	All 21 patients experienced facial irritation, the most common being erythema, erosion, and dryness
Weiss et al, 2002[14]	177	0.5% fluorouracil or vehicle qd for 1, 2, or 4 weeks	A mean lesion decrease to 3.0 after 4 weeks of treatment with fluorouracil compared with 13.7 after vehicle	77.5%–81.6% in each treatment group experienced mild to moderate facial irritation, with majority showing dryness (58%) and erythema (73%)

*BID indicates twice a day; qd, once a day.

side of their face and the 5% cream to the other side and then were evaluated at 7-day intervals. Results indicated that for half of patients—when both sides of the face were affected equally at the start of treatment—both creams produced equal results.[10] Although the most common fluorouracil cream formulations used have been the 1% and 5% strengths, recently, a relatively new 0.5% cream has garnered much attention.[11]

Levy et al[11] performed an in vitro study involving the penetration of three 0.5% fluorouracil creams (formulations A, B, and C), using a microsphere delivery system and one commercially available 5% fluorouracil cream administered every 3 hours for 24 hours on full-thickness human cadaver skin. The three 0.5% cream formulations differed in the method of incorporating fluorouracil within the vehicle base, and a preservative was present only in formulation A. Total absorption was defined as the sum of the amount of cumulative flux through the skin over 24 hours plus the amount retained in the skin at 24 hours. Findings indicate that the flux through the skin of the 5% fluorouracil formulation was 20 to 40 times greater than that of the 0.5% fluorouracil formulation. A greater percentage of absorbed fluorouracil was retained in the skin after 24 hours with the 0.5% formulation (86%–92%) than with the 5% formulation (54%)(P<.001).[11]

Another study by Levy et al[12] used a different methodology; systemic exposure was evaluated via plasma and urine fluorouracil concentrations following topical application of fluorouracil in patients

Table 3.

Topical Imiquimod Studies for the Treatment of Actinic Keratoses

Study	No. of Patients	Treatment	Results	Most Common Adverse Events
Salasche et al, 2002[28]	25	5% imiquimod 3 times a week for a maximum of three 4-week cycles	82% of the treated sites were cleared	Some patients had mild to moderate irritation. Five patients experienced severe medication reactions
Persaud et al, 2002[29]	22	5% imiquimod to half of each patient's body 3 times a week for a maximum of 8 weeks	Mean AK reduction of 3.9 per patient	82% (20) of patients experienced mild to moderate erythema, pruritus, and/or scabbing
Stockfleth et al, 2001[30]	6	5% imiquimod 2–3 times a week for a maximum of 8 weeks	All patients experienced complete clearance	Mild to moderate pruritus and erythema were the only adverse events reported. Overall, the medication was well tolerated
Stockfleth et al, 2002[31]	36	5% imiquimod 3 times a week for a maximum of 12 weeks	21 patients experienced complete clearance	All patients experienced mild to severe reactions. The 5 most common reactions were erythema, scabbing, erosions, flaking, and ulcerations

with a minimum of 3 AKs.[12] Patients were randomized to receive 1-g doses of either 0.5% or 5% fluorouracil cream. Treatment regimens were consistent with prescribing regimens: once daily for the 0.5% fluorouracil cream and twice daily for the 5% fluorouracil cream for up to 28 days. After determining the pharmacokinetics, measurable fluorouracil plasma concentrations were identified in 3 patients treated with the 0.5% cream and in 9 patients treated with the 5% cream.[12] Despite the one-tenth difference in drug concentration among formulations, the cumulative amount excreted in the urine of the 0.5% fluorouracil group was approximately one fortieth that of the 5% fluorouracil group.[12]

In a single-blind study, Loven et al[13] investigated the efficacy and tolerability of 0.5% fluorouracil cream compared with 5% fluorouracil cream. Patients with a balanced number of AKs on each side of their face were treated with the 0.5% cream on one half of their face once daily and the 5% cream on the other half twice daily for 4 weeks, or to the point when treatment became intolerable. Both the total clearance of AKs and the incidence of any adverse event were not found to be significantly different between the 2 groups. However, the majority of patients in the study preferred the 0.5% to the 5% cream ($P=.003$), secondary to the once-daily treatment schedule, less irritation, and ease of product application.[13]

In a similar study examining the efficacy of 0.5% fluorouracil in a randomized, double-blind, vehicle-controlled trial, Weiss et al[14] reported a significant reduction in the number of AKs with the 0.5% cream. Treatment duration consisted of 1, 2, or 4 weeks, with a percentage reduction in the number of AKs from baseline of 78.5%, 83.6%, and 88.7%, respectively ($P<.001$). Total lesion clearance occurred in 26.3%, 19.5%, 47.5%, and 3.4% of patients in the 1-, 2-, and 4-week fluorouracil and vehicle groups, respectively. Facial irritation was experienced by patients in the 1- and 2-week groups and appeared to increase during the entire treatment period. Patients in the 4-week group noted only a slight increase in irritation beyond the second week. Irritation returned to baseline levels 15 to 17 days after completion of therapy, regardless of the duration of application.[14] Further supporting that the topical 0.5% fluorouracil cream may be more cost-effective is a study conducted by Gupta,[19] comparing the other 2 strengths (5% and 1%). Results suggest that 0.5% fluorouracil cream may be more cost-effective than

the higher concentrations in a patient with multiple AKs, most likely due to the once-daily regimen.[19]

In all the studies reviewed, the most common side effects from treatment were mild to moderate facial irritation associated with erythema, dryness, and burning. Few serious adverse events have been reported with topical fluorouracil use and include allergic contact dermatitis[20] and a single case of inflammatory colitis following topical application of a 5% formulation for a basal cell carcinoma of the scalp.[21] This individual had a severe deficiency of dihydropyrimidine dehydrogenase, the rate-limiting enzyme in fluorouracil breakdown. It is thought that this is the only case of a life-threatening toxicity in a patient receiving topical 5-fluorouracil.[21]

Imiquimod

Another medication currently used to treat AKs is imiquimod. This drug has been approved by the US Food and Drug Administration as a therapy for external genital warts.[15] However, there are increasing numbers of case reports and reviews that show the efficacy of topically applied imiquimod for off-label conditions, such as molluscum contagiosum, basal cell carcinoma,[22] SCC, Bowen disease, human papillomavirus infections,[23-26] vulvar intraepithelial neoplasms,[25] and AK[27,28-31] (Table 3).

Imiquimod is an immunomodulator. Application of the drug results in increased levels of interferons α, β, and γ and tumor necrosis factor α in lesional tissues. Further, keratinocytes exposed to imiquimod release increased levels of IFN-α, IL-6, and IL-8. These and other cytokines activate and sensitize the local cellular immune system, including, but not limited to, natural killer and cytotoxic T cells. The cascade results in a localized immune response against the abnormal cells in the application area.[23-26]

Salasche et al[28] conducted a 25-patient, open-label trial using 5% imiquimod 3 times a week. The therapeutic regimen consisted of 4 weeks of treatment, followed by a 1-month resting period. No more than an additional 2 cycles of treatment were given if total clearance did not occur by the end of the first rest period. At the end of the first cycle, 15 of the 33 study areas were devoid of any lesions. After the second cycle, an additional 12 sites were cleared. Only one patient underwent a third cycle of treatment, resulting in a 75% clearance in the study area. Overall, 82% of the treated sites were cleared using this therapy. Some patients experienced a mild to moderate local irritation, which was well tolerated without complication. However, 5 patients reported severe medication reactions, all of which occurred during the first cycle. These reactions followed an intense and early response to therapy.[28]

Persaud et al[29] conducted a 22-patient study applying 5% imiquimod cream to half of each patient's body 3 times a week for a maximum of 8 weeks. The treatment period was followed by an 8-week monitoring period. The 17 patients who completed the study had mean AK reduction of 3.9 on the imiquimod side per patient compared with a 0.5 lesion reduction on the vehicle side ($P<.005$). As a result of treatment, 14 of the 17 patients experienced mild to moderate erythema, pruritus, and/or scabbing. Further, to complete the study, 12 patients required 1 or 2 rest periods, followed by a reduction in application frequency.[29]

Stockfleth et al[30] conducted a 6-patient study examining the efficacy of 5% imiquimod applied 2 to 3 times a week for 6 to 8 weeks. On completion of the treatment, all patients were clinically and histologically cleared of all AKs in their test areas. Patients were followed for a maximum of 12 months and had no recurrence of disease in their treated areas. All patients decreased their dosage from 3 times a week to 2 times a week for more than half of individual treatment periods. The treatment was well tolerated, with only mild to moderate pruritus and erythema reported.[30]

In another study, Stockfleth et al[31] treated 36 patients with 5% imiquimod 3 times a week for a maximum of 12 weeks. By the 14th week of the study, 21 of the 25 patients treated with imiquimod experienced complete clinical and histologic clearance in their study areas. Further, the 15 patients who maintained a 3-times-per-week application protocol all experienced total clearance in their study areas. These results were significant in comparison with the clearance rate in the control group ($P<.001$). During the treatment period, every patient using imiquimod experienced some type of mild to severe adverse reactions. The 5 most common occurrences were erythema, scabbing, erosions, flaking, and ulcerations.[31] Recently, a phase 3 trial evaluating imiquimod for the treatment of AKs was completed.

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