

Treatment Options for Actinic Keratoses

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Actinic keratoses are rough, scaly lesions that commonly occur on sun-exposed areas of the skin. The prevalence of the condition increases with age. Actinic keratoses are thought to be carcinomas in situ, which can progress to squamous cell carcinomas. The decision to treat can be based on cosmetic reasons; symptom relief; or, most importantly, the prevention of malignancy and metastasis. Treatment options include ablative (destructive) therapies such as cryosurgery, curettage with electrosurgery, and photodynamic therapy. Topical therapies are used in patients with multiple lesions. Fluorouracil has been the traditional topical treatment for actinic keratoses, although imiquimod 5% cream and diclofenac 3% gel are effective alternative therapies. There are too few controlled trials comparing treatment modalities for physicians to make sound, evidence-based treatment decisions. (*Am Fam Physician* 2007;76:667-71, 672. Copyright © 2007 American Academy of Family Physicians.)

Patient information:

A handout on actinic keratoses, written by the authors of this article, is provided on page 672.

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Actinic keratoses are lesions that begin in the epidermis on sun-exposed areas of the body. The lesions appear as rough, scaly patches that range in color from normal skin tone to reddish brown (*Figures 1A and 1B*). They are often circumscribed and are usually 1 mm to 2.5 cm in diameter, but they can be larger. Patients may present with a single, well-defined lesion or multiple, less-defined lesions covering a large area of skin. Several types of lesions may be present. Most lesions are asymptomatic, but some cause pruritus or a burning sensation.¹

Prevalence

Fair-skinned, blue-eyed persons living in sunny climates are most likely to develop actinic keratoses. The lesions take years to develop and usually occur in older persons; they are more common in men than in women.¹ Persons with many years of extensive sun exposure are at the greatest risk. More than 80 percent of actinic keratoses occur on areas of the skin with the most sun exposure such as on the head, neck, forearms, and hands.²⁻⁴

It is estimated that 60 percent of predisposed persons older than 40 years have at least one actinic keratosis.⁵ Among white persons, the prevalence of the disease increases with age, ranging from less than 10 percent in persons 20 to 29 years of age to 75 percent in those 80 to 89 years of age.^{6,7}

Risk of Cancer

Actinic keratoses, the most common premalignant lesions seen by dermatologists, have the potential to progress to squamous cell carcinomas.⁸⁻¹¹ Although most actinic keratoses do not progress to cancer, and as many as 26 percent regress spontaneously,¹¹ up to 60 percent of cutaneous squamous cell carcinomas arise from actinic keratoses.¹⁰

Estimates on the risk of actinic keratoses progressing to squamous cell carcinomas vary widely. A prospective, longitudinal study found the risk of progression to be 0.24 percent per year for each actinic keratosis.¹¹ Because most patients have more than one actinic keratosis, another study used these data to determine that the risk of progression to squamous cell carcinoma is 6.1 to 10.2 percent over 10 years per person.¹² Two additional studies show that keratoses are associated with squamous cell carcinomas 72 to 97 percent of the time.^{8,9}

After progression to squamous cell carcinoma has occurred, the risk of metastasis is estimated to be 0.5 to 3.3 percent.^{13,14} One study found histologic evidence that actinic keratoses are present in 44 percent of squamous cell carcinomas that have metastasized.¹⁵

Treatment

Actinic keratoses may be treated for cosmetic reasons or for relief of associated symptoms,

SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>
Actinic keratoses should be treated because of their potential to progress to squamous cell carcinomas.	C	8-11
Cryosurgery is an effective modality for treating solitary or multiple actinic keratoses.	C	16-18
Curettage is an effective treatment for patients with a limited number of actinic keratoses, particularly thick, hyperkeratotic lesions.	C	20
Topical treatment should be considered for patients with multiple lesions.	C	16

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 612 or <http://www.aafp.org/afpsort.xml>.

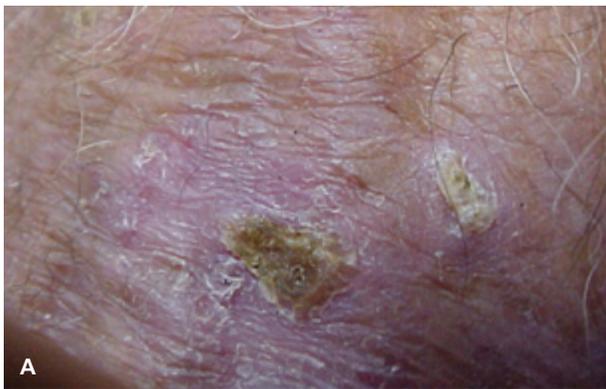


Figure 1. Actinic keratoses on (A) the hand and (B) the face.

Photos courtesy of Daniel A. Davis, MD.

but the most compelling reason for treatment is to prevent squamous cell carcinomas. Treatment options include ablative (destructive) therapies or topical therapies in patients with multiple lesions.

CRYOSURGERY

Cryosurgery using liquid nitrogen is the most common modality for treating actinic keratoses, although compressed nitrous oxide or carbon dioxide is also used. Liquid nitrogen is sprayed directly on the lesions or applied using a cotton-tipped swab.

The procedure is highly effective, with reported cure rates between 75 and 99 percent^{16,17}; however, correct technique is important. A study showed that a five-second treatment had a 39 percent cure rate, whereas a treatment of more than 20 seconds had an 83 percent cure rate.¹⁸

Cryosurgery is easily performed in the office setting, produces excellent cosmetic results, and is well tolerated. Potential adverse effects include infection, hypo- or hyperpigmentation, scarring, and hair loss; however, serious reactions are rare. Cryosurgery is best for treating thin, well-demarcated lesions and can be used to treat solitary lesions or small numbers of scattered lesions. Hyperkeratotic lesions are more resistant to cryosurgery and should be debrided before treatment.^{16,19}

CURETTAGE

Curettage, which involves mechanically scraping away abnormal tissue using a sharp curette, is a highly effective modality for treating actinic keratoses. The procedure provides tissue for histologic evaluation but requires local anesthesia.²⁰ Curettage is particularly useful for treating a limited number of actinic keratoses, especially thick, hyperkeratotic lesions. After curettage, electro-surgery may be used to destroy any remaining abnormal tissue

and to provide hemostasis. Possible complications include infection, scarring, and hypo- or hyperpigmentation.

PHOTODYNAMIC THERAPY

Photodynamic therapy involves applying a photosensitizing agent to each actinic keratosis, followed by exposure to light of a specific wavelength; this leads to cell death.²¹ Protocols for using photodynamic therapy to treat actinic keratoses vary with regard to the photosensitizing agent; amount of application; and light source, intensity, and dose. Two protocols are approved for use in the United States.²²

The use of the photosensitizing agent aminolevulinic acid (Levulan Kerastick) followed by blue light exposure was approved by the U.S. Food and Drug Administration (FDA) in 1999 for the treatment of nonhyperkeratotic lesions on the face and scalp. The protocol specifies a 14- to 18-hour incubation period between application of aminolevulinic acid and light exposure; however, a subsequent study has demonstrated the effectiveness of shorter incubation periods.²³ Another protocol using the photosensitizing agent methyl aminolevulinate (Met-vixia; not yet available in the United States) followed by red light exposure was approved by the FDA in 2004. This protocol specifies a three-hour incubation period.

Photodynamic therapy is well tolerated, has excellent cosmetic results, and has reported cure rates between 69 and 93 percent.^{16,21,24} Potential adverse effects include initial erythema; edema; a burning sensation; pain; and crusting followed by hypo- or hyperpigmentation, ulceration, or scaling.^{16,21}

TOPICAL THERAPIES

Several topical therapies are available for the treatment of actinic keratoses, including various fluorouracil formulations, imiquimod 5% cream (Aldara), and diclofenac 3% gel (Solaraze). Although other topical agents (e.g., colchicine [topical formulation not available in the United States], tretinoin [Retin-A]) are used, there are no comparative phase III studies of these agents.²⁵ Topical therapies are useful for patients with more than 15 actinic keratoses. The anatomic location of the lesions impacts the response time to topical treatments. Actinic keratoses on the face respond the quickest (more quickly than those on the scalp), whereas lesions on the arms usually take the longest to respond.²⁶ After topical treatment, actinic keratoses may reoccur on the treated area.^{26,27}

Fluorouracil. Topical fluorouracil is an established treatment for actinic keratoses and is the standard to which other topical treatments are compared. Fluorouracil cream is available in 5% (Efudex), 1% (Fluoroplex), and 0.5% (Carac) formulations.

Fluorouracil 5% cream is administered twice daily for two to four weeks. The application is associated with local irritation presenting as dryness, erythema, erosion, pain, or edema. Facial irritation and disfigurement associated with fluorouracil 5% cream makes the therapy undesirable to many patients. Studies have evaluated whether intermittent “pulse” applications decrease the adverse effects. However, these studies had small sample sizes and produced inconclusive results.^{28,29}

Studies report similar effectiveness among fluorouracil formulations, although the 0.5% cream, which uses a microspore delivery system, causes less-severe adverse effects.^{30,31} However, studies comparing fluorouracil formulations are limited and include a small number of participants.

Fluorouracil 0.5% cream can be used as a neoadjuvant therapy before cryosurgery. A one-week course of fluorouracil 0.5% has been shown to reduce the number of lesions before cryosurgery and to decrease the risk of reoccurrence.³²

Imiquimod. Imiquimod 5% cream is also approved for treatment of actinic keratoses. Imiquimod is applied once daily, two or three days a week, for 16 weeks. Several randomized, double-blind, vehicle-controlled trials showed that imiquimod 5% cream produced a complete response in 45 to 57 percent of patients and a partial response (i.e., 75 percent reduction in actinic keratoses) in 59 to 72 percent of patients.³³⁻³⁵ One study showed that in the imiquimod treatment group, 20 percent of participants developed new lesions and none developed squamous cell carcinoma after 24 months of follow-up.²⁷ By comparison, in the vehicle group, 90 percent of participants developed new lesions and one developed squamous cell carcinoma after one year of follow-up.²⁷

Local reactions (e.g., erythema, scabbing or crusting, erosions or ulceration) are common with topical imiquimod therapy. Topical imiquimod also has been reported to produce systemic adverse effects, including fatigue, flu-like symptoms, and angioedema.^{36,37}

Diclofenac. A randomized, double-blind, vehicle-controlled study compared topical diclofenac 3% in hyaluronan 2.5% gel with a hyaluronan 2.5% vehicle.³⁸ Participants applied the treatments twice daily for 90 days, with follow-up 30 days after the end of treatment. Approximately 50 percent of participants in the treatment group had complete resolution compared with 20 percent in the vehicle group.³⁸

Cryosurgery is highly effective for treating actinic keratoses if the correct technique is used.

Table 1. Trials of Topical Treatments for Actinic Keratoses

<i>Trials*</i>	<i>Treatment regimen</i>	<i>No. of participants</i>	<i>Complete response (%)</i>	<i>Partial response† (%)</i>
Diclofenac 3% (Solaraze) in hyaluronan 2.5% gel				
Wolf, et al., 2001 ³⁸	Twice daily for 90 days	120	Treatment: 47.0 Vehicle: 19.0	—
Imiquimod 5% cream (Aldara)				
Korman, et al., 2005 ³⁵	Once daily, three times per week, for 16 weeks	492	Treatment: 48.3 Vehicle: 7.2	Treatment: 64.0 Vehicle: 13.6
Lebwohl, et al., 2004 ³³	Once daily, two times per week, for 16 weeks	436	Treatment: 45.1 Vehicle: 3.2 (95% CI, 34.9 to 49)‡	Treatment: 59.1 Vehicle: 11.8 (95% CI, 39.5 to 55.1)‡
Szeimies, et al., 2004 ³⁴	Once daily, three times per week, for 16 weeks	286	Treatment: 57.1 Vehicle: 2.2	Treatment: 72.1 Vehicle: 4.3

CI = confidence interval.

*—Randomized, double-blind, vehicle-controlled, phase III trials.

†—75 percent reduction in actinic keratoses.

‡—CIs are for the treatment group minus the vehicle group.

Information from references 33 through 35 and 38.

Adverse effects associated with diclofenac 3% in hyaluronan 2.5% gel include pruritus, dry skin, application site reactions, rash, and erythema. *Table 1* presents results from trials that evaluated the effectiveness of imiquimod and diclofenac in the treatment of actinic keratoses.^{33-35,38}

Chemical peels. Facial peels using Jessner's solution (i.e., resorcinol, lactic acid, and salicylic acid in ethanol) and trichloroacetic acid 35% (Tri-Chlor) are comparable with fluorouracil in reducing actinic keratoses and recurrence.³⁹ Patients may prefer a chemical peel over fluorouracil because of the convenience of a single application.

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