Update on the Treatment of Actinic Keratoses

From mainstay therapies to newly approved agents, treatment options for actinic keratoses are growing.

BY MADELAINE HADDICAN, MD AND GARY GOLDENBERG, MD

Among the most common diagnoses dermatologists make, actinic keratoses (AKs) are often described as rough, scaly epidermal growths typically less than 1 cm in size occurring in clusters on sun-exposed skin, such as the face, scalp and forearms. Chronic exposure to ultraviolet radiation in fair-skinned individuals is the most important risk factor for the development of AKs. The prevalence of actinic keratoses tends to increase depending on geographic proximity to the equator, with the highest prevalence found in Australia, where 60 percent of individuals over 40 years of age have the diagnosis. Actinic Keratoses are also more commonly diagnosed in males, as well as individuals greater than 60 years of age.

Although some lesions are treated due to symptoms of pain or pruritus, the most common reason to treat AKs is because a small percentage has the ability to transform into squamous cell carcinomas (SCC). The variety of treatments for actinic keratoses is often categorized as either lesion-directed, such as cryotherapy, or field therapy, such as imiquimod cream. The additional benefit of these topical field therapies involves their ability to effectively target subclinical actinic keratoses. Ahead, we explore the relative benefits of a number of both lesion-directed and field therapies.

**THERAPEUTIC UPDATE**

Cryotherapy. Used as a medical therapy since the 1900s, cryotherapy is the most common treatment of choice for actinic keratoses. Liquid nitrogen is usually either sprayed or directly placed with a cotton swab on each lesion. In one study involving over 1,000 lesions treated with liquid nitrogen using the spray technique, a cure rate of 98.8 percent was achieved with follow-up ranging from one to 8.5 years. However, one study demonstrated that duration of spray treatment had a significant effect on cure rates, with one to five seconds of spray treatment associated with a 39 percent cure rate compared to lesions treated for greater than 20 seconds having a 83 percent cure rate.

All patients treated with cryotherapy should be educated about the more common side effects such as hypopigmentation, hyperpigmentation, scarring, and infection.

**TAKE HOME TIPS**

Actinic keratoses are one of the most common skin conditions. Effective treatment of this condition is important due to the possibility of malignant transformation into squamous cell carcinoma. Cryotherapy is one of the oldest known therapies for actinic keratosis and still remains the treatment of choice for many clinicians. In comparison, topical therapies are often not as well tolerated by patients and are more time intensive, but they offer the opportunity to effectively target subclinical lesions. With an increasing number of available agents for the treatment of actinic keratosis, more studies are investigating the efficacy of treating patients with sequential therapy involving topical therapies before or after cryotherapy. Evidence is accumulating to support this combination treatment as the most efficacious approach for clearance of actinic keratosis lesions.
Curettage and Electrodesiccation. For lesion-directed therapy, curettage and electrodesiccation is generally preferred for hyperkeratotic actinic keratoses. Immunocompromised patients with actinic keratoses are also more likely to have a better outcome with curettage and electrodesiccation. Side effects are similar to treatment with cryotherapy and include hypopigmentation, hyperpigmentation, scarring, and infection.

Fluorouracil. Since the 1960s, topical 5-fluorouracil (5-FU) (Efudex, Valeant) has been used for the treatment of actinic keratoses and skin cancers. The mechanism of action for 5-FU involves decreased production of thymidylate synthetase leading to a reduction in DNA synthesis and cell death. Today, topical 5-FU therapy is available as a cream or solution in 0.5% to 5% concentrations. Common side effects of 5-FU include application site reactions, such as erythema, pain erosion, edema and dryness.

One study had subjects use 0.5% 5-FU cream once daily and 5% 5-FU cream twice daily on opposite sides of their face for four weeks with a four week post-treatment follow-up. The percent reduction in actinic keratoses was significantly higher after treatment with 0.5% 5-FU cream compared with 5.0% 5-FU cream. Another study provided evidence in support of a four-week treatment regimen as optimal for 0.5% 5-FU, with 57.8 percent of subjects achieving total clearance of actinic keratoses in the treatment area compared to 37 percent for two weeks of treatment and 14.9 percent for one week of treatment.

Combining 5-FU with other therapies has shown promising results. One study showed that a one week treatment duration of 0.5% 5-FU followed by cryotherapy for facial actinic keratoses resulted in 30 percent of patients having complete clearance, compared to eight percent of subjects who received vehicle followed by cryotherapy.

Imiquimod. Topical imiquimod (Aldara) cream is an agent that falls into the category of field therapy for actinic keratoses. Topical imiquimod cream acts as a toll-like receptor-7 agonist to strengthen the immune response to destroy abnormal keratinocytes. In 2004, the first available formulation, imiquimod 5% cream, was approved as a 16-week regimen for the treatment of actinic keratoses. The newer formulation, imiquimod 3.75% cream (Zyclara, Medicis), was approved in 2010 for the treatment of actinic keratoses on the face and balding scalp. Imiquimod 3.75% cream is now available in a metered-dose pump with 9.4mg of the active drug dispensed with each pump. One to two pumps are applied once nightly for two weeks of treatment, followed by two weeks of no treatment (rest period), and then followed by another two weeks of treatment. In a study by Swanson et al, 35.6 percent of patients treated with imiquimod 3.75% cream on the face or scalp had complete clearance of their actinic keratosis lesions (median of 10 lesions) when evaluated eight weeks post-treatment.

In a study by Hanke, et al, 40.5 percent of patients treated with imiquimod 3.75% who had complete clearance eight weeks post-treatment maintained complete clearance (median of eight to nine lesions) for an additional 12 months.

To increase the percentage of patients who achieve complete clearance of their actinic keratoses after treatment with imiquimod 3.75%, combination therapy has been evaluated. In a study by Jorizzo, et al, 59.5 percent of patients whose actinic keratoses were treated with both cryotherapy and imiquimod 3.75% achieved complete clearance of those lesions when evaluated 20 weeks post-treatment in comparison to 29.8 percent of patients whose actinic keratoses were treated with cryotherapy alone. Thus, for the treatment of actinic keratoses, imiquimod 3.75% has improved upon the previous formulation of imiquimod 5% cream and has also shown enhanced efficacy in combination with cryotherapy.

Diclofenac. Diclofenac sodium (Solaraze, PharmaDerm) 3% topical gel has been used for more than 10 years for the treatment of actinic keratoses. This nonsteroidal anti-inflammatory agent inhibits cyclo-oxygenase 2 (COX-2), an enzyme increased in sun-exposed skin, actinic keratoses, and squamous cell carcinomas. Upregulation of the COX-2 enzyme is believed to support tumor growth by promoting angiogenesis and inhibiting apoptosis. The vehicle for diclofenac sodium gel 3% includes hyaluronic acid which helps maintain the active ingredient in the targeted area of the epidermis.

In a double-blinded study, 195 subjects who had at least five actinic keratoses were randomized to receive diclofenac sodium 3% topical gel for 30 days, diclofenac sodium 3% topical gel for 60 days, 2.5% hyaluronan gel for 30 days, or hyaluronan gel for 60 days. All four groups applied 0.5 grams twice daily of their assigned treatment within a total area of 15 cm². At the follow-up visit on day 90, the 60-day treatment arm had a statistically significant reduction of actinic keratoses compared to the 60-day placebo group (4.9 to 2.5, P=0.009). Adverse events for subjects receiving the active treatments were mild to moderate and included pain, erosion, edema and dryness.
30 days or 60 days of the active medication included pruritus, paraesthesia, rash, edema, and contact dermatitis.\(^25\)

A case series, involving subjects who had a history of recurrent actinic keratoses after cryotherapy alone, retrospectively evaluated the efficacy of combining cryotherapy after an 84-day (12-week) course of diclofenac sodium 3% topical gel. All 27 participants had at least five actinic keratoses with an average of 8.2. After the diclofenac sodium 3% treatment course, 21 patients achieved complete clearance. The remaining subjects with residual lesions were then treated with cryotherapy. During the follow-up period that averaged 10 months, none of the 27 patients were reported to have any recurrences.\(^26\)

**Photodynamic Therapy.** Approved in 1999, photodynamic therapy (PDT) involves applying 5-aminolevulinic acid (ALA) or methyl 5-aminolevulinate (MAL) topically. These agents then undergo conversion to a photosensitizer protoporphyrin IX in abnormal keratinocytes. Free radicals are produced after light activation, which results in targeted tissue destruction.\(^27\)

In one study, 27 patients with at least three actinic keratoses on the face or scalp had ALA applied for four hours. In each patient, separate actinic keratoses were randomized to receive different light doses using a filtered high-pressure metal halide lamp. One month after receiving treatment, the complete clearance rate was 88.5 percent, 92.3 percent, and 80.8 percent for the different light doses of 70 J/cm\(^2\), 100 J/cm\(^2\), or 140 J/cm\(^2\), respectively.\(^28\) Another study, involving the treatment of 198 actinic keratoses with a single session of MAL-PDT, demonstrated a 93 percent complete response rate for thin lesions and a 70 percent complete response rate for thicker lesions at the three month follow-up visit.\(^29\)

**Retinoids.** As early as the 1980s, there was evidence to support the use of retinoids in the treatment of actinic keratoses.\(^30,31\) One of the more recent studies evaluated the use of the synthetic retinoid, adapalene gel (Differin, Galderma) 0.1% and 0.3%, in comparison to vehicle twice daily for nine months in 83 patients, with a reduction of 0.5 and 2.5 actinic keratoses for the 0.1% and 0.3% formulations, respectively, with an increase of 1.5 actinic keratoses for the group treated with vehicle gel (P <0.05).\(^32\)

**Ingenol Mebutate.** Ingenol mebutate (Picato, LEO Pharma) is a natural ingredient found in the sap of the plant *Euphorbia peplus*. In the past few years, evidence has accumulated demonstrating the importance of this agent as a field-directed therapeutic option for actinic keratoses. The mechanism of action is two-fold involving cellular necrosis as well as neutrophil-mediated antibody-dependent cellular cytotoxicity of residual cells.\(^33\)

In a phase Ila, randomized, double-blind, vehicle-controlled study, ingenol mebutate gel 0.05% was applied for two days to actinic keratoses located on the arms, shoulders, face and scalp, with 71 percent of these lesions demonstrating complete clearance at day 85. There were no treatment-related serious events during this phase IIA study and no patient discontinued the study because of an adverse event.\(^34\) In a phase Ib, randomized, double-blind, vehicle-controlled study, 57.9 percent of patients treated with ingenol mebutate gel 0.025% for three days and 43.6 percent of patients treated with the ingenol mebutate gel 0.05% for two or three days had complete clearance at day 57 of the non-facial actinic keratoses that were identified and treated at baseline. This study also had no treatment-related serious events and no patient withdrew because of an adverse event.\(^34\) In a more recent study, complete clearance for actinic keratoses on the face and scalp treated with ingenol mebutate 0.015% for three days was 42.2 percent at the eight-week follow-up visit.\(^35\)

**T4 endonuclease liposome lotion.** T4 endonuclease, a DNA repair enzyme, has been formulated into a liposomal lotion that helps its delivery into keratinocytes. This investigational agent has recently been found to lower the occurrence of actinic keratoses in subjects with xeroderma pigmentosa.\(^36\)

**CONCLUSION**

The most compelling reason to effectively treat AKs is to prevent their possible malignant transformation. A multitude of therapies are available, with cryotherapy being one of the oldest and most commonly used by clinicians. But cryotherapy combined with other field therapies such as imiquimod has led to increased clearance rates of actinic keratoses, as well. The use of PDT has also been promising, but more studies are needed to compare this therapy directly with other available options. In addition, several new agents—such as ingenol mebutate and the recent development of the T4 endonuclease liposome lotion—offer clinicians and their patients more options when previous therapies have been ineffective. ■

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**Madelaine Haddican, MD is a Dematopharmacology Fellow, Mount Sinai of Medicine, Department of Dermatology.**

**Gary Goldenberg, MD is Assistant Professor of Dermatology and Pathology, Mount Sinai School of Medicine, Department of Dermatology Pathology.**


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