New and Emerging Topical Approaches for Actinic Keratoses

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Actinic keratoses (AKs) are intraepidermal foci of malignancy and represent the earliest clinical stage in the continuum of squamous cell carcinoma (SCC). A variety of topical, physical, and surgical modalities are available for treatment. Until recently, topical 5-fluorouracil was the only topical agent approved by the US Food and Drug Administration (FDA) for the treatment of AK. Topical diclofenac 3% gel, an inhibitor of arachidonic acid, is the second topical approved for the treatment of AK. Although not currently approved in the United States, multiple studies have substantiated the efficacy of topical imiquimod for AKs. This article reviews the efficacy and safety of topical diclofenac and topical imiquimod for the treatment of AKs.

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Actinic keratoses (AKs) are intraepidermal foci of malignancy, which represent the earliest clinical stage in the continuum of squamous cell carcinoma (SCC).[1-10] Prevalence is highest in fair-skinned individuals, as lesions characteristically arise secondary to chronic UV radiation exposure.[1-5] From 1990 to 1999, AK was diagnosed in more than 47 million patient visits in the United States.[6] With more than 1 million new cases reported annually, the diagnosis of AK represents approximately 14% of dermatology visits.[1-6] Contiguous SCC in situ or AK has been documented in more than 90% of SCCs arising within photodamaged skin.[9,10] In up to 20% of patients, SCCs have been associated with one or more AK lesions.[9-17]

The most commonly used treatments for AKs have been liquid nitrogen cryotherapy and topical 5-fluorouracil.[18-20] Other modalities have included curettage, excision, dermabrasion, peeling procedures, ablative laser therapies, and photodynamic therapy (PDT).[21] Each treatment approach offers specific advantages, disadvantages, and potential complications. Two newer approaches for the treatment of AKs have emerged. Topical diclofenac 3% gel was approved by the US Food and Drug Administration (FDA) for the treatment of AK. The recommended treatment regimen is twice-daily applications over a period of 60 to 90 days, combined with appropriate sun avoidance and protection.[22,23] Although not currently approved by the FDA for AK therapy, topical imiquimod 5% cream is currently under study for this indication.

What is the mechanism of action of topical diclofenac for the treatment of AKs?

Diclofenac sodium is a nonsteroidal anti-inflammatory drug formulated as a 3% topical gel in 2.5% hyaluronate sodium. At present, the mechanism of action is not fully understood. Inhibition of arachidonic acid metabolism has been associated with potential antineoplastic properties.[22] The decreased formation of arachidonic acid metabolites secondary to inhibition of cyclooxygenase enzymes by diclofenac plays a significant role. Arachidonic acid metabolites have been associated with the conversion of procarcinogens to carcinogens, inhibition of apoptosis, decreased immune surveillance, promotion of

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tumor cell invasion, and increased angiogenesis.[22,24-26] In addition, it has been suggested that the mode of action of topical diclofenac may be mediated by an effect on matrix metalloproteinases.[26]

What is the efficacy of topical diclofenac 3% gel for the treatment of AKs?

Controlled studies have shown the efficacy of topical diclofenac 3% gel for the treatment of AKs.[22,23,27] In a double-blind, vehicle-controlled study evaluating 195 adult patients, those undergoing active therapy applied topical diclofenac 3% gel twice a day (BID) for 30 or 60 days.[23] Inclusion criteria required the presence of at least 5 AKs involving specified regions of the forehead, central face, scalp, or dorsum of the hands. A statistically significant reduction in AK lesions of 50% to 65% was shown in patients completing active treatment with diclofenac 3% gel for 60 days; one third of patients exhibited complete clearance of AKs compared with 10% of those treated with vehicle alone. Investigator global assessments and lesion counts documented significantly higher AK clearance in the group treated with diclofenac 3% gel compared with the group treated with placebo.

Diclofenac 3% gel applied BID for 90 days was evaluated in a double-blind, randomized, placebo-controlled trial involving 96 adult patients.[22] Enrollment criteria required the presence of at least 5 AKs in designated regions affecting the forehead, central face, scalp, hands, or arms. Response assessed at 30 days posttreatment showed complete clearance of AKs in 50% of patients treated with diclofenac 3% gel and in 20% of vehicle-treated patients.[22] Among patients treated with diclofenac 3% gel, investigator evaluation reported significant improvement in the number of AK lesions or complete clearance in 79% of patients and complete clearance in 47% of patients. The corresponding response rates in vehicle-treated patients were 19% complete clearance and 45% complete clearance or partial reduction.

Compilation results from 4 studies conducted with 213 patients treated with diclofenac 3% gel and 214 patients treated with the vehicle gel (placebo group) are reviewed in the FDA-approved product monograph.[27] Response rates were determined 30 days after completion of therapy. Optimal efficacy appears to occur with a 90-day treatment regimen; complete clearance of AK lesions in the diclofenac group was noted in 34% (n=53) and 47% (n=58) of patients treated for 90 days, compared with 31% of patients treated for 60 days (n=48) and 14% of patients treated for 30 days (n=49). Therapy completed over 60 to 90 days produced complete AK clearance rates as follows: scalp (36%), forehead (39%), face (47%), forearm or arm (43%), and dorsum of the hand (18%). Clinical experience with diclofenac 3% gel suggests both a decrease in the number of AK lesions in those patients who did not show complete clearance and a reduction in the development of new AK lesions.[22,23]

What is the tolerability and safety profile of topical diclofenac 3% gel?

The treatment of AKs with currently available therapeutic options is characteristically associated with some degree of local cutaneous inflammation. The most common adverse events reported in 70% to 80% of patients treated with diclofenac 3% gel were reversible, mild to moderate local application site reactions, including pruritus, dry skin, erythema, and paresthesia.[22,23,27] Comparable rates of adverse events were reported in both active and vehicle-treated groups. Although most patients experience some degree of local inflammation and erythema at sites of diclofenac 3% gel application, the severity and extent of reaction are relatively mild and tolerable in most patients and are significantly less than the application site reactions experienced with cryotherapy of multiple AK lesions or diffuse application of topical 5-fluorouracil.[22,23,28,29] In cases showing a more severe local skin reaction or patient intolerance of local side effects, discontinuation of topical diclofenac results in resolution of local tolerability reactions, usually without the need for additional therapeutic intervention.[22,23]

Antidiclofenac antibodies have not been identified on serologic testing, and no serious adverse reactions have been reported.[22,23] Evaluation of hematologic parameters, serum chemistry profiles, and urinalysis studies completed during the trials referenced above indicated no relevant findings.

What is the mechanism of action of topical imiquimod for the treatment of AKs and other epithelial malignancies?

Topical imiquimod 5% cream is FDA approved for the treatment of external genital warts. Effective treatment of cutaneous and mucosal human papillomavirus (HPV) infections has been correlated with enhanced innate and acquired immune responses facilitated by imiquimod application.[30-35]

The complete mechanism of action of imiquimod for the treatment of viral diseases (including HPV infections and molluscum contagiosum) and

epithelial tumors (including AK, basal cell carcinoma [BCC], and SCC in situ) is not fully understood. Topical imiquimod is devoid of direct antiviral and antineoplastic properties.[31,32] It is believed that imiquimod facilitates immunologic recognition of disease and augments natural immune response, at least partially through induction of the synthesis and release of multiple cytokines (eg, interferon-alfa, tumor necrosis factor-α, macrophage chemotactic protein, macrophage inflammatory proteins, and several interleukins [IL-1, -2, -6, -8, -12]); indirect stimulation of interferon-γ; and enhancement of Langerhans cell migration to regional lymph nodes, promoting activation and recruitment of directed T lymphocytes.[33-36]

More recent evidence suggests that topical imiquimod initiates facilitation of local acquired and innate immune responses by interacting with toll-like receptor 7, a surface receptor found on dendritic and inflammatory cells.[37] Other potential effects associated with imiquimod include promotion of directed cellular apoptosis, a mechanism possibly related to the treatment of epithelial tumors.[31]

Topical imiquimod 5% cream has been effective and is under additional investigation for the treatment of AKs, superficial and nodular BCCs, and SCC in situ.[31,32,35-46] Studies have shown the presence of specific cytokines and activated T lymphocytes infiltrating tumor islands in both naturally regressing and interferon-treated BCC and SCC in situ.[38-41] These findings correlate with the mechanism of action of imiquimod when used to treat these specific disease states.[31,32,38-41]

What is the efficacy of topical imiquimod 5% cream for the treatment of AKs?

Initial investigations suggest that imiquimod 5% cream is effective for the treatment of AKs.[40-43] In one report, 6 male patients affected with up to 10 biopsy-proven scalp AKs were treated with imiquimod 5% cream applied 3 times a week for 6 to 8 weeks; frequency of application was reduced to twice a week when significant local inflammation developed at treatment sites.[40] The cases were described as recurrent after prior treatment with other modalities (ie, cryotherapy, 5-fluorouracil). Follow-up evaluations ranging from 2 to 12 months confirmed clinical and histologic resolution of all AK lesions without evidence of recurrence. Mild and reversible erythema and pruritus were reported during therapy.

A larger double-blind, vehicle-controlled trial with 36 patients studied the treatment of AKs with imiquimod 5% cream applied 3 times a week. Study end point was until clearance of lesions, with a maximum duration of 12 weeks.[43] Frequency of application was reduced to once or twice a week in approximately 50% of patients on the development of local cutaneous inflammatory reactions. Complete clearance of AKs was achieved in 84% of patients treated with topical imiquimod compared with 0% in patients treated with vehicle. As noted above, local inflammatory responses commonly develop, including erythema, edema, and superficial erosions.

Suggested treatment protocols allow for reduction in frequency of application and the use of short 1-week rest periods (called *drug holiday*) to reduce the extent of inflammation without sacrificing efficacy. A pivotal evaluation of AK treatment using topical imiquimod "cycle therapy" has been completed in 25 patients each presenting with 5 to 20 AKs in designated cosmetic units involving the scalp, forehead, cheek, and temple regions.[44] In this study, a treatment "cycle" is defined as application of imiquimod 5% cream 3 times a week for 4 weeks, followed by 4 weeks off; a maximum of 3 treatment cycles was used if assessment showed persistent AK lesions. A single cycle of therapy evaluated after 4 weeks posttreatment showed complete clearance of 46% of treated cosmetic units. A second treatment cycle provided clearance of an additional 36% of treated cosmetic units.

Additional evaluations of the cycle therapy approach and other regimens are currently in progress and should help to better define optimal treatment protocols with topical imiquimod for the treatment of AKs.

What is the tolerability and safety profile of topical imiquimod 5% cream?

As reported earlier, an inflammatory response is anticipated, related to lymphocytic infiltration targeted to eradicate AK lesions. Mild to moderate symptoms of pruritus, stinging, and posttreatment hypopigmentation may be present in 10% to 35% of patients; the severity of symptomatology tends to be significantly less than what is usually experienced with topical 5-fluorouracil therapy.[36,47-49] Approximately 50% of patients treated for AKs may warrant the use of a rest period of 1 to 4 weeks due to brisk inflammation.[36,38,41,44] Ideally, there should be a 4-week rest period, as shorter ones may not allow enough time for lesion clearance to be evaluated appropriately.[44] After the rest period, therapy may be reintroduced using one less application per week if residual AK lesions

are present. No significant systemic adverse effects have been reported with imiquimod use.[32,35,36,47-49]

Conclusion

Several effective options are available for the treatment of AKs, including topical, physical, and surgical modalities. Topical diclofenac, currently approved by the FDA for the treatment of AKs, is a viable addition to the therapeutic armamentarium. In addition, the use of topical imiquimod is supported by multiple studies and clinical experience, with additional studies currently in progress in anticipation of FDA approval. Most patients with extensive AKs will likely require treatment with a combination of topical therapy and cryotherapy. Other modalities (eg, laser therapy, PDT) are also available, depending on the specific clinical situation. Regardless of what therapy is used, refractory lesions warrant careful evaluation, often necessitating surgical intervention with histologic evaluation to exclude a more invasive malignancy.

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