Update on New Directions in AK Treatment

New agents in development may improve the efficacy and efficiency with which dermatologists treat these common and costly precancers.

By Jonathan Wolfe, MD

Management of actinic keratoses in the United States costs about $1.2 billion annually, while additional indirect costs associated with management total close to $300 million. Clearly these precancerous lesions—among the most commonly treated skin conditions—are widespread and place a significant financial burden on the healthcare system. Though not definitively defined, the rate of progression of AKs to SCCs is estimated at four to 10 percent over a four-year period, and data suggest the typical time span from a diagnosis of AK to a histologically confirmed SCC is about two years. Given the risk of progression, AKs warrant treatment; patients require follow-up because these lesions are markers of photodamage, which contributes to the development of other cutaneous malignancies.

Although effective treatments exist, an ideal intervention remains elusive. Cryotherapy is effective but is limited to specific clinically evident lesions. Treatment can be expensive and may require multiple patient visits over time to treat numerous lesions. Photodynamic therapy provides a high level of efficacy and the benefit of treating both clinical and pre-clinical lesions. It is not universally available, may be associated with some degree of patient inconvenience, and has been plagued by poor reimbursement.

Topically applied therapies, such as fluorouracil and imiquimod, target multiple clinical and pre-clinical lesions, but these treatments may be associated with inflammatory responses and diminished patient comfort and satisfaction. Recently, combination approaches involving cryotherapy and topical treatments have gained prominence to improve outcomes compared to cryotherapy alone.

Emerging data suggest additional new directions in the management of AKs.

A Promising Novel Topical Agent

Ingenol mebutate (formerly called PEP005) is derived from the extract of the plant Euphorbia peplus, which has been a traditional herbal remedy used for numerous skin conditions. Early trial results suggest that the agent may be effective for the management of AKs and non-melanoma skin cancers. It is shown to act by inducing necrosis locally.

A randomized, double-blind, double-dummy, vehicle-controlled study enrolled patients with non-facial AKs who applied ingenol mebutate gel 0.025% for three days, ingenol mebutate gel 0.05% for two days, ingenol mebutate gel 0.05% for three days, or vehicle gel for three days. There was an eight-week follow-up period. Results showed that active treatment was significantly more effective than vehicle. Partial clearance rates for treated patients ranged from 56 to 75.4 percent, compared to 21.7 percent for vehicle, while the complete response rate ranged from 40 to 54.4 percent for treatment, compared to 11.7 percent for vehicle. The 75-100 percent median reduction in baseline AK lesions among treated patients contrasted with no reduction for controls. Treatment was well-tol-
erated with transient erythema, flaking/scaling, and crusting reported by some patients.

A phase IIa randomized, double-blind, vehicle-controlled, multicenter study involving 58 patients treated with ingenol mebutate has provided similar favorable findings. The study evaluated primarily the safety but also the efficacy of ingenol mebutate when applied to five preselected AKs. Patients in one arm of the study applied treatment (ingenol mebutate 0.0025%, 0.01%, or 0.05%) or placebo on days 1 and 2; while patients in the other arm applied treatment or placebo on days 1 and 8. Treatment was well-tolerated with no significant differences noted between the two arms. Local application site reactions to treatment, which were dose dependent, included erythema, flaking/scaling/dryness, and scabbing/crusting. Ingenol mebutate 0.05% provided greatest efficacy, with complete clearance of 71 percent of treated lesions.

Cycled Imiquimod Coming

Imiquimod cream 5% (Aldara, Graceway) is a well-known and popular treatment for AKs. In the next few months a new formulation of imiquimod 3.75% is expected to come to market with a six-week cycle treatment regimen. Imiquimod 5% is indicated for twice-weekly application for 16 weeks for the treatment of nonhyperkeratotic, nonhypertrophic AKs, although clinical use has varied widely. The new imiquimod 3.75% cream formulation has been submitted to the FDA for treatment of clinically typical lesions via application daily for two weeks followed by a two-week non-treatment period then another two weeks of daily application.

In trials reported by Graceway at Academy ’09 in Boston last summer, treatment with imiquimod cream 3.75% using the cycle regimen produced complete clearance of AKs in 36 percent of treated patients at eight-week follow-up. Treatment was well tolerated, with erythema (25 percent), scabbing/crusting (14 percent), ulceration (11 percent) and flaking/scaling/dryness (eight percent) among the most commonly reported adverse events.

PDT Updates

A study from Journal of the American Academy of Dermatology published online ahead of print reports histologic evidence that 5-aminolevulinic acid photodynamic therapy (ALA PDT) provides photorejuvenating effects in addition to eradicating AKs. These findings support previous reports of photorejuvenating effects measured through clinical observation. Following two ALA PDT treatment cycles spaced one month apart, patients had increases in epidermal thickness and dermal collagen volume and decreases in dermal inflammatory infiltrate. Such findings are welcome by patients and physicians to complement ALA PDT’s favorable efficacy data in AK treatment.

Last month, DUSA Pharmaceuticals announced label changes approved by the FDA for the Levlun Kerastick (ALA solution 20%). The Kerastick is a propriety packaging and medication delivery system that contains an ampule filled with liquid, an ampule filled with powder, and an applicator tip. The physician or healthcare provider must crush the two ampules, allowing the powder to dissolve into the liquid before it can be applied to the treatment site with the applicator tip. The FDA last month cleared the Kerastick Krusher accessory—a hinged plastic device designed to crush the ampules in the Kerastick and ease application of the aminolevulinic acid solution. FDA approved label changes now reduce the required dissolution time for ALA to 30 seconds, versus previous labeling that required the contents to be mixed together for three minutes.

Although initial protocols called for overnight incubation of ALA, which was considered inconvenient to patients and physicians, data show the efficacy of ALA PDT with incubation periods ranging from one to three hours. Practices commonly employ one-hour incubation periods with good results. Levlun is indicated for use with the BLU-U light from DUSA, but similar results have been obtained with irradiation by the long-pulse pulsed dye laser and LED systems. Choice of a light source often depends on clinician preference and access.
New data have emerged in support of a thin, self-adhesive ALA delivery patch that was rated more convenient than traditional ALA PDT and shown to be statistically significantly superior to placebo or cryotherapy in one study. A 12-month follow-up study of patients treated with ALA patch PDT showed that they had fewer recurrences than patients treated with cryotherapy and significantly less hypopigmentation (which developed in zero and three percent of lesions in two patch treatment arms versus 31 percent of lesions in the cryotherapy arm).

Finally, there is growing interest across the US in methyl aminolevulinate (MAL cream 16.8%, Metvixia, Galderma) photodynamic therapy or MAL PDT. Metvixia received FDA approval in June 2008 for use in conjunction with the Adliltile CL128 LED-based narrowband (630nm) red light. Although MAL PDT treatment has not caught on widely here, it is popular in Europe. Data show three-month complete response rates for AKs in the 69-93 percent range.

**Optimizing Management**

The risk of conversion requires that clinicians aggressively treat AKs, while the high overall costs associated with treatment encourage physicians to seek efficient interventions that yield optimal results for each patient presentation. Cyrotherapy has been the gold standard of AK management and will undoubtedly remain popular for the treatment of multiple discreet lesions. A popular management approach supported by data is the adjunctive use of topical therapy following cyrotherapy to target preclinical lesions and increase overall clearance rates. ALA PDT has become increasingly popular for the management of AKs. As further enhancements improve the convenience of this intervention it may become ever more widely available, and favorable photorejuvenating effects may increase patient interest in the procedure.

Finally, new advancement in topical therapy are aimed at optimizing efficacy while improving the patients’ experience. The new formulation of imiquimod cream 3.75% is currently under FDA review and may be available to clinicians early this year. Publication of more data is anticipated.

**Dr. Wolfe has no relevant disclosures.**