Actinic Keratosis (AK) remains the center much of discussion among practitioners in our specialty, both in terms of its clinical components and appropriate avenues of treatment. As speculation continues regarding the status of AKs as “pre-cancerous” lesions, important research developments in recent years have helped to clarify this issue and others. This article will address the latest developments in research and investigate the latest possibilities for treatment.

**NOTEWORTHY DATA**

**Progression to SCCs.** Studies have shown that there is a direct progression between AK and squamous cell carcinoma (SCC). In one publication in particularly, researchers examined 14 normal non-sun-exposed skin samples, 14 normal sun-exposed skin samples, five AKs, and 15 cutaneous SCCs. Using a highly astringent shrunk centroid threshold of 6.52 and the prediction analysis of microarrays, the researchers identified 89 unique genes that most likely contribute to the molecular evolution of SCC. Moreover, genes that were upregulated in AK and SCC were downregulated in normal skin, and genes that were downregulated in AK and SCC were upregulated in normal skin.

These findings support the concept that AK and SCC share mutations. The finding of similar differentially expressed genes in AK and SCC confirms that AK is a precursor lesion of SCC and indicates that they are closely related genetically.

**AK Follicular Extension.** Another recently noteworthy development is the prognostic significance of follicular extension in AK. One study examining 104 AKs with follicular extension noted that patients with follicular extension were 1.8 times more likely to have a previous history of invasive carcinoma than patients without follicular extension. In addition, patients with follicular extension were 11 times more likely to have a previous history of invasive melanoma than patients with AKs without follicular extension. Also, patients with follicular extension were more likely to be male, had an older average age, and more often presented with lesions on their legs when compared to patients with actinic keratoses lacking follicular extension.

**Quality of Life in AK Patients.** Results from 2009 Veterans Affairs study found that AKs may play a greater role in the overall burden of keratinocyte carcinomas (KC) than previously documented. In particular, the study assessed the quality of life (QoL) in patients with

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**ACTINIC KERATOSIS TREATMENT: PLAYING THE FIELD**

As more studies continue to show its benefit, combination therapy will likely take a more prominent role in the treatment of actinic keratosis.

BY GARY GOLDENBERG, MD
EXPLORING THE PHARMACOECONOMICS OF AK TREATMENTS

A 2009 study examined the pharmacoeconomics of treatments for actinic keratosis and found that the primary drivers of cost are physician office visits and associated procedures (Pharmacoeconomics. 2009; 27(6): 451-64). As of 2009, the study also estimated that the direct cost of AK management in the US is $1.2 billion, with indirect costs totaling $295 million. The authors noted, “Pharmacoeconomic research defining standards, outcomes and areas of efficiencies in the treatment of actinic keratosis is in its infancy. To move towards more comprehensive analysis, research needs to focus on updating epidemiological data, evolving evidence-based standards, delineating cost drivers in immunocompetent and immunocompromised populations, and on health outcomes.”

—PD Staff

AK using the Skindex-29, which has six AK-specific items. They found worse QoL on all three subscales, while the KC-specific items was significantly associated with higher AK count, past 5-FU use, and greater sun sensitivity. In multivariate analysis, higher AK count and past 5-FU use were independently related to worse QoL in all domains, including the AK-specific worry/bother group. Younger age was independently related to worse QoL in all domains except symptoms. In addition, greater sun sensitivity was marginally associated with emotions, but strongly associated with symptoms. Higher comorbidity showed modest, yet significant, associations with the symptoms and functioning subscales. Intriguingly, female gender, higher education level, and being unmarried were all independently associated with worse symptoms. Greater photodamage was not independently related to worse QoL. In addition, the number of previous KCs was not independently associated with QoL.

COMBINATION TREATMENTS

Since most dermatologists use cryosurgery as the mainstay of AK treatment, several studies examined the combination, or rather sequential use, of cryosurgery with topical agents. One conclusion rings true in all these studies: there is a clear treatment benefit when a topical modality is used after cryosurgery.

Imiquimod 3.75% with Cryosurgery. One combination approach that’s yielded success in the treatment of AKs has been imiquimod 3.75% cream (Zyclara 3.75%, Medicis/Valeant) with cryosurgery. In one study, patients with a baseline of more than 10 AKs on the face were treated with cryosurgery, with some patients followed by imiquimod 3.75%. For the cryosurgery/3.75% imiquimod and cryosurgery/placebo groups, respectively, median total AK reductions were 86.5 and 50 percent, and proportions of subjects with complete clearance were 30.2 and 3.3 percent. Analyzing cryosurgery-treated lesions only, median reductions were 100 and 80 percent, and subject complete clearance rates were 59.5 percent and 29.8 percent, respectively. The authors concluded that sequential treatment of cryosurgery followed by imiquimod 3.75% two weeks on, two weeks off, two weeks on was well tolerated and provided additional therapeutic benefits to cryosurgery alone.

In another study looking at the effective of imiquimod 3.75% cream and cryosurgery in the treatment of hypertrophic AKs (HAKs) on dorsal hands and forearms, patients were randomized to have either their right or left dorsal hand or forearm treated with imiquimod 3.75% cream, to begin on the same day as cryosurgery for hypertrophic AK lesions, two weeks on, then two weeks off, then two weeks back on. Results indicated that the number of HAK in both treatment groups decreased over time. Importantly, patients who were treated with imiquimod had a higher clearance rate of HAK than those that just receiving cryosurgery alone. These results were statistically significant. The number of non-HAKs decreased in both groups, even though only one side was treated with imiquimod 3.75% cream. At baseline, the number of incidence of non-HAKs on the dorsal hands and forearms averaged 6.3 and 5.5 lesions in the cryosurgery plus imiquimod group and the cryosurgery alone group, respectively. At week 14, the number of non-HAK was reduced to 2.94 and 3.235 in each respective group. The authors believe that this may be due to an immune response due to applying imiquimod to one arm and immune response on the other extremity.

Ingenol Mebutate. Ingenol mebutate gel, 0.015% and 0.05% (Picato, LEO Pharma) is derived from diterpene ester extracted and purified from the plant Euphorbia peplus, a common plant that was used in the early 1800s to treat warts, corns, waxy growths, and even skin cancers. It appears to have a dual mechanism of action of rapid and direct cell death and specific neutrophil-mediated, antibody-dependent cytotoxicity. It has been found safe and effective for the treatment of AKs three weeks after cryosurgery. In one study in which patients were randomized to ingenol mebutate 0.015% gel or vehicle three weeks after cryosurgery, patients receiving ingenol...
mebutate had a higher complete clearance rate (60.5 percent) compared with vehicle (49.4 percent). In addition, the mean percentage reduction in number of AKs versus baseline was also higher for ingenol mebutate gel (82.7 percent vs. 75.6 percent). The same study showed that, at five weeks, the mean composite LSR score in the ingenol mebutate group returned to a score similar to that of earlier visits, which is a significant finding. This allows the use of this medication in a sequential fashion.

**Photodynamic Therapy.** One study assessing the potential of photodynamic therapy (PDT) (ALA with BLU-U) versus ALA vehicle with BLU-U at one, two, and three hour incubation periods to AKs on the face and scalp yielded notable results. Specifically, the study found that a second treatment was week eight appears to be necessary for improved efficacy. It also found that ALA was statistically superior to vehicle at the primary endpoint of 12 weeks for all study arms, while the percent AK lesion reduction showed a plateau with similar efficacy for all ALA treated groups. Moreover, a higher percentage of patients treated with broad-area treatment remained clear from week 12 to week 24 as compared with spot treatment.

Another study assessed the potential of ALA with BLU-U versus ALA vehicle with BLU-U in the upper extremities without occlusion versus with occlusion with three-hour incubation periods. Of note, 83 percent of ALA-PDT patients received a second treatment, and final follow-up was 12 weeks after the first round of PDT. The findings suggest that occlusion of the upper extremity during incubation following topical ALA application significantly increased clearance of AK lesions at the eight-week point and the 12-week point.

**THE RIGHT COMBINATION**

The current state of the art treatment of AKs appears to be heading in the direction of combination therapy—cryosurgery, and field therapy. This treatment approach should address clinical and subclinical AKs and in turn should decrease the number of non-melanoma skin cancers. Dermatology, after all, should be on the forefront of preventative medicine.

The future is bright for our patients with AKs. We are learning more about the relationship of AK and non-melanoma skin cancers. And new topical agents are currently in development to help us take better care of our patients.

**PRACTICAL POINTER**

Recent research has provided deeper understandings of actinic keratosis (AK), particularly regarding the prognostic value of follicular extension and the link between AK and squamous cell carcinoma. Research also shows the benefits of the combination of imiquimod and cryotherapy. Ingenol mebutate and photodynamic therapy have also been shown to be effective in treating AKs.

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