# The Importance of Local Tolerability and Duration of Therapy in Topical Actinic Keratosis Treatment

Leon H. Kircik MD

Icahn School of Medicine at Mount Sinai, New York, NY; Indiana University Medical Center, Indianapolis, IN; Physicians Skin Care, PLLC, Louisville, KY; DermResearch, PLLC, Louisville, KY; Skin Sciences, PLLC, Louisville, KY

Leon H. Kircik MD

Actinic keratoses (AK) are among the most common dermatologic presentations, with estimates suggesting that they account for approximately 15 percent of dermatologic diagnoses in the US.[1] Incidence of AK increases with advanced age and chronic exposure to UV radiation,[2] suggesting that dermatologists will continue to see a continuing high incidence of AKs with the ongoing graying of America.

Treatment of AKs is essential, as these pre-cancerous lesions can progress to squamous cell carcinomas.[3,4] Historically, treatment of AKs had been lesion-directed, with destructive modalities like liquid nitrogen and electrodesiccation and curettage considered mainstays of treatment just over two decades ago.[5]

Somewhat recently, our conception of AKs has shifted from a focus on individual lesions to recognition that the presence of AKs is a manifestation of field cancerization.[6] Therapeutic strategies, therefore, have evolved to emphasize the treatment of both clinically visible and subclinical lesions.[5] The notion of field-directed therapy has been facilitated by the availability of numerous topical formulations now FDA-approved for the treatment of AKs.

As noted by Rajkumar and Armstrong in the pages ahead, five different drug compounds are FDA-approved to treat AKs. Despite differences in phase 3, pivotal trial designs and outcome measures, these agents are all considered efficacious for the treatment of AKs. Similarly, as Rajkumar and Armstrong conclude, the available drugs are generally considered safe when used as directed. However, they note, there is great variability in tolerability.

Tolerability is a crucial consideration when it comes to therapy directed at field cancerization, especially that AKs are chronic and recurring lesions and require life-long treatment. Furthermore, prolonged and severe local skin reactions, especially on the face and scalp, may disrupt daily living activities, social engagements, and negatively impact the quality of life. If patients reduce the frequency or amount of drug application or cut short the duration of treatment due to poor tolerability, the effectiveness will be compromised.

The newest topical drug approved for the management of AKs, tirbanibulin, may offer distinct advantages in terms of tolerability and treatment duration, perhaps as a consequence of its unique mechanism of action. As opposed to earlier drugs that induced necrosis, tirbanibulin induces apoptosis. In clinical trials, most local skin reactions (LSRs) associated with tirbanibulin were mild to moderate, and fewer than 10% of patients reported severe LSRs.[7] Of note, no patients in the clinical trials discontinued therapy; treatment was applied once daily for five days.

Selection of an appropriate treatment for management of AKs depends on multiple factors, including but not limited to patient age, lifestyle, extent of actinic damage, and history of UV exposure. The availability of multiple safe and effective treatments provides options for dermatologists to tailor treatment to the individual needs of their patients. The best outcomes will be achieved with a patient-centric approach along with more tolerable topical treatment.[8] With recent advancements in topical treatment, including the introduction of tirbanibulin, a new chemical entity with established efficacy and favorable tolerability profile, dermatologists may yet improve patient experiences and subsequently adherence and outcomes in field-directed management of AKs.

## Disclosure

LHK has received compensation from JDD for his editorial support and has served as either consultant, speaker, investigator, or advisory board member for Almirall, Leo Pharma, and Ortho Dermatologics.

## References

1. Ahn CS, et al. The National Ambulatory Medical Care Survey: A resource for understanding the outpatient dermatology treatment. *J Dermatol Treat* 2014; 25:453–458.
2. Leiter U, et al. S3 guideline for actinic keratosis and cutaneous squamous cell carcinoma (cSCC) – short version, part 2: epidemiology, surgical and systemic treatment of cSCC, follow-up, prevention and occupational disease. *J Dtsch Dermatol Ges.* 2020; 18:400–413.
3. Fuchs A, Marmur E. The kinetics of skin cancer: progression of actinic keratosis to squamous cell carcinoma. *Dermatol Surg.* 2007 Sep;33(9):1099–101.
4. Stockfleth E. Topical management of actinic keratosis and field cancerisation. *G Ital Dermatol Venereol.* 2009 Aug;144(4):459–62.
5. Schwartz RA. The actinic keratosis. A perspective and update. *Dermatol Surg.* 1997 Nov;23(11):1009–19; quiz 1020-1.
6. Sinclair R, Baker C, Spelman L, Supranowicz M, MacMahon B. A review of actinic keratosis, skin field cancerisation and the efficacy of topical therapies. *Australas J Dermatol.* 2020;Aug 25. doi: 10.1111/ajd.13447.
7. Blauvelt A, et al. phase 3 trials of tirbanibulin ointment for actinic keratosis. *N Engl J Med.* 2021 384:512–520.
8. Grada A, Feldman SR, Bragazzi NL, Damiani G. Patient-reported outcomes of topical therapies in actinic keratosis: A systematic review. *Dermatol Ther.* 2021 Mar;34(2):e14833.