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 ORIGINAL ARTICLE

Advances and Considerations in the Management of Actinic Keratosis: An Expert Consensus Panel Report

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ABSTRACT

Background: Actinic keratosis (AK) is a potentially pre-malignant tumor with a poorly defined risk of progression to invasive squamous cell carcinoma (SCC). Because of the typical need for recurrent cycles of AK treatment, outcomes can be limited by both therapeutic efficacy and patient adherence.

Objective: To synthesize the available and most current literature into overarching principles to provide guidance on the management of AKs, improving patient experiences and treatment outcomes.

Methods: A systematic review querying epidemiology, natural history, prognosis, management of AKs as well as the mechanism of action of and adherence to current AK therapy was conducted. After reviewing the literature, an expert consensus panel consisting of 10 expert dermatologists and dermatopathologists used a modified Delphi process to develop statements regarding the pathogenesis and management of AKs. Final statements were only adopted with a supermajority vote (≥7/10).

Results: The panel developed 7 consensus statements regarding AKs pathogenesis and management.

Conclusion: The poorly defined risk for AK progression into invasive SCC without universally accepted clinical-histopathological factors highlights the importance of long-term efficacious treatment. To effectively counsel and treat patients with actinic keratoses, dermatologists must understand how newer therapeutic approaches with mechanisms of action that have more rapid onset of action, shorter treatment courses, and less intense local skin reaction (LSRs) may promote adherence and improve long-term outcomes.

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INTRODUCTION

Actinic keratoses (AK) are a proliferation of atypical keratinocytes that present as hyperkeratotic, erythematous papules or occasionally plaques on a background of chronic actinic damage.[1] AKs may progress to invasive squamous cell carcinoma (SCC).[1-5] Several risk factors may predispose to developing AKs: lighter skin phenotypes (Fitzpatrick I-II), advanced age, increased cumulative exposure to UV radiation,[6-8] occupational health exposures (eg, to excessive quantities of hydrocarbons)[9], and immunosuppression.[10] AKs are found on sun-exposed areas that are often not covered by clothing.[11]

AKs are one of the most prevalent cutaneous conditions treated by dermatologists with over 35 million cases treated in 2015,[12] accounting for ≥14% of all dermatology visits[13] and costing approximately $3.1B annual healthcare expenditures.[12] Unfortunately, there are not universally accepted clinical or histopathological risk factors to determine which AKs may invasively progress. This is especially concerning as not all AKs are appreciable during every examination.[11,15]

Several key approaches to managing AKs include using proactive photoprotection, lesion-directed, and/or field-directed

therapy. Adequate patient counseling on and implementation of measures to reduce UV exposure could mitigate chronic actinic damage and risk of developing future skin cancers.[16] However, when AKs do appear, not only should the individual tumor be treated, but the surrounding areas may also require treatment given concerns of field cancerization (ie, an area of clonally-expanded pre-malignant lesions) which may be a harbinger of future skin cancers.[14,17] Studies have demonstrated that multi-modal, combination approaches to treatment (eg, combining either cryosurgery or lesion-directed photodynamic therapy with prescribed topical therapy) may yield greater efficacy.[18]

Patient adherence to therapy is also a significant factor affecting efficacy and can cause real-world outcomes to diverge from clinical trial results. Adherence is negatively affected by longer course therapy, complicated regimens, and adverse effects(including local skin reactions (LSR) in AK treatment).[19,20] Dermatologists have employed multiple variations to approved treatment courses to mitigate brisk local skin reactions while optimizing clearance to maintain adherence.

The purpose of this consensus panel was to synthesize the available and most current literature into overarching principles to provide guidance on the management of AKs, improving patient experiences and treatment outcomes.

MATERIALS AND METHODS

A systematic review of the literature pertaining to the epidemiology, natural history, prognosis, management of actinic keratoses (AKs) as well as the mechanism of action (MoA) of and adherence to current therapy was conducted. The goal of this search was to evaluate the literature for evidence, review and development of recommendations by the expert panel. The Medline database was queried for all relevant articles published between 1980 and 2021 using exploded MeSH terms and keywords pertaining to the following themes: diagnosis, prognosis, and epidemiology, risk factors, squamous cell carcinoma, therapy. The Boolean term "AND" was used to find the intersection of these themes with the term "actinic keratosis." Articles deemed relevant diagnosis and management of AK based on full-text review were selected for further discussion by members of the consensus panel.

A 10-person consensus panel of dermatologists and dermatopathologists selected for their expertise in histopathologic risk factors and management of AKs, prior extensive knowledge of atypical and malignant keratinocytic tumors, and/or history of academic achievement, were convened via a virtual platform during January 2021. Panel members discussed issues regarding the appropriate treatment of AKs given the current understanding of pathophysiology and real-world scenarios that may complicate treatment from a physician and patient perspective. Statements were drafted based on the selected articles and relevant discussion.

Consensus among panel members was achieved using a modified Delphi technique.[21] Consensus was defined as agreement among at least a supermajority of 7/10 of the experts participating in the panel. If 7/10 agreement could not be achieved, the proposal was re-discussed among panel members and modified until agreement was achieved.

RESULTS

The process yielded 7 statements that received supermajority (≥7/10) approval regarding the current understanding of AKs and associated management considerations.

Consensus Statements

Actinic keratoses may progress into invasive squamous cell carcinomas.

Multiple studies have determined that there is a risk that AKs can progress to invasive SCC. However, data are limited regarding the exact proportion that may progress, with estimations varying between 0.025% and 16%,[22] though the risk appears to increase over time.[11] These findings are further compounded by

TABLE 1.

Consensus Statements	
Consensus Statement	**Panel in Agreement**
1. Actinic keratoses may progress into invasive squamous cell carcinomas.	10/10
2. To date, there is no definitive way of identifying which actinic keratoses will progress into invasive squamous cell carcinomas.	10/10
3. Actinic keratoses require treatment.	10/10
4. Field, lesional, and combination therapy are effective in the treatment of actinic keratoses.	10/10
5. Multiple factors, including longer duration of therapy and local skin reactions, limit patient adherence to topical therapy for actinic keratoses.	9/10
6. Long duration and severe local skin reactions may prevent patients from completing a prescribed therapeutic course and prevent subsequent treatments.	10/10
7. Patients prefer topical therapies for actinic keratoses that require fewer applications.	10/10

histology when AKs are abutting SCC despite lack of clinically visible lesions.[3-5,11,17] This could represent a slow progression into invasive SCC and field cancerization.[3-5,11,17] Of note, several of the panelists disputed data that AKs can fully regress. They noted that while atypical keratinocytes with only a single p53 mutation may regress, once a cell line has acquired additional mutations, regression becomes highly improbable. In their view, although AKs may be subclinical or missed from visit to visit,[11] they are not likely to revert to a more benign status and also note there are no histopathological data to support the notion that AKs can regress.

To date, there is no definitive way to clinically identify which actinic keratoses will progress into invasive squamous cell carcinomas.

Although the literature has demonstrated AK's potential for progression into invasive SCC, there are no universally recognized clinical markers that can readily identify those higher risk AKs. Inflammation, erythema, diameter >1cm, bleeding, ulceration, and rapid growth have been suggested as risk factors.[15] The presence of spontaneous/pressure-induced pain may suggest the lesion is in fact a SCC not an AK.[23,24] Follicular extension of AKs correlate with both a history of melanoma and non-melanoma skin cancer and an increased risk of future progression into invasive SCC.[25,26] This risk may be further increased in immunosuppressed individuals given an already predisposed risk to developing AKs as well as SCC.[27,28]

Actinic keratoses require treatment.

Given the risk of AK progression to invasive SCC and lack of clinicopathologic signs to differentiate which AKs will progress to invasive disease, these tumors should be treated to decrease unwarranted morbidity and mortality. This statement extends not only to the AKs that are clinically visible, but also includes management of subclinical lesions.

Field, lesional, and combination therapies are effective in the treatment of actinic keratoses.

Multiple studies have demonstrated that various modalities are efficacious for treating AKs. Lesion-directed therapies are often office-based, physician-conducted modalities targeted at clinically visible AKs and can include cryosurgery, surgical/manual removal, and laser.[16,29,30] Field treatments may be office-based (eg, chemical peel, photodynamic therapy (PDT)) or patient-applied medications that target atypical/dysplastic keratinocytes by inhibiting cellular replication, upregulating immune-mediated destruction or by disrupting extracellular signaling pathways.[40] These field therapies are efficacious in treating both clinically visible and subclinical lesions, often with prolonged results.[29-31] Studies have also demonstrated an additive effect from combining lesion-directed therapies and patient-applied field therapies.[32-37] While there are limited data that suggest the specific combination of patient-applied 5-fluorouracil (5-FU) and calcipotriol produces a synergistic effect (with potentially more severe LSR), there is not yet enough evidence to determine if combinations of other patient-applied therapies is superior to mono-patient-applied therapy.[38]

Multiple factors, including longer duration of therapy and local skin reactions, limit patient adherence to topical therapy for actinic keratoses.

While counseling patients on the natural progression of chronic actinic damage, it is important to discuss the risk of evolution into invasive SCC and the ongoing risk of developing new AKs and skin cancers. AKs are a chronic skin disorder, with most patients requiring periodic clinical assessments and repeated courses of treatment(s).[39] Ideal clinical outcomes rely on efficacious agents and patient adherence. Unfortunately, there are many potential barriers to adherence including: insurance coverage, length of treatment course, frequency of application, understanding of more complex interval regimens (eg, 2-weeks on/2-weeks off), and visible LSRs.[19,39-41]

Long duration and severe local skin reactions may prevent patients from completing a prescribed therapeutic course and prevent subsequent treatments.

Counseling must be provided regarding the expected severity and duration of LSRs. Up to 90% of patients may experience LSRs such as erythema, crusting, erosion and pain at treated sites with severity and duration dependent on the prescription regimen.[41] These LSRs may negatively impact patients' quality of life, especially when applied to conspicuous areas such as the face, scalp, or dorsal hands.[40,41] Depending on the onset of LSR relative to duration of therapy, severe reactions may lead to early discontinuation.[40] Prolonged LSRs may also dissuade patients from future treatments.[40] Even if patients are able to complete the prescribed regimen, their negative experience may adversely impact the likelihood of pursuing future therapy and lead to poor long-term outcomes.[40]

Patients prefer topical therapies for actinic keratoses that require fewer applications.

Patients prefer AK therapies that have shorter courses. Studies have shown that patient-applied field therapies requiring less than 4 weeks of treatment have significantly increased rates of adherence compared to treatment durations requiring over 4 weeks.[40] Furthermore, the chance nonadherence increases when therapy is perceived to be too long or time-consuming (OR 1.2, 95% CI 1.1–1.3).[40]

DISCUSSION

Dermatologists must be educated and aware of the variable therapeutic MoA and how they translate to clinical outcomes and anticipated local skin reactions, which can be explained so they align with patients' personal preferences. Patient-applied topical agents function by inducing either necrosis or apoptosis

of rapidly proliferating malignant keratinocytes.[42] Therapies such as ingenol mebutate that operate via rapid necrosis and significant cytokine release will induce marked brisk erythema, desquamation, crusting, and dermal induration.[44] The mechanism of topical 5-Flourouracil(5-FU) as an antimetabolite induces pro-inflammatory cytokines and necrosis in rapidly proliferating epithelium, as seen with the disruption of DNA replication by in S-phase.[43,44] These necrosis-inducing agents have demonstrated efficacy in the treatment of AKs and subclinical atypical keratinocytes but can induce brisk LSRs in treated areas potentially negatively impacting long-term adherence.[43]

Topical agents that induce apoptosis, such as diclofenac which inhibits COX-2 pathways and the keratinocyte-proliferation promoting prostaglandins, can effectively treat AKs while minimizing the intensity and/or duration of LSRs.[45-48] Imiquimod is an immune response modifier that, unlike other agents, does not directly impact the epidermis but induces apoptosis by augmenting the inherent immune response and cytokine activity of the host to identify tumor antigens in rapidly proliferating atypical keratinocytes, which can sometimes result in robust LSRs as well as rare visceral symptoms based on interferon induction.[49]

Tirbanibulin is a new synthetic chemical entity that has shown potent anti-proliferative and anti-tumor activity via several mechanisms, including induction of cell cycle arrest and apoptosis in cancerous cell lines and keratinocytes.[50] Its MoA disrupts microtubule formation by binding tubulin and inhibiting polymerization and separately by the disruption of Src kinase signaling, a non-receptor proto-oncogene tyrosine kinase which has been observed in various cancers in vitro.[50] One of the advantages of tirbanibulin is that its shorter therapy duration and reduced length and degree of LSRs has the potential to enhance adherence.[51]

FUTURE DIRECTIONS

The panel noted inconsistencies in the literature surrounding AKs and recommends additional studies with a special focus on three domains: (1) natural history and clinical presentation of high-risk AKs, (2) efficacy of regimens consisting of a combination of multiple patient-applied therapies, as well as (3) efficacy of patient-applied therapy on non-studied anatomic sites and conditions.

Future studies should endeavor to more clearly elucidate the natural history of AKs. Given an incompletely defined quantitative risk of progression, there is a need for a paradigm to identify those lesions most likely to advance to invasive SCC.

Existing studies demonstrate the additive effects of combining lesion-directed and field therapies[28,40] However, there is little data on the efficacy of regimens of patient-applied combination therapies, especially those that function via different MoA. Furthermore, studies examining a role for concurrent topical corticosteroids or other adjunctive therapies to improve adherence by reducing LSRs without loss of efficacy may be reasonable.[52]

Finally, additional studies further defining the efficacy of patient-applied treatments for actinic cheilitis or other regions of the body (eg, dorsal hands/forearms and chest) could provide more clarity for patient care and further fine-tune individual treatment regimens. Investigations regarding currently off-label uses for these patient-applied agents for other keratinocytic dysplastic processes such as SCC in situ, Bowenoid papulosis, vulvar dysplasias, verruca, and molluscum contagiosum would be helpful.

CONCLUSION

Integrating data on AK prognosis and management with our understanding of barriers to treatment is critical to improve patient outcomes. Further studies are needed to better understand the clinicopathologic risk factors of high-risk AKs and how best to integrate and combine new therapies into existing regimens. Newer therapies with shorter treatment courses and lesser LSRs may improve adherence and outcomes.

DISCLOSURES

JDR serves as a research investigator, speaker, and consultant for Almirall, Bausch Health (Ortho Dermatology), and Sun Pharma and a consultant for Biofrontera. **AWA** has served as a research investigator and/or scientific advisor to AbbVie, BI, BMS, EPI, Incyte, Leo, UCB, Janssen, Lilly, Novartis, Ortho Dermatologics, Sun, Dermavant, Dermira, Sanofi, Regeneron, Pfizer, and Modmed. **BB** serves as an advisory board member and investigator for Biofrontera, SUN (DUSA) Pharma and LEO, Pharma, a speaker for LEO Pharma, and as a consultant for Pierre Fabre, PHD Biosciences and Almirall, Inc. **NB** has affiliations with Abbvie, Almirall, Biofrontera, BMS, BI, EPI Health, Ferndale, Foamix, Galderma, InCyte, ISDIN, J&J, LaRoche-Posay, Leo, Lilly, Ortho, Pfizer, P&G, Regeneron, Sanofi, SunPharma, Vyne, and Vyome. CC serves as a consultant for Almirall, Inc. **GG** serves as a consultant for LEO Pharma and Almirall, Inc. and as an investigator for Biofrontera. **JSK** has served as a research investigator and/or consultant to AbbVie, Boeringer Ingelheim, ChemoCentryx, Incyte, Janssen, Novartis, and UCB, and as a speaker for AbbVie. **MGL** is an employee of Mount Sinai and receives research funds from: Abbvie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Dermavant, Eli Lilly, Incyte, Janssen Research & Development, LLC, Ortho Dermatologics, Regeneron, and UCB, Inc and is a consultant for Aditum Bio, AnaptysBio, Almirall, Arcutis, Aristea, Arrive technology, Avotres Therapeutics, BioMx, Boehringer-Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, Castle Biosciences, Corrona, Dermavant Sciences, Dr. Reddy, Evelo, Evommune, Facilitate

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