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Title: Focused update: Guidelines of Care for the Management of Actinic Keratosis

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Disclaimer

Adherence to these guidelines will not ensure successful treatment in every situation. Furthermore, these guidelines should not be interpreted as setting a standard of care or be deemed inclusive of all proper methods of care, nor exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of all the

circumstances presented by the individual patient, and the known variability and biologic behavior of the disease. This guideline reflects the best available data at the time the guideline was prepared. The results of future studies may require revisions to the recommendations in this guideline to reflect new data.

Abstract

Background: Actinic keratoses (AK) are rough scaly patches that arise on chronically ultraviolet (UV)-exposed skin and can progress to keratinocyte carcinoma.

Objective: In 2021, the AAD published guidelines to assist in clinical decision-making for the management of AK. The purpose of this focused guideline update is to incorporate recently available evidence on the use of topical tirbanibulin to treat AK.

Methods: A multidisciplinary workgroup conducted a systematic review to evaluate data on the use of tirbanibulin for AK and applied the GRADE approach for assessing the certainty of the evidence and formulating and grading a clinical recommendation. The graded recommendation was voted on to achieve consensus.

Results: Two studies were identified, and analysis of the evidence resulted in one recommendation.

Limitations: This analysis is based on the best available evidence at the time it was conducted. Long-term efficacy and safety data are not currently available.

Conclusions: A strong recommendation for the use of topical tirbanibulin as field therapy for AKs was made based on the currently available evidence.

Abbreviations Used

AAD: American Academy of Dermatology

AK: Actinic keratosis

GRADE: Grading of Recommendations, Assessment, Development, and Evaluation

Scope

Actinic keratoses are keratinocyte neoplasms occurring on skin that has had long-term exposure to ultraviolet radiation. Actinic keratosis (AK) is one of the most common conditions treated by dermatologists in the United States.[1] In early 2021, the AAD published guidelines addressing the management of AK and provided recommendations for the use of various available AK treatments, including topical agents, cryosurgery, and photodynamic therapy. Also considered are clinical characteristics, histological classification, natural history, risk of progression, and dermatologic surveillance of AKs.[2]

The impetus for this focused update was the identification of recently published new evidence, and subsequent approval by the U.S Food and Drug Administration of a novel microtubule inhibitor indicated for the topical treatment of AK. This evidence was published after the completion of the evidence review for the full AK guidelines. The focused scope of the present update is to incorporate the evidence specifically and solely addressing the use of topical tirbanibulin for the treatment of AK into the AAD's existing guidance on the management of AK. The updated recommendation for the management of AK is available in **Table I**. A complete list of the original and updated recommendations for the management of AK is available in **e-Table 1**.

Table I. Updated Recommendation for the Management of Actinic Keratosis. *AK*, Actinic keratoses

No.	Recommendation	Strength	Quality of Evidence
Topical Agents			
2.4	For patients with AKs, we recommend field treatment with topical tirbanibulin	Strong	High

Methods

Cognizant of the need for timely updates to clinical guidance when novel evidence that has the potential to inform the revision or development of clinical practice recommendations within the scope of existing, recently published (< 5 years) AAD guidelines becomes available, the AAD's Clinical Guidelines Committee (CGC) oversaw the development of a focused update process. For details of the current focused update process, see **e-Appendix 1**. Per this process, new evidence supporting the approval by the U.S Food and Drug Administration of a novel microtubule inhibitor indicated for the topical treatment of AK was identified as potentially impacting the current AK guidance and led to the initiation of the current update.

This update is based on a systematic review by an expert workgroup supported by an AAD guidelines staff member with health research methodology expertise and applied the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach for assessing the certainty of the evidence and formulating and grading clinical recommendations. The strength of recommendation indicates the assessed magnitude and certainty of the balance of desirable and undesirable consequences of a treatment option. The quality of evidence ratings reflects the assessed overall certainty of the evidence supporting each recommendation. Each category of certainty represents the level of confidence the guideline developers placed in the evidence to support a recommendation (**Table II**).[3-5] For detailed methodology, **see e-Appendix 2**.

Table II. Strength of Recommendation and Certainty of Evidence

Strength of Recommendation	Wording	Implication[3-5]
Strong recommendation *for* the use of an intervention	"We recommend…"	Benefits clearly outweigh risk and burdens; recommendation applies to most patients in most circumstances.
Strong recommendation *against* the use of an intervention	"We recommend against…"	Risk and burden clearly outweigh benefits; recommendation applies to most patients in most circumstances.
Good Practice Statement	"We recommend…"	Guidance was viewed by the Work Group as imperative to clinical practice and developed when the supporting evidence was considerable but indirect, and the certainty surrounding an intervention's impact was high with the benefits clearly outweighing the harms (or vice versa). Good Practice Statements are strong recommendations as the certainty surrounding the impact of the recommended intervention is high. Implementation of these strong recommendations is considered to clearly result in beneficial outcomes.[5]
Conditional recommendation *for* the use of an intervention	"We conditionally recommend…"	Benefits are closely balanced with risks and burdens; recommendation applies to most patients, but the most appropriate action may differ depending on the patient or other stakeholder values.
Conditional recommendation *against* the use of an intervention	"We conditionally recommend against…"	Risks and burden closely balanced with benefits; recommendation applies to most patients, but the most appropriate action may differ depending on the patient or other stakeholder values
Certainty of Evidence	**Wording**	**Implication[3,4]**
High	"high quality evidence"	Very confident that the true effect lies close to that of the estimate of the effect.
Moderate	"moderate quality evidence"	Moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	"low quality evidence"	Confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
Very Low	"very low quality evidence"	The estimate of effect is very uncertain; the true effect may be substantially different from the estimate of effect

New Recommendation

Clinical Question

This focused update considers new evidence pertaining to the following clinical question from the original guideline: What are the efficacy, effectiveness, and adverse effects of topically applied agents for AK?[2] This guidance updates the clinical question by introducing a single, new topical intervention- tirbanibulin- and does not update evidence of the other topically applied agents considered in the original guideline. The previously issued topical agent recommendations are

considered current for 5 years post-publication or until superseded by another update or full revision of the AK guidelines.

Recommendation 2.4[1]

For patients with AK, we recommend field treatment with topical tirbanibulin (strong recommendation, high quality evidence).

Background

A first-in-class microtubule inhibitor, tirbanibulin, was approved for the topical, field-directed treatment of AK on the scalp or face by the U.S Food and Drug Administration in December of 2020.[6,7] Tirbanibulin's mechanism of action addresses two pathways upregulated in AK and SCC by inhibiting tubulin polymerization and disrupting Src kinase signaling.[8] Tirbanibulin 1% ointment is indicated for a once-daily application for 5 consecutive days.[6]

Summary of Evidence and Analysis

A systematic literature search identified two phase III randomized, double-blinded, parallel-group, placebo-controlled trials that met established inclusion criteria.[9] Both trials compared a standard regimen of topical tirbanibulin 1% applied once daily to a 25cm^2 treatment field containing 4-8 AKs on the face or scalp for five consecutive days to vehicle. The trials included 702 adult participants with AKs.

On day 57, participants treated with tirbanibulin experienced higher rates of complete clearance of AKs in the treatment area (pooled clearance rates 174/353 [49.3%]) than those treated with the vehicle (pooled clearance rate 30/349 [8.6%]; Risk ratio [RR] 6.14 95%CI 2.73, 13.80, p<0.0001; **e-Appendix 3**).[9] Participants treated with tirbanibulin also experienced significantly higher rates of partial clearance (≥75% reduction in the number of treated AKs) compared to the vehicle-treated participants (pooled partial clearance rates 255/353 [72.2%] vs 63/349 [18.1%], RR 3.99 95%CI 3.16, 5.04, p<0.00001). At 12 months, the estimated percentage of previously cleared participants with recurrent lesions in the treatment area was 47% and the estimate of those with recurrent or new lesions in the treatment area was 73%.[9] These findings are consistent with the results of an open-label, uncontrolled, dose-finding phase II study of adults with AKs on the face and scalp that reported a complete clearance rate of 43% for participants (n= 84) treated with tirbanibulin 1% for 5 consecutive days at day 57.[8]

The most common adverse events reported through day 57 of the phase III trials were application site pruritus (reported in 9.1% of tirbanibulin-treated participants vs 6.0% of vehicle-treated participants) and pain (reported in 9.9% of tirbanibulin-treated participants vs 3.2% of vehicle-treated participants, **e-Appendix 3**).[9] Severe local skin reactions were rare with less than 1% of tirbanibulin-treated participants experiencing severe vesiculation, pustulation, erosion, or ulceration by day 57 and no vehicle-treated participants experiencing these severe reactions. No participants in either arm of the trials discontinued treatment due to treatment-related adverse events.[9]

Rationale for Recommendation

The Work Group determined that the overall balance of benefits and potential harms as reported at 57 days favors using tirbanibulin for the management of AK on the face and scalp and that the certainty of the available short-term evidence is high (**e-Appendix 3**). Although the Work Group recognizes that cost may be prohibitive without adequate insurance coverage, they

[1]

concluded that the use of tirbanibulin is likely acceptable to patients and providers, and feasible to implement especially considering the abbreviated duration of tirbanibulin treatment compared to the duration of other available topically applied agents for AK.

Achieving clearance of AKs is a key goal of therapy. The reported clearance rates following tirbanibulin treatment were considered to be large in magnitude and an indication of the efficacy of the therapy. The safety profile suggests limited anticipated adverse events. Consequently, the use of tirbanibulin was considered to have substantial clinical potential (clearance of treated AKs) in the short term, while not substantially increasing the potential for undesirable consequences (severe adverse events including local skin reaction and discontinuation of treatment due to adverse events). The large improvement in desirable effects in the absence of substantial risk of undesirable effects, including local skin reactions, favors the use of tirbanibulin.

The Work Group acknowledges that the current recommendation is based on the available short-term efficacy and safety evidence specific to the management of AKs on the face and scalp. Future availability of long-term safety data may impact the direction or strength of the recommendation. Additionally, the Work Group recognizes the evidence is restricted to treatment of a limited field ($25cm^2$) applicable for the management of AKs in commonly affected smaller areas like the central scalp, forehead, or cheek.

Conclusion and Research Needs

The Work Group recommends the use of topical tirbanibulin for the management of AK. Additional, long-term efficacy and safety data and data on patient-reported outcomes in real-world settings are needed to provide additional insights into the efficacy, effectiveness, and safety of tirbanibulin for the management of AK. Studies of larger treatment areas or other protocols are also needed to investigate applicability of the intervention for full face and scalp field-therapy.

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Work Group Members' Disclosures

The following information represents the authors' disclosed relationships with industry during the focused update development process. Authors (listed alphabetically) with relevant conflicts of interest with respect to this guideline are noted with an asterisk (*). In accordance with AAD policy, a minimum 51% of workgroup members did not have any relevant conflicts of interest. Participation in ≥1 of the following activities constitutes a relevant conflict: service as a member of a speaker bureau or advisory board, or service as a consultant for pharmaceutical companies on actinic keratosis (AK), AK drugs in development, or Food and Drug Administration approved AK drugs, or sponsored research funding or investigator-initiated studies with partial or full funding from pharmaceutical companies on AK, or AK drugs in development, or Food and Drug Administration approved AK drugs. If a potential conflict was noted, the workgroup member recused themselves from voting on the recommendations pertinent to the topic area of interest. Complete group consensus was obtained for draft recommendations. Areas where complete consensus was not achieved are shown transparently in the guideline.

Robert P. Dellavalle, MD, PhD, MSPH, serves as a principal investigator for Pfizer, Inc. and the US Department of Veterans Affairs receiving grants and/or research funding; as an editorial board member for the Cochrane Collaboration, Journal of Investigative Dermatology, and the Journal of the American Academy of Dermatology receiving other financial benefits; as an independent contractor for UpToDate, Inc. receiving patent royalties and/or compensation for intellectual property rights; as a consultant for Altus Labs and ParaPRO LLC receiving fees and/or stock. Daniel B. Eisen, MD, has no relationships to disclose. Lindsy Frazer-Green, PhD, has no relationships to disclose. Todd E. Schlesinger*, MD, serves as an investigator for AbbVie, Arcutis, Inc., Allergan, Inc., AOBiome, LLC., Astellas Pharma US, Inc., Biofrontera, Biorasi, LLC., Boehringer Ingelheim, Brickell Biotech, Inc., Bristol-Myers Squibb, Cara Therapeutics, Castle BioScience, Celgene, ChemoCentryx, Corrona, Inc., Demira, Dermavant Sciences, Eli Lilly and Company, EPI Health, Galderma USA, Genentech, Janssen Pharmaceuticals, Inc., Kiniksa Pharmaceuticals, Ltd., Merz Aesthetics, Nimbus Therapeutics, Novartis, Pfizer, Inc., Processa Pharmaceuticals, Prolacta Bioscience, Pulse Biosciences, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme, SiSaf Ltd., and Trevi Therapeutics receiving grants and/or research funding; as a consultant for AbbVie, Allergan, Inc., Almirall,

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