Focused update to the guidelines of care for the management of actinic keratosis: Executive summary

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Key words: actinic keratosis; actinic keratosis guidelines; clinical guidelines for actinic keratosis; topical agents; tirbanibulin.

Actinic keratoses (AKs) are keratinocyte neoplasms occurring on skin that has had long-term exposure to ultraviolet radiation. AK is one of the most common conditions treated by dermatologists in the United States.[1] In 2021, the American Academy of Dermatology 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.[2] The purpose of the update is to incorporate new evidence for the use of a recently US Food and Drug Administration-approved topical, tirbanibulin, for the treatment of AK into the American Academy of Dermatology's existing guidance on the management of AK.

A systematic review identified 2 phase 3 randomized, double-blinded, parallel-group, placebo-controlled trials, including 702 adult participants.[3] Both trials compared a standard regimen of topical tirbanibulin 1% applied once daily to a 25 cm^2 treatment field containing 4 to 8 AKs on the face or scalp for 5 consecutive days to vehicle.

On day 57, participants treated with tirbanibulin experienced higher rates of complete and partial clearance of AKs in the treatment area (pooled complete clearance rates 174/353 [49.3%]; pooled partial clearance rate 255/353 [72.2%]) than those treated with the vehicle (pooled complete clearance rate 30/349 [8.6%]; pooled partial clearance rate 63/349 [18.1%]). The most common adverse events reported through day 57 of the phase 3 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).[3] 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 trial discontinued treatment due to treatment-related adverse events.[3]

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. Although the Work Group recognizes that cost may be prohibitive without adequate insurance coverage and other strongly recommended treatments for AK may be available at a lower cost, they 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 with the duration of other available topical agents for AK.

The Work Group acknowledges that the current recommendation is based on the available

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short-term efficacy and safety evidence specific to the management of AKs on the face and scalp. The future availability of long-term safety data may impact the direction or strength of the recommendation. Consult the full focused update publication for a detailed discussion of the evidence and rationale for the recommendation.

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Key points

- The focused guideline update considers the evidence on the use of topical tirbanibulin to treat actinic keratosis.
- A strong recommendation for the use of topical tirbanibulin was added to the list of recommended therapies for actinic keratosis.

Conflicts of interest

None disclosed.

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Focused update: Guidelines of care for the management of actinic keratosis

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

Objective: In 2021, the American Academy of Dermatology 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 work group conducted a systematic review to evaluate data on the use of tirbanibulin for AK and applied the Grading of Recommendations, Assessment, Development, and Evaluation 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 trials were identified, and analysis of the evidence resulted in 1 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 to join the currently recommended list of topical therapies for AK was made on the basis of the available evidence. (J Am Acad Dermatol 2022;87:374.e1-374.e5.)

Key words: actinic keratosis; actinic keratosis guidelines; clinical guidelines for actinic keratosis; tirbanibulin; topical agents.

SCOPE

Actinic keratoses (AKs) are keratinocyte neoplasms occurring on skin that has had long-term exposure to UV radiation. AK is one of the most common conditions treated by dermatologists in the United States.[1] In early 2021, the American Academy of Dermatology (AAD) published guidelines addressing the management of AK and provided recommendations for the use of various available treatments for AK, including topical agents,

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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.

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Abbreviations used:

AAD: American Academy of Dermatology
AK: actinic keratosis

cryosurgery, and photodynamic therapy.[2] In addition, these guidelines considered the clinical characteristics, histologic classification, natural history, risk of progression, and dermatologic surveillance of AKs.[2]

The impetus for this focused update was the identification of recently published evidence and subsequent approval by the US 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 guidelines on the management of AK. The updated recommendation for the management of AK is available in Table I. A complete list of the current recommendations for the management of AK is available in Supplementary Table I (available via Mendeley at https://data.mendeley.com/datasets/8b9k4mzsgx/1).

METHODS

Cognizant of the need for timely updates to clinical guidelines 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 oversaw the development of a focused update process. For details of the current focused update process, see Appendix 1 (available via Mendeley at https://data.mendeley.com/datasets/8b9k4mzsgx/1). Per this process, new evidence supporting the approval by the US Food and Drug Administration of a novel microtubule inhibitor indicated for the topical treatment of AK was identified as potentially impacting the current guidelines on the management of AK and led to the initiation of this update.

This update is based on a systematic review by an expert work group supported by an AAD staff member with health research methodology expertise and applied the Grading of Recommendations, Assessment, Development, and Evaluation approach for assessing the certainty of the evidence and formulating and grading clinical recommendations. The strength of a recommendation indicates the assessed magnitude and certainty of the balance of desirable and undesirable consequences of a treatment option. The quality of evidence ratings reflect 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 Appendix 2 (available via Mendeley at https://data.mendeley.com/datasets/8b9k4mzsgx/1).

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 guideline updates the clinical question by introducing a single, new topical intervention—tirbanibulin—and does not update the evidence of the other topically applied agents considered in the original guideline. The previously issued topical agent recommendations are considered current for 5 years postpublication or until superseded by another update or full revision of the guidelines for the management of AK.

Recommendation 2.4

For patients with AK, we recommend field treatment with topical tirbanibulin (strong recommendation, high certainty 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 US Food and Drug Administration in December of 2020.[6,7] Tirbanibulin's mechanism of action addresses 2 pathways upregulated in AK and squamous cell carcinoma 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 2 phase III randomized, double-blinded, parallel-group, placebo-controlled trials that met the established inclusion criteria.[9] Both the trials compared a standard regimen of topical tirbanibulin 1% applied once daily to a 25 cm^2 treatment field containing 4 to 8 AKs on the face or scalp for 5 consecutive days to vehicle. The trials included 702 adult participants with AKs.

Table I. Updated recommendation for the management of actinic keratosis

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

AK, Actinic keratosis.

On day 57, the participants treated with tirbanibulin experienced higher rates of complete clearance of AKs in the treatment area (pooled clearance rate 174 [49.3%] of 353) than those treated with the vehicle (pooled clearance rate, 30 [8.6%] of 349; risk ratio, 6.14; 95% CI, 2.73-13.80; P <.0001) (Appendix 3 available via Mendeley at https://data.mendeley.com/datasets/8b9k4mzsgx/1).[9] The participants treated with tirbanibulin also experienced significantly higher rates of partial clearance (≥75% reduction in the number of treated AKs) than those treated with the vehicle(pooled partial clearance rate, 255 [72.2%] of 353 vs 63 [18.1%] of 349; risk ratio, 3.99; 95% CI, 3.16-5.04; P <.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) (Appendix 3 available via Mendeley at https://data.mendeley.com/datasets/8b9k4mzsgx/1).[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 because of 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 (Appendix 3 available via Mendeley at https://data.mendeley.com/datasets/8b9k4mzsgx/1). Although the Work Group recognizes that cost may be prohibitive without adequate insurance coverage and other strongly recommended treatments for AK may be available for lower cost, they 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 with the duration of other available topically applied agents for the management of 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 because of 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 that the evidence is restricted to the treatment of a limited field (25 cm^2) applicable for the management of AKs in commonly affected smaller areas, such as 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

Table II. Strength of recommendation and certainty of evidence

Strength of the recommendation	Wording	Implication[3-5]
Strong recommendation *for* the use of an intervention	"We recommend…"	Benefits clearly outweigh risks and burdens; recommendation applies to most patients in most circumstances.
Strong recommendation *against* the use of an intervention	"We recommend against…"	Risks and burdens 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 because 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; however, 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 burdens are closely balanced with benefits; recommendation applies to most patients; however, the most appropriate action may differ depending on the patient or other stakeholder values.

Certainty of Evidence	Wording	Implication[3,4]
High	"high certainty evidence"	Very confident that the true effect lies close to that of the estimate of the effect.
Moderate	"moderate certainty evidence"	Moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect; however, there is a possibility that it is substantially different.
Low	"low certainty 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 certainty evidence"	The estimate of effect is very uncertain; the true effect may be substantially different from the estimate of effect.

areas or other protocols are also needed to investigate the applicability of the intervention for full face and scalp field therapy.

Conflicts of interest

Work Group Members' Disclosures:

The following information represents the authors' disclosed relationships with the 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 the American Academy of Dermatology policy, a minimum of 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; 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.

Dr Dellavalle 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; and as a consultant for Altus Labs and ParaPRO LLC, receiving fees and/or stock. Dr Schlesinger* 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, Bristol-Meyers Squibb, CMS Aesthetics DMCE, Eli Lilly and Company, EPI Health, Foundation for Research and Education in Dermatology, Galderma USA, IntraDerm Pharmaceuticals, Kintor Pharmaceuticals Ltd, Merz Aesthetics, NextPhase Therapeutics, Novartis, Ortho Dermatologics, Plasmend, Prolacta Bioscience, Regeneron, and UCB, receiving honoraria and/or fees; as a speaker for Almirall, Demira, EPI Health, MED Learning Group, Regeneron, and Sun Pharmaceutical Industries Ltd, receiving honoraria; and as an advisory board member for Almirall, Biofrontera AG, Greenway Therapeutix (no compensation received), and Remedly Inc, receiving honoraria and/or stock. Dr Wu serves as an independent contractor for UpToDate Inc, receiving honoraria. Drs Eisen, Frazer-Green, and Shive have no conflicts of interest to declare.

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