

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 cm² 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.

Click here to read the full article: [Focused update to the guidelines of care for the management of actinic keratosis](#)

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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3. Blauvelt A, Kempers S, Lain E, et al. Phase 3 trials of tirbanibulin ointment for actinic keratosis. *N Engl J Med.* 2021;384(6):512-520.

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 cm² 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
<i>Topical Agents</i>			
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 ($\geq 75\%$ 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 cm²) 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}
<i>Strong recommendation for the use of an intervention</i>		"We recommend..."	Benefits clearly outweigh risks and burdens; recommendation applies to most patients in most circumstances.
<i>Strong recommendation against the use of an intervention</i>		"We recommend against..."	Risks and burdens clearly outweigh benefits; recommendation applies to most patients in most circumstances.
<i>Good Practice Statement</i>		"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
<i>Conditional recommendation for the use of an intervention</i>		"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.
<i>Conditional recommendation against the use of an intervention</i>		"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 Therapeutics (no compensation received), and Remedy 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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Online Supplement

Focused Update: Guidelines of Care for the Management of Actinic Keratosis

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e-Table 1. Recommendations for the Management of Actinic Keratosis.

The updated recommendation appears in bold font. For evidence supporting recommendations from the original, full guideline publication¹ refer to the original guideline publication and its online data supplement (<https://doi.org/10.17632/vw48xpmz2j.3>). AK, Actinic keratoses; ALA, aminolevulinic acid; NSAID, nonsteroidal anti-inflammatory drug; PDT, photodynamic therapy; UV, ultraviolet

No.	Recommendation	Strength	Certainty of Evidence
<i>UV Protection</i>			
1.	For patients with AK, we recommend the use of UV protection <i>Remarks: UV protection may include sun avoidance, sun-protective clothing, and broad-spectrum sunscreen</i>	Strong	Good Practice Statement
<i>Topical Agents</i>			
2.1	For patients with AKs, we recommend field treatment with topical 5-fluorouracil	Strong	Moderate
2.2	For patients with AKs, we recommend field treatment with topical imiquimod	Strong	Moderate
2.3	For patients with AKs, we conditionally recommend the use of diclofenac <i>Remarks: As with other oral and topical medications in the class, NSAIDs carry a black box warning for cardiovascular and gastrointestinal side effects</i>	Conditional	Low
2.4	For patients with AKs, we recommend field treatment with topical tirbanibulin	Strong	High
<i>Cryosurgery</i>			
3.1	For patients with AKs, we recommend the use of cryosurgery	Strong	Good Practice Statement
3.2	For patients with AKs, we conditionally recommend treatment with cryosurgery over CO ₂ laser ablation	Conditional	Moderate
<i>Photodynamic Therapy</i>			
4.1	For patients with AKs, we conditionally recommend ALA-red light-PDT	Conditional	Low
4.2	For patients with AKs, we conditionally recommend 1 to 4-hour 5-ALA incubation time to enhance complete clearance with red light-PDT	Conditional	Low
4.3	For patients with AKs, we conditionally recommend ALA-daylight-PDT as less painful than but equally effective as ALA-red light PDT	Conditional	Moderate
4.4	For patients with AKs, we conditionally recommend treatment with ALA red light PDT over trichloroacetic acid peel	Conditional	Moderate
4.5	For patients with AKs, we conditionally recommend ALA-blue light-PDT	Conditional	Moderate
4.6	For patients with AKs, we conditionally recommend against pretreatment with alpha hydroxy acid solution prior to ALA-blue light-PDT	Conditional	Very Low
4.7	For patients with AKs, we conditionally recommend treatment with ALA red light-PDT over cryosurgery alone	Conditional	Low
<i>Combination Therapy</i>			

5.1	For patients with AKs, we conditionally recommend the combined use of 5-FU and cryosurgery over cryosurgery alone	Conditional	Moderate
5.2	For patients with AKs, we conditionally recommend the combined use of imiquimod and cryosurgery over cryosurgery alone	Conditional	Low
5.3	For patients with AKs, we conditionally recommend against the use of diclofenac in addition to cryosurgery compared to cryosurgery alone	Conditional	Low
5.4	For patients with AKs, we conditionally recommend against the use of topical adapalene in addition to cryosurgery compared to cryosurgery alone	Conditional	Low
5.5	For patients with AKs, we conditionally recommend against the addition of imiquimod following ALA-blue light-PDT	Conditional	Moderate

References

1. Eisen DB, Asgari MM, Bennett DD, et al. Guidelines of care for the management of actinic keratosis. *J Am Acad Dermatol.* 2021;85(4):e209-e233.

e-Appendix 1. Focused Updates: Current Process

Processes for updating the AAD's clinical practice guidelines are established and continue to develop under the direction of the AAD's Clinical Guidelines Committee (CGC). The standard comprehensive guideline updating process considers AAD guideline publications to be current up to five years post-publication with full updates, including consideration of all clinical questions addressed within a guideline publication, to be completed in alignment with the five-year currency cycle. Recognizing 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 CGC oversaw the development of a focused update process.

A focused update is undertaken outside of the standard, comprehensive 5-year guideline updating process as necessitated by the availability of new evidence or a change in the clinical landscape that is likely to impact a single recommendation within the scope of an existing, current AAD guideline.

Initiation of a focused update is based on the identification of peer-reviewed publications of new, high-quality evidence that is considered likely to impact current clinical practice recommendations or support the development of new recommendations. Identification of the new evidence may be prompted by approval of new treatments by the U.S. Food and Drug Administration that impact the management of a dermatologic condition addressed in a current AAD guideline or identification of potentially impactful practice-changing evidence by AAD staff, guideline workgroup members, or CGC members.

CGC approval and prioritization of a focused update dictates that new evidence be critically reviewed by a guideline workgroup but does not indicate that a recommendation will be changed, or a new recommendation developed. Recommendations within the source guideline for the focused update that are not being considered directly during the update remain current. Recommendations revised or added by a focused update are considered current for the standard 5-year currency period or until superseded by another update or full guideline revision.

Once a focused update is approved for development by the CGC, a guideline-focused update workgroup of four to eight members is appointed by the CGC to ensure efficiency in the updating process. Workgroup empanelment adheres to all requirements of the AAD/AAD Association Administrative Regulations for Evidence-Based Clinical Practice Guidelines (March 2021).¹ Focused updates are undertaken by a multidisciplinary expert workgroup supported by an AAD guidelines staff member with health research methodology expertise.

The evidence synthesis and assessment process as well as the process employed to revise or draft recommendations for focused updates adhere to the standard methodology for the development of AAD guidelines. Specifically, a systematic review of the literature relevant to the focused update is conducted and the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach is employed to assess the certainty of the evidence and formulate and grade clinical recommendations.

Focused updates are subject to the standard AAD guideline multilevel review and approval process which includes the opportunity for review and comment by the entire AAD membership and final review and comment by the AAD Board of Directors.¹

References

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e-Appendix 2. Detailed Methodology

Expert Work Group Composition and Disclosures of Interest

Work Group members were reviewed for potential disclosures of interest (DOIs) and approved by the AAD's Clinical Guidelines Committee (CGC). The majority (at least 51%) of the Work Group was required to be free of financial DOIs relevant to the topic of the guideline update. Nominees found to have no relevant financial DOIs were approved, whereas nominees found to have potentially relevant financial DOIs were approved with management. Work Group members approved with management were prohibited from voting on recommendations in which they had relevant DOIs. Work Group members completed a DOI form that was periodically updated and reviewed for potential relevant DOIs throughout the guideline update development process and used to ensure management terms were observed. The multidisciplinary Work Group consisted of the Chair, 4 members, and an AAD guidelines staff member with health research methodology expertise.

Formulation of Questions and Outcomes of Interest

This focused update considers new evidence about the following clinical question from the original *Guidelines of care for the management of actinic keratosis*: What are the efficacy, effectiveness, and adverse effects of topically applied agents for AK?¹ 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.

This focused update used the outcomes of interest that were identified and ranked as critical or important for clinical decision making regarding the management of AK during the development of the original AK guidelines (**e-Table I**).¹

e-Table I. Primary Outcomes

Primary Outcome	Importance Ranking
Mean reduction in AK counts from baseline to assessment	Critical
Participant complete clearance (participants with a complete clearance of all AKs within a predefined field)	Critical
Participant partial clearance (participants with at least a 75% reduction in the AKs within a predefined field)	Critical
Investigator global improvement index (participants rated as 'completely improved' by the investigator)	Critical
Participant global improvement index (participants self-assessed as 'completely improved')	Critical
Withdrawals due to Adverse Events	Critical
Adverse Events	Important

Literature Searches

The literature search strategy employed for the original AK guideline was revised and updated specifically to the clinical question informing the focused update. AAD guidelines' staff (L.F.G) performed a systematic search of the literature for the clinical question using MEDLINE (via PubMed) and Cochrane Library. Databases were searched from inception to June 28, 2021. A

combination of the National Library of Medicine's medical subject headings and other keywords specific to the clinical question was used to identify studies. The MEDLINE (via PubMed) search strategy is available (**e-Table II**). Searches were limited to English language, human clinical trials, randomized controlled trials, meta-analyses, or systematic reviews. The literature search identified three unique publications.

e-Table II. MEDLINE (via PubMed) Search Strategy

Search Strategy
((("keratosis, actinic"[MeSH Terms] OR ("Actinic"[Title/Abstract] OR "acantholytic"[Title/Abstract] OR "Actinic"[Title/Abstract] OR "Bowenoid"[Title/Abstract] OR "hyperkeratotic"[Title/Abstract] OR "hypertrophic"[Title/Abstract] OR "pigmentary"[Title/Abstract] OR "pigmented"[Title/Abstract] OR "senile"[Title/Abstract] OR "senilis"[Title/Abstract] OR "solar"[Title/Abstract] OR "typical"[Title/Abstract])) AND ("Keratoses"[Title/Abstract] OR "keratosis"[Title/Abstract])) AND ("tirbanibulin"[Title/Abstract] OR "KXO1"[Title/Abstract] OR "KX-01"[Title/Abstract] OR "KX2391"[Title/Abstract] OR "KX2-391"[Title/Abstract] OR "Klisyri"[Title/Abstract]))

Study Selection and Data Extraction

Studies retrieved by the literature searches were reviewed for relevance over two rounds of study selection. During the first round of study selection, title and abstract screening was performed against predefined inclusion and exclusion criteria established during the original AK guideline development process by AAD guidelines staff.¹ The full text of studies appearing to meet inclusion criteria during title and abstract screening were retrieved and then underwent a second round of study selection, during which a final inclusion decision was made. Full-text screening inclusion decisions were made independently by AAD guidelines' staff with subsequent quality control by Work Group members. Disagreements were resolved through discussion by the original pair of reviewers to reach a consensus. After two rounds of study screening, 1 publication reporting on two randomized, controlled clinical trials was selected for inclusion in the evidence review.

A structured data table was used to extract relevant data from the included studies. Data extraction was initially performed by AAD guidelines' staff with subsequent quality control via review and discussion by all other Work Group members. Discrepancies were resolved through discussion by the original data extractor and the reviewing Work Group members.

Risk of Bias Assessment and Evidence Synthesis

The risk of bias was assessed in all included studies using the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials.² Following risk of bias assessment, for dichotomous outcomes, when data were homogenous and poolable, the relative risk (RR) and its 95% confidence interval were calculated according to Altman 1991.³ No continuous outcomes were analyzed based on the available evidence. The limited available evidence precluded meta-analysis.

Assessing the Overall Certainty of the Body of Evidence

The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach was used to assess the overall certainty of the evidence for each critical or important

outcome.⁴ The GRADEPro Guideline Development Tool was used to create an evidence profile that categorized the overall certainty of the body of evidence for each outcome into one of four categories: high, moderate, low, or very low. Each category represents the confidence in the estimate of effect for an outcome (**e-Table III**).

e-Table III. *Certainty of Evidence Ratings*

Certainty of the Evidence	Confidence in the Estimate of Effect
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are 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	Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
Very Low	We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Formulating and Grading Recommendations

The Work Group drafted a recommendation using the evidence profile and considering the following: the balance of desirable and undesirable consequences of an intervention, the overall certainty of the evidence, patient values and preferences, resource use, acceptability, and feasibility.⁵ Per the GRADE approach, recommendations are either “strong” or “conditional”.⁶ The implications of each strength of recommendation are summarized in **Table IV**. Recommendations were also graded according to the GRADE approach.⁶

Table IV. *Strength of Recommendation Implications*

Strength	Implication
Strong	Benefits clearly outweigh risks and burdens, or risks and burden clearly outweigh the benefits
Conditional	Benefits finely balanced with risks and burden

Manuscript Review and Currency Statement

This focused update has been developed following the AAD/AAD Association Administrative Regulations for Evidence-Based Clinical Practice Guidelines (March 2021), which includes the opportunity for review and comment by the entire AAD membership and final review and comment by the AAD Board of Directors.⁷ The guidance issued by this focused update will be considered current for 5 years from the date of publication unless reaffirmed, updated, or retired before that time.

References

1. Eisen DB, Asgari MM, Bennett DD, et al. Guidelines of care for the management of actinic keratosis. *J Am Acad Dermatol*. 2021;85(4):e209-e233.

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4. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64(4):401-406.
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7. American Academy of Dermatology. Administrative regulation—evidence-based clinical practice guidelines. Accessed October 15 Available at: <https://server.aad.org/Forms/Policies/Uploads/AR/AR%20-%20Evidence-Based%20Clinical%20Practice%20Guidelines.pdf>

e-Appendix 3. GRADE Evidence Profile

Tirbanibulin 1% ointment qd for 5 days vs vehicle ointment qd for 5 days¹

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	tirbanibulin	vehicle	Relative (95% CI)	Absolute (95% CI)		
Complete Clearance (follow up: 57 days; assessed with: proportion of participants with complete (100%) clearance AKs in the treatment area)												
2 *	randomized trials	not serious	not serious	not serious	not serious	none	174/353 (49.3%)	30/349 (8.6%)	RR 6.14 (2.73 to 13.80)	442 more per 1,000 (from 149 more to 1,000 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Partial Clearance (follow up: 57 days; assessed with: proportion of participants with ≥ 75% reduction from baseline in number of AKs in treatment area)												
2	randomized trials	not serious	not serious	not serious	not serious	none	255/353 (72.2%)	63/349 (18.1%)	RR 3.99 (3.16 to 5.04)	540 more per 1,000 (from 390 more to 729 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Withdrawal due to treatment-related adverse event (follow up: 5 days; assessed with: participants discontinuing treatment due to treatment-related AE)												
2	randomized trials	not serious	not serious	not serious	not serious	none	0/353 (0.0%)	0/349 (0.0%)	not estimable		⊕⊕⊕⊕ HIGH	CRITICAL
Application site pain (follow up: 57 days; assessed with: participants experiencing pain, tenderness, stinging, and burning sensation at the application site.)												
2	randomized trials	not serious	not serious	not serious	serious ^a	none	35/353 (9.9%)	11/349 (3.2%)	RR 2.96 (1.18 to 7.39)	62 more per 1,000 (from 6 more to 201 more)	⊕⊕⊕○ MODERATE	IMPORTANT
Application site pruritus (follow up: 57 days; assessed with: participants experiencing itching at treatment site)												
2	randomized trials	not serious	not serious	not serious	serious ^b	none	32/353 (9.1%)	21/349 (6.0%)	RR 1.50 (0.88 to 2.54)	30 more per 1,000 (from 7 fewer to 93 more)	⊕⊕⊕○ MODERATE	IMPORTANT

Severe vesiculation or pustulation (follow up: 57 days; assessed with: participants experiencing severe vesiculation or pustulation in the application area as graded by investigator on a 4-point scale [0 indicating absent, 1 mild (slightly or barely perceptible), 2 moderate (distinct presence), and 3 severe (marked or intense)])

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	tirbanibulin	vehicle	Relative (95% CI)	Absolute (95% CI)		
2	randomized trials	not serious	not serious	not serious	not serious ^c	none	2/353 (0.6%)	0/349 (0.0%)	RR 2.97 (0.31 to 28.38)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT

Severe erosion or ulceration (follow up: 57 days; assessed with: participants experiencing severe erosion or ulceration in the application area as graded by investigator on a 4-point scale [0 indicating absent, 1 mild (slightly or barely perceptible), 2 moderate (distinct presence), and 3 severe (marked or intense)])

2	randomized trials	not serious	not serious	not serious	not serious ^c	none	0/353 (0.0%)	0/349 (0.0%)	not estimable		⊕⊕⊕⊕ HIGH	IMPORTANT
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AK: Actinic keratosis; **CI:** Confidence interval; **RR:** Risk ratio

* Two phase 3 trials reported in a single publication (Blauvelt 2021)

Explanations

- Small number of events leading to CI consistent with the possibility of a minimal and important increase in risk.
- CI consistent with the possibility of no difference and important increase and decrease in risk.
- Small number of events, as severe reactions were rare. Outcome not downgraded for imprecision as the rarity of events with the intervention supports its safety.

References

- Blauvelt A, Kempers S, Lain E, et al. Phase 3 Trials of Tirbanibulin Ointment for Actinic Keratosis. *N Engl J Med*. 2021;384(6):512-520.