Online Supplement

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

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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 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revised or added by a focused update are considered current for the standard 5-year currency period or until superseded by another update or full guideline revision.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

1. 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 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 pertaining to 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
Participants 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.

2. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343:d5928.
3. Altman DG. *Practical statistics for medical research.* London: Chapman and Hall; 1991.
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.
5. Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *J Clin Epidemiol.* 2013;66(7):719-725.
6. Andrews JC, Schunemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *J Clin Epidemiol.* 2013;66(7):726-735.
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 days[1]

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							№ 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)		
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

AK: Actinic keratosis; **CI:** Confidence interval; **RR:** Risk ratio

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

Explanations

a. Small number of events leading to CI consistent with the possibility of a minimal and important increase in risk.
b. CI consistent with the possibility of no difference and important increase and decrease in risk.
c. 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

1. 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.