SKIN

Clinical Management Recommendations

The Importance of Medication Adherence in the Treatment of Actinic Keratosis: An Expert Consensus Panel

Danny Zakria, MD, MBA[1], April W. Armstrong, MD, MPH[2], Brian Berman, MD[3], James Q. Del Rosso, DO[4], Mark Lebwohl, MD[1], Todd E. Schlesinger, MD[5], Darrell Rigel, MD, MS[1]

[1] Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY
[2] Department of Dermatology, Keck School of Medicine, University of Southern California, Los Angeles, CA
[3] Department of Dermatology & Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL
[4] Department of Dermatology, Touro University, Henderson, NV
[5] Dermatology & Laser Center of Charleston, Clinical Research Center of the Carolinas, Charleston, South Carolina

ABSTRACT

Background: Actinic keratosis (AK) is one of the most common dermatologic diagnoses. While there are several treatment options, many topical therapies have poor adherence due to duration of treatment and local skin reactions (LSRs).
Objective: To review the available literature on the most commonly used patient-administered field-directed therapies for AK and create consensus statements on the role of medication adherence in improving AK outcomes.
Methods: A literature search of PubMed was completed for English-language original research articles reporting efficacy, safety, and tolerability data for 5-FU, diclofenac gel, imiquimod cream, and tirbanibulin. Once the articles were selected, they were distributed to a panel consisting of seven dermatologists with extensive expertise in managing AKs. Each panelist reviewed the articles and assigned them a level of evidence based on Strength of Recommendation Taxonomy (SORT) criteria. The panelists then met to review and discuss the studies and created consensus statements on the management of AKs and the importance of medication compliance. A modified Delphi process was used to approve the adoption of each statement.
Results: The literature search produced 1,326 articles that met search criteria. After screening these articles for relevance and applying the inclusion criteria, 17 articles were chosen to be reviewed by the panel and assigned a level of evidence based on SORT criteria. The panel then created six consensus statements that received a unanimous vote for adoption.
Conclusion: While there are several options for the treatment of AK, there is little consensus on a standard of care. Clearance rates for the most common topical field therapies vary significantly but are also difficult to directly compare due to differences in methodology for measuring and assessing outcomes. Overall, it is clear that an efficacious, tolerable, and convenient treatment for AKs is critical to optimal adherence and management and, given the results of recent studies, tirbanibulin may be the best topical option for meeting these criteria.

INTRODUCTION

Actinic Keratosis (AK) is one of the most common diagnoses in the outpatient setting, with an estimated prevalence of 40 million in the United States (US) in 2004 and a rising incidence.[1,2] AKs are associated with chronic ultraviolet (UV) damage, and therefore their incidence increases substantially with age.[3] In fact, in the US it is the most common dermatologic diagnosis in patients over 45 years of age.[4,5] AKs can be problematic as they have the potential to develop into a keratinocyte carcinoma (KC), typically a squamous cell carcinoma (SCC), the second most common skin cancer in the world.[5-8] While SCC usually has a high cure rate, a subset of these tumors can metastasize, leading to approximately 4,000 – 9,000 deaths in the US each year.[9-13] The risk of transformation into invasive SCC is difficult to accurately assess, but some studies cite a risk as high as 16% per lesion-year.[14,15]

There are two types of treatment methods for AKs – lesion-directed therapy and field therapy. Lesion-directed therapy targets specific AKs that the clinician is able to identify and is commonly used when there are only a few lesions or for patients who may not be compliant with at-home regimens.[16] This includes cryosurgery, laser therapy, curettage, and surgery such as an excision or shave biopsy.[16]

For patients that present to the dermatology office with numerous AKs, lesion-directed therapy can be cumbersome and inefficient. Additionally, chronic UV exposure can lead to field cancerization, in which areas of cutaneous tissue have a high burden of both clinical and subclinical actinic damage.[5] Therefore, in order to mitigate the risk of malignant transformation, it is often important to treat the broader area of skin that may include normal appearing tissue with pathologic atypia.[5] Commonly used field-directed therapies include 5-fluorouracil (5-FU), diclofenac, imiquimod, photodynamic therapy (PDT), and tirbanibulin. While field-directed therapies are more effective at treating subclinical actinic damage, they can be associated with long regimens and local skin reactions (LSRs) that limit adherence.[5,16-18]

Tirbanibulin is the newest field-directed treatment and was approved by the Food and Drug Administration (FDA) for the treatment of AKs on the face and scalp at the end of 2020 after two phase 3 clinical trials demonstrated its safety and efficacy.[19] One benefit of tirbanibulin is that it has a 5-day course, much shorter than other therapies that require treatment for 2-4 weeks. Early data has also shown that tirbanibulin is very tolerable with minimal LSRs. The purpose of this study was for a panel of experts in AK management to review the available literature on the most commonly used patient-administered field-directed therapies for AK and create consensus statements on the role of medication adherence in improving AK outcomes.

METHODS

A literature search of PubMed was completed on January 8, 2023, using the keywords actinic keratosis, actinic keratoses, efficacy, safety, and tolerability, along with the Boolean term “AND” for English-language original research articles without date restrictions. The articles were required to be original studies, systematic reviews, or meta-analyses reporting efficacy, safety, and tolerability data for 5-FU, diclofenac gel, imiquimod cream, and tirbanibulin. Once the articles were selected, they were distributed to a panel consisting of seven dermatologists

with expertise in managing AKs. Each panelist reviewed the articles and assigned them a level of evidence based on Strength of Recommendation Taxonomy (SORT) criteria.[20] The panelists then convened on February 16, 2023, to review and discuss the studies and develop consensus statements on the management of AKs and the importance of medication compliance. A modified Delphi process was used to approve the adoption of each statement.[21] This process requires a supermajority vote to adopt a statement or recommendation through multiple rounds of real-time voting. Each panel voted a score of 1-9 for adoption. Only statements for which at least two-thirds of the panel voted a 7 or higher were adopted.

RESULTS

Study Selection and Levels of Evidence

The initial literature search produced 1,326 articles that met search criteria. After screening these articles for relevance and applying the inclusion criteria, 17 articles were chosen to be reviewed by the panel and assigned a level of evidence. Of the 17 selected articles, the panel assigned level 1 evidence to nine articles[19,22-29], level 2 evidence to three articles[30-32], and level 3 evidence to five articles[33-37] as shown in **Table 1 and 2**.

Consensus Statements

The panel created seven consensus statements related to AK management. For six of these statements, the panel unanimously voted a level 9 for adoption. There was one statement which was not adopted, as five members of the panel assigned it a level 2 and two members assigned it a level 3 (**Table 3**).

Statement 1: *AK is a common dermatologic disease.*

AK is one of the most common dermatologic diseases and is the most common dermatologic diagnosis in adults older than 45 years of age.[4] Its incidence is on the rise, as the number of treated AKs per 1,000 Medicare patients rose 14.6% between 2007 and 2015.[38] It is extremely common outside of the US as well, especially in areas that receive significant UV exposure. In Australia, it is estimated that 40% of the population over the age of 40 has at least one AK.[39] The World Health Organization calculated that there were 131,433,084 cases of AK across Europe in 2006.[40]

Statement 2: *AKs can progress to invasive squamous cell carcinoma.*

The natural history of AKs and their ability to transform into invasive SCC has been described throughout the literature. One study found that patients with at least 20 AKs had an 11-fold greater risk of developing SCC and 10-fold greater risk of developing basal cell carcinoma (BCC) compared to those without any.[41] Not every AK will progress to SCC; in fact, spontaneous regression may occur in 15 to 63% of lesions.[42] However, even though some AKs will regress, they often reappear, and new ones develop in areas of chronically sun-exposed skin. One survey study of 1,040 people in Australia found 1,873 AKs in 59% of the people screened.[43] At 12-month follow-up, although 26% of the lesions were absent in the subgroup with at least one AK, 60% of these participants developed new lesions.[43] Overall, the total number of AKs in the studied population increased by 22% at 12 months.[43] While it is difficult to predict which AKs will transform into SCC and the individual risk of malignant transformation for each lesion, it is clear that AKs have the

Table 1. SORT criteria level of evidence for each of the articles pertaining to tirbanibulin.

Article	Level of Evidence
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.	1
Heppt MV, Dykukha I, Graziadio S, Salido-Vallejo R, Chapman-Rounds M, Edwards M. Comparative Efficacy and Safety of Tirbanibulin for Actinic Keratosis of the Face and Scalp in Europe: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials. J Clin Med. 2022;11(6):1654. Published 2022 Mar 16.	1
Rajkumar JR, Armstrong AW, Kircik LH. INDIVIDUAL ARTICLE: Safety and Tolerability of Topical Agents for Actinic Keratosis: A Systematic Review of Phase 3 Clinical Trials. J Drugs Dermatol. 2021;20(10):s4s4-s14.	1
Kempers S, DuBois J, Forman S, et al. Tirbanibulin Ointment 1% as a Novel Treatment for Actinic Keratosis: Phase 1 and 2 Results. *J Drugs Dermatol*. 2020;19(11):1093-1100.	2
Yavel R, Overcash JS, Cutler D, Fang J, Zhi J. Phase 1 Maximal Use Pharmacokinetic Study of Tirbanibulin Ointment 1% in Subjects With Actinic Keratosis. Clin Pharmacol Drug Dev. 2022;11(3):397-405.	2
Berman B, Grada A, Berman DK. Profile of Tirbanibulin for the Treatment of Actinic Keratosis. J Clin Aesthet Dermatol. 2022;15(10 Suppl 1):S3-S10.	3
Dao DD, Sahni VN, Sahni DR, Balogh EA, Grada A, Feldman SR. 1% Tirbanibulin Ointment for the Treatment of Actinic Keratoses. Ann Pharmacother. 2022;56(4):494-500.	3
Dlott AH, Di Pasqua AJ, Spencer SA. Tirbanibulin: Topical Treatment for Actinic Keratosis. Clin Drug Investig. 2021;41(9):751-755.	3
Eisen DB, Dellavalle RP, Frazer-Green L, Schlesinger TE, Shive M, Wu PA. Focused update: Guidelines of care for the management of actinic keratosis. J Am Acad Dermatol. 2022;87(2):373-374.e5.	3

Table 2. SORT criteria level of evidence for the articles not pertaining to tirbanibulin.

Article	Level of Evidence
Hadley G, Derry S, Moore RA. Imiquimod for actinic keratosis: systematic review and meta-analysis. J Invest Dermatol. 2006;126(6):1251-1255.	1
Pomerantz H, Hogan D, Eilers D, et al. Long-term Efficacy of Topical Fluorouracil Cream, 5%, for Treating Actinic Keratosis: A Randomized Clinical Trial. JAMA Dermatol. 2015;151(9):952-960.	1
Askew DA, Mickan SM, Soyer HP, Wilkinson D. Effectiveness of 5-fluorouracil treatment for actinic keratosis--a systematic review of randomized controlled trials. Int J Dermatol. 2009;48(5):453-463.	1
Rivers JK, Arlette J, Shear N, Guenther L, Carey W, Poulin Y. Topical treatment of actinic keratoses with 3.0% diclofenac in 2.5% hyaluronan gel. Br J Dermatol. 2002;146(1):94-100.	1
Jansen MHE, Kessels JPHM, Nelemans PJ, et al. Randomized Trial of Four Treatment Approaches for Actinic Keratosis. N Engl J Med. 2019;380(10):935-946.	1
Gupta AK, Paquet M. Network meta-analysis of the outcome 'participant complete clearance' in nonimmunosuppressed participants of eight interventions for actinic keratosis: a follow-up on a Cochrane review. Br J Dermatol. 2013;169(2):250-259.	1
Cunningham TJ, Tabacchi M, Eliane JP, et al. Randomized trial of calcipotriol combined with 5-fluorouracil for skin cancer precursor immunotherapy. J Clin Invest. 2017;127(1):106-116.	2
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.	3

Table 3. Consensus Statements

Statement	Vote
Statements that were adopted	
AK is a common dermatologic disease.	7 voted 9
AKs can progress to squamous cell carcinoma.	7 voted 9
Higher complexity, longer duration, and adverse effects negatively impact adherence to AK treatments.	7 voted 9
Lower adherence to AK treatments can lead to lower efficacy.	7 voted 9
Prospective, real-world data demonstrate that topical tirbanibulin for AK is effective, well-tolerated, and convenient, based on highly concordant assessments by both patients and clinicians.	7 voted 9
Payors and other stakeholders are encouraged to reduce barriers to effective, tolerable, and convenient treatments for AKs.	7 voted 9
Statements that were not adopted	
There is an unmet need for effective AK treatments that are of short duration with limited and tolerable adverse effects.	5 voted 2 2 voted 3

potential to progress to SCC as histopathology reports demonstrate that 60% to 82% of invasive SCCs arise from AKs.[44-46] Furthermore, some lesions that are clinically diagnosed as AKs may actually be SCC or BCC. One study of 220 AK biopsy samples found histopathologic identification of SCC in situ (3.2%), invasive SCC (1.4%), and BCC (0.5%).[47] Another study of step sections of 69 lesions originally classified as AKs at histopathologic diagnosis were re-characterized as SCC in situ (13%), invasive SCC (3%), and BCC (4%).[48]

Statement 3: *Higher complexity, longer duration, and adverse effects negatively impact adherence to AK treatments.*

It is well documented that adherence to topical medications can be very poor for a variety of dermatologic conditions.[49] This may stem from a multitude of factors and several studies have attempted to identify these factors and possible interventions. One systematic review of the associations between dose regimens and medication compliance found that compliance decreased as the number of daily doses increased.[50] For AK management specifically, literature reporting adherence and persistence for topical treatments is limited, but one study of 224 AK patients on imiquimod (3.75% and 5%), 5-FU 5%, or 5-FU/salicylic acid (0.5%/10%) in Germany, France, and the UK found between 10 and 25% of patients were non-adherent with their prescribed regimen and 23% were non-persistent.[51] Another study of 305 AK patients that were either currently using a topical AK therapy (diclofenac sodium 3%, imiquimod 5%, 5-FU 5% or 5-FU/salicylic acid (0.5%/10%)) or had done so within the past 12 months found that 88% of patients were either non-adherent, non-persistent, or both with their regimens.[52]

Longer duration and adverse effects certainly play a significant role in adherence to AK treatments. One study of adherence in 20 patients treated with 5-FU 0.5% reported an average adherence rate of 92% in the first week of treatment, but this fell to 82% by the end of treatment at the fourth of week.[53] Common adverse effects of topical AK therapies such as 5-FU 5% cream, diclofenac 3% gel, and imiquimod 3.75% cream include LSRs such as pain, erythema, burning, stinging, crusting, and flaking.[34,54] These adverse effects accompanied with longer regimens between 2 and 16 weeks can require treatment breaks and early cessation.[54] In their literature review, Lebwohl et. al found that the most important contributors to non-adherence were lengthy treatment duration, severity and persistence of LSRs, and confusion over treatment regimens.[54]

Statement 4: *Lower adherence to AK treatments can lead to lower efficacy.*

Lower adherence to treatments has an important negative impact as it can lead to decreased efficacy. This, in turn, results in negative health outcomes such as disease worsening and even death.[55] The problem is so significant that the World Health Organization even declared that non-adherence to medications is a “worldwide problem of striking magnitude” in 2003.[56] Incomplete treatment of AKs can increase the risk of malignant transformation to SCC, thus leading to increased morbidity and mortality.[14]

Statement 5: *Prospective, real-world data demonstrate that topical tirbanibulin for AK is effective, well-tolerated, and convenient, based on highly concordant assessments by both patients and clinicians and this suggests that its usage in AK management could lead to improved adherence.*

The Patient Reported Outcomes in Actinic Keratosis (PROAK) study is a real-world, single-arm, prospective cohort study for adult patients with AKs on the face or scalp who were newly initiated with once daily tirbanibulin.[57] A total of 300 patients were enrolled from 32 community practices across the US. Ten patients were not included in the 8-week analyses due to missing data, loss to follow-up, or voluntary patient withdrawal of consent. Of the remaining 290 patients, 100% of them completed their 5-day once-daily treatment course. Importantly, there were no discontinuations due to adverse drug reactions and there were no serious adverse drug reactions reported at 8 weeks.[57] Not only was tirbanibulin found to be well-tolerated, but it was efficacious as well, with 73.79% of clinicians reporting that their patients AKs were completely or partially (at least 75%) cleared based on investigator global assessment (IGA) at 8 weeks.[58]

In clinical practice, many patients become frustrated with LSRs from topical therapies and after just one treatment course they are very reluctant to use them again. However, in the PROAK study, for 85.17% of tirbanibulin-treated patients, their clinicians reported that they are somewhat or very likely to consider tirbanibulin treatment again if the need arises. Concordantly, 80.0% of patients noted that they were somewhat or very likely to consider tirbanibulin treatment again if the need arises.[57,58] These findings suggest that tirbanibulin usage for AK therapy could lead to enhanced therapeutic adherence.

Statement 6: *Payors and other stakeholders are encouraged to reduce barriers to effective, tolerable, and convenient treatments for AKs.*

While efficacy and tolerability are very important factors to ensure medication adoption and treatment success, accessibility is just as important. Access to tirbanibulin can be limited, as the cost for a 5-day supply of the ointment can be $1,136 for cash-paying patients or those with inadequate insurance coverage.[59] One study that compared costs of various field therapies for AK found the per-regimen cost of tirbanibulin was $990.[60] This is less expensive than the most expensive medication studied, 5-FU 0.5% cream ($1,332.08), but far more expensive than the least expensive treatment, 5-FU 5% cream ($384.94).[60] When patients face choices between AK therapies with long durations and significant LSRs or high costs, they may be discouraged from seeking care. This can subsequently increase the morbidity, mortality, and overall use of healthcare resources from AKs and their associated SCCs. In 2013, the estimated cost of treating AKs in the US was $1.68 billion.[61] Early detection and treatment of AKs is imperative for both improving outcomes and decreasing costs to the healthcare system, as one Veterans Affairs study found 3-year savings of $771 per patient treated with 5-FU versus placebo.[62] Therefore, improving access to effective, tolerable, and convenient treatments such as tirbanibulin should be a priority for payors.

CONCLUSION

While there are multiple options for the treatment of AK, there is little consensus on a standard of care. Clearance rates for the most common topical field therapies vary significantly but are also difficult to directly compare due to differences in methodology for measuring and assessing outcomes. After a thorough review of the literature, this panel of dermatologists with significant expertise in managing AKs created six consensus statements related to the importance of AK treatment to prevent the development of SCC and the role that medication adherence plays

in treatment success. Study limitations include that not all therapeutic options for AK were considered and the topical field therapies that were included in the review have not all been compared head-to-head. Overall, it is evident that an efficacious, tolerable, and convenient treatment for AKs is critical to their adequate management and that tirbanibulin may be the best current option to achieve these criteria.

Conflict of Interest Disclosures: DZ has no relevant conflicts to disclose. **AWA** has served as a consultant and investigator for Almirall. **BB** has served as a consultant and speaker for Almirall. **JDR** is a consultant, research investigator, and speaker for Almirall. **ML** is a consultant for Almirall. **TS** is a consultant and investigator for Almirall, Galderma and Biofrontera. **DR** has served as a consultant and investigator for Almirall.

Funding: This study was funded in part by an unrestricted educational grant from Almirall.

Corresponding Author:
Danny Zakria, MD, MBA
234 E 85th St. 5th Floor
New York, NY 10028
Phone: (212) 241-6595
Email: danny.zakria@mountsinai.org

References:

1. Bickers DR, Lim HW, Margolis D, et al. The burden of skin diseases: 2004 a joint project of the American Academy of Dermatology Association and the Society for Investigative Dermatology. J Am Acad Dermatol. 2006;55(3):490-500. doi:10.1016/j.jaad.2006.05.048
2. Rigel DS, Stein Gold LF. The importance of early diagnosis and treatment of actinic keratosis. J Am Acad Dermatol. 2013;68(1 Suppl 1):S20-S27. doi:10.1016/j.jaad.2012.10.001
3. Siegel JA, Korgavkar K, Weinstock MA. Current perspective on actinic keratosis: a review. Br J Dermatol. 2017;177(2):350-358. doi:10.1111/bjd.14852
4. Landis ET, Davis SA, Taheri A, Feldman SR. Top dermatologic diagnoses by age. Dermatol Online J. 2014;20(4):22368. Published 2014 Apr 16.
5. Willenbrink TJ, Ruiz ES, Cornejo CM, Schmults CD, Arron ST, Jambusaria-Pahlajani A. Field cancerization: Definition, epidemiology, risk factors, and outcomes. J Am Acad Dermatol. 2020;83(3):709-717. doi:10.1016/j.jaad.2020.03.126
6. Que SKT, Zwald FO, Schmults CD. Cutaneous squamous cell carcinoma: Incidence, risk factors, diagnosis, and staging. J Am Acad Dermatol. 2018;78(2):237-247. doi:10.1016/j.jaad.2017.08.059
7. Muzic JG, Schmitt AR, Wright AC, et al. Incidence and Trends of Basal Cell Carcinoma and Cutaneous Squamous Cell Carcinoma: A Population-Based Study in Olmsted County, Minnesota, 2000 to 2010. Mayo Clin Proc. 2017;92(6):890-898.
8. Skin Cancer Foundation: Skin Cancer Facts & Statistics [Internet]. The Skin Cancer Foundation, 2023. [cited 2023 Apr 18]. Available from: https://www.skincancer.org/skin-cancer-information/skin-cancer-facts/
9. Stratigos AJ, Garbe C, Dessinioti C, et al. European interdisciplinary guideline on invasive squamous cell carcinoma of the skin: Part 1. epidemiology, diagnostics and prevention. Eur J Cancer. 2020;128:60-82. doi:10.1016/j.ejca.2020.01.007
10. Brougham ND, Dennett ER, Cameron R, Tan ST. The incidence of metastasis from cutaneous squamous cell carcinoma and the impact of its risk factors. J Surg Oncol. 2012;106(7):811-815. doi:10.1002/jso.23155
11. Dessinioti C, Pitoulias M, Stratigos AJ. Epidemiology of advanced cutaneous squamous cell carcinoma. J Eur Acad Dermatol Venereol. 2022;36(1):39-50. doi:10.1111/jdv.17709
12. Thompson AK, Kelley BF, Prokop LJ, Murad MH, Baum CL. Risk Factors for Cutaneous Squamous Cell Carcinoma Recurrence, Metastasis, and Disease-Specific Death: A Systematic Review and Meta-analysis. JAMA Dermatol. 2016;152(4):419-428. doi:10.1001/jamadermatol.2015.4994
13. Karia PS, Han J, Schmults CD. Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012. J Am Acad Dermatol. 2013;68(6):957-966. doi:10.1016/j.jaad.2012.11.037
14. Criscione VD, Weinstock MA, Naylor MF, et al. Actinic keratoses: Natural history and risk of malignant transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial. Cancer. 2009;115(11):2523-2530. doi:10.1002/cncr.24284
15. Werner RN, Sammain A, Erdmann R, Hartmann V, Stockfleth E, Nast A. The natural history of

actinic keratosis: a systematic review. Br J Dermatol. 2013;169(3):502-518. doi:10.1111/bjd.12420
16. Dianzani C, Conforti C, Giuffrida R, et al. Current therapies for actinic keratosis. Int J Dermatol. 2020;59(6):677-684. doi:10.1111/ijd.14767
17. Cornejo CM, Jambusaria-Pahlajani A, Willenbrink TJ, Schmults CD, Arron ST, Ruiz ES. Field cancerization: Treatment. J Am Acad Dermatol. 2020;83(3):719-730. doi:10.1016/j.jaad.2020.03.127
18. Goldenberg G. Treatment considerations in actinic keratosis. J Eur Acad Dermatol Venereol. 2017;31 Suppl 2:12-16. doi:10.1111/jdv.14152
19. 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. doi:10.1056/NEJMoa2024040
20. Ebell MH, Siwek J, Weiss BD, et al. Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. Am Fam Physician. 2004;69(3):548-556.
21. Hsu C-C, Sandford BA. The Delphi technique: making sense of consensus. Practical assessment, research & evaluation 2007;12:1-8.
22. Heppt MV, Dykukha I, Graziadio S, Salido-Vallejo R, Chapman-Rounds M, Edwards M. Comparative Efficacy and Safety of Tirbanibulin for Actinic Keratosis of the Face and Scalp in Europe: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials. J Clin Med. 2022;11(6):1654. Published 2022 Mar 16. doi:10.3390/jcm11061654
23. Rajkumar JR, Armstrong AW, Kircik LH. INDIVIDUAL ARTICLE: Safety and Tolerability of Topical Agents for Actinic Keratosis: A Systematic Review of Phase 3 Clinical Trials. J Drugs Dermatol. 2021;20(10):s4s4-s14. doi:10.36849/JDD.M1021
24. Hadley G, Derry S, Moore RA. Imiquimod for actinic keratosis: systematic review and meta-analysis. J Invest Dermatol. 2006;126(6):1251-1255. doi:10.1038/sj.jid.5700264
25. Pomerantz H, Hogan D, Eilers D, et al. Long-term Efficacy of Topical Fluorouracil Cream, 5%, for Treating Actinic Keratosis: A Randomized Clinical Trial. JAMA Dermatol. 2015;151(9):952-960. doi:10.1001/jamadermatol.2015.0502
26. Askew DA, Mickan SM, Soyer HP, Wilkinson D. Effectiveness of 5-fluorouracil treatment for actinic keratosis--a systematic review of randomized controlled trials. Int J Dermatol. 2009;48(5):453-463. doi:10.1111/j.1365-4632.2009.04045.x
27. Rivers JK, Arlette J, Shear N, Guenther L, Carey W, Poulin Y. Topical treatment of actinic keratoses with 3.0% diclofenac in 2.5% hyaluronan gel. Br J Dermatol. 2002;146(1):94-100. doi:10.1046/j.1365-2133.2002.04561.x
28. Jansen MHE, Kessels JPHM, Nelemans PJ, et al. Randomized Trial of Four Treatment Approaches for Actinic Keratosis. N Engl J Med. 2019;380(10):935-946. doi:10.1056/NEJMoa1811850
29. Gupta AK, Paquet M. Network meta-analysis of the outcome 'participant complete clearance' in nonimmunosuppressed participants of eight interventions for actinic keratosis: a follow-up on a Cochrane review. Br J Dermatol. 2013;169(2):250-259. doi:10.1111/bjd.12343
30. Kempers S, DuBois J, Forman S, et al. Tirbanibulin Ointment 1% as a Novel Treatment for Actinic Keratosis: Phase 1 and 2 Results. J Drugs Dermatol. 2020;19(11):1093-1100. doi:10.36849/JDD.2020.5576
31. Yavel R, Overcash JS, Cutler D, Fang J, Zhi J. Phase 1 Maximal Use Pharmacokinetic Study of Tirbanibulin Ointment 1% in Subjects With Actinic Keratosis. Clin Pharmacol Drug Dev. 2022;11(3):397-405. doi:10.1002/cpdd.1041
32. Cunningham TJ, Tabacchi M, Eliane JP, et al. Randomized trial of calcipotriol combined with 5-fluorouracil for skin cancer precursor immunotherapy. J Clin Invest. 2017;127(1):106-116. doi:10.1172/JCI89820
33. Berman B, Grada A, Berman DK. Profile of Tirbanibulin for the Treatment of Actinic Keratosis. J Clin Aesthet Dermatol. 2022;15(10 Suppl 1):S3-S10.
34. Dao DD, Sahni VN, Sahni DR, Balogh EA, Grada A, Feldman SR. 1% Tirbanibulin Ointment for the Treatment of Actinic Keratoses. Ann Pharmacother. 2022;56(4):494-500. doi:10.1177/10600280211031329
35. Dlott AH, Di Pasqua AJ, Spencer SA. Tirbanibulin: Topical Treatment for Actinic Keratosis. Clin Drug Investig. 2021;41(9):751-755. doi:10.1007/s40261-021-01068-9
36. Eisen DB, Dellavalle RP, Frazer-Green L, Schlesinger TE, Shive M, Wu PA. Focused update: Guidelines of care for the management of actinic keratosis. J Am Acad Dermatol. 2022;87(2):373-374.e5. doi:10.1016/j.jaad.2022.04.013
37. 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. doi:10.1016/j.jaad.2021.02.082
38. Yeung H, Baranowski ML, Swerlick RA, et al. Use and Cost of Actinic Keratosis Destruction in

the Medicare Part B Fee-for-Service Population, 2007 to 2015. JAMA Dermatol. 2018;154(11):1281-1285. doi:10.1001/jamadermatol.2018.3086
39. Marks R. Freckles, moles, melanoma and the ozone layer: a tale of the relationship between humans and their environment. Med J Aust. 1989;151(11-12):611-613. doi:10.5694/j.1326-5377.1989.tb139626.x
40. Lucas, R.; McMichael, T.; Smith, W.; Armstrong, B. Solar Ultraviolet Radiation: Global Burden of Disease from Solar Ultraviolet Radiation; Environmental Burden of Disease, Series; no., 13; Prüss-Üstün, A., Zeeb, H., Mathers, C., Repacholi, M., Eds.; World Health Organization: Geneva, Switzerland, 2006.
41. Green A., Battistutta D.: Incidence and determinants of skin cancer in a high-risk Australian population. Int J Cancer 1990; 46: pp. 356-361.
42. Navarrete-Dechent C, Marghoob AA, Marchetti MA. Contemporary management of actinic keratosis. J Dermatol Treat. 2019;32:572–4.
43. Marks R., Foley P., Goodman G., Hage B.H., Selwood T.S.: Spontaneous remission of solar keratoses: the case for conservative management. Br J Dermatol 1986; 115: pp. 649-655.
44. Marks R., Rennie G., Selwood T.S.: Malignant transformation of solar keratoses to squamous cell carcinoma. Lancet 1988; 1: pp. 795-797.
45. Czarnecki D., Meehan C.J., Bruce F., Culjak G.: The majority of cutaneous squamous cell carcinomas arise in actinic keratoses. J Cutan Med Surg 2002; 6: pp. 207-209.
46. Mittelbronn M.A., Mullins D.L., Ramos-Caro F.A., Flowers F.P.: Frequency of pre-existing actinic keratosis in cutaneous squamous cell carcinoma. Int J Dermatol 1998; 37: pp. 677-681.
47. Ehrig T., Cockerell C., Piacquadio D., Dromgoole S.: Actinic keratoses and the incidence of occult squamous cell carcinoma: a clinical-histopathologic correlation. Dermatol Surg 2006; 32: pp. 1261-1265.
48. Carag H.R., Prieto V.G., Yballe L.S., Shea C.R.: Utility of step sections: demonstration of additional pathological findings in biopsy samples initially diagnosed as actinic keratosis. Arch Dermatol 2000; 136: pp. 471-475.
49. Mayba JN, Gooderham MJ. A Guide to Topical Vehicle Formulations. J Cutan Med Surg. 2018;22(2):207-212. doi:10.1177/1203475417743234
50. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther. 2001;23(8):1296-1310. doi:10.1016/s0149-2918(01)80109-0
51. Erntoft S, Norlin J, Pollard C, Diepgen TL. Patient adherence and non-persistence behaviour in real life Actinic Keratosis (AK) topical treatment in the UK, Germany and France. Paper presented at the International Society for Pharmacoeconomics and Outcomes Research; 2014; Montreal.
52. Shergill B, Zokaie S, Carr AJ. Non-adherence to topical treatments for actinic keratosis. Patient Prefer Adherence. 2013;8:35-41. Published 2013 Dec 17. doi:10.2147/PPA.S47126
53. Yentzer B, Hick J, Williams L, et al. Adherence to a topical regimen of 5-fluorouracil, 0.5%, cream for the treatment of actinic keratoses. Arch Dermatol. 2009;145(2):203-205. doi:10.1001/archdermatol.2008.562
54. Foley P, Stockfleth E, Peris K, et al. Adherence to topical therapies in actinic keratosis: A literature review. J Dermatolog Treat. 2016;27(6):538-545. doi:10.1080/09546634.2016.1178372
55. Tan X, Feldman SR, Chang J, Balkrishnan R. Topical drug delivery systems in dermatology: a review of patient adherence issues. Expert Opin Drug Deliv. 2012;9(10):1263-1271. doi:10.1517/17425247.2012.711756
56. World Health Organisation S. Adherence to long-term therapies: evidence for action. World Health Organization; Geneva, Switzerland: 2003
57. Kircik, L., Schlesinger, T., Armstrong, A., Berman, B., Bhatia, N., Del Rosso, J., Lebwohl, M., Patel, V., Rigel, D., Narayanan, S., Koscielny, V., & Kasujee, I. (2023). Impact of Actinic Keratosis (AK), as measured by patient-reported AK symptoms, and impact on emotions and functioning (using Skindex-16) among patients with AK administered tirbanibulin in real-world community practices across the U.S. (PROAK Study). SKIN The Journal of Cutaneous Medicine, 7(2), s161. https://doi.org/10.25251/skin.7.supp.161
58. Schlesinger, T., Kircik, L., Armstrong, A., Berman, B., Bhatia, N., Del Rosso, J., Lebwohl, M., Patel, V., Rigel, D., Narayanan, S., Koscielny, V., & Kasujee, I. (2023). Investigator Global assessment (IGA) of Actinic Keratosis (AK) among patients administered tirbanibulin in real-world community practices across the U.S., and clinician likelihood to consider tirbanibulin again for future AK treatments (PROAK Study). SKIN The Journal of Cutaneous Medicine, 7(2), s162. https://doi.org/10.25251/skin.7.supp.162
59. Klisyri prices, coupons, Copay & Patient Assistance. Drugs.com. (n.d.). Retrieved May 3,

2023, from https://www.drugs.com/price-guide/klisyri
60. Lampley N 3rd, Rigo R, Schlesinger T, Rossi AM. Field Therapy for Actinic Keratosis: A Structured Review of the Literature on Efficacy, Cost, and Adherence. Dermatol Surg. 2023;49(2):124-129. doi:10.1097/DSS.0000000000003677
61. Lim HW, Collins SAB, Resneck JS Jr, et al. The burden of skin disease in the United States. J Am Acad Dermatol. 2017;76(5):958-972.e2. doi:10.1016/j.jaad.2016.12.043
62. Yoon J, Phibbs CS, Chow A, Weinstock MA; Veterans Affairs Keratinocyte Carcinoma Chemoprevention Trial Group. Impact of topical fluorouracil cream on costs of treating keratinocyte carcinoma (nonmelanoma skin cancer) and actinic keratosis. J Am Acad Dermatol. 2018;79(3):501-507.e2. doi:10.1016/j.jaad.2018.02.058