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Reshaping treatment paradigm in actinic keratosis by using a modified Delphi questionnaire

Thomas Dirschka[a], Marco Ardigò[b,c], Maria Concetta Fargnoli[d], Carla Ferrándiz-Pulido[e], Yolanda Gilaberte[f], Ina Hadshiew[g], Ketty Peris[h,i] and Rolf-Markus Szeimies[j]

[a]CentroDerm Clinic, Heinz-Fangman-Strasse 57, Wuppertal, Germany[b]Dermatology Unit, IRCCS Humanitas Research Hospital, Rozzano, Italy[c]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Italy[d]San Gallicano Dermatological Institute, IRCCS, Rome, Italy[e]Department of Dermatology, Vall d'Hebron University Hospital, Barcelona, Spain[f]Department of Dermatology Miguel Servet University Hospital, University of Zaragoza, IIS Aragón, Zaragoza, Spain[g]MVZ Derma Köln, Cologne, Germany[h]Dermatologia, Dipartimento Universitario di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, Rome, Italy[i]Dermatologia, Dipartimento Scienze Mediche e Chirurgiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [j]Department of Dermatology and Allergology, Knappschaft Kliniken Recklinghausen, Recklinghausen, Germany

ABSTRACT

Purpose: Actinic keratosis (AK) is the main precursor of invasive cutaneous squamous cell carcinoma (cSCC). Since it is impossible to predict which lesions will progress to cSCC, early treatment of AK is crucial. Although AK treatments are effective, some are associated with local skin reactions that may impact treatment compliance and effectiveness. The aim of this modified Delphi study was to review the efficacy and safety of the different AK treatments, gain an understanding of the dermatologists' perspectives on their use, and provide guidelines for clinical practice.

Materials and methods: This document corresponds to a modified Delphi consensus survey, based on a literature review and a single round of questionnaire.

Results: The Delphi questionnaire was completed by 73 dermatologists from Germany, Italy, and Spain. Agreement was achieved for 78% of statements, while 11% showed discrepancies or were rejected.

Conclusions: Key findings emphasize the importance of patient-centered approaches and treatment attributes beyond efficacy (e.g. tolerability or adherence). Understanding the mechanisms of action of treatments is vital for managing patients' and clinicians' expectations and optimizing outcomes. Alternative strategies for evaluating efficacy, including the Actinic Keratosis Area and Severity Index (AKASI) score and lesion reduction from baseline, were also highlighted.

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Actinic keratoses; field-directed treatment; lesion-directed treatment; modified Delphi consensus

Introduction

Actinic keratoses (AK) are cutaneous lesions caused by chronic exposure to ultraviolet radiation (1). They primarily affect older males with fair skin (2), and can present as single or, more frequently, multiple lesions (3). The estimated global prevalence of AK is 14%, indicating a high burden of disease (4). Reducing sun exposure by using sunscreens, for example, has been shown to reduce the incidence and development of AK lesions (5).

Actinic keratosis is the most common precursor of invasive cutaneous squamous cell carcinomas (cSCCs) (6). It is still difficult to determine which lesions will evolve to cSCC, so early diagnosis and treatment of all AKs are important to prevent progression from AK to cSCCs (7). Despite its significance, AK remains underdiagnosed and undertreated, contributing to an increased disease burden (8).

A variety of therapeutic options are available for the treatment of patients with AK lesions (9). These can be classified as lesion- or field-directed, depending on the targeted area (10), and include 5-fluorouracil (5-FU)/salicylic acid (SA), cryotherapy, surgery and lasers (lesion-directed therapies), photodynamic therapy (PDT), and topical treatments (field-directed therapies) (11). The treatment selection should be individualized, based on the characteristics of both the patients and their lesions (10). Most topical treatments require a long 4 to 12-week regimen and are often associated with a significant local skin reaction (LSR) [also known as local tolerability sign (LTS)] and even systemic symptoms (12). Although LSRs are associated with a positive treatment outcome and generally resolve spontaneously, studies show that a high proportion of patients discontinue drug application prematurely (11–13), leading to a loss of therapeutic effectiveness (14).

Treatments with a good tolerability profile and shorter regimens improve adherence (15–20), patient satisfaction (21) and willingness to re-treat (22). Despite all these advantages, the perception of physicians and patients regarding the use of these topical treatments in clinical practice is not completely understood. To improve the management of patients with AK, it is essential to assess the therapeutic effectiveness and ease of use for both clinicians and patients while increasing knowledge of treatment benefits.

This modified Delphi study aims to enhance understanding of the attitude of dermatologists toward the use of topical treatments for AK, and to achieve a consensus on clinical decision-making, based on published literature and experience

CONTACT Thomas Dirschka t.dirschka@centroderm.de CentroDerm Clinic, Heinz-Fangman-Strasse 57, D-42287 Wuppertal, Germany
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Table 1. List of relevant topics and clinical questions to be answered.

Topic	Questions
1. Treatment objectives beyond efficacy	1. Why is the early treatment of actinic keratosis (AK) lesions important? 2. What is the efficacy/effectiveness of the different treatments for AK? 3. What is the short-term safety / tolerability of the different treatments for AK? [it includes the importance of low severity and short duration of local tolerability signs (LTSs)]. Are LTSs associated with better response to treatment?
2. Treatment selection	4. What is the patient satisfaction with the different treatments for AK and what are the patient preferences regarding treatments for AK? (it includes a good tolerability profile, cosmesis or convenience of the treatments, quality of life). 5. What is the progression rate to invasive cutaneous squamous cell carcinoma (cSCC) in patients treated with the different AK treatments?
3. Treatment patient profiles	6. Which treatment is more suitable for the following patient profiles: large field cancerization and multiple hyperkeratotic AK lesions, field cancerization of ≤25 cm^2 and non-hypertrophic and non-hyperkeratotic AK lesions, immunosuppressed patients, patients who work and have an active lifestyle, patients with field cancerization and heterogeneous lesions grading, patients concerned about esthetic issues, and non-adherent patients?
4. Treatment added value	7. Importance of adherence to AK treatments. Which is the adherence to each AK treatment? Are long treatment regimens associated with higher rates of discontinuation? And treatments associated with severe LTSs? 8. What is the duration of each AK treatment? Importance of a short treatment duration. 9. What are the different mechanisms of action of the different topical treatments and their consequences? 10. Which is the inflammatory response of each topical treatment? Does a higher inflammatory response correlate with a better clinical outcome? 11. Effects of photosensitivity. Are all treatments the same regarding photosensitivity?

AK: actinic keratosis, LTS: local tolerability sign, cSCC: cutaneous squamous cell carcinoma.

from a panel of experts. Evidence on the safety and effectiveness of the different topical treatments, the key reasons for treatment selection, and the patient profiles in which the different AK treatments would be most beneficial will also be discussed.

Materials and methods

This document reports the results of a modified Delphi consensus survey, based on a literature review and a single round of questionnaire process. The questionnaire statements were defined by a scientific committee, which comprised 8 dermatology specialists with extensive experience in the diagnosis and management of patients with AK. Participants came from 3 different countries in Europe (Germany, Italy and Spain).

In order to understand the knowledge gaps and relevant topics for review, 11 clinical questions grouped in 4 different subject areas were investigated (Table 1).

Literature review

To conduct the literature review, a search strategy protocol was developed. It contained the main topics and outcomes to be included in a search engine, and the inclusion and exclusion criteria of the different publications (Table S1). The search was conducted in October 2024. Publications related to AK retrieved from the MEDLINE and Epistemonikos databases were included. Clinical practice guidelines, systematic reviews, meta-analyses and randomized controlled trials were prioritized.

A stepwise search was conducted: in the first round the publications were assessed according to inclusion criteria by title and abstract, leading to a total of 80 eligible publications which were assessed for suitability.

Modified Delphi study

All members of the scientific committee met virtually to discuss the statements of the questionnaire, based on the synthesis of evidence and their expert opinion. The questionnaire comprised 27 statements divided into 5 thematic blocks. These were in line with the relevant topics from the literature review, and an additional block concerning AK treatment guidelines was added (Table 2).

A mass email was sent to a pool of 2,300 panelists from Germany, Italy, and Spain to achieve a minimum target of 60 panelists responding to the questionnaire within a period of 8 weeks. A minimum of 60 panelists was considered adequate based on findings from various publications (23,24). Panelists needed to meet the following criteria: (i) dermatologists with long or medium experience in the management of patients with AK, based on their years of practicing dermatology (from 4 to ≥30) and annual number of AK consultations (from <60 to ≥2,000), and (ii) dermatologists with different levels of experience with tirbanibulin 1% ointment, from low (<10 patients per month) to high prescribers (≥30 patients per month). The Delphi survey was made available on an online platform and was open for 8 weeks.

The level of consensus was assessed using a Likert 6-point scale (25) and the following response range: 'strongly disagree', 'disagree', 'neutral', 'agree', 'strongly agree', or 'abstain/unable to answer'. Agreement was defined as ≥80% of the participants voting 'agree' or 'strongly agree'. An agreement of 100% was considered unanimity. Discrepancy was defined as agreement levels between 66% and 79%, and rejection was defined as agreement levels below 66%.

Results

Literature review

Overall, 23 publications were included in the evidence synthesis, based on their relevance and suitability for answering the corresponding questions and according to expert judgment. The list of the included publications is shown in Table S2.

Participants

Among the 2,300 invited panelists, 73 dermatologists from Germany, Italy and Spain completed the questionnaire, representing a 3% response rate, which aligns with the commonly accepted range of 1%-5% (26). The proportion of respondents per country and their years of experience in dermatology and the annual number of AK consultations are shown in Table 3. Results reflect the diversity in geographical localization and clinical experience among the different panelists, avoiding any bias that might be caused by these characteristics.

Table 2. Level of agreement of the different statements of the questionnaire.

Thematic block	Statement	Agreement (%)	Level of agreement
1. Understanding current actinic keratosis (AK) treatment guidelines and their knowledge gaps	I believe in the importance of National and/or International Guidelines in the treatment of AK	93%	Agreement
	Current Guidelines are mainly based on treatment efficacy and safety. Real-world evidence (RWE) studies, patient preferences, patient satisfaction, patient follow-up, and patient profiles should also be considered in clinical practice	96%	Agreement
2. Treatment objectives beyond efficacy	The success of a treatment should be based solely on efficacy, measured by complete lesion clearance	63%	Rejection
	The safety and tolerability of a treatment should be considered when evaluating treatment success	95%	Agreement
	The lower risk of progression to squamous cell carcinoma (SCC) should be considered when evaluating treatment success	97%	Agreement
	The duration of lesion clearance should be considered when evaluating treatment success	90%	Agreement
	Adherence and patient treatment completion should be considered when evaluating treatment success	97%	Agreement
	Patient satisfaction with the treatment (good tolerability profile, cosmesis, convenience, etc.) should be considered when evaluating treatment success	89%	Agreement
3. Treatment selection	Early treatment of AK lesions is important to improve patient outcomes	91%	Agreement
	The duration of treatment for AK lesions should be considered when selecting a therapy	86%	Agreement
	Long treatment regimens and long application periods are associated with higher rates of discontinuation in clinical practice	82%	Agreement
	The severity and duration of treatment-associated local tolerability signs (aka local skin reactions, LSRs) should be considered when selecting a treatment	92%	Agreement
	In clinical practice, a high frequency and severity of local tolerability signs (aka LSRs) are not always associated with higher treatment efficacy	68%	Discrepancy
	In clinical practice, a high frequency and severity of local tolerability signs (aka LSRs) are associated with a higher number of treatment discontinuations	85%	Agreement
	Before choosing an AK treatment, the patient's preferences, as well as how and to what extent the treatment affects them, should be considered	87%	Agreement
	Minimizing the inflammatory response should be considered when selecting an AK treatment	70%	Discrepancy
4. Treatment patient profiles	In patients with a large field of cancerization and multiple hyperkeratotic lesions, 5-fluorouracil (5-FU) or conventional photodynamic therapy (PDT) should be the treatment of choice, provided if they meet summary of product characteristics (SmPC) requirements	80%	Agreement
	In patients with a field of cancerization ≤25 cm^2 and non-hypertrophic, non-hyperkeratotic AK lesions, 1% tirbanibulin should be considered the treatment of choice due to its well-balanced profile in terms of efficacy, safety, and convenience	81%	Agreement
	In immunosuppressed patients, such as solid organ transplant recipients, an immunomodulatory treatment, such as imiquimod, should not be the treatment of choice	62%	Rejection
	In patients who work and have an active lifestyle, 1% tirbanibulin should be the treatment of choice, provided if it meets SmPC requirements, due to its mild/moderate local tolerability signs (aka LSRs) and short course of treatment (5 days)	81%	Agreement
	In patients with a field of cancerization with heterogeneous lesions grading, a sequential approach might be considered, including lesion-directed treatments such as cryotherapy or 0.5% 5FU + salicylic acid, and a field cancerization treatment like 1% tirbanibulin, provided if they meet SmPC requirements	86%	Agreement
	In patients concerned about esthetic issues, 1% tirbanibulin should be the treatment of choice, provided if they meet SmPC requirements, due to its mild\/moderate local tolerability signs (aka LSRs) and good cosmetic outcomes	77%	Discrepancy
	In patients who have shown poor adherence to other AK treatments, 1% tirbanibulin should be the treatment of choice, provided if they meet SmPC requirements	84%	Agreement
5. Treatment added value	The balance between good efficacy and other attributes (short treatment regimen, mild/moderate local tolerability signs (aka LSRs) and absence of photosensitivity) constitutes an added value for any AK treatment	94%	Agreement
	A single-dose sachet per day that enables precise product dosing and supports patient adherence and compliance constitutes an added value for any AK treatment	81%	Agreement
	The apoptosis-based mode of action, due to its low inflammatory response, constitutes an advantage for an AK treatment	82%	Agreement
	The high frequency and severity of local tolerability signs (aka LSRs) can help in foreseeing the AK treatment success	64%	Rejection

5-FU: 5-fluorouracil, AK: actinic keratosis, LSR: local skin reaction, PDT: photodynamic therapy, RWE: real world evidence, SCC: squamous cell carcinoma, SmPC: summary of product characteristics.

Questionnaire results

Table 2 shows the different questionnaire statements for each thematic block and the level of agreement for each one.

Panelists agreed with most of the statements of the questionnaire (78%). There were discrepancies for 3 of the statements, and another 3 were rejected.

Discussion

This modified Delphi study aimed to explore the perspectives of dermatologists on the use of AK treatments and to establish a consensus that could guide clinical decision-making, based on published literature and insights from an expert panel. Data on the efficacy and safety of the different available treatment approaches were also reviewed.

Understanding current AK treatment guidelines and knowledge gaps

Panelists agreed on the importance of national and/or international guidelines when treating patients with AK. Of note, almost all topical treatments are recommended for the treatment of

Table 3. Demographic data of the participating panelists.

Characteristic	Number of participants (%)
Nationality:	73 (100%)
Spain	36 (49%)
Italy	23 (32%)
Germany	14 (10%)
Years of experience in dermatology:	73 (100%)
4–9	15 (21%)
10–19	23 (31%)
20–29	16 (22%)
≥30	19 (26%)
Annual number of AK consultations:	73 (100%)
<60	37 (51%)
500–999	17 (23%)
1000–1999	15 (21%)
≥2000	4 (5%)

single or multiple AK and field cancerization in the current European consensus-based guidelines (7). 5-FU has level of recommendation A [strongly recommended ('shall')] in these guidelines, while imiquimod (both 5% and 3.75%) and tirbanibulin 1% have levels of recommendation B [recommended ('should')]. Diclofenac 3% in sodium hyaluronate 2.5% gel is regarded as less effective than the other treatments. Conventional or daylight PDT with 5-aminolevulinic acid and/or methyl aminolevulinate and cryosurgery (recommendation level A), and laser ablation (B) are also recommended in the guidelines (7).

Besides the guidelines, panelists strongly agreed on taking into account real-world evidence (RWE) studies and following a patient-centered approach in clinical practice. AK affects various aspects of patients' lives, so treatment approaches need to be tailored to patient preferences to achieve maximum treatment satisfaction. These results are in line with the literature that reports that personalized approaches which complement patient preferences can lead to better adherence and ultimately improve treatment outcomes (27).

Treatment objectives beyond efficacy

Complete clearance of lesions is widely used to evaluate the efficacy of AK treatments. However, in a study conducted with 5-FU, complete clearance rates were inversely correlated with the number of baseline lesions, and the authors emphasized the limitations of relying solely on complete clearance to evaluate the therapeutic efficacy (28). The scientific committee also stressed the importance of regarding AK as a chronic recurrent condition in which achieving durable complete clearance can be challenging. Therefore, the reduction in the number of lesions compared to baseline (29) and the Actinic Keratosis Area and Severity Index (AKASI) score (30) should also be routinely used as parameters in clinical practice.

Unsurprisingly, then, panelists rejected the statement of evaluating treatment success solely on efficacy, measured by complete lesion clearance (only 63% agreement in the questionnaire). Despite this rejection, it is noteworthy that a large number of panelists still agreed with the statement, probably because complete lesion clearance is the most widely used parameter to measure the efficacy of AK treatments, thus allowing comparisons between the different therapeutic options.

Evaluation of the panelists' responses also showed that, besides efficacy, safety and tolerability, the lower risk of progression to cSCC if treated, the duration of lesion clearance, adherence and patient satisfaction were considered important parameters when evaluating treatment success.

A meta-analysis examining safety and tolerability demonstrated a lower incidence of severe local adverse events (AEs) with tirbanibulin compared to other AK treatments, and experts place tirbanibulin and diclofenac among the most tolerable topical treatment options (20). While diclofenac efficacy is lower than other AK treatments (7), tirbanibulin 1% efficacy and safety are well balanced (31). 5-FU and imiquimod are associated with more LSRs. Lower concentrations of 5-FU (4%) are associated with fewer severe skin reactions compared to higher concentrations (5%) (13), but even for 5-FU 4%, more severe skin reactions are reported than with tirbanibulin 1% in clinical trials (32,33). Imiquimod is associated with severe skin irritation, systemic flu-like symptoms and infections in a dose-dependent manner (9), ranking this treatment as one of the least tolerable options.

Adherence is another important parameter. Together with the reduced rate of progression to cSCC, agreement on the statement about considering adherence when evaluating treatment success was 97%. Premature discontinuation of a treatment reduces its effectiveness (14). For all topical treatments, tirbanibulin 1% has demonstrated the highest adherence rate (15–20). The high tolerability and the short treatment duration (5 days) (3) make it a preferred option for patients with AK. PDT has proven to be effective; however, the pain associated with conventional PDT and the fact that it is time-consuming for healthcare professionals are notable drawbacks (34).

Patient satisfaction with the chosen therapy is crucial in the treatment of chronic conditions, as it is associated with willingness to re-treat (22). In this context, shorter treatment regimens have been shown to lead to a better adherence and subsequently to improve patient quality of life and satisfaction (35).

Treatment selection

Experts underlined the importance of early treatment of AK lesions to improve patient outcomes. This is in accordance with the literature, which describes that all AK lesions, not just hypertrophic ones, can progress to cSCC (6). The percentage of lesion clearance is also higher in low-grade lesions versus high-grade lesions (36). The scientific committee emphasized the importance of early treatment not only for field cancerization but also for subclinical AK lesions. Therefore, prompt treatment is strongly recommended to prevent the lesions from progressing to a more severe stage.

As when evaluating treatment objectives, panelists agreed on the importance of considering treatment duration, discontinuations, the severity and duration of LSRs, and patient preferences and well-being when selecting a treatment. In contrast, panelists disagreed on the following statements: 'In clinical practice, a high frequency and severity of local tolerability signs (aka LSRs) are not always associated with higher treatment efficacy' and 'Minimizing the inflammatory response should be considered when selecting and AK treatment'.

For this last point, the scientific committee underscored the importance of patient and clinical expectations. Treatments like 5-FU (13,37) and imiquimod (14,38), due to their mechanism of action (MoA), may not be effective in the absence of inflammation, whereas this is not the case for diclofenac (14,38) and tirbanibulin (14,39). Experts placed PDT between these 2 groups. This shift challenges the 'no pain, no gain' concept, emphasizing that skin reactions are not necessary in all treatments for positive outcomes. Thus, dermatologists and patient education on tolerability and expected outcomes of the different treatments is crucial to accommodate patient preferences and ultimately optimize adherence and effectiveness.

Treatment patient profiles

Panelists agreed on: (i) conventional PDT or 5-FU as the treatments of choice in patients with large field of cancerization and multiple hyperkeratotic lesions; (ii) tirbanibulin 1% as the treatment of choice in patients with a field of cancerization ≤25 cm^2 and non-hypertrophic, non-hyperkeratotic AK lesions, or in patients who work and have an active lifestyle, or in patients who have shown poor adherence to other treatments; and (iii) a sequential approach with lesion-directed and field cancerization treatments in patients with a field of cancerization with heterogeneous lesion grading. In all cases treatments should be provided if the case fulfills the summary of product characteristics (SmPC) requirements.

In contrast, panelists rejected the statement that imiquimod should not be the treatment of choice for immunosuppressed patients, such as solid organ transplant recipients. This statement aligns with the most recent European consensus guidelines (7), which recommend caution when using imiquimod in this patient profile. Specifically, the use of imiquimod (either 5% or 3.75%) for the treatment of single or multiple AKs and field cancerization in selected immunocompromised patients is assigned a recommendation level of C. The scientific committee offered several justifications for the use of the immunomodulatory treatment imiquimod in immunosuppressed patients: (i) in clinical practice the use of imiquimod in small treatment areas has not been associated with organ rejection in this patient profile; (ii) imiquimod may not be the first treatment of choice in this patient profile but instead may be used as a second or third line of treatment. Of note, imiquimod is associated not solely with skin reactions, but also with flu-like symptoms (9), representing an increased risk in immunocompromised patients.

Panelists also disagreed that tirbanibulin 1% should be the treatment of choice in patients with esthetic issues, provided if they meet SmPC requirements, due to its mild/moderate LSRs and good cosmetic outcomes, although the statement was close to agreement (77%). The scientific committee pointed out that the duality of this statement, containing 2 major points (tolerability and cosmesis) might be a reason for the discrepancy, as panelists might agree with 1 point but not the other. The scientific committee also commented there should be a distinction between esthetic appearance during and after AK treatment. In the last case, all treatments improve skin appearance after administration, once LSRs are resolved. However, during treatment, the use of tirbanibulin and diclofenac might be preferred to ensure good cosmesis due to the low frequency and severity of LSRs associated with these treatments (20).

In this regard, the recent study from Li Pomi et al. shows that besides clearing AK lesions and even solar lentigo, tirbanibulin 1% improves the appearance of photoaged skin (40), and therefore it could be a suitable option for patients with esthetic issues.

Treatment added value

Generally, panelists agreed with the statements in this thematic block. A good balance between efficacy and other treatment attributes (e.g., short regimen, mild LSRs, absence of photosensitivity), the use of a single-dose sachet per day enabling precise product dosing, and the apoptosis-based mode of action were considered to be benefits. Experts underscored the importance of the statement regarding the balance between good efficacy and other attributes (94% agreement), as it summarizes all the important characteristics that an ideal treatment should offer. Patient satisfaction with the treatment should also be included.

On the other hand, experts disagreed that a high frequency and severity of LSRs can help foresee AK treatment success. This rejection goes hand in hand with the aforementioned 'no pain, no gain' concept from the block *Treatment selection*, where the scientific committee underscored the importance of patient and treatment expectations.

Study limitations

This study sheds light on the use of the different treatments for AK in clinical practice. However, it presents some limitations. Firstly, panelists participating in the study were representative of clinical practice in Spain, Italy and Germany, so it might not be possible to extrapolate the conclusions of this study to other healthcare settings or potential patients with other skin colors or racial backgrounds. Secondly, the panelist response rate of 3% might suggest a source of bias resulting from targeting more involved panelists. Thirdly, the study conducted a nonsystematic literature review, which could limit reproducibility and exclude some relevant publications. Further studies including a systematic literature review and a broader scope should be conducted.

Conclusions

This study emphasizes the crucial need for prescribing physicians to have a comprehensive understanding of the MoA of the treatments they recommend, as this knowledge is essential for anticipating tolerability outcomes. Additionally, integrating patient perspectives, particularly regarding cosmesis, is a valuable consideration when selecting an appropriate treatment. Panelists and experts further stressed the importance of incorporating additional parameters, beyond complete clearance, for a more comprehensive evaluation of treatment efficacy. Ultimately, the study highlights the necessity of balancing effective treatment outcomes with other factors, such as tolerability, shorter treatment regimens, and ensuring patient adherence and satisfaction in the management of AK. These factors are key to improving treatment compliance and, consequently, enhancing overall treatment effectiveness (14).

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Author contributions

All authors contributed to the study conception and have reviewed and validated the content of this manuscript.

Consent for publication

All authors gave their consent for the publication of this manuscript.

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