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Tirbanibulin 1% Ointment for Actinic Keratosis

Less Pain, More Gain

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The Importance of Local Tolerability and Duration of Therapy in Topical Actinic Keratosis Treatment

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Actinic keratoses (AK) are among the most common dermatologic presentations, with estimates suggesting that they account for approximately 15 percent of dermatologic diagnoses in the US.[1] Incidence of AK increases with advanced age and chronic exposure to UV radiation,[2] suggesting that dermatologists will continue to see a continuing high incidence of AKs with the ongoing graying of America.

Treatment of AKs is essential, as these pre-cancerous lesions can progress to squamous cell carcinomas.[3,4] Historically, treatment of AKs had been lesion-directed, with destructive modalities like liquid nitrogen and electrodesiccation and curettage considered mainstays of treatment just over two decades ago.[5]

Somewhat recently, our conception of AKs has shifted from a focus on individual lesions to recognition that the presence of AKs is a manifestation of field cancerization.[6] Therapeutic strategies, therefore, have evolved to emphasize the treatment of both clinically visible and subclinical lesions.[5] The notion of field-directed therapy has been facilitated by the availability of numerous topical formulations now FDA-approved for the treatment of AKs.

As noted by Rajkumar and Armstrong in the pages ahead, five different drug compounds are FDA-approved to treat AKs. Despite differences in phase 3, pivotal trial designs and outcome measures, these agents are all considered efficacious for the treatment of AKs. Similarly, as Rajkumar and Armstrong conclude, the available drugs are generally considered safe when used as directed. However, they note, there is great variability in tolerability.

Tolerability is a crucial consideration when it comes to therapy directed at field cancerization, especially that AKs are chronic and recurring lesions and require life-long treatment. Furthermore, prolonged and severe local skin reactions, especially on the face and scalp, may disrupt daily living activities, social engagements, and negatively impact the quality of life. If patients reduce the frequency or amount of drug application or cut short the duration of treatment due to poor tolerability, the effectiveness will be compromised.

The newest topical drug approved for the management of AKs, tirbanibulin, may offer distinct advantages in terms of tolerability and treatment duration, perhaps as a consequence of its unique mechanism of action. As opposed to earlier drugs that induced necrosis, tirbanibulin induces apoptosis. In clinical trials, most local skin reactions (LSRs) associated with tirbanibulin were mild to moderate, and fewer than 10% of patients reported severe LSRs.[7] Of note, no patients in the clinical trials discontinued therapy; treatment was applied once daily for five days.

Selection of an appropriate treatment for management of AKs depends on multiple factors, including but not limited to patient age, lifestyle, extent of actinic damage, and history of UV exposure. The availability of multiple safe and effective treatments provides options for dermatologists to tailor treatment to the individual needs of their patients. The best outcomes will be achieved with a patient-centric approach along with more tolerable topical treatment.[8] With recent advancements in topical treatment, including the introduction of tirbanibulin, a new chemical entity with established efficacy and favorable tolerability profile, dermatologists may yet improve patient experiences and subsequently adherence and outcomes in field-directed management of AKs.

Disclosure

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ORIGINAL ARTICLE

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Safety and Tolerability of Topical Agents for Actinic Keratosis: A Systematic Review of Phase 3 Clinical Trials

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ABSTRACT

Background: Topical agents for actinic keratosis (AK), along with cryotherapy and phototherapy, are the most commonly used therapies for areas of skin with multiple AKs. Multiple options for the topical treatment of AK exist; newer therapies aim to balance efficacy with an acceptable safety and tolerability profile for the patient.

Objective: To describe the safety and tolerability of FDA-approved topical agents for the treatment of AK.

Methods: A systematic review of phase III clinical trials of topical agents for AK available on PubMed and clinicaltrials.gov was conducted on January 10th, 2021.

Results: 29 phase III clinical trials meeting the inclusion criteria were included in the qualitative synthesis. No serious adverse events or systemic adverse events were determined to be due to topical therapies for AK. The highest rates of treatment-related application-site adverse events and local skin reactions occurred with the various formulations of topical 5-FU and imiquimod; newer topical agents such as ingenol mebutate and tirbanibulin had more favorable tolerability profiles.

Conclusions: FDA-approved topical agents for the treatment of multiple AKs have minimal safety concerns. Tolerability profiles vary among the available options, and new agents such as tirbanibulin offer a favorable combination of safety, tolerability, and efficacy.

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INTRODUCTION

Actinic keratoses (AKs) are hyperkeratotic, erythematous papules or plaques with overlying scale and rough texture found in sun-damaged areas of skin.[1] They represent a chronic and recurring manifestation of field cancerization. AKs are most commonly diagnosed in fair-skinned individuals,[2] and incidence increases with age and exposure to UV radiation.[1] An analysis of the National Ambulatory Medical Care Survey (NAMCS) data from 1993–2010 found that 14.6% of dermatologist visits included a diagnosis of AK.[3] Data pooled from several nation-wide surveys estimated the prevalence of AK in the United States to be 39.5 million in 2004.[4]

Areas of clinically sun-damaged skin are predisposed to tumorigenesis; this phenomenon is referred to as field-cancerization.[5] In areas of skin with extensive sun-damage and/or multiple AKs, topical agents may be prescribed to treat overt lesions and prevent subclinical dysplasia from progressing to AK.[5,6] AKs themselves may progress to squamous cell carcinoma (SCC); however, there are no clinical features unique to AK lesions which predict this transformation, and data regarding the rate of progression from AK to SCC are inconclusive.[7] Therefore, the common consensus is to treat all AK lesions to prevent transformation to SCC.[8] Multiple treatment modalities exist for the treatment of AK. Cryotherapy or excision may be used for individual AK lesions (lesion-directed therapy), and topicals or photodynamic therapy may be used in diffusely sun-damaged skin containing both overt and subclinical lesions (field-directed therapy).[8]

Topical agents have been used for the treatment of multiple AKs from the 1960s, beginning with the use of topical fluorouracil (5-FU). Dillaha et al in 1963 reported successful clearance of multiple AKs using a 20% 5-FU solution; however, patients also experienced severe inflammation, erosions, corneal and conjunctival irritation, and photosenstivity.[9] Milder preparations of 5-FU and new topical agents for AK, such as the antimitotic agent tirbanibulin, have maintained treatment efficacy while substantially improving tolerability.[10] The purpose of this review is to document the safety and tolerability of topical agents used for the treatment of AK.

METHODS

Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist guided this systematic review.[11] A systematic search of literature available on PubMed was conducted using the search terms ((((((("Fluorouracil"[Mesh]) OR "Imiquimod"[Mesh]) OR "3-ingenyl angelate" [Supplementary Concept]) OR "Diclofenac"[Mesh]) OR "tirbanibulin" [Supplementary Concept]) AND "Keratosis, Actinic''[Mesh]) AND "Randomized Controlled Trial" [Publication Type]. A search of clinical trials listed on clinicaltrials.gov was conducted using the search terms "Actinic Keratoses'' and was further filtered using the "Status - Completed", "Study Results - With Results'', and "Study Phase - Phase 3" options. This initial search yielded a total of 105 articles.

Selection of Studies and Data Extraction

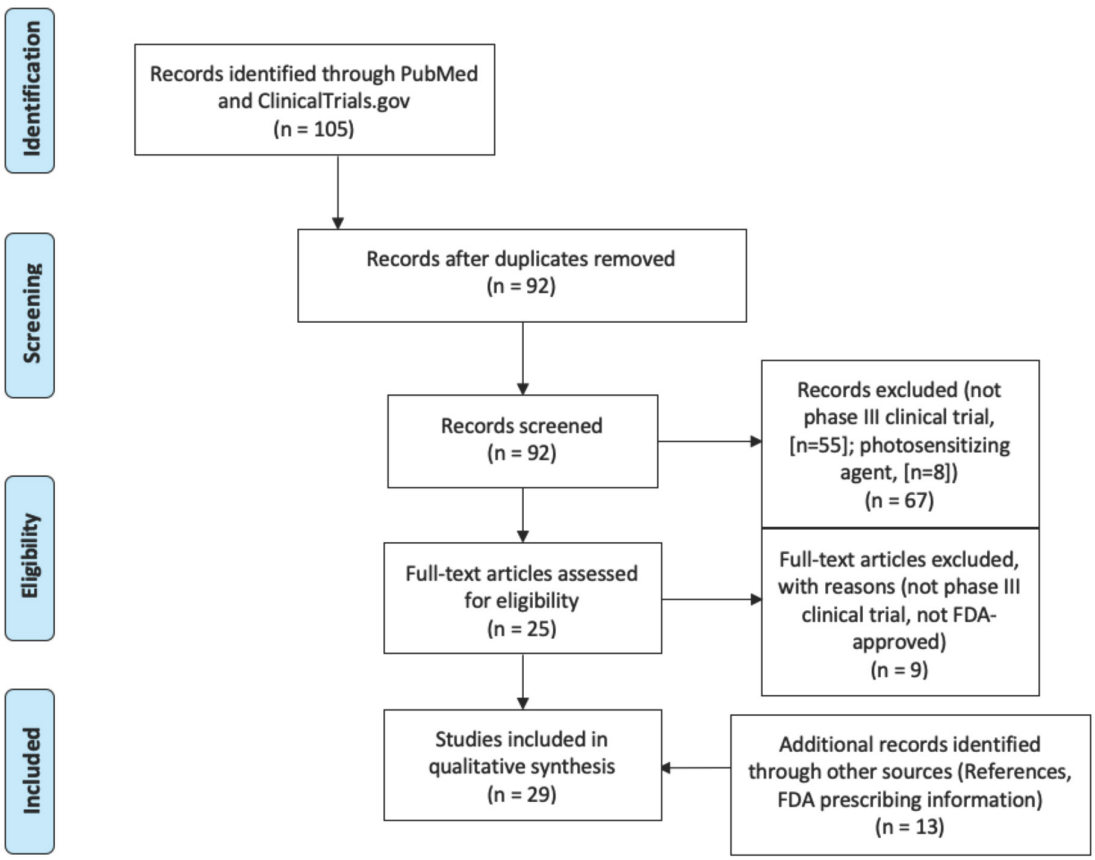
Articles were included into the review if they met the following criteria: (1) Actinic keratosis as the disease studied, (2) Topical, non-photosensitizing agent, (3) Phase III Clinical Trial, (4) Safety and Tolerability data reported. 92 abstracts were reviewed; 25 met the aforementioned criteria and were included in this review. Excluded abstracts were not phase III clinical trials (n=55) and studied topical photosensitizing agents (n=8). Full-text review of references in the 25 remaining abstracts as well as specific searches for phase III pivotal trial data in FDA prescribing information documents revealed 13 additional articles. A final full-text review excluded 9 articles, 6 of which were not phase III clinical trials, and 3 of which described a topical therapy which was not FDA-approved. A total of 29 articles were included. Safety and Tolerability data were extracted from each article included in the review and included the number of subjects, treatment and follow-up duration, and safety/tolerability event rate (Table 2).

RESULTS

5-Fluorouracil

5-fluorouracil (5-FU) is an antimetabolite pyrimidine analog which is incorporated into DNA and RNA by thymidylate synthase.[12] Topical 5-FU preparations have been used for the treatment of AK since the 1960s[9], and systematic reviews have shown it is among the most efficacious field-directed therapies for AK.[13–15] Common symptoms and local skin reactions (LSRs) associated with topical 5-FU include pain, pruritus, erythema, edema, crusting, and erosion at the application site.[12,16]

FIGURE 1. Study inclusion flow diagram.



These side effects must be tolerated by the patient, as proper adherence is necessary to maintain efficacy. Topical 5-FU is available in 0.5% (Carac), 1% (Fluoroplex), 4% (Tolak), and 5% (Efudex) formulations; lower concentrations of 5-FU aim to balance efficacy with an acceptable side effect profile.[12]

5% 5-FU (Efudex) is applied twice daily to areas of skin with multiple AKs for a duration of 2 to 4 weeks. As the most potent drug in its class, 5% 5-FU is relatively less tolerated compared to the other available formulations of 5-FU. A comparison of 4% 5-FU applied once daily to either generic 5% 5-FU applied twice daily or vehicle cream found that application site reactions such as irritation, pain, erythema, pruritus, and edema occurred in all participants in both the 4% and 5% 5-FU groups at 2 weeks and 4 weeks of treatment. However, 4% 5-FU was more tolerable, and less severe stinging, burning, crusting, and itch at the site of application was observed compared with 5% 5-FU.[16] Furthermore, 14.9% of subjects discontinued use of 5%-FU compared with 10.1% of subjects who discontinued use of 4% 5-FU.[16]

Phase III clinical trials evaluating the efficacy and safety of 0.5% 5-FU also found a similar, but more tolerable, side effect profile compared to the more potent 4% and 5% formulations. Application site erythema (93.4% of participants), dryness (83.3%), and burning (74.7%) were commonly experienced in patients applying 0.5% 5-FU for 1-, 2-, and 4-week treatment courses.[17] The majority of patients in the 1-week treatment group experienced mild LSRs, and the majority of patients in the 2- and 4-week treatment groups experienced mild-to-moderate LSRs.[17] This is in contrast to pivotal phase III trials evaluating the safety and efficacy of 4% 5-FU (Tolak), in which the proportion of patients who experienced severe erythema, dryness, and burning in a 4-week daily treatment period was 44%, 24%, and 25%, respectively (n=397).[18]

A phase III trial sought to determine if pre-treatment with cryosurgery followed by a 1-week course of either Carac cream or Cetaphil cream maintained treatment efficacy while minimizing application-site adverse effects.[19] Although patients receiving Carac reported significantly more LSRs compared to patients receiving Cetaphil, LSR severity was similar to the 1-week course of Carac cream and lower than the LSR severity observed in the 2- and 4-week courses of Carac evaluated in the pivotal phase III trials.[19–21]

Imiquimod

Imiquimod is a toll-like receptor (TLR) agonist which was first approved for the treatment of external genital and perianal warts caused by human papillomavirus (HPV); it stimulates TNF-a and IL-6 expression to leverage adaptive and immune pathways in anti-viral and anti-tumor responses. Its anti-lesional activity in AK and superficial basal cell carcinoma (sBCC) is mediated through both cytolytic and apoptoptic pathways which result in lesion destruction within the treatment field.[22] LSRs such as erythema, scabbing, crusting, dryness, erosion, ulceration, edema, vesiculation, and weeping may be experienced with topical application of imiquimod.[23] The tolerability of imiquimod, much like the other topical agents reviewed, varies directly with its potency; topical imiquimod is available in 2.5% (Zyclara 2.5%), 3.75% (Zyclara 3.75%), and 5% (Aldara) formulations.

2 phase III trials of imiquimod 5% cream applied daily twice weekly vs thrice weekly evaluated application-site AEs such as itching (20.5% vs 28.9%), burning (5.6% vs 7.4%), pain (2.3% vs 3.7%), and tenderness (1.9% vs 2.1%).[23,24] LSRs were experienced by nearly all patients in both studies, and the rates of severe LSRs followed a similar trend to the application-site AEs between twice vs thrice-weekly application in erythema (17.7% vs 33.2%) and flaking/scaling/dryness (7.4% vs 8.7%).[23,24] 4% of patients applying imiquimod 5% twice daily discontinued due to either AEs or LSRs, and 13.2% of patients in the study evaluating thrice weekly treatment discontinued.[23,24]

Application-site AEs and LSRs were evaluated in two phase III clinical trials in which imiquimod 2.5% and 3.75% cream formulations were applied daily for two 2-week or 3-week treatment cycles flanking one 2- or 3-week cycle off treatment.[25,26] 3.75% imiquimod applied in a 3-week treatment cycle was associated with the highest rates of application-site AEs (pruritus, irritation, pain, and swelling) and LSRs (erythema, edema, weeping/exudate, flaking/scaling/dryness, scabbing/crusting, and erosion/ulceration).[26] A follow-up study at 14 months included patients from both previous trials with complete lesion clearance; only one patient in the 2-week/3.75% treatment arm had a treatment-related AE (scarring in treatment area).[27]

Ingenol Mebutate

Ingenol mebutate (Picato) is a macrocyclic diterpene ester derived from *Euphorbia peplus* and was approved in the US for the treatment of AK. Its mechanism of action is two-fold; first through destabilizing mitochondrial cell membranes and increasing intracellular calcium, resulting in lesional necrosis, and second through neutrophil activation via ongoing necrosis and antibody dependent cellular cytotoxicity (ADCC). Neutrophil activation triggers an "oxidative burst" which releases reactive oxygen species (ROS) and further eliminates remaining dysplastic cells.[28] Ingenol mebutate is available in 0.015% and 0.05% formulations for treatment of AK on the face and trunk, respectively; duration of application is 3 days for the face and 2 days for the trunk. Commonly reported application-site AEs include pain and pruritus; LSRs such as erythema, scabbing, crusting, dryness, erosion, ulceration, edema, vesiculation, and weeping also may be observed.

A phase III trial conducted by Lebwohl et al of ingenol mebutate evaluated application-site AEs and LSRs following once daily application of 0.015% ingenol mebutate for 3 consecutive days for multiple AKs on the face or scalp or 0.05% ingenol mebutate for 2 consecutive days for multiple AKs on the trunk or extremities.[29] 19% of patients who applied 0.015% ingenol mebutate and 12% of patients who applied 0.05% ingenol mebutate reported any application-site AE (pruritus, pain, irritation, skin/subcutaneous tissue disorder). 6 LSRs (erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration) were assessed on a scale of 0-4 (0 representing absence of LSR, 4 representing severe LSR); the scores were subsequently summed to calculate a local skin response score (0-24) for each patient. Mean composite local skin response score (±SD) was 9.1±4.1 in patients applying 0.015% ingenol mebutate to the face/scalp on day 4 of treatment and 6.8±3.5 in patients applying 0.05% ingenol mebutate to the trunk/extremities on day 3 of treatment. On day 57, mean composite local skin response scores had fallen to levels indistinguishable from vehicle.[29]

A phase III trial evaluating the safety and efficacy of ingenol mebutate 0.027% gel applied for 3 days to lesions on the face, scalp, or chest found that treatment area could be increased (from 25cm^2 in the Lebwohl et al trials evaluating 0.015% and 0.05% ingenol mebutate) to 250cm^2 without an increase in systemic side effects.[30] 79.8% of patients reported any treatment-related AE; the mean composite LSR was 11.7 for the face and 8.8 for the scalp. Treatment withdrawal due to AEs or LSRs was less than 1 percent in each of the aforementioned treatment arms (0.015%, 0.027%, or 0.05%).[29,30]

Ingenol mebutate has been withdrawn from European Union and Canadian markets due to concerns for an increase in the risk of non-melanoma skin cancer (NMSC).[31] In October of 2020, LEO Pharma announced that Picato would cease to be manufactured in the US as well; patients may continue using Picato currently available for the treatment of AK, but alternative treatments will need to be used in the US after supply is depleted.[32]

Diclofenac Sodium

Diclofenac sodium 3% in hyaluronic acid gel (diclofenac HA; Solaraze) is a cyclooxygenase-2 (COX-2) inhibitor believed to treat AK through inhibiting tumor angiogenesis and inducing tumor apoptosis.[33] It is applied twice-daily for 60 to 90 days.[34] Application-site AEs and LSRs are similar to the other topical agents available for the treatment of AK and include irritation, inflammation, pruritus, burning, dryness, edema, and pain.[34–36]

Application-site AEs and LSRs were assessed at 30 days after treatment in a pivotal phase III trial for diclofenac HA (Solaraze) applied twice-daily for either 60 or 90 days. Application-site reactions (total) occurred in 75% of patients in the 60-day treatment arm vs 84% of patients in the 90-day treatment arm; a similar trend was observed for application-site contact dermatitis (19% vs 33%), exfoliation (6% vs 24%), pruritus (31% vs 52%), and rash (35% vs 46%). 18% of patients (77 of 470) discontinued diclofenac HA for any reason.[34]

A phase III clinical trial comparing the safety and efficacy of 0.5% 5-FU/10% salicylic acid (0.5% 5-FU/10% SA; Actikerall) to diclofenac HA or vehicle applied twice-daily until lesion clearance up to 12 weeks found that application-site AEs in the diclofenac HA treatment arm occurred at lower rates compared to Actikerall for total application-site reactions (62.7% vs 75.5%), irritation (38.4% vs 61.2%), and pruritus (38.9% vs 44.9%); application-site irritation was slightly higher in the diclofenac HA treatment arm (38.4% vs 35.7%).[35] Treatment discontinuation was similar between both treatment arms at 4.9% (9 of 185) in the diclofenac HA arm and 3.7% (7 of 189) in the Actikerall arm.[35]

Tirbanibulin

Tirbanibulin (Klisyri) is a tubulin polymerization and Src kinase signaling inhibitor. As an anti-mitotic agent, tirbanibulin reversibly binds tubulin, arresting the cell cycle in G2/M phase in rapidly dividing cells.[37] Tirbanibulin also inhibits Src kinase signaling known to be upregulated in AK and invasive SCC and increase p53 expression with subsequent induction of apoptosis.[38] Tirbanibulin 1% ointment is currently available for treatment of AK of the face or scalp for once daily application over a 5-day treatment course. The reversible tubulin-binding effects of tirbanibulin may contribute to its favorable tolerability compared to other topical agents for treatment of AK; nevertheless, application-site AEs and LSRs are experienced with its use. Application-site AEs and LSRs assessed in phase III clinical trials included application-site pruritus, pain, erythema, flaking, scaling, crusting, swelling, vesiculation, pustulation, erosion, and ulceration.

Two simultaneous phase III clinical trials involving 702 patients were conducted to determine the safety and efficacy of tirbanibulin 1% ointment for treatment of AK on the face and scalp.[10] Application-site pruritus and pain were experienced by 9% and 10% of participants, respectively. Most LSRs were mild-to moderate, and severe LSRs were reported in less than 10% of patients. Total and severe LSR rates observed included erythema (90.9%; 6% severe), flaking/scaling (81.9%, 9%), crusting (46.5%, 2%), swelling (38.5%, 1%), vesiculation/pustulation (8.2%, 1%), and erosion/ulceration (11.6%, 0%). All LSRs resolved spontaneously without treatment or intervention. No patients discontinued the use of tirbanibulin due to treatment-related AEs.[10]

DISCUSSION

In addition to efficacy, tolerability is important to consider when choosing a therapy for multiple AKs or clinical evidence of field cancerization. Foley et al found common reasons for non-adherence or non-persistence to topical regimens to be length of treatment, local skin reaction severity and duration, and uncertainty regarding the treatment regimen.[39] For example, topical preparations of 5-FU, especially in the potent 5% formulation, traditionally have carried unfavorable tolerability profiles; 14.9% of patients discontinued 5% 5-FU cream when applied twice daily for 4 weeks.[16] Other topical agents with harsher tolerability profiles, such as 5% imiquimod applied daily 3 times per week for 16 weeks, saw 13.2% of participants discontinue therapy in the treatment group.[24] This is in contrast to patients in the treatment arm of phase III studies evaluating safety/efficacy of tirbanibulin 1%, in which no patients discontinued due to treatment-related adverse events.[10] The severity of local skin reactions and duration of treatment matched discontinuation data as well: severe erythema, scabbing/crusting, and flaking/scaling/dryness were experienced in 33.2%, 27.4%, and 8.7% of patients in the 5% imiquimod study, respectively, versus 6%, 2%, and 9% in the tirbanibulin 1% study.[10,24] Additionally, compared to the months-long duration of treatment for imiquimod, tirbanibulin only requires once daily application for 5 days, limiting both the duration of potential local skin reactions and increasing ease of use.

TABLE 1.

Indications and Instructions for Use		
Topical Agent	**Approved Indication(s)**	**Instructions for Use**
5% 5-FU cream (Efudex)	Topical treatment of actinic keratoses	For AK: apply twice daily for 2 to 4 weeks until erosions appear in AK lesions
	Topical treatment of superficial basal cell carcinoma	For sBCC: apply 5% cream twice daily for at least 3 to 6 weeks and up to 10 to 12 weeks until lesions are completely cleared
0.5% 5-FU cream (Carac)	Topical treatment of multiple actinic keratoses of the face or scalp	Thin film applied once daily to areas of the skin with actinic keratoses lesions up to 4 weeks
Imiquimod 5% cream (Aldara)	Actinic keratoses of the face or scalp in immunocompetent individuals	For AK: twice per week for 16 weeks
	Biopsy-confirmed superficial basal cell carcinoma <2.0cm in diameter on trunk, neck, or extremities (excluding hands or feet) only when deemed more appropriate than surgical treatment and follow-up is arranged	For sBCC: 5 times per week for 6 weeks
	External genital warts/perianal warts/condyloma acuminata in patients >12 years old	For external genital and perianal warts/condyloma acuminata: 3 times per week until complete clearance, up to 16 weeks
Imiquimod 3.75% cream (Zyclara 3.75%)	Actinic keratoses of the face or scalp in immunocompetent adults	For AK: once daily to affected areas of the face or balding scalp for two 2-week treatment cycles with one 2-week cycle of no treatment in between
	External genital warts/perianal warts/condyloma acuminata in patients >12 years old	For external genital and perianal warts/condyloma acuminata: once daily until complete clearance, up to 8 weeks
Imiquimod 2.5% cream (Zyclara 2.5%)	Actinic keratoses of the face or scalp in immunocompetent adults	Apply once daily to affected areas of the face or balding scalp for two 2-week treatment cycles with one 2-week cycle of no treatment in between
Ingenol mebutate 0.05% gel (Picato 0.05%)	Actinic keratoses of the trunk or extremities	Apply to areas of skin with AK once daily for 2 days
Ingenol mebutate 0.015% gel (Picato 0.015%)	Actinic keratoses of the face or scalp	Apply to areas of skin with AK once daily for 3 days
Diclofenac sodium 3% gel (Solaraze)	Topical treatment of actinic keratoses	Apply to areas of skin with AK lesions twice daily for 60 to 90 days
Tirbanibulin 1% ointment (Klisyri)	Topical treatment of actinic keratoses of the face or scalp	Apply 1 dose packet to affected areas of the face or scalp for 5 consecutive days

TABLE 2.

Results/Findings			
Drug/Study/Year	**n**	**Dosing and Treatment Duration**	**Safety/Tolerability Event Rate**
5-FU			
Dohil 2016	841	4% 5-FU cream qd vs 5% 5-FU cream bid OR vehicles (qd/bid) for 4 weeks Follow-up at 8 weeks	5% 5-FU adverse events: application site irritation (60%) 5% 5-FU discontinuation due to adverse events: 14.9% (51 of 342)
NCT02616601	422	Carac (fluorouracil) 0.5% cream vs generic 5-FU 0.5% cream OR vehicle qd for 2 weeks Follow-up at 6 weeks	Carac vs generic 5-FU 0.5% cream adverse events: application-site dermatitis (0.71% vs 0%), erythema (0.71% vs 0%), pain (1.43% vs 0%), pruritus (0.71% vs 0%)
Gupta 2001 Carac FDA Label Jorizzo 2002 Weiss 2002	384	Pooled data from two phase III clinical trials: Carac vs vehicle once daily for 1 weeks, 2 weeks, or 4 weeks Follow-up 4 weeks after last treatment	LSRs (n=257; All durations): erythema (93.4%); dryness (83.3%), burning (74.7%), erosion (44.0%), pain (43.6%), edema (35.4%) Eye irritation (5.4%) Mean severity of LSRs:mild-to-moderate for 1 week treatment duration; moderate for 2 week/4 week treatment duration 0.5% 5-FU discontinuation due to AEs/LSRs: 12% (31 of 257)
Hoover 2014	60	Cryosurgery followed by 5-FU cream 0.5% or vehicle qd for 1 week Follow-up at 26 weeks	Mean Tolerability Assessment Scores 5-FU 0.5% cream (0-3, where 0 is absent and 3 is severe): dryness (2.0), erosion (1.0), fissuring (0.2), redness (0.4), ulceration (0.03) Discontinuation due to AEs/LSRs: 0% (0 of 60)
Imiquimod			
Lebwohl 2004	436	Imiquimod 5% cream qd 2 times per week for 16 weeks Follow-up at 24 weeks	AEs at application site: total (33%); itching (20.5%); burning (5.6%); bleeding (3.3%); stinging (2.8%); induration (2.3%); pain (2.3%); tenderness (1.9%) Severe LSRs: erythema (17.7%); scabbing/crusting (8.4%); flaking/scaling/dryness (7.4%); erosion/ulceration (2.3%); edema (0%); vesicles (0%); weeping/exudate (0%) Discontinuation due to AEs: 3% (7 of 215) Discontinuation due to severe LSRs: 1% (2 of 215)
Korman 2005	492	Imiquimod 5% cream qd 3 times per week for 16 weeks Follow-up at 24 weeks	Imiquimod 5% application-site reactions: total (38.8%); itching (28.9%); burning (7.4%); pain (3.7%); tenderness (2.1%); infection (1.7%); stinging (1.2%) Imiquimod 5% LSRs (total, severe): erythema (98.3%, 33.2%); flaking/scaling/dryness (94.6%, 8.7%); scabbing/crusting (86.7%, 27.4%) Discontinuation in imiquimod treatment group: 13.2% (32 of 242)
Swanson 2010	479	Imiquimod 3.75% qd OR Imiquimod 2.5% cream qd OR placebo qd for two 2-week treatment cycles Follow-up at 14 weeks	Application-site reactions imiquimod 3.75%: any (10.6%); pruritus (4.4%); irritation (3.1%); pain (3.1%); swelling (1.3%) Application-site reactions imiquimod 2.5%: any (6.3%); pruritus (3.8%); irritation (2.5%); pain (1.3%); swelling (0%) Severe LSRs imiquimod 3.75%: any (33.8%); erythema (25.2%); edema (5.7%); weeping/exudate (5.7%); flaking/scaling/dryness (8.2%); scabbing/crusting (13.8%); erosion/ulceration (10.7%) Severe LSRs imiquimod 2.5%: any (20.6%); erythema (14.4%); edema (3.8%); weeping/exudate (1.3%); flaking/scaling/dryness (4.4%); scabbing/crusting (9.4%); erosion/ulceration (9.4%) Discontinuation imiquimod 3.75%; 2.5%: 1.25% (2 of 160); 0.63% (1 of 160)

TABLE 2. (CONTINUED)

Results/Findings			
Drug/Study/Year	**n**	**Dosing and Treatment Duration**	**Safety/Tolerability Event Rate**
Imiquimod			
Hanke 2010	490	Imiquimod 3.75% cream qd OR Imiquimod 2.5% cream qd OR placebo qd for two 3-week treatment cycles Follow-up at 17 weeks	Application-site reactions imiquimod 3.75%: any (24.1%); pruitus (9.3%); pain (9.3%); irritation (5.6%); bleeding (3.1%) Application-site reactions imiquimod 2.5%: any (17.1%); pruritus (7.3%); pain (6.7%); irritation (3.7%); bleeding (1.2%) Severe LSRs imiquimod 3.75%: any (54.9); erythema (44.7%); edema (13.0%); weeping/exudate (9.9%); flaking/scaling/dryness (13.0%); scabbing/crusting (34.8%); erosion/ulceration (30.4%) Severe LSRs imiquimod 2.5%: any (41.5%); erythema (28.2%); edema (7.4%); weeping/exudate (7.4%); flaking/scaling/dryness (11.0%); scabbing/crusting (22.7%); erosion/ulceration (23.9%) Discontinuation imiquimod 3.75%; 2.5%: 2.5% (4 of 162); 1.2% (2 of 164)
Hanke 2011	179	Imiquimod 3.75% OR Imiquimod 2.5% cream OR placebo after two 2-week (qd) treatment cycles OR two 3-week (qd) treatment cycles Follow-up at 14 months for patients with complete clearance after treatment	Adverse events related to imiquimod 3.75% cream, 2-week cycles: 4.8% (2 of 57) Adverse events related to imiquimod 2.5% cream, 2-week cycles: 12.8% (5 of 49) Adverse events related to imiquimod 3.75% cream, 3-week cycles: 10.4% (5 of 55) Adverse events related to imiquimod 2.5% cream, 3-week cycles: 0% (0 of 41)
NCT02120898	467	Generic Imiquimod 2.5% cream qd OR Zyclara (imiquimod) 2.5% cream qd OR placebo cream qd for two 2-week treatment cycles Follow-up at 14 weeks	AEs in treatment area (unspecified), generic Imiquimod 2.5%: 3.7% (7 of 187) AEs in treatment area (unspecified), Zyclara 2.5%: 2.7% (5 of 187) LSRs (severity unspecified) generic Imiquimod 2.5%: erythema (17.6%); flaking/scaling/dryness (17.1%); scabbing/crusting (11.8%); pruritus (6.4%); erosion/ulceration (1.6%); pain (1.1%); edema (1.1%); weeping/exudate (0.5%) LSRs (severity unspecified) Zyclara 2.5%: erythema (16.0%); flaking/scaling/dryness (15.5%); scabbing/crusting (7.0%); pruritus (2.7%); erosion/ulceration (1.1%); pain (1.1%); edema (1.1%); weeping/exudate (0.5%) Discontinuation generic imiquimod 2.5%; Zyclara 2.5%: 2.1% (4 of 187); 1.1% (2 of 187)
NCT01686152	589	Imiquimod cream, 3.75% (Teva) qd OR Zyclara (imiquimod) 3.75% cream qd OR placebo cream qd for two 2-week treatment cycles Follow-up at 14 weeks	AEs in application site, Imiquimod 3.75% (Teva): dermatitis (0.81%); erythema (0.40%); hemorrhage (0.40%); pain (0.81%); pruritus (0%); reaction (0%) AEs in application site, Zyclara 3.75%: dermatitis (0%); erythema (0%); hemorrhage (0%); pain (1.61%); pruritus (0.80%); reaction (0.80%) Discontinuation Imiquimod 3.75% (Teva); Zyclara 3.75%: 4.4% (11 of 252); 4.4% (11 of 252)
NCT00948428	462	Generic Imiquimod 5% cream OR Aldara (imiquimod) 5% cream OR vehicle cream applied twice weekly for 16 weeks Follow-up at 24 weeks	Application-site reactions generic imiquimod 5% cream: alopecia (0%); discomfort (1.1%); pruritus (0%); reaction (0.55%) Application-site reactions Aldara (imiquimod) 5% cream: alopecia (0.56%); discomfort (0.56%); pruritus (0.56%); reaction (0%) Discontinuation generic imiquimod 5%; Aldara: 3.2% (6 of 185); 6.5% (12 of 185)
Jorizzo 2010	247	Cryosurgery followed by imiquimod 3.75% cream qd or placebo cream qd for two 2-week treatment cycles Follow-up at 26 weeks	Treatment-related AEs cryo/imiquimod 3.75% cream: any (27.8%); pruritus (9.5%); irritation (5.6%); pain (4.8%) Any grade LSRs cryo/imiquimod 3.75% cream above 0: 99.2% (125 of 126) Severe LSRs cryo/imiquimod 3.75%: any (34.9%); erythema (28.6%); scabbing/crusting (12.7%); flaking/scaling/dryness (7.1%); weeping/exudate (3.2%); edema (1.6%); erosion/ulceration (1.6%) Discontinuation cryo/imiquimod 3.75% cream: 3.2% (4 of 126)

TABLE 2. (CONTINUED)

Results/Findings			
Drug/Study/ Year	**n**	**Dosing and Treatment Duration**	**Safety/Tolerability Event Rate**
Ingenol mebutate			
Lebwohl 2012	1005	Ingenol mebutate 0.015% gel qd for face/scalp OR vehicle gel qd for 3 consecutive days AND ingenol mebutate 0.05% gel qd for trunk/extremities OR vehicle gel qd for 2 consecutive days with safety and efficacy assessed at 57 days Follow-up at 12 months for patients with complete clearance	Ingenol mebutate 0.015% gel (face/scalp): any administration-site condition (19%), application-site pruritus (8.0%), application-site pain (13.9%), application-site irritation (1.8%), skin or subcutaneous tissue disorder (4.0%) Ingenol mebutate 0.05% gel (trunk/extremities): Any administration-site condition (12.0%), application-site pruritus (8.4%), application-site pain (2.2%), application-site irritation (3.6%), skin or subcutaneous tissue disorder (4.4%) Mean composite local-skin-response score ingenol mebutate 0.015% gel (face/scalp): 9.1±4.1 Mean composite local-skin-response score ingenol mebutate 0.05% gel (trunk/extremities): 6.8±3.5 Discontinued due to AEs: ingenol mebutate 0.015% (0.36%); ingenol mebutate 0.05% (0.89%)
Berman 2014	329	Cryosurgery followed by ingenol mebutate 0.015% gel or placebo qd for 3 consecutive days for 11 weeks Follow-up at 12 months	Cryo/IngMeb 0.015% application-site reactions: discoloration (0%); induration (0.60%); pain (4.19%); pruritus (2.40%); swelling (0.60%) Cryo/IngMeb 0.015% mean composite local-skin-response score, mean (SD): 8.5 (4.7) Cryo/IngMeb 0.015% discontinued due to AE: 0.60% (1 of 167)
Pellacani 2015	199	Simultaneous (both at week 0) or sequential (at weeks 0 and 8) treatment of AK lesions on the face/scalp and trunk/extremities with ingenol mebutate 0.015% gel qd for 3 consecutive days/ ingenol mebutate 0.05% gel qd for 2 consecutive days Follow-up at 16 weeks	Simultaneous vs sequential treatment AEs: treatment-related AEs (18.8% vs 7.1%), AEs within treated areas (14.9% vs 4.1%), application-site pruritus (7.9% vs 0%), application-site pain (5.0% vs 0%). Simultaneous vs sequential treatment mean composite LSR scores 3 days post-treatment: (10.4 vs 9.7) Simultaneous vs sequential treatment AEs leading to withdrawal: 2.0% (2 of 101) vs 1.0% (1 of 98)
Garbe 2016	450	Ingenol mebutate 0.015% gel for face/scalp qd for 3 consecutive days at initial treatment followed by ingenol mebutate 0.015% gel OR vehicle qd for 3 consecutive days for recurrent lesions in previously treated fields Follow-up at 12 months	First treatment cycle adverse effects: application-site pain (13.5%), application-site pruritus (4.4%), headache (4.0%), eyelid edema (3.8%), periorbital edema (3.3%); SAEs in treatment field (# of events): SCC (1), BCC (4), KA (1) First treatment cycle withdrawal due to AEs: 2% (9 of 450) Second treatment cycle adverse effects: application-site pain (11.2%), application-site pruritus (5.2%); SAEs in treatment field (# of events): basosquamous carcinoma (1)
Hanke 2020	729	Ingenol mebutate 0.027% gel or vehicle once daily for 3 days Follow-up at 8 weeks and 12 months	IngMeb 0.027% gel, 8-week follow-up AEs: any treatment-related AE (79.8%); application-site pain (63.8%), application-site pruritus (37.0%), application-site discomfort (5.1%), application-site paresthesia (2.6%), headache (4.0%), eyelid edema (2.6%) IngMeb 0.027% gel, mean composite LSR (day 4 - peak): face 11.7; scalp 8.8 IngMeb 0.027% gel discontinuation due to treatment AEs: 0%
NCT03200912	507	Picato (ingenol mebutate) 0.015% gel vs generic ingenol mebutate 0.015% gel OR vehicle gel qd for 3 consecutive days Follow-up at 57 days	Picato (ingenol mebutate) 0.015% gel adverse effects: application-site erythema (0.59%), application-site inflammation (0.59%), application-site pain (3.53%), application-site pruritus (1.76%), application-site swelling (0.00%) Generic ingenol mebutate 0.015% gel adverse effects: application-site erythema (0%), application-site inflammation (0%), application-site pain (3.55%), application-site pruritus (1.18%), application-site swelling (0.59%) Discontinued due to AE, Picato 0.015% gel vs generic IngMeb 0.015% gel: 0% vs 1.76% (3 of 170)

TABLE 2. (CONTINUED)

Results/Findings			
Drug/Study/Year	**n**	**Dosing and Treatment Duration**	**Safety/Tolerability Event Rate**
Diclofenac sodium			
Stockfleth 2011	470	0.5% 5-FU/SA 10% vs diclofenac 3% in HA OR vehicle bid until lesion clearance up to 12 weeks Follow-up at 20 weeks	Diclofenac HA adverse events: application-site reactions, total (62.7%), application-site irritation (38.4%), application-site inflammation (38.4%), application-site pruritus (38.9%) Diclofenac HA general disorders/application-site reactions of severe intensity: 11.9% Diclofenac HA discontinuation due to AEs: 4.9% (9 of 185)
Stockfleth 2012	470	0.5% 5-FU/SA 10% qd vs diclofenac 3% in HA bid OR vehicle qd for up to 12 weeks Follow-up at 12 months	Diclofenac 3% in HA adverse events at week 6: application-site inflammation (28.9%), application-site burning (25.0%) At EOT (week 12): application-site inflammation (21.7%), application-site burning (16.6%) Diclofenac 3% HA discontinuation due to AEs: 0.54% (1 of 185)
NCT02952898	665	GDC 695 vs diclofenac sodium gel, 3% OR vehicle gel applied topically as directed Follow-up at 90 days	Diclofenac sodium gel, 3% adverse events: application-site erythema (1.36%), application-site edema (0.91%), application-site pain (0.45%), application-site pruritus (0%) Diclofenac sodium gel, 3% discontinuation due to AEs: 3.62% (8 of 221)
NCT01962987	476	Diclofenac sodium gel 3% (Actavis) vs Solaraze (diclofenac sodium gel 3%) or placebo bid for 60 days Follow-up at 90 days	Actavis vs Solaraze adverse events: application-site burn (0.53% vs 0%), dermatitis (3.19% vs 1.59%), dryness (0.53% vs 0%), exfoliation (0% vs 1.59%), hemorrhage (0% vs 0.53%), irritation (0.53% vs 0%), pain (1.06% vs 0.53%), pruritus (1.06% vs 1.06%), rash (0.53% vs 0%), reaction (0.53% vs 0.53%), scab (0.53% vs 0%), swelling (0% vs 1.59%), urticaria (0% vs 0.53%), vesicles (0% vs 0.53%) Actavis vs Solaraze, discontinuation (any reason): 15.9% (30 of 190) vs 14.7% (28 of 191)
Solaraze FDA label	427	Solaraze (diclofenac sodium) 3% gel vs vehicle bid for either 60 days or 90 days Follow-up at 30 days post-treatment (90 days or 120 days)	Solaraze 60-day treatment adverse events: application-site reaction, total (75%), application-site acne (0%), alopecia (2%), contact dermatitis (19%), dry skin (27%), edema (4%), exfoliation (6%), hyperesthesia (0%), pain (15%), paresthesia (8%), photosensitivity reaction (0%), pruritus (31%), rash (35%), vesiculobullous rash (0%) Solaraze 90-day treatment adverse events: application-site reaction, total (84%), application-site acne (1%), alopecia (1%), contact dermatitis (33%), dry skin (25%), edema (3%), exfoliation (24%), hyperesthesia (3%), pain (26%), paresthesia (20%), photosensitivity reaction (3%), pruritus (52%), rash (46%), vesiculobullous rash (4%) Solaraze discontinuation (any reason): 18%
Tirbanibulin (Klisyri)			
Blauvelt 2021	702	KX2-391 Ointment 1% (Tirbanibulin [Klisyrii]) vs placebo qd for 5 consecutive days Follow-up at 57 days; follow-up at 12m for patients with complete clearance at 57 days	Adverse events: Application-site pruritus (9%), application-site pain (10%) LSRs (total, severe): erythema (90.9%, 6%), flaking/scaling (81.9%, 9%), crusting (46.5%, 2%), swelling (38.5%, 1%), vesiculation/pustulation (8.2%, 1%), erosion/ulceration (11.6%, 0%) Klisyri discontinuation due to treatment AEs: 0%

Guidelines for the treatment of AK published in 2016 by Werner et al based on available safety and efficacy data strongly recommend topical agents which combine safety, tolerability, and efficacy. Topical 0.5% 5-FU, 3.75% imiquimod, and 0.015% or 0.05% ingenol mebutate were more strongly recommended compared to topical agents such as diclofenac 3% in 2.5% HA gel, 5% 5-FU, 0.5% 5-FU/10% SA (Actikerall), 5% imiquimod, and 2.5% imiquimod.[8] Components of safety used to determine the strength of the recommendations included 'skin irritation', 'withdrawal due to adverse events', and patient satisfaction with treatment. At the time the Werner et al review was published, clinical trials of tirbanibulin had yet to be conducted; however, this topical agent also combines safety, tolerability, and efficacy like the aforementioned strongly recommended agents. Updated guidelines for the care of AK were published by the American Academy of Dermatology in 2021 and corroborated the recommendations by Werner et al; these guidelines also did not include recommendations regarding tirbanibulin as it had yet to be approved for use by the FDA.[40] The data analyzed in this systematic review supports the findings in the Werner et al and AAD guidelines; topical agents with the greatest strength of recommendation balance efficacy with a more acceptable safety and tolerability profile.[8,40]

A systematic review of patient-reported outcomes (PROs) regarding topical, field-directed therapies for AK published in 2021 (tirbanibulin was not available at the time of review), found that ingenol mebutate was among the most favorably rated treatments.[41] Ingenol mebutate was rated higher compared to other topical agents reviewed in the report such as 5-FU, diclofenac sodium, and imiquimod due to its short treatment duration and lack of prolonged LSRs. The authors acknowledge that PROs are an important metric to use when selecting a topical agent for AK, as adherence may be limited by poor tolerability or an inconvenient dosing schedule.[41]

More favorable safety and tolerability profiles for certain topical agents may also be explained by each agent's mechanism of action. 5-FU metabolites interfere with DNA and RNA synthesis and repair, resulting in DNA strand breaks, alterations in RNA expression, and ultimately cell death.[42] 5-FU also may increase p53 expression, leading to increased apoptosis in dysplastic cells within the treatment field. Markers of epidermal injury, such as keratin 16, and proinflammatory cytokines, such as interleukin 1B, also are observed to be elevated following topical treatment with 5-FU.[42] The resulting necrosis induced by 5-FU may increase local inflammation within the treatment field. Combined with twice daily application for a duration between 2 and 4 weeks, this may result in severe local skin reactions lasting for an extended time period, ultimately proving less tolerable for patients. Alternatively, newer agents, such as tirbanibulin, have mechanisms of action that result in more favorable tolerability profiles. Tirbanibulin inhibits tubulin polymerization and disrupts the proto-oncogene SrC, slowing rapid cell division.[38,43] The tubulin-binding exhibited by tirbanibulin was shown to be reversible, with no residual cellular toxicity 5 days after application in vitro.[37] Tirbanibulin also increases p53 signaling, arrests cells in the G2-M transition, and induces apoptosis.[10,38] As tirbanibulin primarily clears AK lesions through apoptosis, rather than necrosis, inflammation within the treatment field is limited.[33] As such, only mild LSRs were observed in phase III clinical trials and treatment-related adverse events, such as pain and pruritus, were limited.[10] Combined with a short duration of treatment, tirbanibulin provides an ideal combination of efficacy and tolerability within a topical agent.

Topical agents are important to consider when treating patients who present with multiple AKs; however, adherence to older topical agents may be limited by unfavorable tolerability profiles. Visible skin reactions, especially in the face and scalp prolonged patient discomfort may interfere with daily living activities and social engagements, hence negative impact on quality of life. An ideal topical agent for the treatment of multiple AKs combines efficacy, safety, and tolerability with a short duration of treatment. Clinical trials reviewed in both this systematic review as well as PRO data show that the tolerability of topical agents is strongly associated with adherence to treatment.[16,24,41] Newer topicals agents available for use are able to better balance efficacy, safety, and tolerability to improve adherence and, ultimately, better real-world effectiveness.

DISCLOSURES

LHK has served either as a consultant, speaker, investigator, or an advisory board member for Almirall, Leo Pharma, and Ortho Dermatologics.

AWA has served as a research investigator and/or scientific advisor to AbbVie, ASLAN, BI, BMS, EPI, Incyte, Leo, UCB, Janssen, Lilly, Novartis, Ortho Dermatologics, Sun, Dermavant, Dermira, Sanofi, Regeneron, Pfizer, and Modmed.

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