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The New Landscape of Field Cancerization: Proven efficacy without severe skin reactions

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The New Landscape of Field Cancerization: Proven efficacy without severe skin reactions

EDITORIAL

ORIGINAL ARTICLES

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VEHICLE MATTERS

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Actinic keratosis (AK) is a precancerous lesion that occurs with greatest frequency in individuals aged 60 or older and in men. Given the role of chronic UV exposure in engendering these lesions, they are more commonly found on sun-exposed areas such as the face, ears, scalp, hands, and arms. AKs have the potential to resolve spontaneously but also to advance to squamous cell carcinoma (SCC), thus requiring treatment.[1]

The notion of field cancerization that emerged in the second half of the last century has been applied to AK; chronic UV radiation and associated locally-mediated genetic aberrations in a given area promote the formation of multifocal AKs, SCC in situ, and SCC.[2] Through both clinical visualization and imaging analysis, it has been shown that AKs of various stages can coexist within the cancerized field, including pre-clinical, early, and advanced AK lesions and SCC.[3] Whereas treatments such as cryosurgery and other physical modalities of destruction can be highly effective for individual AK lesions, these lesion-directed treatments will not resolve adjacent clinical or preclinical lesions. As such, there has been a shift toward field-directed therapies, such as photodynamic therapy (PDT), imiquimod, 5-fluorouracil, diclofenac sodium, and, most recently, tirbanibulin. Many topical AK therapies are associated with significant local inflammatory response that may interrupt or prevent treatment.[1]

Tirbanibulin, as explored in the pages ahead, represents a unique option among the available topical AK treatments, with a targeted mechanism of action and a favorable tolerability profile. This agent inhibits microtubules and provides antiproliferative and pro-apoptotic effects. There is also evidence that tirbanibulin may interfere with Src kinase signaling.[4]

In the two phase 3 trials to support initial approval, 49% of those receiving active treatment achieved complete clearance of targeted AKs, compared to 9% of controls. Additionally, 72% of those receiving tirbanibulin had at least a 75% reduction in the number of AK lesions compared to 18% for vehicle.[5] Notable efficacy was seen in the phase 3 trials to support the 100 cm^2 indication. The mean percentage reduction in lesion counts from baseline was 22.3% on Day 5, 28.1% on Day 8, 50.5% on Day 15, 69.6% on Day 29, and 77.8% on Day 57.[6] Across studies, the most common local adverse side effects were pruritus and pain, and most reported adverse events were moderate or mild in severity.[4,5]

Topical tirbanibulin ointment was initially approved for treatment of areas up to 25 cm^2 and has more recently been approved for areas up to 100 cm^2 – a true field-directed approach. Tirbanibulin 1% ointment requires once-daily application for five consecutive days, offering a significantly shorter treatment duration compared to other topical agents. This short treatment course has the potential to promote patient adherence.

From a practical standpoint, the product is provided in pre-measured sachets of 250 mg or 350 mg (to cover up to 100 cm^2) to simplify dosing and patient convenience.

Current understanding of the pathogenesis of AK supports widespread adoption of field-directed treatment for these precancerous lesions for a significant proportion of patients. With its efficacy, tolerability, and convenient short course of treatment, tirbanibulin ointment 1% is a welcome addition to our armamentarium of AK treatments.

Of course, we can not ignore the favorable ointment formulation since "Vehicle Matters"

DISCLOSURES

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Tirbanibulin 1% Ointment: Clinical Trial and Real-World Evidence on Efficacy, Tolerability, Safety, and Patient-Reported Outcomes

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ABSTRACT

Actinic keratosis (AK) is a skin lesion that arises due to chronic sun exposure. Treatment of all AKs is recommended due to their risk of progressing to squamous cell carcinomas (SCCs). Many field-directed treatments for AKs involve burdensome treatment duration and frequency, compromising treatment compliance. Tirbanibulin 1% ointment is a first-in-class microtubule inhibitor that treats AKs by inhibiting Src kinase signaling and inducing pro-apoptotic effects. It is an approved treatment for field-directed therapy of AKs, administered once daily for 5 consecutive days. In addition to its convenience of use, tirbanibulin 1% ointment has demonstrated efficacy and safety in phases 1 to 3 clinical trials and favorable clinical outcomes in real-world clinical studies. This paper summarizes the comprehensive evidence from clinical trials and global clinical studies to guide clinical consideration of tirbanibulin 1% ointment in AK management.

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INTRODUCTION

Actinic keratosis (AK) is a common skin lesion that develops due to long-term sun exposure. AKs are estimated to affect 14% of the global population.[1] Factors that increase the risk of developing AKs include male sex, older age, lighter skin color, red hair, and immunocompromise.[2] Clinically, AKs present as poorly demarcated, scaly areas with variable keratosis that may cause symptomatic or cosmetic discomfort.[3] However, the primary clinical significance of AKs is their potential for malignancy. AKs are characterized by atypia of keratinocytes,[3] and untreated lesions can progress to squamous cell carcinomas (SCCs) at a rate of 0.025% to 16% per year.[4] Therefore, treatment of all AKs is recommended.[2]

AK therapies can be categorized as lesion- or field-directed. Lesion-directed therapies target singular AK lesions for individuals with low disease burden and include cryotherapy and excisions.[3] In contrast, field-directed therapies target larger areas with multiple AKs and subclinical lesions for individuals with high disease burden. Field-directed therapies include photodynamic therapy and topical treatments such as imiquimod, 5-fluorouracil, and diclofenac sodium.[3] Although various field-directed therapies exist, they are often associated with prolonged treatment duration (ie, 12 or 16 weeks), frequent use (ie, twice daily), and prolonged inflammation.[2] These barriers limit patient adherence to many field-directed therapies.

Tirbanibulin 1% ointment is a field-directed therapy for AKs that gained initial approval from the United States Food and Drug Administration (FDA) in 2020.[5] Tirbanibulin inhibits microtubules and blocks Src kinase signaling, resulting in antiproliferative and proapoptotic effects.[6,7] Compared to other field-directed therapies, tirbanibulin is administered with lower frequency and treatment duration, with once-daily application for 5 consecutive days over a treatment area of up to 25 cm^2.[5] Additionally, tirbanibulin has been investigated and approved by the FDA in 2024 for larger treatment areas of up to 100 cm^2.[8] In this paper, we aim to review the efficacy, safety, tolerability, and clinical outcomes of tirbanibulin 1% ointment from clinical trials and real-world clinical studies.

Phase 1 and 2 Trials

A phase 1 trial assessed the safety and efficacy of tirbanibulin 1% ointment for AKs on the dorsal forearm across 4 different cohorts.[6] The cohorts varied in treatment dosage (50 vs 200 mg/day), treatment duration (3 vs 5 days), and surface area of application (25 vs 100 cm^2). Patients with 4 to 8 AK lesions received treatment over an area of 25 cm^2, whereas patients with 8 to 16 AK lesions received treatment over an area of 100

cm². On day 45, results showed the highest rate of complete clearance of AK lesions in patients using 50 mg/day for 5 days over a treatment area of 25 cm² (50%, N=4/8), followed by patients using 50 mg/day for 3 days over a treatment area of 25 cm² (25%, N=1/4).[6] Local skin reactions (LSR) included mild-to-moderate erythema and flaking/scaling that appeared on day 4, peaked between days 5 and 8, and spontaneously resolved within 2 weeks.[6] Adverse events (AEs) were limited to application site pruritus and pain.[6]

A phase 2 trial assessed the safety and efficacy of tirbanibulin 1% ointment for AKs on the face and scalp across 2 different cohorts.[6] Both cohorts used tirbanibulin 1% ointment 50 mg/day over an area of 25 cm², but the cohorts varied in treatment duration (3 vs 5 days). On day 57, patients in the 5-day cohort had a higher rate of complete clearance (43%, N=36/84) than the 3-day cohort (32%, N=27/84). LSRs primarily involved minimal/mild erythema and flaking/scaling, with few patients experiencing mild erosions/ulcerations or vesiculation/pustulation.[6] LSRs appeared on day 2, peaked at the end of treatment, and spontaneously resolved by day 29. AEs included application site pruritus and pain, transient dizziness, mild headache, and mild hair darkening near the treatment area.[6] Pharmacokinetics revealed minimal absorption of tirbanibulin after 3 or 5 days of treatment.[6]

In phase 1 and 2 trials, tirbanibulin 1% ointment led to clearance of AKs with self-resolving LSRs and minimal adverse effects. Based on these findings, the treatment regimen of tirbanibulin 1% ointment for 5 days was further evaluated in phase 3 trials.

Phase 3 Trials

Treatment Area of 25 cm²

Two identical phase 3 trials were conducted concurrently at 62 sites across the United States. Enrolled participants had 4 to 8 AKs on the face or scalp within a contiguous area of 25 cm².[7] They were randomized in a 1:1 manner to tirbanibulin 1% ointment or vehicle ointment (placebo). The primary outcome of these trials was to assess the efficacy of tirbanibulin 1% ointment once daily for 5 days over a treatment area of 25 cm², as measured by complete clearance of all AK lesions within the application area on day 57.[7]

Across the 2 trials, complete clearance was achieved in 49% (N=174/353) of participants on tirbanibulin and 9% (N=30/349) of participants on placebo (difference, 41%; 95% CI: 35 to 47).[7] Partial clearance was defined as a reduction of at least 75% in the number of AK lesions. Across the 2 trials, partial clearance was achieved in 72% (N=255/353) of participants on tirbanibulin and 18% (N=63/349) of participants on placebo (difference, 54%; 95% CI: 48 to 60).[7] Results for each phase 3 trial are shown in Figures 1 and 2. Additionally, participants with complete clearance on day 57 completed a 1-year follow-up, at which the development of new or recurrent AK lesions was assessed within the treatment area. At 1 year, 71% (N=124/174) of participants developed 1 or more AK lesions within the treatment area.[7] Of these participants, 58% (N=72/124) had recurrent lesions (reappearance of the same lesions from baseline), and 42% (N=52/124) had new lesions (different from those identified at baseline).[7]

FIGURE 1. Percentage of patients achieving complete clearance on tirbanibulin vs vehicle in each of the 2 phase 3 clinical trials.

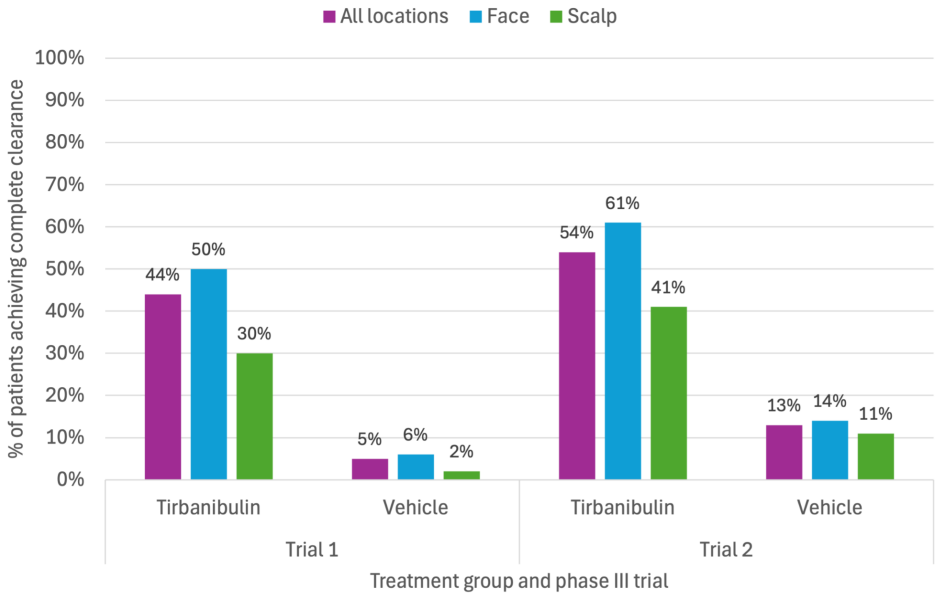
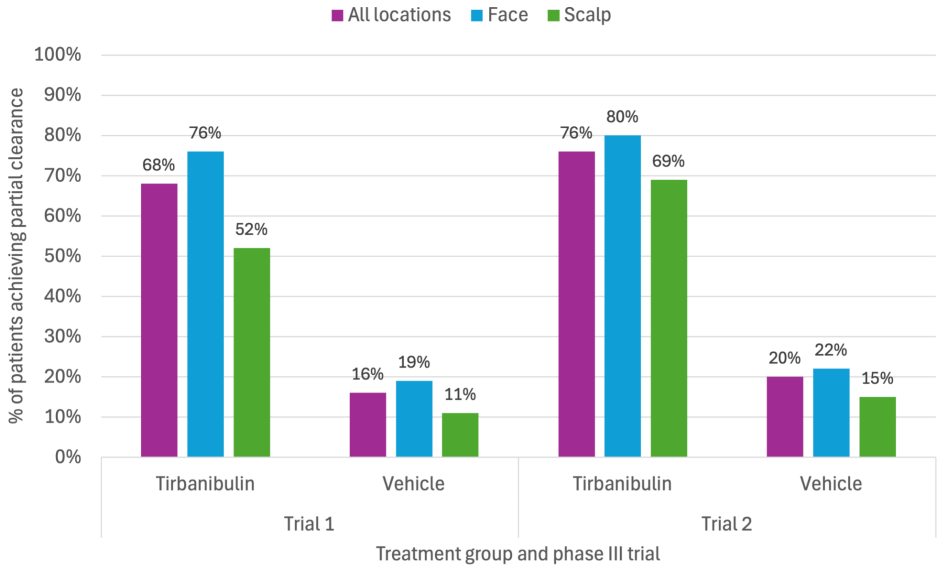


FIGURE 2. Percentage of patients achieving partial clearance on tirbanibulin vs vehicle in each of the 2 phase 3 clinical trials.



Consistent with that of the phase 1 and 2 trials, LSRs most commonly included moderate erythema (63%, N=223/353) and moderate flaking/scaling (47%, N=166/353), and less commonly included crusting, swelling, vesiculation/pustulation, and erosion/ulceration (Figure 3).[7] These local reactions peaked by day 8 and spontaneously resolved by day 29. Moreover, AEs included application site pain (10%, N=35/353) and pruritus (9%, N=32/353). Detailed results from each phase 3 trial are shown in Table 1.

Treatment Area of 100 cm²

Currently, there are limited treatment options for AK field-directed therapies that cover a treatment area greater than 25 cm². Thus, following FDA approval of tirbanibulin for 25 cm², a phase 3 trial using a larger treatment area was initiated.[8] Enrolled participants had 4 to 12 AKs on the face or balding scalp within a contiguous area of 100 cm². All enrolled participants received treatment with tirbanibulin 1% ointment once daily for 5 days over a treatment area of 100 cm².[8]

FIGURE 3. Maximal local skin reactions at the application site in the two phase 3 clinical trials (pooled data).

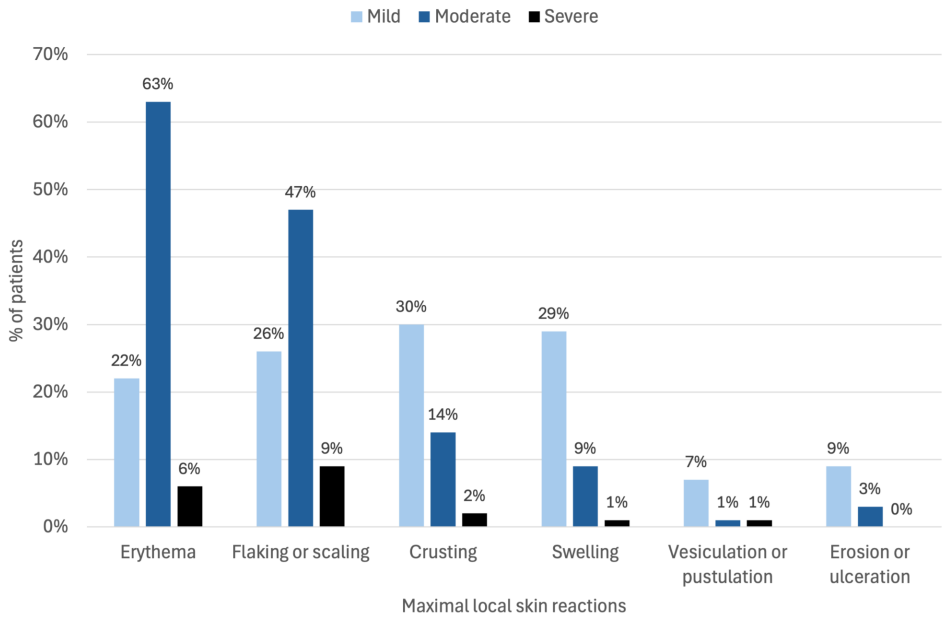


TABLE 1.

Summary of Clinical Trials Evaluating Tirbanibulin 1% Ointment

Clinical Trial Phase and Intervention	Efficacy	Tolerability and Safety
Phase 1[6] Cohort 1: 50 mg/day for 3 days over 25 cm^2 Cohort 2: 200 mg/day for 3 days over 100 cm^2 Cohort 3: 50mg/day for 5 days over 25 cm^2 Cohort 4: 200 mg/day for 5 days over 100 cm^2	**Complete clearance (on Day 57)** Cohort 1: 25% (N=1/4) Cohort 2: 0% (N=0/10) Cohort 3: 50% (N=4/8) Cohort 4: 12.5% (N=1/8)	**LSRs** Mild to moderate erythema Mild-to-moderate flaking/scaling Timeline: Appeared day 4, peaked days 5-8, resolved in 2 weeks **Treatment-related AEs*** Application site pruritus and pain
Phase 2[6] 3-day cohort: 50 mg/day for 3 days over 25 cm^2 5-day cohort: 50 mg/day for 5 days over 25 cm^2	**Complete clearance (on Day 57)** 3-day cohort: 32% (N=27/84) 5-day cohort: 43% (N=36/84)	**LSRs** Minimal/mild erythema (71%, N=120/168) Minimal/mild flaking/scaling (60%, N=100/168) Timeline: Appeared day 2, peaked day 5, resolved day 29 **Treatment-related AEs*** Application site pruritus and pain
Phase 3 (Trial 1)[11] Tirbanibulin 1% ointment once daily for 5 days over 25 cm^2	**Complete clearance (on Day 57)** Tirbanibulin: 44% (N=77/175) Placebo: 5% (N=8/176) **Partial clearance (on Day 57)** Tirbanibulin: 68% (N=119/175) Placebo: 16% (N=29/176) **Follow-up at 1 year** 71% (N=124/174) with new or recurrent lesions in the treatment area -New: 42% (N=52/124) -Recurrent: 58% (N=72/124)	**LSRs** Moderate erythema (63%, N=223/353) Moderate flaking/scaling (47%, N=166/353) Timeline: Peaked day 15, resolved day 29 **Treatment-related AEs*** Application site pruritus (9%, N=32/353) Application site pain (10%, N=35/353)
Phase 3 (Trial 2)[7] Tirbanibulin 1% ointment once daily for 5 days over 25 cm^2	**Complete clearance (on Day 57)** Tirbanibulin: 54% (N=97/178) Placebo: 13% (N=22/173) **Partial clearance (on day 57)** Tirbanibulin: 76% (N=136/178) Placebo: 20% (N=34/173)	
Phase 3[8] Tirbanibulin 1% ointment once daily for 5 days over 100 cm^2	**Mean % change (SD) in AK lesion count from baseline** Day 5: 22.3% (36.4) Day 8: 28.1% (47.3) Day 15: 50.5% (45.2) Day 29: 69.6% (35.0) Day 57: 77.8% (26.8)	**LSRs** Erythema (96.1%, N=99) Flaking/scaling (84.4%, N=87) Timeline: Peaked day 5-8, resolved day 29 **Treatment-related AEs*** Application site pruritus (N=11, 10.5%) Application site pain (N=9, 8.6%)

*No treatment-related changes in labs, vital signs, physical examination, or EKGs
LSR = local skin reaction; AE = adverse events; EKG = electrocardiogram; W = week; SD = standard deviation; AKASI = Actinic Keratosis Area and Severity Index; N/A = none applicable

Efficacy outcomes were measured by the mean percentage of change in AK lesion count from baseline. The mean (SD) percentage change from baseline was 22.3% (36.4) on day 5, 28.1% (47.3) on day 8, 50.5% (45.2) on day 15, 69.6% (35.0) on day 29, and 77.8% (26.8) on day 57.[8] There were no significant differences in mean percentage change in lesion count between different number of baseline lesions (≤ 8 AKs vs > 8 AKs), Fitzpatrick skin types (I/II vs III/IV), age (< 65 years vs ≥ 65 years), and sex (male vs female).[8] There was a small difference in mean percentage change in lesion count between treatment locations on the face (84.5% change on day 57) vs the scalp (63.7% change on day 57).[8]

The local tolerability signs (LTS) score consisted of a graded evaluation (0=absent, 1=mild, 2=moderate, and 3=severe) for erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration. The maximum LTS score was defined as the highest severity reported for each category throughout the post-baseline visits. Similarly to earlier trials, the most common LTS observed were erythema (N=99, 96.1%) and flaking/scaling (N=87, 84.4%).[8] Photographs of local tolerability signs are shown in Figure 4. The majority of patients had a maximum LTS score of "moderate" for erythema (N=66, 64.1%), "moderate" for flaking/scaling (N=44, 42.7%), and "absent" for all other LTS. LTS peaked between days 5 and 8 and spontaneously resolved by day 29.[8] The most commonly reported treatment-emergent adverse events (TEAEs) were pruritus (N=11, 10.5%) and pain (N=9, 8.6%) at the application site.

In brief, tirbanibulin 1% ointment demonstrated efficacy in both treatment areas of 25 cm^2 and 100 cm^2, and patients commonly experienced local reactions of erythema and flaking/scaling. New or recurrent AK lesions occurred in patients who had achieved complete clearance of AKs 1 year prior; 58% had re-current lesions (reappearance during

FIGURE 4. Local tolerability signs at baseline (pre-treatment) and days 5, 8, 15, 29, and 57 (post-treatment) in 2 patients using tirbanibulin on a treatment area of 100 cm^2.

follow-up) and 42% had new lesions only (distinct from baseline).[11] A summary of clinical trial results is outlined in Table 1.

Real-World Clinical Studies

Patient-Reported Outcomes in Actinic Keratosis (PROAK) Study

Given the efficacy and safety demonstrated in clinical trials, tirbanibulin 1% ointment was investigated in a real-world clinical study called Patient-Reported Outcomes in Actinic Keratosis (PROAK) to evaluate patient-reported outcomes (PRO) and clinician-reported outcomes (ClinRO).[9] The PROAK study included patients from 32 real-world community practices in the United States diagnosed with AKs on the face or scalp and treated with tirbanibulin.[9]

ClinRO included assessments on treatment effectiveness measured by Investigator's Global Assessment (IGA). IGA success was defined as an IGA score of 0 to 1, equivalent to ≥ 75% clearance of AK lesions.[9] Clinicians reported IGA success in 73.8% of patients at week 8 and 71.9% of patients at week 24. There was a statistically significant difference in IGA success between males (70.4%) vs females (81.3%, P=0.0488), patients with AKs on the face (81.5%) vs scalp (64.1%) vs both (48.7%, P<0.0001), and patients with absent/mild skin photodamage (83.1%) vs severe/moderate skin photodamage (70.9%, P=0.0491).[9] Additionally, there was a statistically significant reduction in skin photodamage severity at week 24 compared to baseline (P<0.0001).[9] PRO included assessments on quality of life (QoL) measured by Skindex-16.[9] There was a statistically significant decrease in scores in all Skindex-16 domains (ie, symptoms, emotions, and functioning) at week 8 compared to baseline in the overall cohort (P<0.0001).[9]

Both clinicians and patients reported treatment satisfaction with the Treatment Satisfaction Questionnaire for Medication (TSQM-9) and Expert Panel Questionnaire (EPQ). On the TSQM-9, both clinicians and patients reported high satisfaction scores with tirbanibulin at week 8 and week 24 in effectiveness, convenience of use, and global satisfaction.[9] On the EPQ, the majority of patients and clinicians reported the highest satisfaction ratings at week 24 in all domains. Detailed results from the TSQM-9 and EPQ are summarized in Table 2.

TABLE 2.

Summary of Real-World Clinical Studies Evaluating Tirbanibulin 1% Ointment

Clinical Study *Study site*	Efficacy, Tolerability, and Safety	Patient- and Clinician-Reported Outcomes
PROAK study[9] *United States*	**≥ 75% clearance** *IGA success* W8: 73.8% W24: 71.9% **LSRs** Mild/moderate erythema (47.6%) Severe erythema (4.9%) Mild/moderate flaking/scaling (49.6%) Severe (3.3%) **AEs** 5% (N=15) had ≥ 1 AE	**Quality of life** *Skindex-16* Week 8: Statistically significant decrease in scores in all Skindex-16 domains (symptoms, emotions, and functioning) **Treatment satisfaction** *TSQM-9* Patients, mean (SD) score out of 100 at W24 Effectiveness: 73.3 (21.3) Convenience of use: 85.0 (14.6) Global satisfaction: 72.0 (24.6) Clinicians, mean (SD) score out of 100 at W24 Effectiveness: 74.3 (21.2) Convenience of use: 84.5 (15.6) Global satisfaction: 74.9 (23.9) *EPQ* % of patient response Much/somewhat improved overall appearance of skin: 78.5% Extremely/very satisfied/satisfied with improvement in "how skin looks": 73.3% Extremely/very satisfied/satisfied with improvement in "skin texture": 71.8% Somewhat/very likely to consider tirbanibulin to treat AK lesions in the future: 78.4% % of clinician response Much/somewhat improved overall appearance of skin: 83.6% Extremely/very satisfied/satisfied with improvement in "how skin looks": 68.5% Extremely/very satisfied/satisfied with improvement in "skin texture": 68.9% Somewhat/very likely to consider tirbanibulin to treat AK lesions in the future: 77.3%
Campione et al[10] *Italy*	**Complete clearance (on Day 57)** 70% (N=21) **Partial clearance (on Day 57)** 30% (N=9) **LSRs** Mild erythema (30%, N=9) Moderate erythema (53.3%, N=16) Mild scaling (26.6%, N=8) Moderate scaling (3.33%, N=1) Timeline: Appeared day 2-15, peaked day 8, resolved day 15-29	**Treatment satisfaction** *TSQM 1.4* Patients, mean (SD) score out of 100 on day 57 Effectiveness: 80 Convenience of use: 97 Global satisfaction: 83 Side effects: 94
Kirschberger et al[11] *Germany*	**Complete clearance** *AKASI score < 1* W4: 47% (N=14) 1-6 months: 57% (N=13) **LSRs** Erythema (80%, N=26) Flaking/scaling (43%, N=13) Timeline: Appeared day 2-10, resolved in 5 days	N/A
Li Pomi et al[12] *Italy*	**Complete clearance (at W8)** 51% of all lesions Olsen grade 1: 60% (N=51/85) Olsen grade 2: 49% (N=57/116) Olsen grade 3: 29% (N=8/27) **Partial clearance (at W8)** 73% of all lesions Olsen grade 1: 78% (N=67/85) Olsen grade 2: 72% (N=84/116) Olsen grade 3: 55% (N=15/27) **LSRs** Moderate erythema (60%, N=23/38) Moderate scaling (44%, N=17/38) Timeline: Appeared Day 7-9, peaked Day 10-12, resolved in 2-4 weeks	**Treatment compliance** *Patient-reported* Excellent: 71% (N=28) Good: 18% (N=7) Moderate: 8% (N=3) Poor: 3% (N=1)

PROAK = Patient-Reported Outcomes in Actinic Keratosis; LSR = local skin reaction; AE = adverse events; W = week; SD = standard deviation; IGA = investigator's Global Assessment; AKASI = Actinic Keratosis Area and Severity Index; TSQM = Treatment Satisfaction Questionnaire for Medication; EPQ = Expert Panel Questionnaire; N/A = none applicable

Fifteen patients (15%) reported at least one AE, and most of them were mild (4%).[9] Few patients developed SCC (2.3%) and basal cell carcinoma (1.3%), but only one patient developed skin cancer within the treatment site.[9] None of the cases were considered related to treatment. Severe AEs reported were not related to treatment, and there were no serious adverse drug reactions. Consistent with clinical trial results, the most commonly reported LSRs were erythema (47.6% mild/moderate and 4.9% severe) and flaking/scaling (49.6% mild/moderate and 3.3% severe).[9]

Single-Center Clinical Studies

Single-center studies have been conducted globally in real-world clinical settings. Campione et al, Kirschberger et al, and Li Pomi et al reported efficacy and safety results from cohorts in Italy and Germany consistent with those of the PROAK study.[10-12] All 3 studies used dermoscopic evidence in combination with clinical findings to demonstrate clearance of AK lesions. Detailed findings are reported in Table 2.

In addition to efficacy and safety data, Campione et al reported treatment satisfaction on day 57 using the TSQM, with mean satisfaction scores (on a scale of 0-100) of 97 in convenience of use, 94 in side effects, 83 in global satisfaction, and 80 in effectiveness.[10] Moreover, Li Pomi et al measured AK clearance at week 8, stratified by Olsen grading of AK lesions.[12] Olsen grade 1 lesions demonstrated the highest rate of complete clearance (60%, N=51/85), followed by Olsen grade 2 lesions (49%, N=57/116), then Olsen grade 3 lesions (29%, N=8/27). Similarly, Olsen grade 1 lesions demonstrated the highest rate of partial clearance (78%, N=67/85), followed by Olsen grade 2 lesions (72%, N=84/116), then Olsen grade 3 lesions (55%, N=15/27).[12] There was a statistically significant difference in the rate of complete clearance between Olsen grade 1 vs grade 3 lesions (60% vs 29%, *P*=0.01), as well as the rate of partial clearance between Olsen grade 1 vs grade 3 lesions (78% vs 55%, *P*=0.02).[12] Li Pomi et al also measured self-reported patient compliance to tirbanibulin treatment, which showed 71% (N=28) of patients reporting their compliance as "excellent", 18% (N=7) as "good", 8% (N=3) as "moderate", and 3% (N=1) as "poor".[12]

In summary, real-world clinical studies using tirbanibulin 1% ointment demonstrated high treatment satisfaction, improved quality of life, and robust treatment compliance. The highest efficacy was achieved by AK lesions in females, on the face, with absent/mild skin photodamage, and with milder Olsen grade.

DISCUSSION

Tirbanibulin 1% ointment has demonstrated strong clinical trial and real-world evidence for safe and effective treatment of AKs. While other field-directed therapies can be limited by poor treatment compliance due to prolonged treatment duration, tirbanibulin 1% ointment is administered with a lower frequency and duration of use. Phase 3 and real-world clinical studies demonstrated complete clearance of AKs by day 57 in most patients. Given efficacy data on different types of AK lesions and patient characteristics, tirbanibulin may be particularly effective for mild AKs on the face without significant hyperkeratosis, female patients, and individuals with limited skin photodamage. However, despite significant improvement in AK lesions, patients may experience recurrence of AKs in the treatment area after complete clearance.

Moreover, patients commonly experienced LSRs such as erythema and flaking/scaling that self-resolved in 2 to 4 weeks. Application site pruritus and pain were the most common AEs experienced by patients. Of note, tirbanibulin used in larger treatment areas of 100 cm^2 revealed promising efficacy and safety in a phase 3 clinical trial, which led to the FDA approval for field treatment up to 100 cm^2. Lastly, real-world clinical studies have contributed valuable patient and clinician perspectives on tirbanibulin use. Overall, both patients and clinicians reported high treatment satisfaction, with the highest scores reported in convenience of use. Patients also demonstrated strong treatment compliance, and quality of life improved in all domains of symptoms, emotions, and functioning.

This article summarizes the clinical evidence on tirbanibulin 1% ointment use from several studies. This comprehensive review of tirbanibulin 1% ointment can guide treatment considerations for the treatment of AKs for both clinicians and patients.

DISCLOSURES

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ORIGINAL ARTICLE

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Tirbanibulin 1% Ointment: The Mechanism of Action of a Novel Topical Therapy for Actinic Keratosis

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ABSTRACT

Actinic keratosis (AK) is a common, precancerous skin lesion that may progress to squamous cell carcinoma (SCC). Traditional topical therapies for AKs often require long treatment durations. These therapies may also cause significant local skin reactions that can reduce patient adherence. Tirbanibulin, a first-in-class topical agent for AKs on the face and scalp, was approved by the US Food and Drug Administration (FDA) in 2020. Tirbanibulin serves as a promising alternative with a shorter treatment duration of five days.

Unlike other topical AK therapies, tirbanibulin targets microtubules in keratinocytes. The agent inhibits tubulin polymerization, disrupts the microtubule network, and induces cell cycle arrest. These cellular effects may be reversible, reducing tirbanibulin's toxicity profile. Tirbanibulin has also demonstrated antiproliferative activity with the potential to selectively target highly proliferative keratinocytes, contributing to its antitumorigenic effects. In addition, studies suggest that tirbanibulin may induce apoptosis and interfere with the activity of Src, a tyrosine kinase that can contribute to the progression of AKs and SCCs.

Tirbanibulin's shorter treatment duration and favorable safety profile make it an appealing choice in AK management. In clinical studies, tirbanibulin 1% ointment was well-tolerated and demonstrated significant efficacy in clearing AK lesions in areas up to 100 cm^2 on the face and scalp. Tirbanibulin's novel mechanism of action introduces a new, exciting option for the field treatment of AKs.

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INTRODUCTION

Epidemiology

Actinic keratosis (AK) is a premalignant skin lesion that may result from prolonged ultraviolet (UV) damage.[1] AKs are common worldwide with an estimated global prevalence rate of 14%.[1] AKs are often characterized as hyperkeratotic papules or plaques with a rough surface or overlying scale on an erythematous base.[2–4] These skin lesions often appear on sun-exposed areas and are more common among males, those of advanced age, those with Fitzpatrick skin type I or II, and those who are immunosuppressed.[1,4] If left untreated, AKs may progress to invasive squamous cell carcinoma (SCC).[2,4]

Pathogenesis

Histologically, AKs demonstrate epidermal hyperplasia and varying degrees of cellular atypia.[2] The atypia can resemble SCC in situ but without full-thickness epidermal involvement.[2] The cellular changes that are present in both AKs and SCCs may be indicative of their mutual pathogenesis.[2] AK development commonly begins with DNA damage in the basal layer of the epidermis.[2,5] Affected keratinocytes often contain DNA mutations that have been classically associated with UVB-related damage (eg, C to T and CC to TT).[2,5] The mutations have also been associated with oxidative stress from UVA-mediated production of reactive oxygen species or the intrinsic aging of cells.[2] The DNA mutations found in AKs particularly involve the *TP53* gene, which encodes for the p53 protein that plays a critical role in tumor suppression.[5] The *TP53* mutations contribute to keratinocyte dysplasia, ultimately resulting in AK development on the epidermal surface.[2,5] In the research of AK progression to SCC, Src kinases have been of particular interest, as increased expression of these nonreceptor tyrosine kinases has been found in both AKs and SCCs.[6,7] Studies suggest that increased Src signaling may play an important role in the alteration of hemidesmosomes and migration of keratinocytes necessary for SCC progression and invasion.[6,7]

Treatment Overview

The potential for AKs to progress to SCC has been well-established.[4] However, a clinical method to definitively identify which AK lesions may progress to SCC is yet to be determined.[4] As a result, dermatologists have recommended that all AKs, including both clinically visible and subclinical lesions, be treated.[4] Recommendations to treat subclinical lesions stem from concerns regarding field cancerization, which refers to the presence of genetically altered cells in the areas surrounding AK lesions.[8] Although these surrounding areas may not present with clinical signs or symptoms suggestive of carcinogenesis, they may still contain genetic mutations that increase their risk for AK development.[4,8]

AK management options include lesion-directed and field-directed therapies. Lesion-directed therapies include liquid nitrogen cryosurgery, manual or surgical removal, and ablative lasers.[2,4] These therapies are often used to target clinically visible AKs in patients with few or isolated lesions and are performed by the clinician.[2,4] Field-directed therapies, such as photodynamic therapy (PDT) and topical agents, may be used in place of or in addition to lesion-directed therapies.[2,4] Field-directed therapies are often used to target both clinically visible and subclinical lesions in patients with multiple AKs.[2,4] Furthermore, field-directed therapies may help to reduce the risk of new AK development and recurrence.[2,8] Although PDT is conducted by clinicians, topical agents may be self-administered by the patient.[2,4]

Traditional Topical Therapies

Most topical therapies for AKs induce cell necrosis or apoptosis in rapidly proliferating keratinocytes.[4] Topical 5-fluorouracil (5-FU) disrupts DNA replication in the S phase and promotes the release of proinflammatory cytokines and cell necrosis.[4,6] Similarly, ingenol mebutate also induces inflammation and necrosis of atypical keratinocytes.[2,4] However, safety data reviewed by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee found an increased incidence of skin cancer in patients treated with ingenol mebutate compared to imiquimod after three years.[2] As a result, ingenol mebutate was removed from the US market in 2020.

Apoptosis-inducing agents include imiquimod and diclofenac.[4] Imiquimod primarily functions as a toll-like receptor 7 agonist and can stimulate the immune system.[6] The agent enhances cytokine activity levels and modifies the patient's immune response to identify and target tumor antigens in atypical keratinocytes.[4,6] On the other hand, the nonsteroidal antiinflammatory drug (NSAID) diclofenac functions by inhibiting cyclooxygenase-2 (COX-2) and preventing the formation of prostaglandins.[4] However, the use of diclofenac is not recommended as strongly as 5-FU and imiquimod due to the medication's black box warning for cardiovascular and gastrointestinal side effects, similar to other NSAIDs.[2]

Although 5-FU, imiquimod, and diclofenac may serve as potential therapy options for AKs, they often require several weeks of treatment.[6] Previous studies have found that therapies with longer dosing regimens may be associated with lower patient adherence.[4] In addition, 5-FU, imiquimod, and diclofenac have been found to induce local skin reactions (LSRs), such as erythema, pruritus, crusting, erosions, and ulcerations, at treated sites.[4,6] Imiquimod, in particular, has also been associated with systemic, influenza-like symptoms.[2] These adverse effects may decrease patient adherence even further.[2,4] The long dosing regimens and adverse effects associated with 5-FU, imiquimod, and diclofenac have created the need for an effective, well-tolerated topical agent with a shorter treatment duration.

Tirbanibulin

In December 2020, the FDA approved tirbanibulin, a first-in-class, topical treatment for AKs on the scalp or face.[9] Unlike previous topical agents, tirbanibulin 1% ointment only requires once-daily application for five consecutive days.[9] Although tirbanibulin was originally approved for use on an area up to 25 cm^2, the FDA expanded the treatment field to up to 100 cm^2 in June 2024.[10]

Mechanism of Action

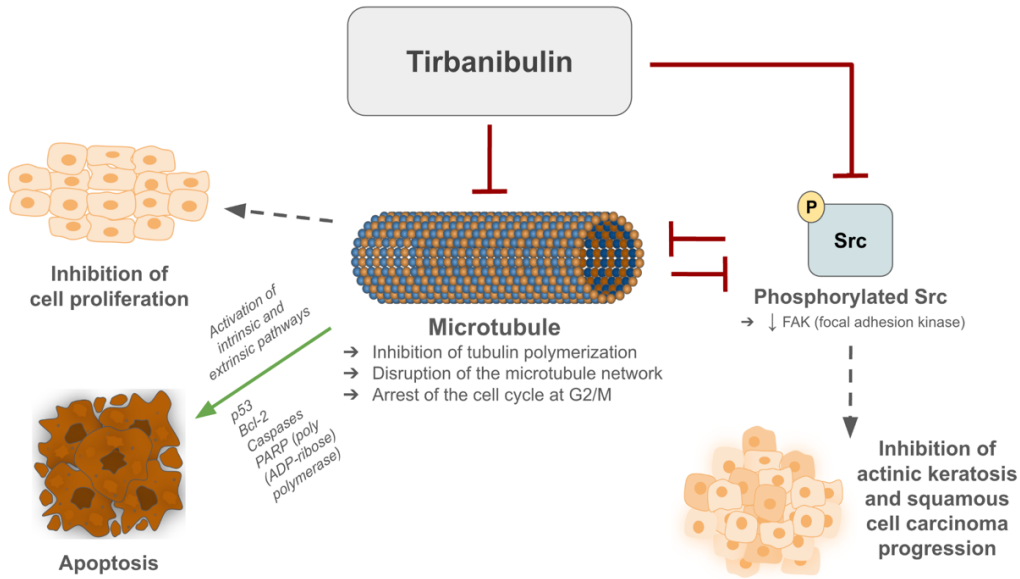
Several studies have focused on clarifying the mechanism of action of tirbanibulin (Figure 1). Research has found that tirbanibulin inhibits microtubules and exhibits antiproliferative and proapoptotic effects.[6,7] Additionally, tirbanibulin may interfere with Src kinase signaling, reducing AK and SCC progression.[6,7]

Microtubule Inhibition

Microtubules have demonstrated a high susceptibility to modulation by many existing chemotherapies.[6] During mitosis, microtubules are essential to the formation of the mitotic spindle that functions during the metaphase-anaphase transition.[6] Disruption of this stage may lead to cell cycle arrest and apoptosis.[6]

Microtubules consist of tubulin heterodimers, which are formed by α- and β-tubulin monomers.[6] Using liquid chromatography with tandem mass spectrometry, the in vitro ATNXUS-KX01-001 study found both α- and β-tubulin to be targets of tirbanibulin in colon cancer HT-29 cells.[6] These findings were further supported by results from photoaffinity labeling assays with purified tubulin and competitive binding

FIGURE 1. Tirbanibulin's proposed mechanism of action in actinic keratosis treatment.[6,7] Tirbanibulin binds to microtubules and inhibits tubulin polymerization, disrupts the microtubule network, and arrests the cell cycle at growth phase 2/mitosis (G2/M). Tirbanibulin may also inhibit cell proliferation and induce cellular apoptosis through both intrinsic and extrinsic pathways involving hyperphosphorylation of Bcl-2, cleavage of caspases 8 and 9, activation of caspase 3, and cleavage of poly (ADP-ribose) polymerase (PARP). Increased expression of p53 may augment proapoptotic effects. Additionally, tirbanibulin may interfere with Src signaling, decreasing expression of its downstream targets such as focal adhesion kinase (FAK). The inhibition of FAK may disrupt the microtubule network, while the inhibition of microtubules may suppress FAK activity. Ultimately, tirbanibulin's interference with Src signaling may inhibit actinic keratosis and squamous cell carcinoma progression.



assays with known tubulin-binding drugs, such as colchicine, vincristine, docetaxel, guanosine diphosphate (GDP), and guanosine triphosphate (GTP).[6] In another study examining tirbanibulin's binding site, competition experiments revealed a lack of competition between a tirbanibulin analogue and tubulin-binding drugs, suggesting that tirbanibulin may bind to a novel site on tubulin.[11] In contrast, other biochemical experiments suggest that tirbanibulin binds to β-tubulin on the colchicine-binding site.[12] These findings were further supported by a crystal structure and electron density map created of the tubulin-tirbanibulin complex.[12] However, unlike colchicine, tirbanibulin was found to bind to tubulin in a reversible rather than an irreversible manner.[12] Given the varied findings from previous experiments, additional research to confirm tirbanibulin's binding site is needed.

Studies to examine tirbanibulin's effects on microtubules have found that tirbanibulin inhibits tubulin polymerization, disrupts the microtubule network, and arrests the cell cycle at growth phase 2/mitosis (G2/M).[6,7,11,12] In the ATNXUS-KX01-001 study, a tubulin polymerization assay was performed to examine the cellular effects of purified tubulin, paclitaxel (an agent that promotes tubulin polymerization), and nocodazole (an agent that inhibits tubulin polymerization).[6] Tirbanibulin was found to inhibit tubulin polymerization in a manner similar to that of nocodazole.[6] Another study examining the effects of tirbanibulin in HeLa cells found that tirbanibulin inhibits tubulin polymerization in a manner similar to that of colchicine and vinblastine (other agents that inhibit tubulin polymerization).[12] Moreover, tirbanibulin's disruption of the microtubule network has been demonstrated in various cell lines, including human immortalized keratinocytes (CCD-1106 KERTr).[6,7] A previous study found that tirbanibulin disrupts the microtubule network in a concentration-dependent manner, and 30 minutes after tirbanibulin was washed out of the cell culture, filamentous tubulin structures were even restored.[11] Similarly, tirbanibulin's arrest of the cell cycle has also been found to occur in a reversible manner.[6,7,12] Flow cytometry of CCD-1106 KERTr cells incubated with tirbanibulin demonstrated complete G2/M cell cycle arrest.[6,7] However, a mitotic block reversibility assay of HeLa cells treated with tirbanibulin showed the G2/M cell cycle arrest to be reversible.[12] The reversibility of tirbanibulin's cellular effects, as demonstrated in these studies, may potentially explain its low toxicity shown in clinical trials.[12]

Antiproliferative Activity

Tirbanibulin has been shown to exhibit antiproliferative activity in several cancer cell lines, including SCC.[6,7] A cell growth experiment with CCD-1106 KERTr cells compared the effects of tirbanibulin on slower-growing cells in growth factor-reduced medium versus faster-growing cells in complete medium.[6,7] After keratinocyte cultures were incubated with tirbanibulin for 72 hours, tirbanibulin was found to inhibit cell growth and induce cell death more effectively in the fast-growing cells.[6,7] These results suggest that tirbanibulin may selectively target highly proliferative cells.[6] Additionally, in vivo, tirbanibulin was able to slow tumor growth in mouse xenograft models.[7,13] Antiproliferative activity was also demonstrated through decreased expression of the Ki-67 proliferation marker and increased levels of apoptotic cells as detected through TUNEL assay.[7,13]

Proapoptotic Effects

Flow cytometry analysis has shown that tirbanibulin may induce early apoptosis, as indicated by positive annexin V staining, and late apoptosis, as indicated by positive 7-aminoactinomycin D staining.[7] Immunoblot analyses suggest that tirbanibulin may activate both the intrinsic and extrinsic apoptosis signaling cascades through hyperphosphorylation of Bcl-2, cleavage of caspases 8 and 9, activation of caspase 3, and cleavage of poly (ADP-ribose) polymerase (PARP).[7] In vivo studies of tirbanibulin in mouse xenograft models have also demonstrated similar proapoptotic effects.[7,13]

Moreover, previous research has revealed that tirbanibulin may increase the expression of the tumor suppressor, p53.[11] p53 has been shown to localize on microtubules, and in response to DNA damage, translocate to the nucleus via the microtubule network.[14] In a previous study, treatment with microtubule-targeting agents led to the accumulation of p53 in the nucleus and activation of p53's downstream targets, including caspase-3 activation and PARP cleavage.[15] These findings suggest that through microtubules, tirbanibulin may contribute to the nuclear retention of p53 and augment apoptotic cell death. Given that mutations in the *TP53* gene have been identified in both AKs and SCCs,[5] tirbanibulin's potential to modulate p53 may be of therapeutic significance.

CCD-1106 KERTr cells incubated for 24 hours with tirbanibulin have also demonstrated significantly increased levels of interleukin (IL)-1α, a marker of cell death.[6,7] However, keratinocytes incubated with tirbanibulin released less tumor necrosis factor (TNF)-α and IL-8 compared to keratinocytes incubated with 5-FU.[6,7] TNF-α and IL-8 are proinflammatory cytokines that can contribute to the development of severe LSRs, as seen with AK therapies such as 5-FU.[6,7] These results suggest that tirbanibulin may induce cell death, but with a weaker response of inflammatory cytokines known to induce severe LSRs.[6,7] Because tirbanibulin primarily functions through apoptosis, which is associated with less inflammation than necrosis, LSRs may be milder, as shown in clinical studies.[6,7]

Src Kinase Inhibition

Phosphorylation of Src tyrosine kinase has been shown to promote cellular invasion and metastasis of various tumors[12] and may contribute to the progression of AKs to SCCs by inducing hemidesmosome alterations and cell migration.[6,7] However, tirbanibulin has been found to reduce levels of phosphorylated Src and its downstream targets such as focal adhesion kinase (FAK).[13] Tirbanibulin may inhibit Src through indirect mechanisms, with studies highlighting an intricate relationship between Src signaling and microtubules.[7] While Src downstream targets such as FAK play a role in stabilizing microtubules,[16,17] microtubules have also been shown to play a role in facilitating Src signaling.[18] Consequently, while inhibition of FAK may disrupt the microtubule network,[17] the inhibition of microtubules may also suppress FAK activity.[18] These complexities highlight the need for further research to clarify the mechanism through which tirbanibulin primarily exerts its effects.

Summary of Clinical Trials

The efficacy and safety of tirbanibulin 1% ointment for AK treatment have been demonstrated in phase 1 and phase 2 clinical trials.[19,20] Once-daily application of tirbanibulin 1% ointment to a 25 cm^2 area of the face or scalp with AK lesions led to complete AK clearance at day 57 for 32% of participants treated with a three-day course and 43% of participants treated with a five-day course.[19] A subsequent phase 3 study included two double-blind trials that were identically designed.[21] The first trial resulted in complete AK clearance in 44% of patients in the tirbanibulin group and 5% of patients in the control group.[21] The second trial resulted in complete AK clearance in 54% of patients in the tirbanibulin group and 13% of patients in the control group.[21] Partial AK clearance was also seen in a significantly higher percentage of patients in the tirbanibulin groups than in the control groups.[21] A phase 3 study examining tirbanibulin use over a 100 cm^2 area, rather than a 25 cm^2 area, found that the average number of AKs decreased from 7.7 AKs at baseline to 1.8 AKs at day 57.[22] The average reduction in lesion count was 77.8%, demonstrating tirbanibulin's efficacy.[22] In addition, phase 1, 2, and 3 trials have all shown a favorable safety profile, with the most common adverse events being mild or moderate LSRs, such as erythema, flaking, scaling, pruritus, and pain.[19–23] Importantly, there were no reports of serious adverse events, deaths, or discontinuations related to tirbanibulin use.[19–23]

Pharmacokinetics

A previous study examined the absorption of tirbanibulin 1% ointment used for AKs in a 25 cm^2 area of the face or scalp.[19] Results demonstrated minimal absorption after three or five days of consecutive treatment.[19] In fact, the plasma concentration of tirbanibulin was below the lower limit of quantification of 0.1 ng/mL in most collected samples, and the maximum individual plasma concentration did not exceed 2 ng/mL.[19] A phase 1 maximal use study also examined tirbanibulin use over a contiguous 25 cm^2 area of the face or scalp. After a five-day course, the mean maximum plasma concentration was 0.26 ng/mL.[23] For use over a contiguous area of 100 cm^2, another phase 1 maximal use study revealed a mean maximum plasma concentration of 1.06 ng/mL after five days.[20] These findings were consistent with the four-fold increase in treated area from 25 cm^2 to 100 cm^2.[20] Furthermore, topical application to the face rather than the scalp resulted in a higher exposure to tirbanibulin and its metabolites.[20] However, overall systemic levels of tirbanibulin remained low, which may explain the lack of systemic adverse effects observed in clinical studies.[20]

CONCLUSION

Tirbanibulin 1% ointment represents a novel, first-in-class topical therapy for AKs. Tirbanibulin's mechanism of action targets microtubules, inhibiting tubulin polymerization, disrupting the microtubule network, and arresting the cell cycle. Unlike some of the traditional topical agents for AKs, tirbanibulin's reversible effects on microtubules help to reduce its toxicity profile while still achieving effective lesion clearance. In addition, tirbanibulin's antiproliferative activity, proapoptotic effects, and inhibition of Src kinase signaling further contribute to its anti-tumorigenic properties.

Although tirbanibulin's efficacy in AK clearance has been demonstrated in clinical studies, cost may be a barrier to widespread use.[9] However, compared to traditional topical therapies, tirbanibulin provides a shorter treatment duration and favorable safety profile, potentially improving patient adherence. These benefits may still make tirbanibulin a compelling option for patients and healthcare providers. To further establish tirbanibulin's role in AK treatment, long-term studies on its safety and efficacy are needed.[9]

Overall, tirbanibulin's novel mechanism of action offers an effective, well-tolerated treatment option for field-directed therapy in AK management.

DISCLOSURES

Alyssa M. Roberts BS has no conflicts of interest to disclose.

Leon Kircik MD has served on as an investigator, consultant, speaker, and/or advisory board member for Abbott Laboratories, Abbvie, Ablynx, Aclaris, Acambis, Allergan, Inc., Almirall, Amgen, Inc., Anacor Pharmaceuticals, Anaptys, Arcutis, Arena, Assos Pharma, Astellas Pharma US, Inc., Asubio, Bausch Health, Berlex Laboratories, Biogen-Idec, Biolife, BioMimetix, Biopelle, BMS, Boehringer-Ingleheim, Breckinridge Pharma, Cassiopea, Centocor, Inc., Cellceutix, Cipher, Coherus, Colbar, Combinatrix, Connectics Corporation, Coria, Dermavant, Dermira, Dermik Laboratories, Dow Pharmaceutical Sciences, Inc., Dr. Reddy's Lab, Dusa, Embil Pharmaceuticals, Eli Lilly, EOS, Exeltis, Ferndale Laboratories, Inc., Foamix, Ferrer, Galderma, Genentech, Inc., GlaxoSmithKline, PLC, Glenmark, Health Point, LTD, Idera, Incyte, Intendis, Innocutis, Innovail, Isdin, Johnson & Johnson, Kyowakirin, Laboratory Skin Care Inc., Leo, L'Oreal, 3M, Maruho, Medical International Technologies, Merck, Medicis Pharmaceutical Corp., Merz, Nano Bio, Nektar, Nimbus, Novartis AG, Noven Pharmaceuticals, Nucryst Pharmaceuticals Corp, Obagi, Onset, OrthoNeutrogena, PediaPharma, Pfizer, Promius, PuraCap, PharmaDerm, QLT, Inc, Quinnova, Quatrix, Rapt, Regeneron, Sanofi, Serono, SkinMedica, Inc., Stiefel Laboratories, Inc., Sun Pharma, Taro, TolerRx, Triax, UCB, Valeant Pharmaceuticals Intl., Ventyx, Warner-Chilcott, XenoPort, and ZAGE.

Mark Lebwohl MD has served as a consultant for Aditum Bio, Almirall, Altrubio, Anaptysbio, Apogee Therapeutics, Arcutis, Arena Pharmaceuticals, Aristea Therapeutics, Arrive Technologies, AstraZeneca, Atomwise, Avotres Therapeutics, Biomx, Boehringer Ingelheim, Brickell Biotech, Bristol-Myers-Squibb, Cara Therapeutics, Castle Biosciences, CorEvitas, Corrona, Dermavant Sciences, Dr. Reddy's Laboratories, EPI, Evelo Biosciences, Evommune Inc., Facilitation of International Dermatology Education, Forte Biosciences, Foundation For Research and Education in Dermatology, Galderma Laboratories, L.P., Galderma Laboratories, L.P., Helsinn Therapeutics, Hexima Ltd, LEO Pharma AS, Meiji Seika Pharma, Mindera, Pfizer, Seanergy, STRATA Skin Sciences, Inc, Sun Pharmaceutical Industries Inc, Takeda Pharmaceutical Company, Trevi, Verrica, and Vial.

April W. Armstrong MD MPH has served as a research investigator, scientific advisor, and/or speaker to AbbVie, Amgen, Almirall, Arcutis, ASLAN, Beiersdorf, BI, BMS, EPI, Incyte, Leo, UCB, Janssen, Lilly, Novartis, Ortho, Sun, Dermavant, Dermira, Sanofi, Takeda, Regeneron, and Pfizer.

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