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Topical Pharmacological Treatment of Actinic Keratoses: Focus on Tirbanibulin 1% Ointment

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ABSTRACT

Actinic keratosis (AK) is a frequent precancerous skin lesion that mostly affects chronically sun-exposed areas. Chronic sun damage leads to various mutations in onco-suppressor and oncogenic genes which cause an uncontrolled proliferation of atypical keratinocytes. Untreated AKs may evolve in cutaneous squamous cell carcinoma (cSCC), with the consequent need for dermato-surgical excision or even for systemic immunotherapy in case of invasive/metastatic cSCCs. Epidemiology data on AK prevalence are various, however, the literature unanimously reports an increasing prevalence due to the aging of the population. Clinically AKs appear as a scaly, erythematous macule or papule or hyperkeratotic plaque. Management of AKs and the field of cancerization is important to avoid the natural evolution into squamous cell carcinomas (SCCs). Both physical and topical treatments are approved for managing AKs. Patient compliance with topical regimens is usually low due to the length of the posology and frequent skin adverse events. A recently approved tirbanibulin-based ointment, showed potential for inhibiting cell proliferation and blocking SRC-kinases, implicated in the progression of AKs in SCCs. The advantage of this new treatment is the practical posology, with a daily application for 5 consecutive days on AKs of the face-scalp area. Local skin reactions are usually mild and do not require treatment discontinuation. The short course of this new therapy and its excellent tolerance massively increased patient compliance. This article reviews what is currently known about this new therapy from its mechanism of action to clinical trial outcomes regarding safety, effectiveness, and patient adherence to the treatment.

Introduction

Actinic keratoses (or solar keratoses) are the clinical manifestation of a common, chronic disease of the skin of adults [1], which develops in areas exposed to sunlight [2]. Risk factors for the development of actinic keratoses and SCC are I-II phototypes according to Fitzpatrick's scale, male sex, age, and immunodepression [3-5]. The incidence of AKs is likely underestimated, as they are not recorded routinely in cancer registries. Unsurprisingly, the prevalence of AKs shows an increase in its trend [3]. AKs represent one of the most common conditions diagnosed and treated by dermatologists in the United States (US), where currently up to 12% of individuals have AKs [6]. A Rotterdam prevalence study of >2,000 Dutch men and women, with a mean age of 72 years, found AK in 49% of men and 28% of women [7]. In Galway, South Wales and Merseyside (UK), 19-24% of individuals aged >60 had at least one AK. Over 30% of those attending a dermatology clinic (mean age of attendance 61 years) in Austria had AK. Up to 60% of Australians over the age of 40 have AKs [8,9].

Histologically, AKS are characterized by epidermal hyperplasia and by variable degrees of keratinocyte atypia, which can involve all layers of the epidermis, as in the *in-situ* forms of squamous cell carcinoma [10]. Indeed, AKs are considered by some to be a precursor of SCC [11,12] by others an initial and superficial form [13,14]. The histopathological similarities between AKs and squamous cell carcinoma reflect their same pathogenesis, a multi-stage process caused by somatic mutations induced by the carcinogenic action of ultraviolet (UV) radiation. These critically affect the tumor suppressor *TP53* gene, which has mutations with UV signature (e.g., pyrimidine dimers) in almost 90% of AK specimens. [7,15-19] Although on histological examination up to 90% of invasive cutaneous squamous cell carcinomas arise contiguously or in continuity with AKs [17,20,21], prospective evaluation of AKs over time demonstrates a low rate of transformation to invasive squamous cell carcinoma, with less than one invasive squamous cell carcinoma for every 1000 AKs in a year [22]. In a US study, 0.6% of patients developed invasive squamous cell carcinoma in the same anatomical site as the actinic keratosis within the first year, rising to 2.57% at 4 years [21]. Rather than referring to the anatomical regions affected by the keratoses actinic keratoses, the risk of developing squamous cell carcinoma can be attributed more correctly to the subject suffering from actinic keratoses, with a risk of invasive squamous cell carcinoma which increases proportionally to the number of actinic keratoses [23] and which is estimated at 10% in 10 years for an average patient with 7-8 actinic keratoses [1,21,24].

A clinical categorization method for AK grading based on the total thickness of different lesions was proposed by Olsen et al [25]. Grade 1 lesions are hardly tangible, Grade 2 lesions are rather thick, and Grade 3 lesions are very thick and hyperkeratotic according to this system. This clinical classifying system is often used to set patient inclusion criteria in randomized clinical trials of AK treatments.

The concept of the field of cancerization was proposed by Slaugther in 1953 [28] and was applied to squamous cell carcinomas of the oral cavity, although Willis in his seminal article in 1944 first hypothesized that the proliferation of keratinocytes can occur multifocally in the epidermis [28]. From a pathological point of view, field of cancerization could currently be defined as one or more areas of epithelial and stromal tissue characterized by genetic and epigenetic abnormalities, some of which are also present in cancer, even in the absence of histopathological alterations. In this perspective, the concept of field cancerization has diagnostic and prognostic implications, especially when considering that "healthy" perilesional skin surrounding clinically evident, multiple AKs could indeed be treated treatment of AKs, since therapy of AKs should be directed not only to visible lesions but also to the field of cancerization from which they originate. For practical purposes, however, a univocal consensus on the criteria required to clinically identify and treat the cutaneous field of cancerization is still lacking and it was defined in a recent review [26-29] as multifocal clinical atypia, characterized by AKs and/or squamous cell carcinoma in situ (SCCis) with or without invasive cSCC, occurring in a field exposed to chronic UVR.

Sunscreens and protective clothing, together with adequate sun-exposure education, are crucial in managing patients with AKs; however, they are often insufficient to treat existing lesions [30,31]. Currently, available therapies for AKs are divided into field-directed treatments and lesion-directed treatments [31,32]. The latter mostly include physical treatments, of which cryotherapy is probably the most widely used technique [33]. Lesion-directed therapies, however, do not impact the field of cancerization, leaving invisible AKs that might arise in the future. Moreover, they are usually painful and can lead to melanocyte necrosis with consequent hypo- or hyperpigmentation and cosmetic concerns [34]. A summary of the characteristics, efficacy, and mechanism of action of topical treatments are shown in Table 1.

Tirbanibulin

In 2020 and 2021 respectively, tirbanibulin 1% ointment has been approved by Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of Olsen grade 1 AKs of the scalp and the face [35]. Tirbanibulin has a short course of application, just 5 consecutive days on an area of a maximum of 25 cm^2. Furthermore, the rate of skin adverse events is very low, with a vast majority of just

Table 1. Comparative Treatment Efficacy and Safety of Face-Scalp Typical Actinic Keratosis Approved in Europe [24]

Medication	Mechanism of Action	Duration of Treatment	Complete Clearance Rates at the end of the standard duration treatment Or (95% Ci)	Rate of Discontinuation Due to Adverse Events
Cryosurgery	Physical destruction of the affected tissue	Once	13.4 (6.2-30.3)	Not applicable
Tirbanibulin 1% ointment	Inhibits microtubule assembly and inhibits Scr kinase	5 consecutive days	11.1 (6.2-20.9)	0%
5-fluorouracil (FU) 0.5% + salicylate 10%	5-FU acts as a pyrimidine analogue, while salicylate has a keratolytic effect	Up to 12 consecutive weeks	7.6 (4.6-13.5)	1.9%-9.1%
Diclofenac 3% gel	Inhibits cyclooxygenases, and thus prostaglandin E2 production	Up to 12 consecutive weeks	2.9 (1.9-4.3)	2.1%-12.3%
Imiquimod 3.75% cream	Activates innate immune system	2 weeks, followed by a 2-week stop, followed by another 2 weeks cycle	8.5 (3.5-22.4)	0-1.6%
PDT with aminolevulinate (ALA)	The combined activity of a photosensitizer (ALA) and a specific wavelength cause the formation of free radicals	2 outpatient accesses	24.1 (10.9-52.8)	0.6%
PDT with methyl aminolevulinate (MAL)	The combined activity of a photosensitizer (MLA) and a specific wavelength cause the formation of free radicals	2 outpatient accesses	11.7 (6.0-21.9)	1.1%
5-Fluorouracil (FU) 4%	5-FU acts as a pyrimidine analogue	Up to 4 weeks	30.3 (9.1-144.7)	Not applicable
5-Fluorouracil (FU) 5%	5-FU acts as a pyrimidine analogue	Up to 4 weeks	35.0 (10.2-164.4)	0%

mild irritative reactions. For these characteristics, tirbanibulin represents a new effective, safe, and practical option for addressing the problem of patient compliance in AKs management.

This article reviews what is currently known about tirbanibulin, from its mechanism of action to clinical trial outcomes and preliminary real-life reports regarding safety, effectiveness, and patient adherence to the treatment.

Mechanism of Action

Tirbanibulin is a new synthetic drug that targets α and β tubulin, like other antitumoral drugs including vinca alkaloids, taxanes, colchicine, and docetaxel. In immunofluorescence, studies mechanism is concentration dependent on both in in-vitro tumoral lines and murine tumor tissues [36-38]. Immortalized keratinocytes incubation with tirbanibulin has proven to cause the arrest of the end of the interphase of phase growth 2 and mitosis when the assembly of microtubules allows for the migration of genetic material to opposite poles of the cell [36-38]. Of note, the good tolerability of this drug could be attributable to the reversibility of its effect [38].

Alongside the above, preclinical studies have proven tirbanibulin to have a pro-apoptotic effect in both in-vitro and murine models by activating both intrinsic and extrinsic pathways such as Bcl-2 hyperphosphorylation, and caspase-mediated mechanisms [36,37,39]. Not only does tirbanibulin show an antiproliferative and pro-apoptotic effect [38], but some evidence also [39,40] suggests that it plays a role in the rapid decrease of phosphorated Scr tyrosine kinase, which plays a role in the alterations of

hemidesmosomes necessary to the progression to a cSCC [41,42]. Certain medications used to treat AK, such as 5-fluorouracil, can produce localized skin responses by causing the release of proinflammatory cytokines such as tumor necrosis factor TNF α and interleukin IL 8. A preclinical investigation described the potential effects of tirbanibulin on the release of pro-inflammatory cytokines during a 24-hour incubation period of CCD-1106 KERTr keratinocytes. The findings demonstrated that whereas 5-fluorouracil generated a substantial rise in TNF α and IL-8, tirbanibulin incubation only slightly increased IL-8 at the highest dosage. Furthermore, IL-1, an indicator of cell death, was significantly higher in tirbanibulin-treated cells than in control (DMSO) and 5-fluorouracil. These findings imply that 5-fluorouracil is more likely to trigger a robust proinflammatory cytokine response than tirbanibulin, which could minimize the severity of local skin responses [41].

Phase 1 Trials

The Phase 1 trial [44] was an open-label single-center study. The enrolled patients had clinically typical AKs, and their age had to be ≥18. Thirty participants were enrolled in 4 successive cohorts. Cohort 1 was treated in a 25 cm^2 area with 4-8 AKs with tirbanibulin ointment 1% applied once a day for 3 consecutive days. Cohort 2 was 1 treated in a 100 cm^2 area with 8-16 AKs with tirbanibulin 200 mg once a day for 3 consecutive days. Cohorts 3 and 4 resembled cohorts 1 and 2 at baseline, except the treatment was carried on for 5 consecutive days. The results were evaluated in terms of lesion count reduction, which was classified as complete if 100% and partial if ≥75%. Each cohort was followed on days 10, 17, 31, and through day 45. Only 1 patient withdrew his consent, while the rest (n=29) completed the treatment and the follow-up.

Complete clearance was achieved in participants by rates of 25% in Cohort 1, 0% in Cohort 2, 50% in Cohort 3, and 12.5% in Cohort 4, while partial clearance was respectively 50%, 30%, 63%, and 50%. Data regarding effectiveness are summarized in Table 2.

Regarding safety, the only adverse effects reported were mild local skin reactions, mostly in cohorts 3 and 4 including itching, erythema, and stinging or burning sensation, which did not lead to the discontinuation of the treatment and that self-resolved. No contact sensitization, phototoxic, or photoallergic effects were reported (Table 3).

Phase 2 Trials

The phase 2 trial [44] was aimed at open-label, uncontrolled dose regimen-finding multicentric (16 centers) in which patients (n=168) aged at least 18 years were sequentially enrolled in 2 cohorts, each consisting of 84 patients.

In both cohorts, the treated area was 25 cm^2, with 4-8 clinically typical AKs on the scalp, face, and/or neck area. The daily dose of tirbanibulin, applied as a 1% ointment once a day, was around 50 mg/day, however, group 1 underwent the treatment for 3 consecutive days, while group 2 was for 5 consecutive days. The results were evaluated in terms of lesion count reduction, which was classified as complete if 100% and partial if ≥75%. Each cohort was evaluated on days 8, 15, 29, and 57.

Both cohorts showed a significant reduction in the lesion count by day 57, however, it was superior in those patients who used tirbanibulin for 5 days. Complete clearance was achieved by 43% (95% confidence interval [CI]: 32%, 0,54%)

Table 2. Actinic Keratosis Clearance Rates* Through Phase 1,2 and 3 [44,45]

		100% clearance % (n)	≥75% clearance % (n)
*Phase 1 Trial**	Cohort 1: 50 mg once daily for 3 days >25 cm^2 (n=4)	1 (25%)	2 (50%)
	Cohort 2: 200 mg once daily for 3 days >100 cm^2 (n=10)	0 (0%)	3 (30%)
	Cohort 3: 200 mg once daily for 5 days >25 cm^2 (n=8)	4 (50%)	5 (50%)
	Cohort 4: 200 mg once daily for 5 days >25 cm^2 (n=8)	1 (12.5%)	4 (63%)
Phase 2 study#	5-day cohort: 50 mg once-daily for 5 days over 25 cm^2 (n=84)	36 (43%)	47 (56%)
	5-day cohort: 50 mg once-daily for 3 days over 25 cm^2 (n=84)	27 (32%)	44 (52%)
Phase 3 study°	Tirbanibulin group (n=353)	174 (49%)	255 (72%)
	Vehicle (n=349)	30 (9%)	63 (18%)

*Clearance rates were either classified as complete (100%) or partial (≥75%) at day 45. Data of cohorts 1-4 are summarized above.
#Clearance rates were either classified as complete (100%) or partial (≥75%) at day 57. Data from 3- and 5-day cohorts are summarized above.
°Clearance rates were either classified as complete (100%) or partial (≥75%) at day 57. Clearance was assessed for both tirbanibulin and vehicle (placebo) cohorts. The percentage difference between the 2 groups is shown. Data are from intention-to-treat analysis.

Table 3. Treatment-Related Adverse Effects* Through Phases 1, 2, and 3. [44,45]

Phase 1 study	Mild n (%)	Severe n (%)
Cohort 1: 50 mg once daily for 3 days >25 cm^2 (n=4)	0	0
Cohort 2: 200 mg once daily for 3 days >100 cm^2 (n=4)	0	0
Cohort 3: 200 mg once daily for 5 days >25 cm^2 (n=4)	0	0
Cohort 4: 200 mg once daily for 5 days >25 cm^2 (n=4)	0	0
Phase 2 study		
5-day cohort: 50 mg once daily for 5 days >25 cm^2 (n=84)	9 (11)	0
5-day cohort: once daily for 3 days >25 cm^2 (n=84)	3 (4)	0
Phase 3 study, intention-to-treat		
Tirbanibulin	124 (35)	0
Vehicle	124 (36)	0

*Adverse events are classified as mild (no need to discontinue the treatment) and severe (need to discontinue the treatment). Of note, most adverse events were treatment-related mild.

in the 5-day group vs 32% (95% CI: 22%, 43%) in the 3-day group while a ≥75% clearance was achieved by 56% (95% CI: 45%, 67%) and 52% (41%, 63%) respectively. Data regarding effectiveness is summarized in Table 1.

Furthermore, all the patients who achieved complete clearance (n=63) were included in a further 12-month follow-up to evaluate the rate of recurrence. Consistent with the data above, the recurrence rate was lower in the 5-day cohort (57% [95% CI: 41%, 73%]) when compared to the 3-day cohort (70% [95% CI: 51%, 87%]).

One hundred percent of patients completed the treatment and the follow-up. No severe adverse effects (SAEs) or discontinuation of the therapy due to adverse effects were reported, and 7% (n=12) of the patients reported adverse effects, with a slightly higher occurrence in the 5-day cohort (11%, n=9) vs the 3-day cohort (4%, n=3). However, these effects were mostly mild lysosomal stress responses (LSRs), which never required discontinuation of the treatment or further interventions, and that were self-resolved (Table 3).

Phase 3 Trials

Phase 3 trials [45], conducted in the United States, were multicentric (62 centers), randomized, double-blind, parallel-group, vehicle-controlled (placebo trials). Patients were eligible for enrollment if they had 4-8 clinically typical AKs within a contiguous area of 25 cm^2 in the face-scalp area and were aged ≥18 years. The patients (n=702) were divided into 2 identical-sized groups (n=301, each) and were randomly assigned to receive a vehicle ointment or tirbanibulin 1% ointment with a 1:1 ratio. Enrollment, however, was controlled to achieve, within each trial, a 2:1 facial: scalp treated area ratio. Patients were evaluated at baseline and day 57. Primary and secondary outcomes were respectively complete clearance or incomplete lesion count reduction at day 57. These patients were re-evaluated after 12 months to assess the recurrence rate.

In trial 1 complete clearance occurred in 44% of patients (n=77) treated with tirbanibulin vs the placebo group 5% (n=8). Similar results were reported in trial 2 with 54% (n=97) vs 13% (n=22). Overall, a complete clearance was achieved by 49% (n=174) of the tirbanibulin group vs 9% (n=30) of the controls, with a difference of 41% (95% CI: 35%, 47%). Results were consistent with regards to the partial clearance outcome: across the 2 trials, a ≥75% clearance was obtained by 72% (n=255) of the tirbanibulin group vs 18% (n=63) of the vehicle, with a difference of 54% (95% CI: 48%, 60%) (Table 2).

No SAEs or discontinuation due to AEs occurred. The only AEs that occurred at a significantly higher rate in the tirbanibulin group vs placebo were LRSs, the most common of which were erythema (91%) and flaking or scaling (82%). Pain in the application site and pruritus were much less common. All the adverse effects were mild to moderate and resolved without the need for further treatment.

Real-World Studies

A real-world study that showed the real effectiveness of tirbanibulin in a real clinical contest was published by Kirchberger et al [46]. It was a single-center study of adult patients with AK of face and scalp treated with tirbanibulin ointment 1% applied daily for 5 consecutive days on the same lesion or field. The results of treatment were assessed 4 weeks after the beginning of administration of tirbanibulin plus optional assessments later in time. The effectiveness of tirbanibulin over the AKs was measured before and after the treatment with a specific score, the actinic keratosis area and severity

index (AKASI), and with digital dermoscopy. A group of 33 patients was eligible for the study design and treated but only 30 were analyzed because 3 were lost to follow-up. The results of this study showed that before treatment, the median AKASI score was 5.6 (1.4–11), after treatment it was 1.2 (0–7.4) ($p < 0.0001$), and at a second follow-up after a mean of 3.7 months was 0.6 (0-1.4). At the first and second follow-ups, 47 percent of patients (n = 14) and 57 percent of patients (n = 13) had complete clearance, as indicated by AKASI scores less than 1. Local adverse events occur between 2 and 10 days from the beginning of the treatment, with a median onset at the seventh day and a mean resolution time of 5 days. The most common local reaction reported is erythema (80%, n=26) followed by scaling and flaking (43%, n= 13%) and by pustulation ad pruritus (7%, n = 2). Six patients (20%) did not report any local adverse event. Every local reaction ended on its own, without any aftereffects. Another real-world experience involved 30 patients with AKs on their faces or scalps in a single-center, prospective, observational trial in which tirbanibulin ointment was applied to a 25 cm^2 area for five days in a row. To evaluate the drug's safety profile, effectiveness, and patient satisfaction, they were monitored for a minimum of 57 days. Six local skin response (LSR) symptoms were assessed and their intensity was rated as mild, moderate, or severe. These signs were erythema, scaling, crusting, swelling, blisters/pustules, and erosions/ulcerations. Dermatoscopically and clinically, the efficacy was assessed. The Medication Treatment Satisfaction Questionnaire (TSQM 1.4) was used to measure treatment satisfaction. The majority of LSRs, which included swelling (3.3%), scaling (30%), and erythema (83.3%), appeared on day 8 but went away on their own. moscopic response was observed in 70% of the patients on day 57.[47]. To evaluate the efficacy and safety of tirbanibulin 1% ointment, a spontaneous open-label, prospective non-randomized study focused on the treatment of 228 AKs in 38 consecutive patients—28 males (73%) and 10 females (26%), aged between 52 and 92 years (mean age: 72 ± 8.92 years). Of the lesions that were reported, 51% had total clearance and 73% had partial clearance. There was no treatment termination owing to the occurrence of adverse events, and an outstanding tolerability profile and high compliance rate were noted.[48]

Discussion

Tirbanibulin is approved by the FDA and EMA in the formulation of 1% ointment for treating grade I AKs (according to Olsen's grading) of the head and the neck in a contiguous area of no more than 25 cm^2. The application cycle must be of 5 consecutive days [35,49]. Since this drug has been marketed very recently, studies on compliance, efficacy, and cost-effectiveness compared to other approved treatments are still lacking.

A recent systematic review [24] of several phases 2 and 3 randomized controlled trials (RCTs) showed how tirbanibulin proved comparable effectiveness in lesion count reduction and complete clearance of the lesions when compared to both physical and topical FC-directed treatments. Odds ratio (OR), for complete clearance, with their respective 95% confidence interval, assessed at 8 weeks after baseline were: cryosurgery 13.4 (6.2-30.3); diclofenac 3% 2.9 (1.9-4.3); fluorouracil 0.5% + salicylic acid 7.6 (4.6-13.5); fluorouracil 4% 30.3 (9.1-144.7); fluorouracil 5% 35.0 (10.2-164.4); imiquimod 3.75% 8.5 (3.5-22.4); imiquimod 5% 17.9 (9.1-36.6); ingenol mebutate 0.015% 12.5 (8.1-19.9); photodynamic therapy with aminolevulinic acid 24.1 (10.9-52.8); photodynamic therapy with methyl aminolevulinate 11.7 (6.0-21.9); tirbanibulin 1% 11.1 (6.2-20.9).

Longer duration of topical therapy has repeatedly been shown to lower patient adherence to the therapy, leading to worse outcomes in real life [2,51]. This data is coherent with a recent systematic encompassing 14 studies and over 4,000 patients of patient-reported outcomes evaluating topic therapies for treating AKs, which improved significantly in both shorter-duration treatments [51]. Even though tirbanibulin was not directly evaluated in that systematic review, it is suggested that its 5-day course treatment would lead to high compliance and adherence to the treatment, in line with findings of Phases 1, 2, and 3 of the random controlled trials.

The safety of the drug is supported by the lack of significant changes in the clinical examination as well as in blood chemistry, urine, physical examination, and instrumental tests (ECG, blood pressure) in phase 1 and 2 trials [44] and by phase 3 trials [45]. This new drug, thus, not only seems to bring higher compliance but is very well tolerated. It has been proposed that the safety of tirbanibulin might be due to the reversibility of its mechanism of action [50].

Another review [35] investigated the most common application-site side effects, noting that they were mild LSRs: erythema (91%) scaling or flaking (82%), and much more rarely pain or itching at the application site. Consistently to the previous review, no severe AEs were reported, all AEs were resolved, and did not affect the adherence to therapy. All of these data from different trials are comparable with the local adverse events reported in real-life studies demonstrating the real safety of this treatment [59]. Moreover, a recent group of phase 1 studies in healthy volunteers [54] demonstrated that tirbanibulin ointment 1% had no sensitization or phototoxic or photoallergic potential connected with the treatment and supported the safety of this topical medication. Unsurprisingly, compliance to topical treatments seems to be related to both the length of the treatments and their tolerability profile [52,53]. One crucial point was that

in the reviews [44,45,49,50] tirbanibulin showed the lowest discontinuation rate with a compliance percentage of up to 100%. This is likely due to the well-tolerated profile of the drug and its easy administration regimen.

Incidentally, anecdotal experience from these two studies proves that the antitumoral effects above make tirbanibulin a potential candidate for future treatment of skin carcinomas, especially basocellular and squamocellular carcinomas even though it is not approved yet for these indications [55,56].

In patients with AK, a new Phase 1 trial assessed the safety and systemic exposure of tirbanibulin ointment 1% when applied under maximal usage settings, i.e., 350 mg once day for five days in a row to 100 cm2 of the face or balding scalp having eight or more AK lesions. The majority of TEAEs were mild, with application site reactions being the most common treatment-related TEAEs, similar to other topical AK treatments [57].

Finally, given the great effectiveness and safety of this medication, new sites for possible application over the approved face and scalp start to be reported. As shown in this case review study [58] tirbanibulin 1 % ointment demonstrated efficacy for the treatment of grade I and II AKs of upper arms with approximately 45% of complete clearance after a single cycle of therapy. Following the profile of safeness described for the face and scalp also for the upper extremities, tirbanibulin showed a significative level of tolerability and adherence to treatment thanks to its proapoptotic effect which reduces the inflammatory necrosis typical of the other medications prescribed for AKs.

Conclusions

Considering the short-term course of application, the low rate of local cutaneous side effects, and the efficacy profile, tirbanibulin represents a safe, effective, and practical option for managing grade I face and scalp AKs. In particular, tirbanibulin seems to raise patient adherence rates to topical AKs therapies. Furthermore, tirbanibulin shows potential benefits also on more advanced AKs or AKs located in other anatomical areas. Head-to-head studies comparing the efficacy of different therapeutical options with tirbanibulin are required to further understand the best positioning of this drug in a real-life setting.

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