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ORIGINAL ARTICLE

Predictors of outcomes and satisfaction with tirbanibulin in actinic keratosis: a multicenter real-world study

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A BSTRACT

BACKGROUND: Tirbanibulin 1% ointment is a short-course field therapy for actinic keratosis (AK). Real-world data on predictors of response, tolerability, and satisfaction may support patient selection and counselling. The aim was to evaluate effectiveness and tolerability in a large multicenter cohort, identify predictors of high clinical clearance and local skin reactions (LSRs), and describe patient and physician satisfaction.

METHODS: This retrospective observational real-life study (33 Italian dermatology centers) included 679 patients. Clinical response was classified as complete (100%), good (75-99%), moderate (50-74%), or <50% clearance; high clearance was defined as ≥75%. AK severity was assessed using AK Area and Severity Index (AKASI). LSRs were graded 0-4, and a total score was calculated. Satisfaction was rated 0–4 (scores 3–4 indicated high satisfaction.) Multivariable logistic regression identified predictors of high clearance, erythema, and vesiculation/pustulation.

RESULTS: Patients were predominantly male (70.8%), mean age 74.9±9.7 years; 77.6% were AK-experienced. All patients completed treatment. High clearance occurred in 69.7% and was greater in AK-naïve patients (78.3% vs. 67.1%, $P<0.001$). Mean AKASI decrease was 63.2%; photodamage improvement was 30.5%. Tolerability was favorable (mean LSR score 0.65±0.90); 11.9% of LSRs were ≥3, with no grade 4 vesiculation/ulceration occurring. Lower Olsen grade independently predicted high clearance. Female sex and age ≥75 years were associated with higher odds of selected LSRs. High satisfaction was reported by 79.4% of patients and 83.1% of physicians.

CONCLUSIONS: Tirbanibulin 1% achieved high clearance with favorable tolerability and satisfaction, supporting its use in individualized management of field cancerization.

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KEY WORDS: Actinic keratosis; Tirbanibulin; Patient satisfaction; Patient compliance.

Introduction

Actinic keratosis (AK) is a highly prevalent, chronic keratinocytic dysplasia driven primarily by ultraviolet (UV) radiation exposure. It represents a key entity within the spectrum of UV-induced epithelial dysplasia. Increasingly, AK is understood not merely as a collection of isolated premalignant lesions but as part of the broader concept of field cancerization, in which clinically visible lesions coexist with extensive subclinical dysplastic alterations across chronically sun-damaged skin. This framework reflects UV-driven genomic damage and clonal expansion across photo-exposed areas and provides a biological rationale for the relapsing nature of AK, characterized by the emergence of new lesions over time despite successful clearance of individual targets.[1-4] In clinical practice, this gives rise to a long-term condition requiring repeated therapeutic cycles and continuous preventive strategies, particularly among older individuals in whom cumulative actinic damage is extensive.[5]

The field cancerization model has direct implications for oncologic risk assessment and treatment intervention. The diagnosis of AK has been associated with an increased risk of skin cancer. Clinical lesions frequently occur in patients with a history of keratinocyte carcinoma (KC), underscoring the clinical relevance of structured surveillance and comprehensive field-directed approaches to care.[6, 7] At the population level, KCs constitute a major healthcare burden, and AK management represents a substantial proportion of the dermatologic workload, including both procedural and pharmacologic intervention.[8, 9] This healthcare demand reinforces the need for therapeutic agents that combine effectiveness with feasibility, patient acceptability, and suitability for repeated use in routine treatment pathways.[10]

Management of AK includes lesion-directed interventions, such as cryotherapy and curettage, and field-directed therapies designed to treat both visible lesions and subclinical dysplasia within photoexposed skin. Field therapy is particularly relevant in patients with multiple lesions, recurrent disease, or diffuse photodamage, in whom exclusive reliance on lesion-directed procedures may be insufficient and impractical.

A real-world, office-based approach to AK management has been proposed to guide treatment selection based on disease extent, severity, and patient factors.[11] In parallel, European consensus-based interdisciplinary guidelines emphasize individualized management of AK that incorporates assessment of disease severity and potential field cancerization, with prevention, and long-term follow-

up.[12] The adoption of standardized scoring systems further supports harmonized assessment and comparability of outcomes; the Actinic Keratosis Area and Severity Index (AKASI) was specifically developed to quantify AK severity on the head and has been increasingly used in both clinical trials and real-world investigations.[13]

Despite the availability of a broad range of treatment options, real-world outcomes are frequently influenced by therapy duration, complexity, tolerability, and patient adherence. Longer topical treatment courses may be challenging for older or frail patients and for individuals with limited ability to sustain multiweek self-application. Moreover, local inflammatory reactions can affect comfort, cosmetic acceptability, and willingness to complete or repeat therapy, with potential implications for follow-up requirement and resource utilization in high-volume settings. The importance of acceptability is underscored by evidence showing that perceived burden and prior experience with topical therapy can influence the willingness to undergo retreatment, thereby affecting long-term field control in chronic AK management.[14] In this setting, short-course therapies that can reduce treatment fatigue and simplify counselling have pragmatic relevance.

Tirbanibulin 1% ointment is a short-course topical field therapy administered once daily for five consecutive days; pivotal phase 3 trials demonstrated its efficacy and tolerability for AK of the face and scalp under controlled conditions, providing robust evidence for regulatory approval.[15] Subsequent comparative synthesis, including systematic review and network meta-analysis of randomized controlled trials, further contextualized the treatment's efficacy and safety relative to more established topical therapies.[16] The brief five-day regimen may represent a practical advantage by simplifying administration and improving adherence, particularly in older patients who frequently require repeated cycles of therapy over time.

In addition to efficacy, safety and tolerability remain central to the real-world implementation of field therapy, particularly when applied over larger skin areas or during periods associated with increased UV exposure.[15, 17] Dedicated clinical pharmacology and maximal-use studies have contributed clinically relevant pharmacokinetic and safety information in broader application contexts, while phase 3 tolerability investigation over 100 cm^2 on the face or scalp provides further reassurance regarding local tolerability under intensive field exposure conditions.[18, 19] Evidence addressing contact sensitization and phototoxic/photoallergic potential also informs safety considerations during routine clinical practice and in seasons characterized by higher ambient UV exposure.[20] Mechanistic data describing reversible binding of tirbanibulin to the colchicine-binding site of β-tubulin provide a plausible biological explanation for its low systemic toxicity and a manageable local safety profile.[21] Real-world evidence for tirbanibulin 1% ointment usage has expanded substantially, with observational and prospective studies reporting effectiveness, tolerability, AKASI reduction, and improved satisfaction outcomes in routine settings.[17, 22-26]

Additional case series and retrospective reviews have explored tirbanibulin use on anatomical areas other than the face and scalp, reflecting growing clinical interest in broader applicability.[22] Multicenter reporting in Italy has also described effectiveness and tolerability in field cancerization management, supporting the external validity of study treatment outcomes in everyday clinical practice.[24] In parallel, studies focusing on skin-quality endpoints related to photodamage, as well as economic evaluations in specific healthcare systems, have contributed to the pragmatic positioning of tirbanibulin among field-directed therapies. However, these secondary endpoints need to be interpreted carefully when incorporated into AK-focused manuscripts, as their relevance differs from core AK efficacy measures.[27-29]

Within this evolving evidence base, clinicians increasingly require a concise, practical synthesis of information to aid counselling rather than descriptive reporting. Specifically, practical decision-making is strengthened by identifying baseline characteristics that predict meaningful clinical clearance and by recognising local skin reactions that may influence comfort, follow-up planning, and the overall patient experience.

Accordingly, this Italian multicenter real-world study was designed to provide a clinically oriented synthesis of outcomes following tirbanibulin 1% therapy and to identify parsimonious, clinically interpretable predictors of high clearance and selected local skin reactions, together with patient- and physician-reported satisfaction. Focusing on clinically decision-relevant endpoints within a large real-world population, this study aims to provide actionable evidence to support patient selection, enhance expectation management, and refine the use of field-directed therapy in routine dermatologic practice.

Materials and methods

Ethical and regulatory approval

The study was approved prior to commencement by the appropriate ethics committee (Ethics Committee of CET

5 Lombardy, Italy, approval no. 729/25) and conducted in accordance with the principles set forth in the Helsinki Declaration as revised in 2024. All patients provided signed informed consent.

Study design and setting

This retrospective observational study evaluated adult patients with AK treated with tirbanibulin 1% ointment in routine clinical practice in 33 dermatology centers across Italy. All treatments were initiated during the warm season (April to September), and were prescribed in accordance with the approved regimen, *i.e*., once-daily application for five consecutive days over a contiguous treatment field. Data was extracted from institutional clinical records using a standardized case report structure shared among participating centers.

Eligibility criteria

This retrospective study included consecutive adult patients with a clinical diagnosis of AK who were treated with tirbanibulin 1% ointment as field-directed therapy according to the standard regimen in routine clinical practice. Consecutive inclusion was adopted to minimize selection bias. Patients were included if their baseline clinical assessment and at least one post-treatment evaluation were available to measure clinical response and tolerability outcomes. Exclusion criteria comprised incomplete clinical documentation preventing assessment of primary outcomes, absence of follow-up information, and deviation from the standard five-day dosing schedule (*i.e*., treatment courses not completed as prescribed). When multiple AK sites were treated in the same patient, all treatment sites were recorded and considered in the analyses; patient-level variables were recorded once per patient.

Baseline variables and clinical characterization

Baseline patient characteristics included age, sex, and Fitzpatrick phototype. Comorbidity burden was defined pragmatically as a binary variable ('multiple comorbidities'), indicating the presence of comorbidities in more than one category in the clinical record. Dermatologic oncologic history was captured as prior melanoma, basal cell carcinoma (BCC), and squamous cell carcinoma (SCC).

AK clinical characterization included the anatomical location of treated fields, grouped as face, scalp, or other body sites. Disease extent was recorded at the patient level as the number of treated sites, dichotomized as 1 site versus ≥2 sites for modelling purposes. Lesion severity was assessed clinically according to the Olsen classification. Because some patients had more than one treated site, Olsen grade was considered a site-level variable. For predictive analyses, baseline severity was dichotomized as Olsen grade ≤2 *versus* >2 consistent with a clinically meaningful separation between less severe and more severe/hyperkeratotic disease patterns.

AK history was also classified using a pragmatic longitudinal definition. Patients were categorized as "AK-naïve" when AK lesions had been present for less than one year, and as "AK-experienced" when AK had been present for more than one year and/or when prior treatments had been documented, reflecting a chronic or recurrent disease course frequently encountered in routine practice.

Outcomes

Clinical response was assessed at post-treatment follow-up and categorized using a standardized ordinal scale based on the estimated reduction in AK lesions within the treated field. Categories included: complete clearance (100% reduction), good response (75-99%), moderate response (50-74%), mild response (25-49%), and poor response (0-24%). For predictive analyses intended to guide patient counselling, a binary outcome of high clearance was defined *a priori* as ≥75% clearance (complete plus good response), whereas <50% clearance was defined as 25-49% and 0-24% clearance (mild and poor response). The ≥75% threshold was selected to represent a clinically meaningful level of improvement for routine decision-making. When available, AKASI scores were recorded at baseline and post-treatment and were used to quantify overall change in disease burden over time. At the cohort level, AKASI scores were summarized as mean baseline and post-treatment values with the corresponding mean change.

Global photodamage within the treated area was graded clinically (absent, mild, moderate or severe), at baseline and post-treatment, using routine documentation when available. Improvement in photodamage was recorded as a binary outcome (improved *versus* not improved). Local skin reactions (LSRs) were recorded across six domains: erythema, scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration. Each domain was graded on a 0-4 scale (0 = absent to 4 = very severe) at post-treatment evaluation. Overall LSR burden was summarized using a total LSR score, defined as the sum of the six domain scores (range 0-24). For table-only reporting, tolerability was summarized as the proportion of patients experiencing

each LSR domain at any grade, the mean (SD) total LSR score, the proportion of LSR domain entries graded ≥3, and the occurrence of grade 4 vesiculation or ulceration. Patient and physician satisfaction were recorded using a 0–4 scale (0 = no satisfaction to 4 = extreme satisfaction). Patient-physician concordance was defined as agreement between the patient- and physician-reported satisfaction categories for each treatment episode.

Statistical analysis

Categorical variables were summarized as frequencies and percentages; continuous variables were summarized as mean and standard deviation. Site-level variables were summarized using site-entry denominators, whereas patient-level variables used the total number of patients. Post-treatment photodamage assessments were summarized using the denominator of patients with available follow-up photodamage documentation. Between-group comparisons were performed when relevant for descriptive purposes using chi-square tests (or Fisher's Exact Test when appropriate) for categorical variables and independent-samples t tests for continuous variables. Correlations between treatment satisfaction and effectiveness, and between satisfaction and tolerability measures, were evaluated using Spearman's correlation coefficient. To generate clinically interpretable predictors suitable for routine counselling, we fitted multivariable logistic regression models for three prespecified outcomes: high clearance (≥75%); occurrence of erythema (any grade); occurrence of vesiculation/pustulation (any grade). The covariate set was selected *a priori* to balance clinical plausibility with model parsimony, and included female sex, age ≥75 years, phototype III–IV, multiple comorbidities, Olsen grade >2, and ≥2 involved sites. Results are reported as adjusted odds ratios (aORs) with 95% confidence intervals (95% CI). Statistical significance was defined as a two-sided P value <0.05. Analyses were performed using Stata version 17 (StataCorp, College Station, TX, USA).

Results

Patient profile and disease characteristics

A total of 679 patients were included in the study. The cohort was predominantly male (70.8%), with a mean age of 74.9 years (SD 9.66). Fitzpatrick phototype II was most frequent (69.1%), followed by phototype III (21.9%), phototype I (8.5%), and phototype IV (0.4%). A substantial proportion of patients had a prior history of skin cancer, including melanoma (10.9%), BCC (40.6%), and SCC (28.9%). Most patients were classified as AK-experienced (77.6%), while 22.4% were AK-naïve (Table I). Regarding disease distribution, AK fields were mostly located on the face (61.8%) and scalp (31.8%), with other body sites accounting for 6.4% of treated fields (percentages based on field-level entries, not patient counts). At the patient level, 70.9% had one involved treated site and 29.1% had two or more sites. Lesion severity assessed by Olsen grade was predominantly mild-to-moderate, with grades I and II accounting for 44.4% and 48.6% of evaluable site entries, respectively, whereas grade III represented 6.2% (Table I). Baseline AK burden, quantified by AKASI, was 4.5 (mean), and baseline photodamage was graded as moderate in 45.2% and severe in 16.5% of patients (Table I).

TABLE I.—*Baseline patient and disease characteristics, including actinic keratosis distribution and severity.*

Variable	Total cohort
Patients	679
AK status	
AK-experienced	527 (77.6%)
AK-naïve	152 (22.4%)
Sex	Male: 481 (70.8%); Female: 198 (29.2%)
Mean age, years	74.9±9.66
Fitzpatrick phototype	
I	58 (8.5%)
II	469 (69.1%)
III	149 (21.9%)
IV	3 (0.4%)
History of melanoma	74 (10.9%)
History of basal cell carcinoma	276 (40.6%)
History of squamous cell carcinoma	196 (28.9%)
Number of involved sites (patient-level)	
1 site	479 (70.9%)
≥2 sites	197 (29.1%)
AK distribution by site (site-level)	
Face	548 (61.8%)
Scalp	282 (31.8%)
Other	57 (6.4%)
Olsen clinical grade (site-level)	
I	359 (44.4%)
II	393 (48.6%)
III	50 (6.2%)
Not available	6 (0.7%)
AKASI, baseline (mean)	4.54
Baseline photodamage	
Severe	112 (16.5%)
Moderate	307 (45.2%)
Mild	242 (35.6%)
Absent	14 (2.1%)
Not available	4 (0.6%)

AK: actinic keratosis; AKASI: AK Area and Severity Index; SD: standard deviation.

TABLE II.—*Clinical outcomes after tirbanibulin treatment: clearance, AKASI change, tolerability summary, and satisfaction.*

Parameter	Endpoint	Result
Effectiveness (clearance categories)	High clearance (≥75%) (100% + 75-99%)	473 (69.7%)
	Complete clearance (100%)	198 (29.2%)
	Good response (75-99%)	275 (40.5%)
	Moderate response (50-74%)	132 (19.4%)
	<50% response	74 (10.9%)
Effectiveness (AKASI)	AKASI, baseline (mean)	4.54
	AKASI, post-treatment (mean)	1.67
	Mean change (Δ)	−2.87
	Mean % reduction	−63.2%
Field effect	Photodamage improved	206 (30.5%)
IGA (subset)	IGA available, n	74
	IGA = 0 post-treatment	23 (31.1%)
	IGA grade 3-4 post-treatment	0/74 (0.0%)
Tolerability (LSRs)	Total LSR score, mean±SD	0.65±0.90
	Erythema (any grade)	80%
	Scaling (any grade)	60%
	Swelling (any grade)	40%
	Crusting (any grade)	39%
	Erosion/ulceration (any grade)	19%
	Vesiculation/pustulation (any grade)	18%
	Events graded ≥3 (overall)	11.9%
	Grade 4 vesiculation or ulceration	0.0%
Satisfaction	Patient high satisfaction (score 3-4)	539 (79.4%)
	Physician high satisfaction (score 3-4)	564 (83.1%)
	Patient–physician concordance	66.1%
Adherence	Completion of 5-day regimen	100%

AKASI: Actinic Keratosis Area and Severity Index; IGA: Investigator Global Assessment; LSR: local skin reaction; SD: standard deviation

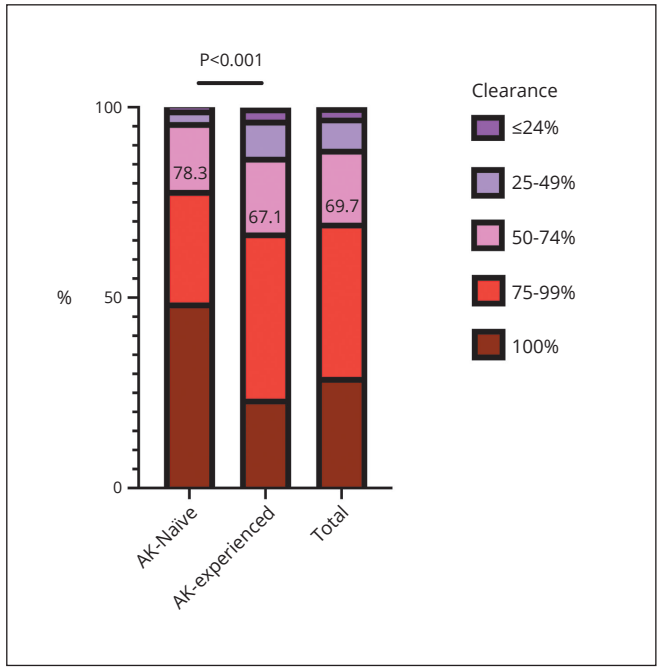

Figure 1.—Clinical efficacy of tirbanibulin 1% ointment in the treatment of actinic keratoses (AKs). Proportion of patients achieving different clearance rates (≤24%, 25-49%, 50-74%, 75-99%, and 100%) stratified by treatment history (AK-naïve *versus* AK-experienced) and overall population. Complete (100%) and high (75-99%) clearance rates were significantly more frequent among AK-naïve patients (P<0.001).

Clinical effectiveness and field effect

Clinical effectiveness outcomes are summarized in Table II. All patients completed the prescribed five-day regimen. Complete clearance (100%) was achieved in 29.2% of patients, while overall high clearance (≥75%) was observed in 69.7% of patients. Clinical efficacy was significantly higher in AK-naïve patients compared with AK-experienced patients, both in terms of complete clearance (48.7% *vs*. 23.5%; P<0.001) and high clearance (78.3% *vs*. 67.1%; P<0.001) (Figure 1) (Supplementary Digital Material 1: Supplementary Table I). In parallel, AKASI decreased from a baseline mean of 4.54 to 1.67 at post-treatment assessment, corresponding to a mean absolute change of -2.87 and a mean relative reduction of 63.2% (Table II).

Improvement in photodamage within the treated field was documented in 30.5% of patients with available assessment (Table II, Figure 2). AK-naïve patients showed a significantly greater improvement in photodamage (41.4% *vs*. 27.3%; P=0.0006) (Supplementary Table I).

In the subset with available Investigator Global Assessment (IGA) body evaluation (N.=74), IGA grade 0 was recorded in 31.1% of patients at post-treatment follow-up, while IGA grades 3-4 were not recorded at all (Table II).

In multivariable modelling, Olsen grade >2 was independently associated with a lower probability of achieving high clearance (≥75%) (aOR 0.476; 95% CI 0.285–0.796; P=0.005), whereas female sex, age ≥75 years, phototype III-IV, multiple comorbidities, and involvement of ≥2 sites were not significantly associated with high clearance in the adjusted model (Table III).

Tolerability and local skin reactions

Overall tolerability was favorable (Table II). The mean total LSR score was 0.65±0.90. Erythema was most recorded (80% at any grade), followed by scaling (60%), swelling (40%), crusting (39%), erosion/ulceration (19%), and vesiculation/pustulation (18%). Across all recorded LSR assessments, 11.9% were graded ≥3, with no grade 4 vesiculation or ulceration observed. AK-experienced patients demonstrated a relatively greater occurrence of moderate LSRs (Figure 3) (Supplementary Digital Material 2: Supplementary Table II).

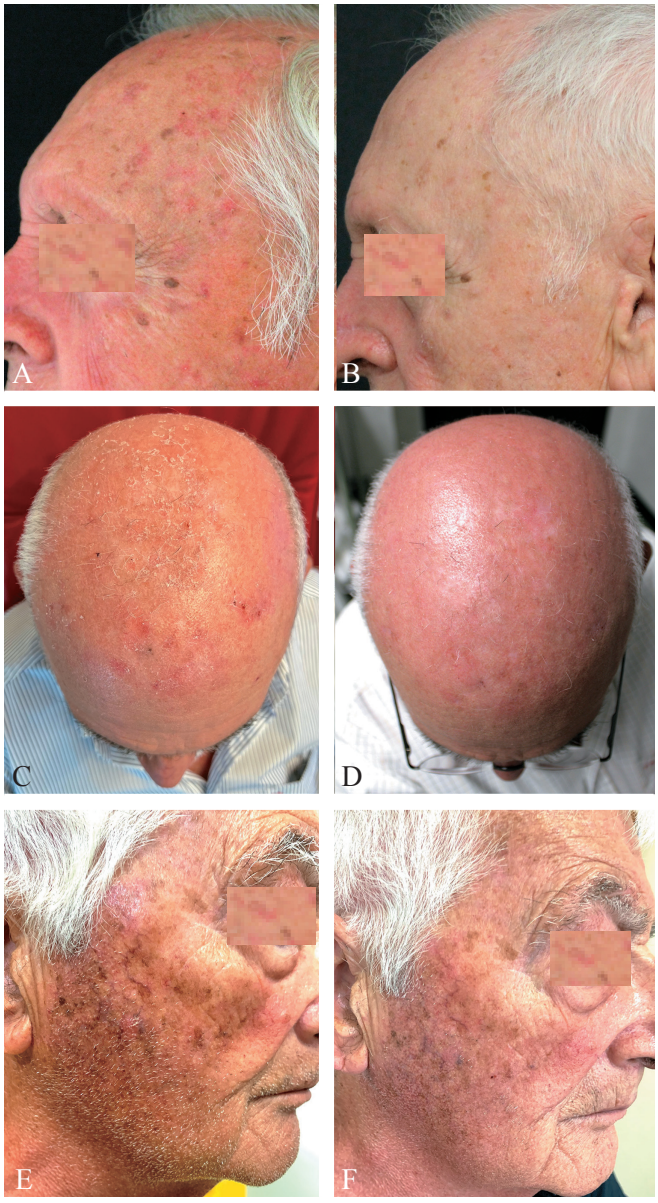

Figure 2.—Baseline clinical presentation of three patients with actinic keratoses (AKs) treated with tirbanibulin 1% ointment (A, C, E). Corresponding outcomes approximately 8-10 weeks after a 5-day course of tirbanibulin 1% ointment (B, D, F). A reduction in the number of visible AK lesions is evident, together with marked improvement in photodamage, including decreased erythema and hyperkeratosis.

Exploratory univariate analyses suggested higher LSR rates in AK-experienced patients, in those with higher baseline AKASI or prior AK treatments, and in patients with multiple treated sites; phototype I-II was associated with higher rates of swelling and vesiculation. No comorbidity showed a significant association with LSR severity.

Multivariable analyses identified patient characteristics associated with selected clinically relevant LSRs (Table III). Female sex was associated with higher odds of erythema (aOR 1.817; 95% CI 1.316-2.508; P<0.001) and vesiculation/pustulation (aOR 1.950; 95% CI 1.263–3.010; P=0.003). Age ≥75 years was independently associated with erythema (aOR 1.619; 95% CI 1.204–2.176; P=0.001) but not with vesiculation/pustulation (Table III). Olsen grade >2 and involvement of ≥2 sites were inversely associated with erythema (aOR 0.565; 95% CI 0.422–0.758; P<0.001; and aOR 0.632; 95% CI 0.458–0.872; P=0.005, respectively). Olsen grade >2 was also inversely associated with vesiculation/pustulation (aOR 0.442; 95% CI 0.290–0.674; P<0.001), while ≥2 sites did not reach statistical significance for this endpoint (aOR 0.673; 95% CI 0.430–1.054; P=0.084) (Table III).

Satisfaction

High satisfaction (score 3 or 4) was reported by 79.4% of patients and by 83.1% of physicians. Patient-physician satisfaction concordance was 66.1% (Table II).

Transplanted patients

Among 23 transplanted patients, 82.6% were male and most had Fitzpatrick phototype III. A prior history of AK was reported in 12 individuals, with the face being the most frequently treated site (69.6%). Clinical effectiveness showed complete clearance in 39.1% of patients and good response (75-99% clearance) in 47.8% of patients. Tolerability was favorable, with a low mean total LSR score (0.46±0.75); one grade 4 LSR was recorded. High satisfaction was reported by 95.6% of patients and 100% of physicians. IGA was available for three patients and was consistent with clinical improvement.

Discussion

This large multicenter real-world study offers a clinically oriented synthesis of outcomes following tirbanibulin 1% ointment field therapy and identifies pragmatic predictors to support routine counselling. In a cohort of elderly patients with substantial photodamage and frequent prior KC, tirbanibulin therapy achieved high clearance in approximately two-thirds of patients and produced marked reduction in AK severity, as measured by AKASI, alongside a favorable tolerability profile and high satisfaction reported by both patients and physicians. These findings are consistent with the current view of AK as a field disease within the broader construct of field cancerization and sup-

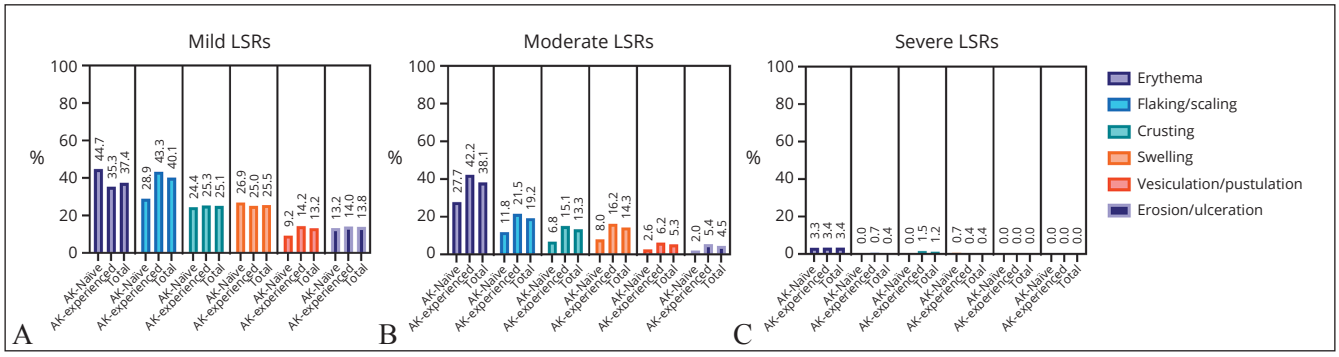

Figure 3.—Frequency and severity of local skin reactions (LSRs) following treatment with tirbanibulin 1% ointment. Percentage of patients experiencing mild (A), moderate (B), and severe (C) LSRs, stratified by treatment history (AK-naïve *versus* AK-experienced) and shown for the total population. The most frequently reported LSRs were mild erythema, flaking/scaling, and crusting. Moderate reactions were less common, while severe LSRs were rare across all subtypes, with no cases of severe flaking/scaling, swelling, vesiculation/pustulation, or erosion/ulceration observed. AK: actinic keratoses.

TABLE III.—*Multivariable logistic regression models identifying predictors of high clearance and selected clinically relevant local skin reactions.*

Predictor	aOR (95% CI)	P value
Predictors of high clearance (≥75%)		
Female sex	1.024 (0.591–1.777)	0.931
Age ≥75 years	0.838 (0.502–1.398)	0.498
Phototype III–IV	0.862 (0.465–1.598)	0.638
Multiple comorbidities	0.761 (0.360–1.609)	0.475
Olsen grade >2	0.476 (0.285–0.796)	0.005
≥2 involved sites	1.300 (0.724–2.332)	0.379
Predictors of erythema (LSR)		
Female sex	1.817 (1.316–2.508)	<0.001
Age ≥75 years	1.619 (1.204–2.176)	0.001
Phototype III–IV	1.081 (0.774–1.511)	0.646
Multiple comorbidities	1.175 (0.800–1.726)	0.412
Olsen grade >2	0.565 (0.422–0.758)	<0.001
≥2 involved sites	0.632 (0.458–0.872)	0.005
Predictors of vesiculation/pustulation (LSR)		
Female sex	1.950 (1.263–3.010)	0.003
Age ≥75 years	1.073 (0.703–1.637)	0.744
Phototype III–IV	0.695 (0.410–1.177)	0.175
Multiple comorbidities	0.797 (0.445–1.427)	0.445
Olsen grade >2	0.442 (0.290–0.674)	<0.001
≥2 involved sites	0.673 (0.430–1.054)	0.084

aOR: adjusted odds ratio; CI: confidence interval; LSR: local skin reaction.

port the need for repeatable, feasible field-directed strategies embedded in long-term management pathways.[1-4, 12]

The effectiveness observed in this cohort is consistent with evidence from pivotal randomized phase 3 trials and with subsequent comparative synthesis of randomized data.[15, 16] Importantly, the expanding body of real-world literature has shown that tirbanibulin retains meaningful effectiveness under routine conditions, including studies reporting significant AKASI reductions, reinforcing the value of AKASI as a standardized, field-oriented instrument for severity quantification.[13, 23] In addition, multicenter observational experiences of Italian cohorts have described favorable effectiveness and tolerability in the management of field cancerization, supporting the external validity of tirbanibulin outcomes in routine practice.[24-26]

This dataset extends previous observations by emphasizing counselling-oriented predictors from parsimonious models, complementing average response estimates with clinically interpretable stratification signals.

In multivariable analysis, baseline clinical severity emerged as a clinically meaningful stratification response parameter. Patients with milder lesions (Olsen grade I-II) were more likely to achieve high clearance whereas patients with Olsen grade >2 had reduced likelihood of high clearance. This pattern may be explained clinically because increasing hyperkeratosis can limit topical agent penetration and may indicate greater lesion heterogeneity.

From a guideline perspective, this finding supports patient selection and management of expectations based on disease severity, consistent with European consensus emphasizing individualized care based on disease extent and severity.[12] In routine clinical practice, patients with a predominance of higher-grade lesions may benefit from clearer management of expectations regarding potential clearance rates and from follow-up strategies that allow early identification of partial responders who may require adjunctive lesion-directed therapy or pre-treatment with keratolytic agents to reduce hyperkeratosis. A notable finding of the study is the significantly superior clinical performance of tirbanibulin in AK-naïve patients compared with those with a history of prior treatment (AK-experienced patients). This discrepancy suggests that AK-naïve fields

may offer a biologically more receptive disease state, whereas AK-experienced patients often harbor more recalcitrant lesions or advanced field cancerization, characterized by chronic hyperkeratosis, which may partially limit drug penetration. Furthermore, the significantly greater improvement in photodamage observed in the AK-naïve subgroup underscores the potential of tirbanibulin as an early-intervention strategy.

Tolerability outcomes in the present study were favorable and consistent with the broader safety and tolerability findings reported during clinical development and subsequent post-approval evaluation. The low mean LSR burden, limited proportion of higher-grade classifications, and the absence of grade 4 vesiculation or ulceration are in line with the tolerability profile described across controlled and maximal-use contexts.[18, 19] Evidence addressing sensitization and phototoxic/photoallergic potential further informs prescribing confidence, particularly in routine settings and during periods of higher ambient UV exposure.[20] Mechanistic evidence describing reversible binding at the colchicine-binding site of β-tubulin provides a coherent biological explanation for low systemic toxicity and contributes to the plausibility of a manageable safety profile in real-world use.[21]

The main findings were also observed in clinically vulnerable subgroups, including organ transplant recipients. Immunosuppressed individuals are at substantially increased risk of AK progression to invasive SCC and therefore require effective field-directed strategies.[30, 31] However, treating these fragile patients can be challenging due to a higher susceptibility to delayed wound healing and potentially lower tolerance to prolonged, highly inflammatory topical regimens.[10, 32, 33]

In the transplanted subgroup, tirbanibulin demonstrated clinical activity, with approximately 87% of patients achieving a 75% reduction or more in lesion count. Importantly, this effectiveness was not associated with an increased safety burden, as treatment was generally well tolerated and characterized by a low incidence of clinically significant local reactions.

The full adherence rates observed in this cohort further support the feasibility advantage of a short five-day schedule, an attribute likely to be clinically relevant in busy outpatient departments, particularly in the care of elderly patients. Poor therapeutic adherence remains a well-recognized barrier to successful outcome in the topical management of field cancerization, often driven by prolonged treatment regimens and the occurrence of severe, treatment-limiting LSRs.[10, 16, 34-38] In this context, a short application schedule combined with a favorable local tolerability profile may reduce treatment fatigue and lower the risk of early discontinuation. This observation is supported by tirbanibulin data from pivotal phase III trials and subsequent real-world studies, which consistently report adherence rates exceeding 99%, underscoring the importance of simplified posology and predictable, generally mild local reactions in promoting high treatment adherence.[15, 24, 34, 35, 38] Predictive modelling identified female sex as an independent risk marker for erythema and vesiculation/pustulation, and older age (75 years and over) as an independent predictor of erythema.

These results have practical implications for counselling and planned follow-up, because local reactions remain a key determinant of perceived burden, cosmetic acceptability, and unscheduled contact during field therapy. Univariate analyses also suggest that LSR frequency may vary in relation to AK history and baseline field burden (*e.g.*, as measured by AKASI and previous treatment), supporting the use of counselling that encompasses both patient profile (sex/age) and disease status. In chronic disease management, when long-term field control frequently necessitates repeated therapy cycles, treatment acceptability, and willingness to undergo retreatment are clinically important, given that retreatment refusal has been documented for previous topical regimens.[14] The combination of a short-course schedule and overall favorable tolerability profile seen with tirbanibulin may therefore offer practical advantage when aligning therapeutic choice with patient preference and preserving willingness for future treatment cycles.

The increasing breadth of real-world data available has also included endpoints other than clearance, such as satisfaction, AKASI reduction, and skin-quality outcomes related to photodamage.[22-29] While such endpoints should remain contextualized within the primary therapeutic goals of AK field management, they highlight the relevance of patient-centered outcomes in routine practice. Economic evaluation has also suggested that the short-term regimen afforded by tirbanibulin may offer favorable value proposition in specific health system settings, reinforcing the agent's pragmatic positioning among more established field-directed therapies.[28-39] Collectively, these data support a role for tirbanibulin within individualized AK management pathways, particularly when regimen simplicity and acceptability should be prioritized.

Limitations of the study

This study has limitations inherent to its retrospective design, including potential selection bias, heterogeneity in

follow-up timing, and variability in documentation across participating centers. Some measures were available only in subsets, limiting precision for these endpoints. LSR grading reflected routine assessment which may be subject to interobserver variability. Additionally, the evaluation of global photodamage relied on a subjective clinical estimation based on routine documentation, lacking the use of a validated, standardized grading tool. Moreover, although the predictor models were intentionally parsimonious to preserve interpretability and reduce the risk of overfitting, they cannot capture all determinants of response and tolerability, including detailed lesion morphology, sequencing of prior therapies, and behavioral factors. External validation of the identified predictors in independent cohorts would strengthen their applicability to clinical practice.

Conclusions

In conclusion, in this large real-world multicenter study, tirbanibulin 1% ointment administered as a five-day treatment regimen demonstrated high field-clearance rates, substantial AKASI reduction, favorable tolerability, and high satisfaction ratings. Patients with milder baseline disease (Olsen grade I-II) and/or recent disease history (AK-naïve patients) were more likely to achieve high clearance. Male sex, age <75 years, and AK-naivety were associated with a lower probability of selected local reactions. These findings provide concise, clinically actionable signals for patient selection, expectation management, and counselling in routine AK field treatment, consistent with contemporary field cancerization frameworks and guideline-based management principles.

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Conflicts of interest

Marco Ardigò has received consulting fees from Pierre Fabre and has participated in lectures, presentations, and advisory boards for Almirall, Kyowa Kirin, Pierre Fabre, Recordati Rare Diseases, and Cantabria Labs. Laura Atzori has participated in advisory boards, lectures, presentations, and received support for attending meetings from AbbVie, Amgen, Sanofi, LEO Pharma, Pfizer, Eli Lilly, J&J, BMS, Novartis, and UCB. Riccardo Balestri has received support for attending meetings from Lilly, AbbVie, Amgen, and Novartis. Stefania Barruscotti has participated in presentations/lectures for L'Oreal. Manfredo Bruni has participated in presentations/lectures for Almirall, AbbVie, and Novartis. Stefano Caccavale has received consulting fees from Boehringer Ingelheim, and has participated in lectures/presentations for AbbVie, Novartis, Pfizer, J&J, Almirall, and LEO Pharma, and received support for attending meetings from Galderma and Eli Lilly. Andrea Carugno has received payment or honoraria for lectures/presentations from Almirall, UCB, J&J, and Novartis, and has participated in advisory boards for Almirall, AbbVie, BMS, Sanofi, LEO Pharma, UCB, and Boehringer Ingelheim; he has also received support for attending meetings from Almirall, Sanofi, AbbVie, and Novartis. Giulia Ciccarese has received consulting fees from Almirall and support for attending meetings from Pierre Fabre. Giacomo Dal Bello has participated in presentations/lectures for Almirall. Pietro Danese has received grants or contracts from Sanofi, LEO Pharma, and Almirall and support for attending meetings from Sanofi, LEO Pharma, Almirall, and AbbVie. Maria Concetta Fargnoli has served on advisory boards, received honoraria for lectures and/or research grants from Almirall, Galderma, and Pierre Fabre. Lerica Germi has received consulting fees from LEO Pharma and AbbVie and has participated in lectures and presentations for Novartis and advisory boards for AbbVie and Almirall. Serena Giacalone has received payment or honoraria for lectures from LEO Pharma, AbbVie, Almirall, Sanofi, UCB, and Novartis, and has participated in advisory boards for Almirall. Roberta Giuffrida has received payment or honoraria for lectures and presentations from Pierre Fabre. Gianluca Nazzaro has received payment or honoraria for lectures from Novartis, Giuliani, L'Oreal, IDI Farmaceutici, and Almirall. Mario Valenti has received payment or honoraria for lectures and presentations from Sanofi, Sun Pharma, Almirall, AbbVie, Novartis, UCB, Boehringer Ingelheim, LEO Pharma, Eli Lilly, Difa Cooper, and Janssen, support for attending meetings from Sanofi, Almirall, AbbVie, Novartis, Janssen, LEO Pharma, UCB, and Eli Lilly, and has participated in advisory boards for Almirall and UCB. Elisa Zavattaro has received consulting fees from Active Pharma Group and support for attending meetings from the Ganassini Institute and Sanofi–Regeneron. Lisa Argnani, Francesco Bellinato, Elena Zappia, Maria Vittoria Masala, Giampaolo Addari, Emanuele Trovato, Giovanni Paolino, Andrea D'Arino, Cristina Magnoni, Giulia Toni, Alice Verdelli, Alessia Villani, Sebastiano Recalcati, Stefano Bighetti, Luca Bettolini, Giovanni Fiorillo, Stefano Fazio, Carmen Cantisani, Vincenzo Maione, Salvatore D. Infusino, Laura Eibenschutz, Alice Cesari, Martina Dragotto, Grazia B. Zolo, Anna Elisa Verzì, Paola Savoia, Iris Zalaudek, Elia Sala, Enzo Errichetti, Santo Raffaele Mercuri, Maria Esposito, Caterina Foti, Francesco Lacarrubba, Simone Ribero, Paolo Gisondi, Angelo Valerio Marzano, Nicola Zerbinati declare no conflicts of interest. The authors did not receive any external funding for conducting this study.

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Data availability

The data associated with the paper are available from the corresponding author upon reasonable request.

Ethical approval

All procedures performed in this study involving human participants received ethical approval from the competent authorities, as described in the appropriate section of the manuscript, and have been conducted in accordance with the 1964 Helsinki Declaration and its later amendments. The authors confirm that this article does not report any studies involving embryos, gametes and human embryonic stem cells conducted by the authors. The authors confirm that this article does not report any studies involving animals conducted by the authors.

Informed consent
Written informed consent was obtained from all participants prior to inclusion in the study and for publication of their data, as described in the appropriate section of the manuscript.

Authors' contributions
Andrea Carugno has given substantial contributions to the conception and the design of the manuscript, Andrea Carugno and Lisa Argnani to analysis and interpretation of the data. All authors have participated to acquiring data and drafting the manuscript; Andrea Carugno, Lisa Argnani and Stefano Bighetti revised it critically. All authors read and approved the final version of the manuscript.

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SUPPLEMENTARY DIGITAL MATERIAL 1

Supplementary Table I.—Baseline characteristics and tirbanibulin treatment outcomes.

Characteristics	**Total**	**AK-Experienced**	**AK-Naïve**	***p***
Site of AK	887*	710	177	0.000
Single site:				
A: Face	548 (61.8%)	420 (59.2%)	128 (72.3%)	
B: Scalp	282 (31.8%)	247 (34.8%)	35 (19.8%)	
C: Rest of the body	57 (6.4%)	43 (6.1%)	14 (7.9%)	
Multiple sites:				0.035
1	479 (70.9%)	355 (67.4%)	127 (83.6%)	
2	186 (27.4%)	161 (30.6%)	25 (16.4%)	
3	11 (1.6%)	11 (2.1%)	0 (0)	
Body site: **	57	43	14	0.165
Chest	16 (28.1%)	8 (18.6%)	8 (57.1%)	
Hands	19 (33.3%)	16 (37.2%)	3 (21.4%)	
Hands/arms	1 (1.8%)	1 (2.3%)	0 (0)	
Hands/chest	2 (3.5%)	2 (4.7%)	0 (0)	
Legs	7 (12.3%)	6 (13.9%)	1 (7.1%)	
Upper limbs	11 (19.3%)	9 (20.9%)	2 (14.3%)	
Not available	1			
Olsen grade of AK	808	633	175	0.02

I	359 (44.4%)	261 (41.2%)	98 (56.0%)	
II	393 (48.6%)	323 (51.0%)	70 (40.0%)	
III	50 (6.2%)	44 (6.9%)	6 (3.4%)	
Not available	6 (0.7%)	5 (0.8%)	1 (0.6%)	
Mean AKASI before treatment	4.537	4.796887	3.633784	0.0000
Mean AKASI after treatment	1.669	1.855273	1.002083	0.0000
Delta (%)	-2.868 (-63.2%)	-2.941614 (-61.3%)	-2.631701 (-72,4%)	0.076
Body (C) IGA before treatment	74	52	22	0.915
0	0	0	0	
1	11 (14.8%)	7 (13.5%)	4 (18.2%)	
2	24 (32.4%)	18 (34.6%)	6 (27.3%)	
3	36 (48.6%)	25 (48.1%)	11 (50.0%)	
4	3 (4.1%)	2 (3.8%)	1 (4.5%)	
Body (C) IGA after treatment				0.082
0	23 (31.1%)	16 (30.8%)	7 (31.8%)	
1	36 (48.6%)	24 (46.2%)	12 (54.5%)	
2	15 (20.3%)	12 (23.1%)	3 (13.6%)	
3	0	0	0	
4	0	0	0	
Skin photodamage				
Skin photodamage before treatment	679	527	152	0.000

Severe	112 (16.5%)	97 (18.4%)	15 (9.9%)	
Moderate	307 (45.2%)	252 (47.8%)	55 (36.1%)	
Mild	242 (35.6%)	166 (31.5%)	76 (50.0%)	
Absent	14 (2.1%)	8 (1.5%)	6 (3.9%)	
Not available	4 (0.6%)	4 (0.8%)	0 (0)	
Skin photodamage after treatment	675	523	152	0.0006
Improved	206 (30.5%)	143 (27.3%)	63 (41.4%)	
Not improved	455 (67.4%)	372 (71.1%)	83 (54.6%)	
Absent (before and after treatment)	14 (2.1%)	8 (1.5%)	6 (3.9%)	
Not available	4			
Clinical Efficacy	679	527	152	0.000
0 (complete clearance 100%)	198 (29.2%)	124 (23.5%)	74 (48.7%)	
1 (good response 75–99%)	275 (40.5%)	230 (43.6%)	45 (29.6%)	
2 (moderate response 50–74%)	132 (19.4%)	105 (19.9%)	27 (17.8%)	
3 (mild response 25–49%)	56 (8.2%)	51 (9.7%)	5 (3.3%)	
4 (poor response 0–24%)	18 (2.7%)	17 (3.2%)	1 (0.7%)	
Satisfaction				
Patient satisfaction	679	527	152	0.001
0 (no satisfaction)	8 (1.2%)	6 (1.1%)	2 (1.3%)	

1	18 (2.7%)	15 (2.8%)	3 (1.9%)	
2	109 (16.1%)	92 (17.5%)	17 (11.2%)	
3	228 (33.6%)	193 (36.6%)	35 (23.0%)	
4 (extreme satisfaction)	311 (45.8%)	220 (41.7%)	91 (59.9%)	
Not available	5 (0.7%)	1 (0.2%)	4 (2.6%)	
Clinician satisfaction	679	527	152	0.000
0 (no satisfaction)	6 (0.9%)	6 (1.1%)	0 (0)	
1	20 (2.9%)	17 (3.2%)	3 (1.9%)	
2	84 (12.4%)	74 (14.0%	10 (6.6%	
3	226 (33.3%)	193 (36.6%)	33 (21.7%)	
4 (extreme satisfaction)	338 (49.8%)	236 (44.8%)	102 (67.1%)	
Not available	5 (0.7%)	1 (0.2%)	4 (2.6%)	

*All sites were considered as a whole; the statistical unit is the site; percentages were calculated on this total.
** If the site of AK = the rest of the body.
AK: actinic keratosis; AKASI: Actinic Keratosis Area Severity Index; IGA: Investigator Global Assessment

SUPPLEMENTARY DIGITAL MATERIAL 2

Supplementary Table II.—Tolerability (whole study sample and the two cohorts).

LSRs*	Total	AK-Experienced	AK-Naïve	*p*
Erythema	679	527	152	0.015
0	138 (20.3%)	101 (19.2%)	37 (24.3%)	
1	254 (37.4%)	186 (35.3%)	68 (44.7%)	
2	176 (25.9%)	144 (27.3%)	32 (21.1%)	
3	88 (12.9%)	78 (14.8%)	10 (6.6%)	
4	23 (3.4%)	18 (3.4%)	5 (3.3%)	
Swelling	679	527	152	0.150
0	406 (59.8%)	308 (58.4%)	98 (64.5%)	
1	173 (25.5%)	132 (25.0%)	41 (26.9%)	
2	78 (11.5%)	68 (12.9%)	10 (6.6%)	
3	19 (2.8%)	17 (3.28%)	2 (1.38%)	
4	3 (0.4%)	2 (0.4%)	1 (0.7%)	
Scaling	679	527	152	0.000
0	273 (40.2%)	183 (34.7%)	90 (59.2%)	
1	272 (40.1%)	228 (43.3%)	44 (28.9%)	
2	104 (15.3%)	89 (16.9%)	15 (9.9%)	
3	27 (3.9%)	24 (4.6%)	3 (1.9%)	
4	3 (0.4%)	3 (0.7%)	0 (0)	
Crusting	679	527	152	0.014
0	412 (60.7%)	307 (58.6%)	105 (69.1%)	
1	170 (25.1%)	133 (25.3%)	37 (24.4%)	
2	72 (10.7%)	62 (11.8%)	10 (6.8%)	
3	17 (2.6%)	17 (3.3%)	0 (0)	
4	8 (1.2%)	8 (1.5%)	0 (0)	

Vesiculation/pustulation	679	527	152	0.061
0	554 (81.6%)	420 (79.7%)	134 (88.2%)	
1	89 (13.16%)	75 (14.2%)	14 (9.2%)	
2	23 (3.4%)	19 (3.6%)	4 (2.6%)	
3	13 (1.9%)	13 (2.6%)	0 (0)	
4	0	0	0	
Erosion/ulceration	679	527	152	0.320
0	553 (81.4%)	425 (80.6%)	128 (84.2%)	
1	94 (13.8%)	74 (14.0%)	20 (13.2%)	
2	26 (3.8%)	24 (4.6%)	2 (1.3%)	
3	5 (0.7%)	4 (0.8%)	1 (0.7%)	
4	0	0	0	

*Number of total events.
LSRs, local skin reactions; AK, actinic keratoses.