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ORIGINAL ARTICLE

A single-center prospective observational study evaluating the efficacy and safety of tirbanibulin 1% in actinic keratoses in immunosuppressed patients: the ESTIMATE study

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Summary

Background: Actinic keratoses (AKs) are common precursors to squamous cell carcinoma and pose a heightened risk in immunosuppressed patients, such as organ transplant recipients (OTRs).

Patients and methods: This prospective, monocentric, single-arm observational study investigated the safety and efficacy of topical tirbanibulin 1% ointment in treating Olsen grade 1 and 2 AKs on the face and scalp of 40 OTRs. At baseline (T0), demographic characteristics, clinical history, AKASI score, and AK count were collected. Patients applied tirbanibulin once daily for 5 consecutive days. Local skin reactions (LSRs) were evaluated on day 8 (T1), and efficacy outcomes – *Actinic Keratosis Area and Severity Index* (AKASI) and actinic keratosis count – were assessed on approximately day 60 (T2).

Results: All patients experienced mild or moderate local skin reactions (LSRs), primarily erythema and scaling, which resolved spontaneously without further intervention. By T2, the mean AKASI score decreased from 2.64 to 1.03, while the mean AK count dropped from 6.65 to 2.78; the differences were statistically significant. Notably, 52.5% of patients achieved at least 75% clearance, and 42.5% reached complete clearance. No serious adverse events or treatment discontinuations were reported.

Conclusions: This study demonstrates that tirbanibulin is a safe, well-tolerated, and effective option for AK management in OTRs, addressing a critical need in this high-risk population.

KEYWORDS
Actinic keratosis, field cancerization therapy, organ transplant recipients, tirbanibulin

INTRODUCTION

Actinic keratosis (AK) is a proliferative lesion commonly resulting from the chronic and cumulative sun exposure and primarily arising in photodamaged skin. It typically presents as a rough and scaly maculo-papular element, sometimes becoming thicker and hyperkeratotic. The prevalence of AK is high, thus affecting one quarter of patients attending dermatology clinics in Italy.[1] AKs have the potential to transform into keratinocyte cancers, primarily squamous cell carcinomas (SCCs). However, while some AKs progress to malignancy, many will either regress or remain unchanged. Currently, it is not possible to predict which lesion will undergo malignant transformation.[2]

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Organ transplant recipients (OTRs) represent a high-risk population for developing AKs, often with multiple lesions that can easily transform into invasive SCC.[3,4] Indeed, the AKs regression rate in OTRs is strictly related to various clinical factors, including sun-exposure habits, a previous history of skin cancer and the degree of immunosuppression itself.[5,6] On these bases, there is a strong need to recognize and properly treat every AKs in OTRs. While multiple therapeutic options are available, preventive measures, such as sunscreen use, and sun-exposure avoidance remain pivotal in this population.[7]

Tirbanibulin is an anti-proliferative agent currently approved for the topical treatment of non-hyperkeratotic and non-hypertrophic actinic keratoses of the face or scalp in adults. It has recently been authorized by the EMA (European Medicines Agency) and is available in many countries, including Italy.[8] Its main mechanism of action relates to the inhibition of tubulin polymerization and the Src kinase pathway, leading to interference in the cycle cell and promoting apoptosis.[9]

Since no data are currently available on tirbanibulin treatment in OTRs, including its efficacy, tolerability, and adverse event severity, in the present study we aimed to evaluate the efficacy and safety of topical tirbanibulin for the treatment of actinic keratoses in OTRs. Here, we present the results of our study.

PATIENTS AND METHODS

Study design

We conducted a prospective, monocentric, single-arm, observational study at the OTRs Outpatient Clinic of the Dermatology Unit, University Hospital Maggiore della Carità, Novara, Italy. The study was approved by the Local Ethical Committee (Acronym: ESTIMATE; CE086/23; 2023, May 31). Enrollment started in 2023, June 1 and concluded one year later. Each OTR who was prescribed tirbanibulin 1% ointment for the field therapy of Olsen grade 1 and 2 AKs arising on the face or scalp was asked to provide written informed consent to participate in the present study.

At the baseline (T0), demographic and clinical data – including type of transplantation, immunosuppressive therapy, history of skin cancers and previous AK treatments – were collected. Patients received detailed instructions on how to apply the therapy. Additionally, clinical photographs of the area to be treated, the AKASI score, and the AK count were registered. The treatment protocol required patients to apply the ointment from a single sachet on the affected area once a day (at the same time, preferably in the evening). The ointment was left on overnight and rinsed off after approximately 8 hours. Treatment lasted for 5 consecutive days. No other local treatments were allowed during the study conduction, except for common sunscreen or emollients. Each patient was properly informed about the possible appearance of local skin reactions (LSRs), which typically appear a few days after treatment completion. LSRs consisted in the presence of erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration, and were assessed in a semi-quantitative manner with a 4-point scale with 0 meaning "not present", to 3 meaning "severe", according to the literature.[10]

Each patient was evaluated 8 days after the baseline (T1), to recognize and report the LSRs total score, ranging from 0 to 18. A further evaluation was performed after approximately 60 days from the baseline (T2), in which clinical examination, AKASI score and AKs count were registered. The study protocol is summarized in Figure 1. To perform the direct comparison between the counted lesions at T0 and T2, the AK clearance was calculated. More in detail, 100% and 75% clearance, as previously described in the literature,[10] were evaluated. Clinical photographs were taken at each time point. All data were collected in a dedicated database using the REDCap (Research Electronic Data capture) web application, available at the University of Eastern Piedmont.

Primary endpoint

The primary endpoint was the clinical efficacy of tirbanibulin 1% ointment for topical use in the treatment of AKs of the scalp and face in immunosuppressed patients (OTRs), in terms of partial clearance rate of AK lesions, defined as the proportion of subjects at T2 with a $\geq$ 75% reduction in the number of AK lesions in the treatment area.

Secondary endpoints

Secondary endpoints were: *(1)* the evaluation of AKASI reduction in time (between T2 and baseline) overall and separately for different sites; *(2)* the evaluation of LSRs, adverse events after 8 days (T1); residual dyschromia and scarring in the treatment area at T2; *(3)* the complete (100%) clearance rate of AK lesions, defined as the proportion of subjects at T2 with no clinically visible AK in the treatment area.

Inclusion and exclusion criteria

Key inclusion criteria were clinically and dermoscopically confirmed AKs arising on the face and scalp of OTRs, thus requiring field cancerization therapy. The exclusion criteria consisted in the presence of AKs suspicious for transformation into invasive SCCs, known allergy to the drug or its excipients, recent treatment for AKs within the past 60 days, or failure to provide informed consent.

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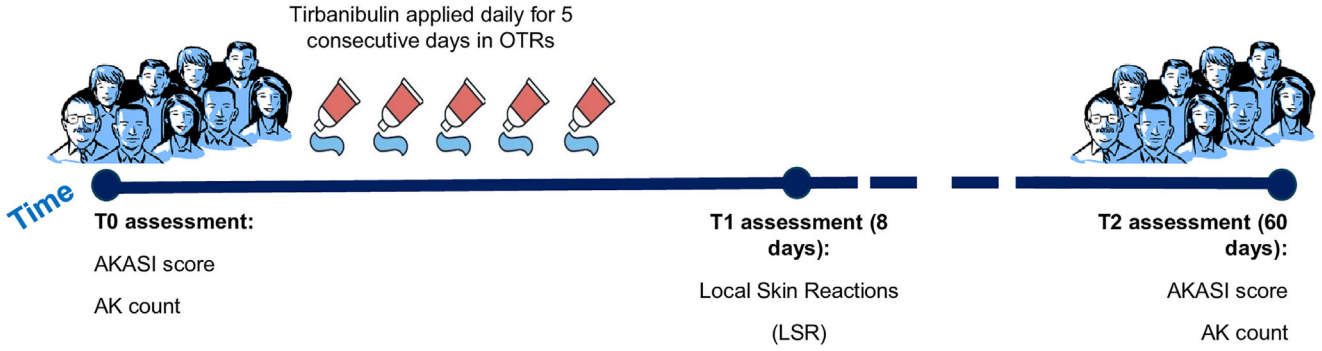

FIGURE 1 Schematic representation of the study protocol.

Statistical analysis

Data were summarized using descriptive analysis to describe the main characteristics of the sample. Absolute and relative frequencies were reported for categorical variables, with mean and standard deviation or median and interquartile range for numerical ones.

The difference in time in AKASI scores between T2 and baseline was calculated and reported as mean and standard deviation. Difference from zero was calculated using the paired t-test. Moreover, the percentage change was calculated and to assess efficacy of the treatment, the proportion of subjects who had a partial (≥ 75%) or complete (100%) reduction in the number of lesions at T2 were estimated, both with 95% confidence intervals. Finally, a detailed description of adverse effects in terms of skin lesions was assessed on day 8. All analyses were performed using SAS 9.4.

Missing data were not observed in the study; models or adjusted analyses were not performed due to the low number of patients enrolled and because no supplementary analyses were specified in the protocol.

Sample size

Expecting that 72% of patients had a partial (≥ 75%) reduction of number of lesions at T2, assuming a width of interval of 30% and a confidence interval of 95%, at least 32 patients were required.[10]

RESULTS

Study population

A total of 40 OTRs, with a predominance of men (30 patients; 75%), were consecutively enrolled in the present study. The mean age of patients at the time of the enrolment was 69.6 years (range 45–84). Most patients had previously undergone kidney transplantation (35 patients), while two had received a liver transplant, two had undergone combined kidney–liver transplantation, and one had undergone heart transplantation. The mean age at transplantation was 53 years (range 19–69).

Regarding skin phenotype and sun exposure habits, most participants had Fitzpatrick skin type III (29 subjects; 72.5%) and reported occasional sun exposure (25 subjects; 62.5%) with regular sunscreen use (33; 77.5%). Only 13 subjects (32.5%) reported outdoor work activity, and most subjects (37; 92.5%) had not been exposed to UV lamps in the past. In contrast, many (23 patients; 57.5%) reported previous sunburns. At the time of tirbanibulin treatment, all patients were on an immunosuppressant regimen consisting of various drug combinations. Notably, none of the patients were receiving Azathioprine. Complete demographic data are summarized in Table 1.

In the study population, previous AKs were reported by 36 patients (90%) in different body sites, while 28 subjects (70%) referred past surgical treatment for non-melanoma skin cancers (NMSC), mainly represented by basal cell carcinomas (BCCs) and SCCs. The previous treatments for AKs consisted mainly of cryotherapy (30 cases; 83.3%), although different drugs and techniques (5-fluorouracil, diclofenac, imiquimod, photodynamic therapy -PDT- and surgery), also in association, were reported. No subject had been treated with tirbanibulin before the enrollment. These data are summarized in Table 2.

Tirbanibulin treatment

At the baseline (T0), 29 patients (72.5%) had AKs localized exclusively on the face, two patients (5%) had lesions only on the scalp, while the remaining nine (22.5%) presented with scattered AKs involving both sites (face and scalp). The mean AKASI score at T0 was 2.64 (range 0.8–5.4) and the mean number of AKs was 6.65 (range 1–16). Notably, even when a single lesion was treated, it was a large AK located in an area of chronic actinic damage, thus qualifying for field therapy in accordance with European guidelines.[11]

At T1 evaluation all patients showed Local Skin Reactions (LSR), mainly of mild or moderate severity. The most fre-

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TABLE 1 Demographic data of the study cohort.

Sex	n (%)	Range
Male	30 (75)	
Female	10 (25)	
Age at enrollment		
Mean (SD)	69.61 (8.12)	45–84
Age at transplant, years		
Mean (SD)	52.98 (12.66)	19–69
Transplant type		
Kidney	35 (87.50)	
Liver	2 (5.00)	
Kidney-Liver	2 (5.00)	
Heart	1 (2.50)	
Skin type		
II	11 (27.5)	
III	29 (72.5)	
Sun exposure		
Occasional	25 (62.5)	
Frequent	13 (32.5)	
Never	2 (5)	
Work activity		
Indoor	27 (67.5)	
Outdoor	13 (32.5)	
Sunscreen use		
Yes	33 (77.5)	
No	7 (22.5)	
Previous sunburns		
Yes	23 (57.5)	
No	17 (32.5)	
UV lamp exposure		
Yes	3 (7.5)	
No	37 (92.5)	

Abbr.: AK, actinic keratosis; AKASI, actinic keratosis area and severity index; SD, standard deviation; UV, ultraviolet

TABLE 2 Skin tumors developed in the study population before enrollment.

Past NMSC (patients)	n (%)
Yes	28 (70)
No	12 (30)
NMSC types* (n = 28)	
BCC	21(75.00)
SCC	14 (50.00)
Other	6 (21.43)
Previous AKs (patients)	
Yes	36 (90)
No	4 (10)
Previous AK sites**	
Face	26 (72.2)
Scalp	17 (47.2)
Trunk	6 (16.7)
Hand	3 (8.3)
Previous AKs therapies***	
Cryosurgery	30 (83.3)
Surgery	16 (44.4)
Diclofenac	12 (33.3)
5-FU	11 (30.6)
Imiquimod	9 (25)
PDT	5 (13.9)
Ingenol mebutate	4 (11.1)

Abbr.: AK, actinic keratosis; BCC, basal cell carcinoma; NMSC, non-melanoma skin cancer; PDT, photodynamic therapy; SCC, squamous cell carcinoma; 5-FU, 5-fluorouracil
*NMSC types developed in the group of 28 patients. Some patients developed multiple tumors of different types
**Possible multiple affected sites in the same subject
***Possible various therapies in the same subject

quently observed LSRs were erythema and scaling; with other features being less frequent. No patient was found to have oedema or vesicles/pustules. The mean LSR score was 4 (range 1–9).

Lack of qualitative and quantitative differences regarding LSR were reported based on the treated area (face versus scalp). No specific treatment was required for the LSR resolution, and no dyschromia or scarring was detected at the treatment site. There were no adverse events related to tirbanibulin administration, nor alterations in the general health status or in blood test performed by the enrolled patients. No patient discontinued therapy before its completion.

At the T2 evaluation all patients demonstrated clinical improvement, with mean AKASI value of 1.03 (range 0–3.8). The average AKs count was 2.78 (range 0–15). The differences between AKASI score and AK count at the T0 and T2 reached statistical significance (Figure 2).

AK clearance was at least 75% in 21 patients (52.5% [95% CI 0.37–0.68]) and 100% in 17 patients (42.5% [95% CI 0.27–0.58]). Due to the small number of patients complaining of AKs in each single site (face vs. scalp), no significant difference was detected between the two groups regarding the efficacy of tirbanibulin treatment. Data are summarized in Table 3.

The clinical outcomes of the two different areas (scalp versus face) treated with tirbanibulin in representative patients are reported in Figure 3 and Figure 4, respectively.

DISCUSSION

In the ESTIMATE study, we evaluated the efficacy and safety of topical tirbanibulin in a cohort of organ transplant recipients consecutively enrolled at the Dermatology Unit in Novara, Italy. Patients were assessed at three different timepoints, during which the standardized scores and

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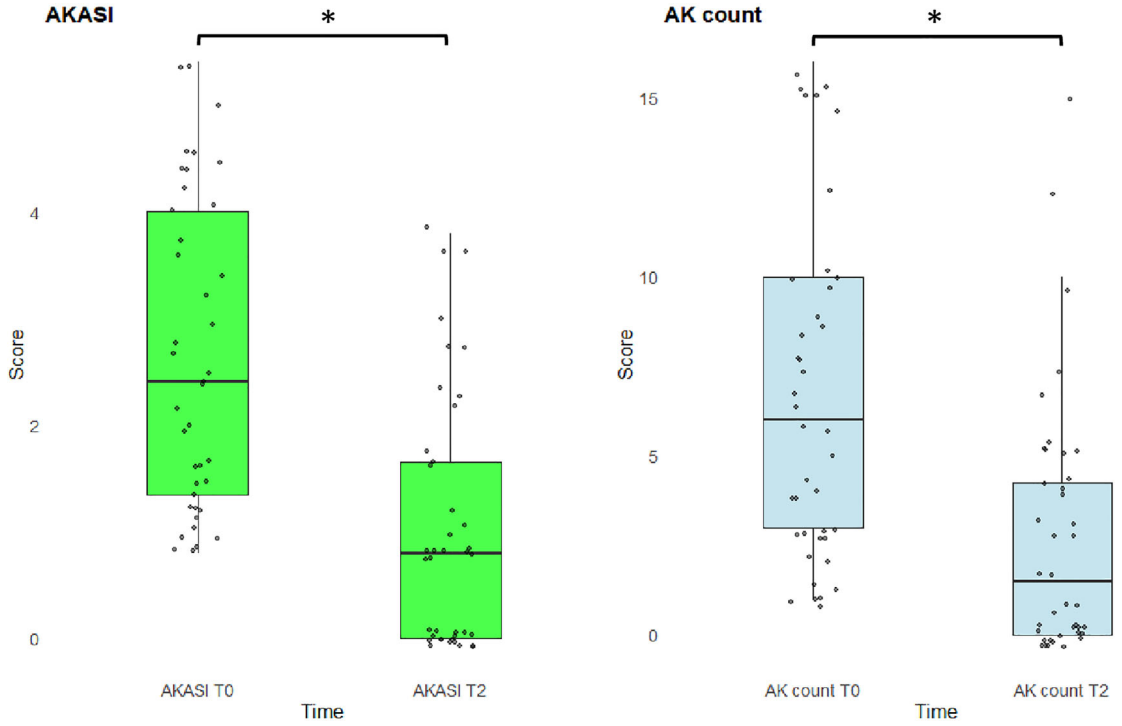

FIGURE 2 Box plots showing changes in AKASI score and actinic keratosis (AK) count from T0 to T2. Individual data points are overlaid to show the distribution within each group. An asterisk indicates statistical significance ($p < 0.001$).

TABLE 3 Efficacy of tirbanibulin in the study population. Results are reported as mean (SD) for scores, differences, and percentage change. For clearance, n (%) are reported.

	T0	T2	T2 versus T0	p-value	% change
AKASI scalp	0.79 (1.36)	0.41 (0.85)	−0.38 (0.75)	0.0028	−13.68 (27.10)
AKASI forehead	0.53 (0.68)	0.18 (0.33)	−0.35 (0.53)	0.0002	−26.79 (40.03)
AKASI left face	0.71 (0.57)	0.25 (0.39)	−0.46 (0.49)	< 0.0001	−42.74 (45.01)
AKASI right face	0.61 (0.54)	0.19 (0.34)	−0.42 (0.42)	< 0.0001	−43.57 (44.12)
AKASI total	2.64 (1.46)	1.03 (1.19)	−1.61 (0.89)	< 0.0001	−70.68 (30.62)
AK count	6.65 (4.73)	2.78 (3.56)	−3.88 (2.78)	< 0.0001	−70.06 (32.04)
		Clearance 75%		***Clearance 100%***	
AKASI total		21 (52.5)		17 (42.5)	
AK count		21 (52.5)		17 (42.5)	

Abbr.: AK, actinic keratosis; AKASI, actinic keratosis area and severity index; SD, standard deviation; T0, baseline; T2, 60 days after treatment

clinical data were recorded, thus allowing for a comprehensive evaluation of the treatment efficacy in such a cohort of patients. Indeed, more than 50% of the enrolled subjects were found to reach the clearance 75% score, with 42.5% reaching the AK complete clearance. Furthermore, the therapy was well tolerated, and all patients were able to complete the treatment and undergo clinical examination. Overall, adherence to the short treatment regimen was high, likely due to the mild nature of local skin reactions (LSRs), which did not interfere with daily activities or require additional management. No systemic adverse events were observed, and routine blood tests did not show any changes.

The phase III trials of tirbanibulin versus placebo published by Blauvelt et al. reported comparable efficacy outcomes, with clearance rates of ≥ 75% and 100% in a large cohort of 702 immunocompetent subjects. More specifically, 44%–54% of patients achieved 100% clearance, and 68%–76% achieved ≥ 75% clearance, with improved results when the two trials were analyzed as pooled data (100% clearance in 49% and ≥ 75% clearance in 72% of patients).[10] Similarly, the LSRs that developed 1 week after application were mild, with a mean score of 4, and the most frequently observed reactions were erythema and flaking or scaling, which resolved spontaneously, consistent with the findings of our study.

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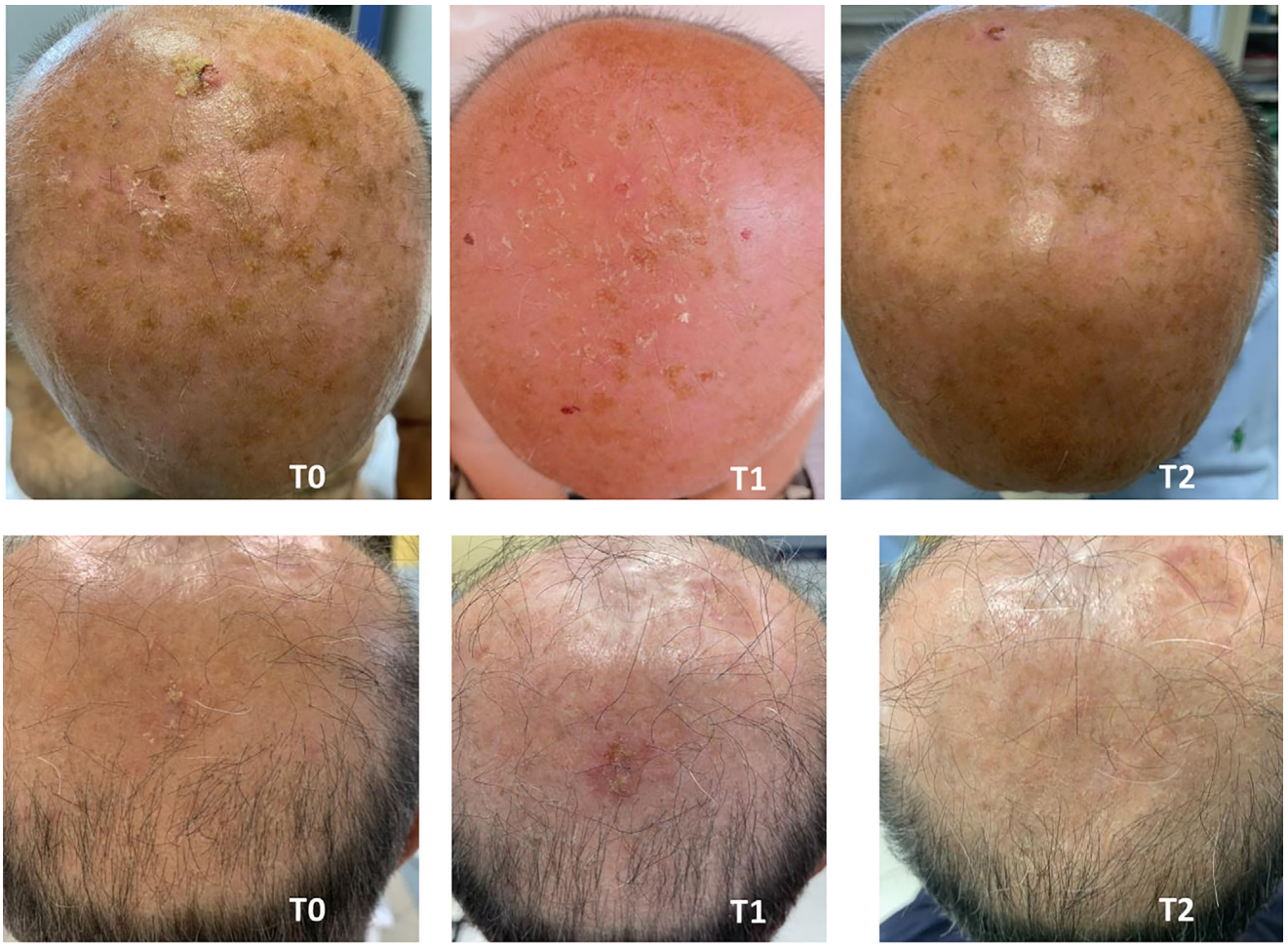

FIGURE 3 Actinic keratoses (AKs) located on the scalp of a 63-year-old man and a 77-year-old man. Both patients had undergone kidney transplantation in 2016 and 2005, respectively. T0 baseline; T1 8 days after the beginning of treatment; T2 60 days after treatment.

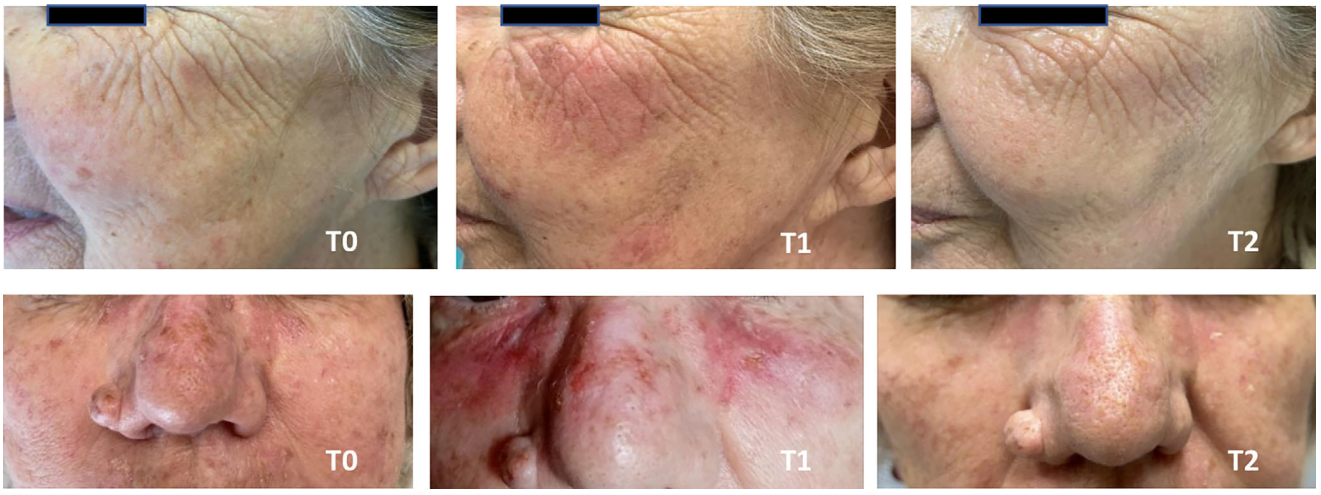

FIGURE 4 Actinic keratoses (AKs) located on the left cheek of a 65-year-old woman who had undergone kidney transplantation and on the central face of a 67-year-old woman who had undergone kidney transplantation in 2011. T0 baseline; T1 8 days after the beginning of treatment; T2 60 days after treatment.

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Tirbanibulin is a recently approved treatment for grade I AK of the face or scalp in adults, acting through the inhibition of microtubule formation and on the Src tyrosine kinase pathway, thus inducing apoptotic death of proliferating cells. To date, numerous articles have reported the efficacy, safety, and tolerability of this molecule, even in the so-called "real life" setting, with complete AK clearance ranging from 24% to 70%, and 75% clearance varying from 70% to 88.8%.[12–16] Moreover, many studies have evaluated its use in off-label disorders, such as warts, other keratinocyte neoplasms and cutaneous conditions.[17–28]

Ciccarese et al. have recently published the efficacy and tolerability of tirbanibulin for treating AK in a cohort of patients with HIV infection.[29] Among the enrolled patients, the authors also treated a patient who had undergone liver transplantation 7 years earlier, and they reported the treatment to be effective.

To date, there is a lack of published data on the efficacy of tirbanibulin in series of OTRs. Indeed, only a single conference abstract published in a supplement issue of the European Academy of Dermatology and Venereology Congress 2022 is available.[30] This report described the use of tirbanibulin for cutaneous field cancerization in only 2 OTRs, provided only a brief account of clinical outcomes, and suggested that the drug may also be used in combination with other treatments for the management of thicker Aks. According to our results, these cases did not develop severe local skin reactions (LSRs). More recently, in a poster presentation at the 2025 European Association of Dermato-Oncology Congress, Vicente et al. reported data on tolerability in a cohort of organ transplant recipients (OTRs), assessing pain in correlation with LSRs, and concluded that a favorable safety profile was observed.[31]

Regarding our cohort, we observed encouraging results in terms of both efficacy and safety. Although the rates of complete (100%) and partial (75%) clearance of AKs were lower than those reported in immunocompetent subjects in both clinical trials and real-world studies, it is important to note that organ transplant recipients represent a high-risk population for the development and management of AKs.

Although several topical treatments are currently available for AKs, only a few have been formally approved for use in immunosuppressed patients. Clinical outcomes in OTRs tend to be less favorable, with generally lower clearance rates compared to immunocompetent patients.[32–34] On the other hand, the high incidence of progression to SCC in OTRs, together with the low rate of spontaneous regression, represents a strong indication for field cancerization treatment.[35]

Tirbanibulin has also been administered over large areas of skin affected by AKs in a cohort of 105 immunocompetent patients, demonstrating a favorable safety and tolerability profile, along with good efficacy.[36] These data further support the safety of tirbanibulin, since no systemic adverse events, nor changes in the healthy status were registered in such a large cohort. This has even more relevance when considering the potential drug interactions and adverse events in immunosuppressed patients, and the consequent difficulties in their management. On the other hand, providing the correct treatment of AKs and cutaneous field cancerization in OTRs is fundamental and, thus, highlights the need to investigate the efficacy of tirbanibulin in such a category of patients.[11]

Our study suffers from several limitations, primarily due to the relatively small sample size. Indeed, we enrolled only 40 subjects, but the restriction in the target category of patients and inclusion criteria might be considered. Moreover, we had previously conducted a statistical evaluation to establish the minimal number of subjects required to obtain a powerful analysis of the data, and our final sample size exceeded that threshold.

However, in our study we did not show the dermoscopic outcome of the treated areas, since some studies have reported it, as well as histological clearance of AK.[12–16] On the other side, the AKASI score and the AK count have been used in many studies, including the phase III trial,[10] as they can provide a reliable assessment of the obtained results.

A further limitation could be represented by the short follow-up period, which was less than 1 year in some patients at the time of writing. Actinic keratoses (AKs) are known to recur after treatment, and recurrence may occur more frequently in high-risk populations such as OTRs. As a result, these patients may require repeated or alternative therapies over time, making treatment adherence a potentially significant challenge that warrants further investigation.[37,38] In this context, the short duration of the tirbanibulin therapy, as well as the mild local adverse effects, could be of help in improving compliance and the adherence to the treatment.

Recent evidence suggests that the extent of follicular involvement in AKs is directly associated with the risk of progression to invasive SCC in OTRs.[39,40] In this context, the potential ability of tirbanibulin to penetrate adnexal structures may provide an additional advantage in targeting early or subclinical lesions, warranting further investigation. Although further studies are needed to adequately evaluate the role of different topical treatments in the management of AKs and field cancerization in OTRs, future clinical guidelines may facilitate a more personalized approach, enabling treatment to be tailored to the specific needs of each patient.

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CONFLICT OF INTEREST STATEMENT

E.Z. received consulting fees from Sun Pharmaceutical Industries and support for attending meetings from Istituto Ganassini. V.T. received consulting fees from Sun Pharmaceutical Industries and support for attending meetings from Istituto Ganassini. P.S. received speaker's honoraria and research grants from Novartis, Almirall S.A., Sun Pharmaceutical Industries, Istituto Ganassini, and IDI Farmaceutici. All other authors declare no conflict of interest.

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