

Real-World Efficacy of Tirbanibulin in Actinic Keratosis Treatment: Expert Consensus and Clinical Insights

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Key words: Actinic keratosis, Tirbanibulin, Topical treatment, Expert opinion

Key Message: Tirbanibulin use in the treatment of actinic keratosis is expanding owing to its proven efficacy, tolerability, and short treatment regimen. This expert consensus provides guidance on optimal use of tirbanibulin in real-life clinical practice.

Citation: Ardigo M, Argenziano G, Campione E, et al. Optimal Use of Tirbanibulin in the Real-Life Treatment of Actinic Keratosis: Expert Consensus. *Dermatol Pract Concept*. 2025;15(3):5921. DOI: <https://doi.org/10.5826/dpc.1503a5921>

Accepted: May 19, 2025; **Published:** July 2025

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Funding: This article was sponsored by Almirall S.p.A. Assistance with coordination of the consensus process and medical writing was provided by Editamed and funded by Almirall S.p.A.

Competing Interests: MA reports speaker fees from Almirall, La Roche-Posay, and Cantabria and advisory boards for Almirall. EC reports speaker fees from Almirall, Amgen, BMS, and UCB and advisory boards for Almirall, Amgen, BMS, Cantabria, and UCB. CL reports speaker fees from Almirall Hermal and advisory boards for Regeneron. GN reports speaker fees from Giuliani, Ideka, and Novartis and advisory boards for Almirall, L'Oreal, and Novartis. KP reports grants from Abbvie, Almirall, Lilly, Novartis, and Sanofi, consulting fees from Galderma, Leo Pharma, Lilly, and Sanofi, and participation in advisory boards for Abbvie, Almirall, Biogen, Galderma, Leo Pharma, Lilly, MSD, Pierre Fabre, Regeneron, Sun Pharma, Janssen, and Sanofi. AV reports speaker fees from Almirall. IZ reports speaker fees from Almirall Hermal, Sanofi, La Roche-Posay, Bioderma, Canova, MSD, Sanofi Genzyme, and FotoFinder and advisory boards for Philogen and Regeneron. SG reports speaker fees from L'Oreal and Almirall and consultation fees from Istituto Ganassini, Merz Aesthetics. GA, GM, and FV report no conflicts of interest.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT **Introduction:** Tirbanibulin, a topical treatment for actinic keratosis (AK) with a novel antiproliferative mechanism of action, has demonstrated efficacy and a favorable tolerability profile in clinical trials and real-life studies. An insight into best-practice use of tirbanibulin in different clinical presentations of AK would be useful.

Objectives: The aim of this article was to deliver advice, via expert consensus, on the optimal use of tirbanibulin in the real-life management of AK.

Methods: A panel of 11 dermatologists with expertise in the treatment of AK convened to develop consensus statements about key aspects of tirbanibulin treatment in AK patients based on selected literature data and on their own clinical experience.

Results: Two areas were examined and discussed: clinical assessment/diagnostic procedures and key aspects of tirbanibulin therapy. A total of 19 statements concerning clinical evaluation of AK patients, routine and advanced diagnostic instruments, patient selection, treatment modalities, and key messages for patient communication were drafted and voted on.

Conclusion: Tirbanibulin should be considered as a first-line option for most patients with AK owing to its proven efficacy, good local and systemic tolerability, and a short treatment regimen of five days. All these factors encourage patient acceptability and treatment compliance. The favorable safety profile and tolerability of tirbanibulin also enable flexible therapeutic schedules, including repeated treatment cycles, if needed.

Introduction

Actinic keratosis (AK) is a chronic skin disease characterized by the abnormal proliferation of epidermal keratinocytes that typically presents as scaly erythematous papules or hyperkeratotic plaques in chronically sun-exposed areas [1,2]. AK lesions are considered either a precursor or an initial and superficial form of cutaneous squamous cell carcinoma (cSCC), although low rates of progression to invasive cSCC have been reported, ranging from 0% to 0.075% per lesion-year [1,3]. Mutations in oncogenic and tumor-suppressing genes (e.g., *p53*, *CDKN2A* and *PTEN*) induced by cumulative ultraviolet B (UVB) radiation are believed to be the main factor in the pathogenesis of both AK and cSCC [1]. Important risk factors for the development of AK include male sex, age >45 years, light Fitzpatrick phototypes, and the use of photosensitizing drugs [1,4]. The concept of field cancerization (FC), generally referred to as an area of subclinical changes surrounding AK lesions that displays genetic changes similar to those found in AK, has diagnostic and prognostic implications and is an important aspect in the management of AK [1,3,5]. A vast array of treatments for AK, either lesion- or field-directed, is currently available, including topical drugs, surgical procedures, cryotherapy, laser ablation, and photodynamic therapy. However, many therapies are associated with important local or systemic adverse reactions, and they often require a long duration of treatment, resulting in poor patient adherence and suboptimal outcomes [1,4]. The recently introduced tirbanibulin ointment, a promising topical treatment option that targets both AK lesions and surrounding FC, has rapidly gained favor among dermatologists mainly due to its good tolerability

and ease of use, with a short-term course of therapy (once daily application for five days) [1,3,6,7]. A first-in-class microtubule inhibitor, tirbanibulin targets tubulin polymerization and Src tyrosine kinase signaling, two pathways that are upregulated in AK and cSCC [6,7]. Tirbanibulin has demonstrated efficacy in clearing AK lesions, with a good tolerability profile, in large randomized clinical trials as well as in real-world studies and is listed among recommended options for the treatment of AK in all major international guidelines [1,7-11].

Given the chronic, relapsing nature of AK, the growing body of knowledge about its pathophysiology, and the increasing availability of treatment options, clinicians face many challenges in the long-term management of this disease. The aim of this consensus document was to deliver real-world guidance on the optimal use of tirbanibulin in the treatment of AK throughout the patient journey.

Methods

Eleven dermatologists with extensive clinical experience in the treatment of AK convened to discuss best-practice patient management and optimal use of tirbanibulin based on the presentation of exemplary clinical cases and the review of relevant literature data. The panel then developed expert recommendations in the form of statements, subsequently voted on, related to two areas: 1) clinical assessment of patients and real-life diagnostic procedures; 2) key aspects of tirbanibulin therapy, including patient selection, treatment modalities, and patient education. Only statements with a consensus of 100% were included.

Clinical Assessment and Diagnostic Procedures

Initial Patient Evaluation

AK can have multiform clinical presentations (including distinct clinical variants such as pigmented, bowenoid, or lichenoid AK), with lesions of variable thickness and size [1,12-14]. Hyperkeratotic lesions are best examined after applying an ointment containing keratolytic agents, since the thick layer of scaly tissue may mask the real aspect of the lesion. AK lesions are most visible on the face and scalp but can also be found on the limbs and trunk. AK lesions located on the lower lip or ears are considered high-risk lesions that are often resistant to treatment [1,9]. In addition to assessing the number, aspect, and location of the lesions, it is important to accurately evaluate the photodamaged skin surrounding the lesions, since severe FC identifies a patient population at high risk for recurrence of AK and the development of multiple cSCCs that requires a prompt and aggressive therapeutic approach [4,15,16]. There is evidence from the literature that several UVB-induced mutations and gene expression alterations that are frequently observed in photodamaged skin (e.g., deregulation of tumor suppressor genes *p53*, *CDKN2A* and *PTEN*, disruption of the RAF-1/MER/ERK cell survival pathway) become increasingly more severe in AK and SCC, suggesting that photodamaged skin, AK, and SCC may be part of a disease continuum that is manifested as FC [17,18]. Despite the lack of a clear and consistent definition of FC, an expert consensus based on an extensive review proposed a clinical definition of FC as “the anatomical area with or adjacent to AK and visibly sun-damaged skin identified by at least two of the following signs: telangiectasia, atrophy, pigmentation disorders and sand paper-like texture” [17]. Even without diagnostic instruments, therefore, perilesional skin should be assessed for visible signs of inflammation and UV damage. The initial clinical evaluation should also always consider patient-specific factors such as demographics, Fitzpatrick type, comorbidities, current medications, past clinical history (especially regarding skin cancer), previous AK treatments, and sun-protection behavior. Particular attention should be paid to immunosuppression, as immunocompromised patients, mainly organ transplant recipients, have a greatly increased risk of developing more severe AK and SCC, with worse treatment outcomes compared to immunocompetent AK patients. In fact, immunocompromised patients represent a distinct population requiring a dedicated treatment algorithm [1,19].

The complexity of AK features cannot be captured by rigid classification systems. In the Olsen clinical classification scale, one of the most commonly used parameters for assessing AK severity, single lesions are graded based on their thickness [20]. The Olsen scale has been used in most

clinical trials of AK treatments and is a valuable tool for the assessment of individual lesions, but it does not consider the severity of FC. For a more complete assessment of AK severity that includes FC, the Actinic Keratosis Field Assessment Scale (AK-FAS) is preferable [15]. This validated tool, a 4-grade scale which evaluates AK area, hyperkeratosis, and sun damage, provides objective and clinically relevant information and is easy to use in routine practice.

Instrumental Diagnostic Techniques and Histopathology

Dermatoscopy is an easy-to-use, readily available, non-invasive technique that should always be part of the clinical assessment of AK. Dermatoscopy enables clinicians to visualize typical clinical aspects of AK (e.g., erythematous pseudonetwork, ‘strawberry pattern’, large white follicles, and yellow or whitish scales), and thus it helps in the differential diagnosis of AK and superficial basal cell carcinoma, lentigo melanoma, irritated seborrheic keratosis, or other inflammatory skin diseases [1,14,21]. Dermatoscopy also plays an important role in monitoring treatment response and identifying early signs of invasive SCC such the presence of peripheral radial lines or vessels in the context of typical AK signs [14,21]. Histopathological examination of biopsy specimens should be carried out when atypical lesions are present, especially if they show features that may suggest a diagnosis of cSCC or other types of skin cancer [1]. Although more advanced imaging techniques, such as reflectance confocal microscopy (RCM), optical coherence tomography (OCT), and line-field confocal OCT (LC-OCT), are not part of the routine clinical assessment, when available, they can provide useful information in specific cases. Overall, these non-invasive techniques help increase diagnostic accuracy and provide additional information on the microenvironment of AK lesions, enabling detection of subclinical changes [1,14,22,23]. They also play an important role in monitoring treatment response, thus optimizing patient management [1,14,24,25] (Figure 1).

Expert consensus statements with recommendations on clinical assessment and diagnosis of AK are reported in Table 1(A).

Treatment of AK with Tirbanibulin

AK is a chronic disease that requires regular surveillance and long-term, personalized management based on prevention (i.e., photoprotection) and therapy of both visible lesions and FC; compliance is crucial to treatment success. In the natural history of the disease, the evolution of AK lesions (e.g., persistence, resolution, or progression to cSCC) is unpredictable, and disease recurrence is the norm owing to the continuous presence of mutagenic disease drivers induced by UV radiation [2,4,13,26]. The main objective of AK therapy

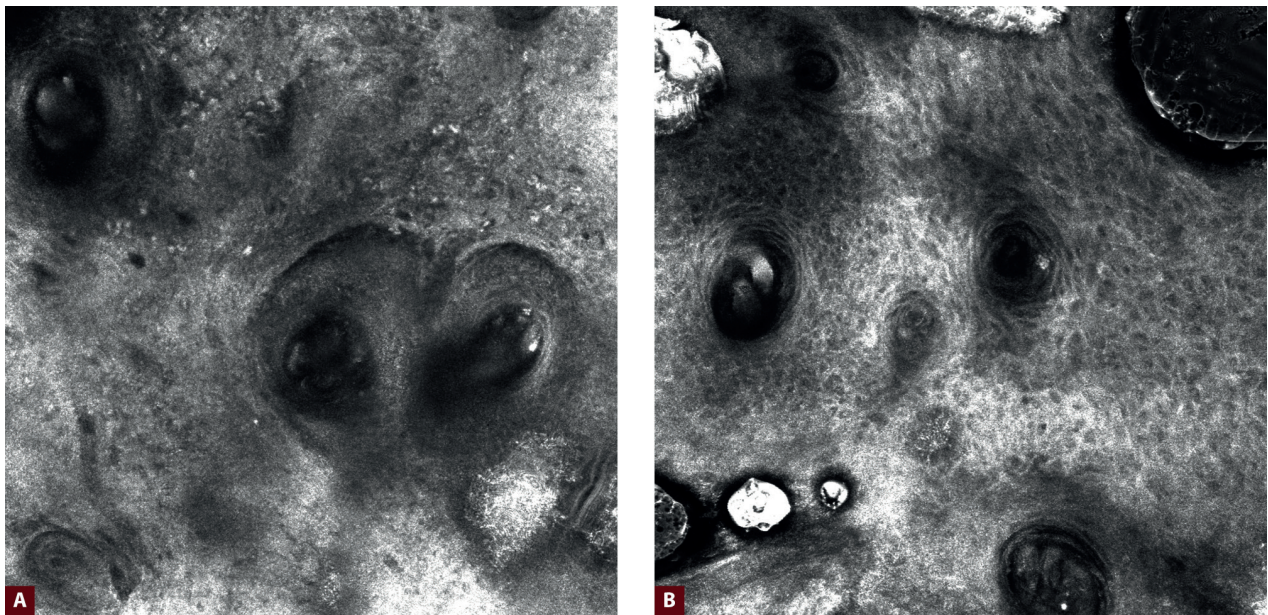


Figure 1. Reflectance confocal microscopy image of a small area of field cancerization on the right temporal area of a 63-year-old male with multiple AK lesions on the face and scalp and a history of chronic myelofibrosis and resected melanomas: (A) before treatment, showing atypical honeycomb pattern together with small bright round inflammatory cells; (B) at 29 days after starting treatment with tirbanibulin 1% ointment, showing partial restoration of the typical honeycomb pattern with no atypical features. (Courtesy of Dr. F. Venturi)

is still a matter of debate. Although prevention of progression to invasive cSCC is still generally considered the key reason for treatment, there is no actual evidence that treating of AK and FC decreases the risk of developing cSCC in immunocompetent patients without a previous skin cancer history [13,27]. Few studies have specifically investigated the incidence of cSCC over time in patients treated for AK. A secondary analysis of a randomized clinical trial found that the 4-year risk of developing cSCC in a previously treated AK area was 3.7%, increasing to 20.9% in patients with Olsen grade III lesions and to 33.5% in those with severe AK needing retreatment, while a retrospective cohort study that followed 5700 patients for five years after treatment with 5-fluorouracil or imiquimod found no significant difference between the two treatments in the 2- or 5-year cumulative risk for a subsequent keratinocyte carcinoma [28,29]. However, since these studies did not include a control arm of untreated patients, the impact of AK treatment per se on the risk of developing cSCC remains unclear. Aside from the potential reduction in the risk of progression, the treatment goals of AK therapy are sustained total or partial clearance of visible lesions and improvement in FC. Field-directed therapies are currently the preferred option for most clinical cases of AK since, unlike lesion-directed treatments, they can target the subclinical changes underlying FC. However, many field therapies with proven efficacy (e.g., photodynamic therapy or 5-fluorouracil) are associated with adverse events such as intense local reactions or pain, which restrict their use and impact adherence [1,3-5]. Tirbanibulin,

a topical ointment approved in the US (2020) and Europe (2021) for the treatment of AK on the face or scalp, has demonstrated significant clinical potential owing to its efficacy and good tolerability, supported by a novel mechanism of action, as well as to its short treatment course [1,3,6].

Evidence of Tirbanibulin Efficacy and Tolerability from Clinical Studies

In the phase III registration trials (two identical multicenter randomized double-blind placebo-controlled clinical studies enrolling a total of 702 patients with AK on the face or scalp), the percentage of patients with complete clearance (100% reduction in the number of lesions, as assessed at day 57 after completion of a 5-day regimen) was significantly higher for patients treated with tirbanibulin than for those who received control ointment (44% and 54% in trial 1 and 2, respectively, vs 5% and 13%, $P<0.001$ for both trails), while the percentages of patients with partial clearance ($\geq 75\%$ reduction in the number of lesions) were 68% and 76% vs 16% and 20%, respectively; $P<0.001$) [8]. At 1-year follow-up, the estimated percentage of tirbanibulin recipients with recurrent lesions, among those who had experienced complete clearance, was 47%. Tirbanibulin was well tolerated. Local reactions, including erythema, flaking/scaling, pruritus, and pain at the application site, were mostly graded as mild or moderate and resolved spontaneously. Unlike with most topical therapies, severe local reactions (e.g., vesicles /pustules, erosion/ulceration) were infrequent. As expected from the negligible absorption rate of tirbanibulin, systemic adverse

Table 1. Expert Consensus Statements on Optimal Use of Tirbanibulin in the Treatment of Actinic Keratosis.

A) Clinical assessment/ diagnostic procedures	<ul style="list-style-type: none"> • Assessment of patient characteristics (e.g., Fitzpatrick skin type, comorbidities, previous therapies, risk factors for AK, immunosuppression, history of NMSC) should always be part of the clinical examination • The Olsen severity classification system can be useful for evaluating single lesions, but FC should also be assessed, preferably by using the Actinic Keratosis Field Assessment Scale (AK-FAS) • Both AK lesions and the surrounding skin should be carefully examined • The use of a keratolytic ointment allows a better evaluation of hyperkeratotic lesions by reducing the masking effect of the scaly tissue • Dermatoscopy should always be carried out, both at baseline for diagnosis and for monitoring treatment response • Advanced instrumental techniques (e.g. RCM, OCT, LC-OCT) or histopathological examination are not routinely necessary, but may be useful in specific cases
B) Treatment	<ul style="list-style-type: none"> • Due to the chronic nature of AK, repeated treatment over time is part of the long-term management of AK • Compliance is crucial to treatment success • It is still a matter of debate whether treatment of both AK lesions and FC can prevent progression to SCC • Tirbanibulin can be considered as a first-line treatment for most patients (both treatment-naïve and previously treated) because of its efficacy, short regimen, and favorable tolerability profile • The area of skin to be covered by tirbanibulin 1% ointment depends on the distribution of AK lesions and FC • The area of application of tirbanibulin is limited to 25 cm² for each anatomical area (scalp, forehead, left/right cheek with ear, nose, and chin) • More than 25 cm² can be treated by one sachet of tirbanibulin 1% ointment • When treating large fields (>25 cm²), sequential or simultaneous schedules can be considered • The standard tirbanibulin treatment period is five days. Up to four consecutive treatment cycles 1–2 months apart can be planned if needed • Multiple treatment cycles can be performed in immunocompromised patients, those with a history of skin cancer, or advanced photodamage • Patients should be informed about the chronic nature of AK and the need for repeated treatments over time • Although tirbanibulin-related local reactions are usually mild and transient, severe reactions may occur, and patients should be reassured • Patients should be given detailed instructions about tirbanibulin application at home

AK: actinic keratosis; FC: field cancerization; LC-OCT: line-field confocal optical coherence tomography; NMSC: non-melanoma skin cancer; OCT: optical coherence tomography; RCM: reflectance confocal microscopy; SCC: squamous cell carcinoma.

events were uncommon. Notably, none of the patients discontinued treatment for tirbanibulin-related adverse events [8]. Post-hoc analyses of these phase 3 trials suggested that comorbidities and concomitant treatments (which were common in the elderly population enrolled in the studies) do not affect the efficacy and tolerability of tirbanibulin. Also, no correlation was found between the number of AK lesions at baseline and the severity of local reactions in tirbanibulin-treated patients [30]. The efficacy and favorable tolerability profile of tirbanibulin as well as the high rates of treatment compliance have been confirmed in several real-life studies, including case series and prospective or retrospective observational studies [9-11,30,31]. Despite their limitations (e.g., lack of a control group, small number of

cases in some reports), the findings of real-life studies offer an insight into the effects of tirbanibulin in a much wider spectrum of patients and clinical presentations compared with the populations enrolled in randomized clinical trials. Although the European indication of tirbanibulin is for treatment of non-hyperkeratotic, non-hypertrophic AK (Olsen grade I) of the face or scalp, its use has been successfully extended to a range of clinical conditions, including AK patients with Olsen grade II or III lesions, AK lesions located on the trunk or limbs, or AK in organ transplant recipients [9,30,31]. High rates of patient satisfaction with tirbanibulin (as assessed by the Treatment Satisfaction Questionnaire for Medication) have also been reported, especially in domains related to treatment tolerability and convenience [10].

The efficacy and favorable tolerability profile of tirbanibulin are believed to be related to the novel mechanism of action of this molecule. Preclinical studies show that tirbanibulin, a potent antiproliferative agent, induces cell cycle arrest at G2/M phase and triggers programmed cell death of keratinocytes (via activation of intrinsic and extrinsic apoptotic pathways) by reversibly binding to tubulin, thus inhibiting tubulin polymerization, and by disrupting Src intracellular trafficking and Src-mediated signaling. Another possible antiproliferative mechanism is the induction of tumor suppressor *p53* expression. Tirbanibulin antiproliferative effects have been demonstrated in several tumor cell lines, including SCC, suggesting that keratinocytes with an aberrant cell growth rate may be selectively targeted by tirbanibulin [32,33]. As for the mechanisms accounting for tolerability, tirbanibulin displayed an apoptotic effect without inducing overt toxicity in vitro owing to its fully reversible binding to tubulin [34]. The induction of apoptosis has also been demonstrated in a study using line-field confocal optical coherence tomography and confirmed by histopathology [35]. The severe adverse local reactions caused by many AK treatments are known to be triggered by the release of pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-8 (IL-8). Notably, pro-inflammatory response assays show that tirbanibulin induces only a small increase in IL-8, unlike the significant increase in both TNF- α and IL-8 caused by 5-fluorouracil [32]. These data suggest a milder pro-inflammatory effect of this molecule compared with 5-fluorouracil, which could explain the favorable tolerability and safety profile observed in tirbanibulin-treated patients.

Patient Selection and Clinical Scenarios

As demonstrated in clinical trials and real-life studies, tirbanibulin is effective in achieving high clearance rates of AK lesions, with fewer severe local skin reactions compared with other commonly used topical treatments for AK. Importantly, tirbanibulin's mechanism of action targets oncogenic pathways that are believed to be key factors in the progression from AK to SCC. The short duration of treatment is another aspect of tirbanibulin therapy which is relevant to real-life practice since, together with its favorable tolerability profile, it facilitates patient compliance, thus enhancing the chance of a successful outcome. Acceptance of therapy and treatment adherence are important considerations in real-world practice and are often underestimated when selecting AK therapies based on evidence derived solely from clinical trials [36]. In a systematic review investigating adherence and persistence associated with topical AK therapies, combined non-adherence and non-persistence rates were found to be as high as 88%, and key contributing factors were identified as duration of treatment, severity and persistence of local

skin reactions, and patient confusion regarding treatment regimens [37]. Consistently with the data reported in clinical trials and real-life studies, this expert panel suggests that tirbanibulin should be considered as a first-line treatment for most AK patients, both naïve and previously treated, because of its efficacy, short treatment regimen, and favorable tolerability profile. As widely acknowledged, appropriate management of AK should consider patient preferences, clinical presentation (including localization, extension and severity of lesions and FC, duration and severity of symptoms) and patient characteristics (e.g., general health, comorbidities, risk factors for skin cancer) [4,12,27]. In the expert panel's experience, tirbanibulin has been successfully used in a wide range of clinical scenarios, including isolated or multiple AK lesions of varying severity (Olsen grade I and II) located in different areas of the face and scalp, extensive FC, patients who had received multiple AK therapies, and those with a history of chronic sun damage. In particular, tirbanibulin therapy has been selected as the treatment of choice in subjects with comorbidities and those with a history of skin cancer owing to its tolerability and lack of systemic adverse events. The efficacy of tirbanibulin appears to be maintained in difficult-to-treat sites, including ears, lips, and limbs, and in areas with adnexa or pigmented lesions. Examples of tirbanibulin-treated clinical cases with various AK presentations are illustrated in Figures 2–5. Even in cases where total clearance of AK lesions was not achieved, a substantial clinical improvement in both lesions and FC was observed. According to the authors' clinical experience, tirbanibulin therapy is readily accepted by patients, with a high degree of satisfaction and treatment compliance. Local reactions (mostly erythema and flaking/scaling) are generally mild, peak at approximately day 8 after treatment initiation (consistently with clinical study reports), and resolve spontaneously over an average of 10 days, without sequelae. Some patients experience a burning or itching sensation at the application site. The intensity of local reactions seems to be correlated to the extent of inflammation and photodamage in the treated field (Figure 3). However, severe local reactions such as swelling or erosion/ulceration are rarely observed. In addition to clearing or reducing AK signs, tirbanibulin treatment was also found to be associated with cosmetic benefits, such as improvement in skin quality and texture and a more uniform complexion (Figures 4 and 5). These emerging potential effects of tirbanibulin in targeting signs of skin aging, especially hyperpigmentation, have been investigated in recent preliminary studies [38,39]. In particular, tirbanibulin, unlike other AK therapies, appears to exert a skin-lightening effect on solar lentigines, hyperpigmented areas that are frequently observed in the context of AK and FC [39]. Although the mechanisms of action underlying these effects need to be further elucidated, the potential

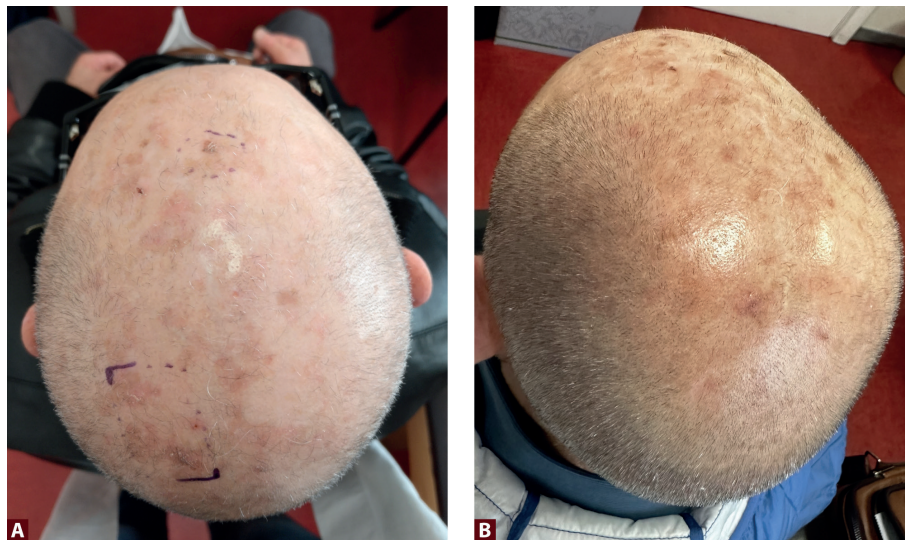


Figure 2. Images of AK lesions (Olsen grade I-II) in two small fields of cancerization on the scalp of a 75-year-old male with a long-standing history (>5 years) of AK on the scalp, previously treated with cryotherapy, topical diclofenac gel, and daylight photodynamic therapy: (A) before tirbanibulin treatment; (B) at the 2-month follow-up after treatment with tirbanibulin 1% ointment, showing complete clearance of occipital area and residual AK lesions (Olsen grade I) in the parietal field. The total area covered by tirbanibulin measured 26 cm² (2x3 cm=6 cm² for the occipital area and 4x5 cm=20 cm² for the parietal area). (Courtesy of Dr. G. Nazzaro)



Figure 3. Images of AK lesions (Olsen grade I-II) in a large field of cancerization on the left cheek of a 76-year-old male with a history of basal cell carcinomas on the trunk and limbs and with AK of the face and scalp (previously treated with physical therapies and topical drugs, with partial results): (A) before tirbanibulin treatment; (B) at 10 days after the end of treatment with tirbanibulin 1% ointment, showing erythema and scaling/flaking (the patient reported a burning sensation in the application area, but no intervention was required); (C) at 60 days after the end of treatment, showing complete clearance of the AK lesions (both Olsen grade I and II) and resolution of the local adverse reactions. (Courtesy of Dr. A. Villani)

benefit of cosmetic improvement induced by tirbanibulin therapy should be mentioned to patients, as it may represent an additional motivation for treatment, further enhancing compliance.

Treatment Modalities and Patient Education

The area of skin to be treated with tirbanibulin ointment depends on the distribution of AK lesions and FC on the face

and scalp. In line with current indications, a thin layer of tirbanibulin 1% ointment should be applied to cover a 25 cm² treatment field in each of four anatomical areas (scalp, forehead, left/right cheek with ear, nose, and chin). When treatment fields are not in close proximity, the total area to be covered by tirbanibulin can be divided into smaller sections, as shown in Figure 2. Addressing the needs of patients with large AK fields to be treated, recent studies have evaluated

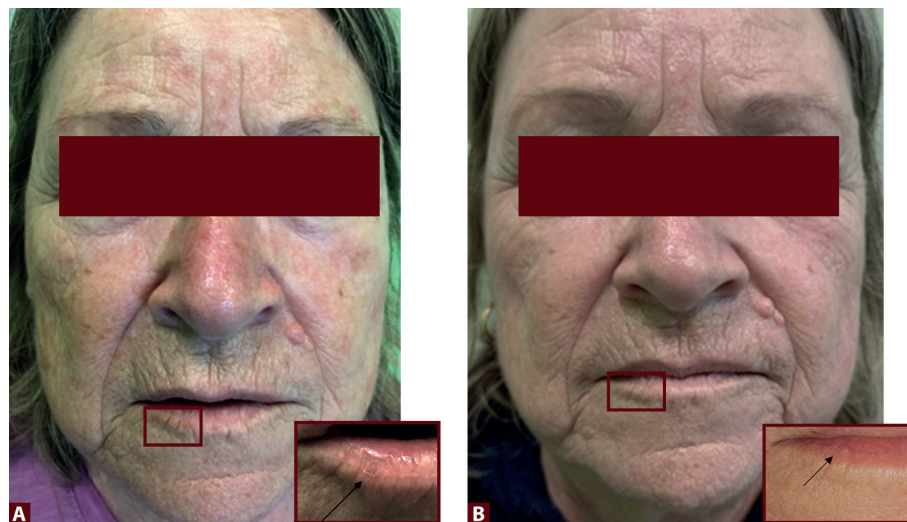


Figure 4. Images of multiple AK lesions (Olsen grade I-II), field of cancerization, and actinic cheilitis on the face of a 70-year-old treatment-naïve woman: A) before treatment, in the foreground square close-up; B) at four months after completion of 4 cycles of tirbanibulin 1% ointment (standard treatment of five days per cycle), showing efficacy on AK lesions, FC, and actinic cheilitis (with a close-up in the foreground square) as well as improvement in skin quality, with reduction in dyspigmentation and a more uniform complexion. A sequential treatment schedule was adopted, with four cycles 10 to 30 days apart, as follows: cycle 1→right forehead and nose, cycle 2→left forehead and nose, cycle 3→right cheek, cycle 4→left cheek. (Courtesy of Dr. S. Guida)

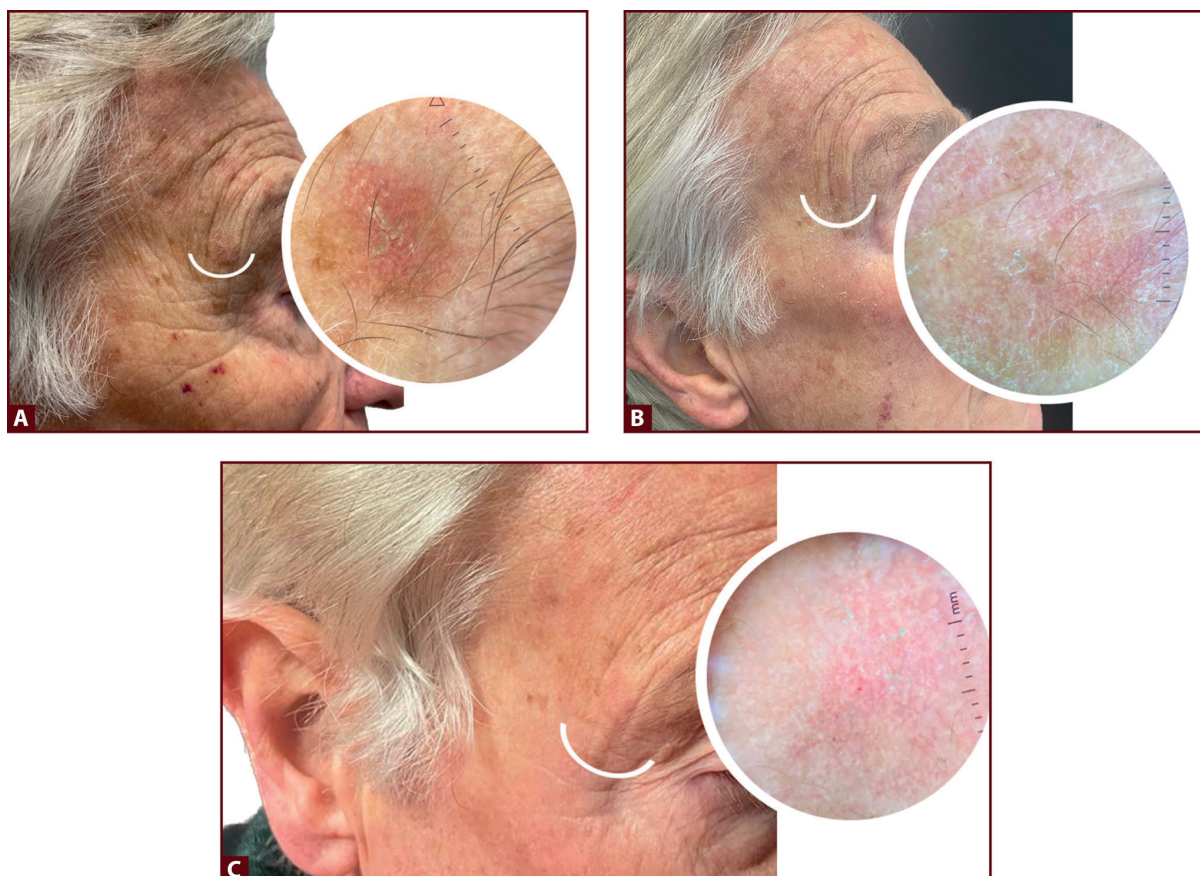


Figure 5. Images (with dermatoscopic view) of AK lesions (Olsen grade I-II) in the right frontotemporal region of an 83-year-old male, Fitzpatrick skin type I, with a history of chronic sun exposure and an extensive field of cancerization involving the head and neck which was treated with cycles of oral nicotinamide 250 mg four times daily. AK lesions had previously been treated with imiquimod 5% and piroxicam and sun filters for local use. The patient also had comorbid ischemic heart disease and depression (treated with calcium antagonists, clopidogrel, and sertraline) and had undergone surgery for a pigmented basal cell carcinoma on the forehead. (A) Before tirbanibulin treatment; (B) at 12 days after starting treatment with tirbanibulin 1% ointment, showing mild, well-tolerated local reactions (erythema and flaking); (C) at 58 days after treatment, showing complete clearance of the AK lesion. (Courtesy of Prof. E. Campione)

the pharmacokinetics and tolerability of tirbanibulin ointment when applied to fields larger than 25 cm², supporting its use (as one 350 mg sachet applied daily) in fields measuring up to 100 cm² [40,41]. The safety and tolerability profiles of tirbanibulin when used at approximately 100 cm² fields were found to be consistent with those reported for smaller fields, and exploratory efficacy data also suggest similar benefits to those observed with the application of tirbanibulin over a more restricted area [41]. According to this expert panel's experience, more than 25 cm² can be treated by one sachet of tirbanibulin 1% ointment.

The standard period of treatment with tirbanibulin is five days. However, owing to the favorable tolerability profile of the drug, various protocols are possible. Forward planning of the treatment regimen (including repeated treatment of severely affected areas) is always advisable. When treating large fields (>25 cm²), sequential or simultaneous therapeutic schedules can be considered. Up to four consecutive treatment cycles one to two months apart can be planned if needed, based on disease and patient characteristics. Multiple treatment cycles can be performed in immunocompromised patients, those with a history of skin cancer, and those with advanced photodamage.

Good communication with the patient is essential in the long-term management of AK. Clinicians should understand the patient's priorities and concerns, setting realistic treatment expectations [26]. Patient should be informed about the chronic nature of AK, the unpredictable evolution of AK lesions, and the high rates of recurrence, hence the need for repeated treatment courses over time. It is particularly important to inform patients about the occurrence and transient nature of local skin reactions associated with tirbanibulin treatment. Although skin reactions are usually mild, severe local adverse events may occur, and patients need reassurance that these will eventually resolve without sequelae. Correct treatment modalities are another important aspect of care that can affect the outcome of therapy. Patients should be given detailed instructions about tirbanibulin application at home.

Expert consensus statements with recommendations on tirbanibulin treatment are reported in Table 1(B).

Conclusion

With its novel mechanism of action, proven efficacy, good tolerability, and short duration of therapy, tirbanibulin is an important treatment for the management of AK and should be considered as a first-line option for most patients, including treatment-naïve and pre-treated subjects as well as those with difficult-to-treat lesions, comorbid conditions, or a history of previous skin cancer. Flexible therapeutic protocols with repeated treatment cycles are made possible by the

favorable tolerability profile of this topical drug. In clinical studies as well as in routine clinical practice, tirbanibulin therapy is associated with high rates of patient acceptability and treatment compliance, thus increasing the chance of a successful outcome.

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