SAJKIEWICZ, Ilona, MIGA-ORCZYKOWSKA, Nadia, LEMIESZEK, Paulina, JASIUK, Ilona, PUSTELNIAK, Martyna, WÓJTOWICZ, Justyna, KRUKAR, Katarzyna, RUDNICKA, Katarzyna, ŁUKASZEWSKA, Ewa and KISTER, Klaudia. Tirbanibulin as a Novel Treatment in Actinic Keratosis: A Literature Review. Journal of Education, Health and Sport. 2024;70:55328 eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.70.55328
https://apcz.umk.pl/JEHS/article/view/55328

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 21.08.2024. Revised: 10.09.2024. Accepted: 12.09.2024. Published: 24.09.2024.

Tirbanibulin as a Novel Treatment in Actinic Keratosis: A Literature Review

Ilona Sajkiewicz, Stefan Wyszyński Provincial Specialist Hospital in Lublin, Aleja Kraśnicka 100, 20-718 Lublin, Poland
https://orcid.org/0009-0007-5954-3594, inasajka@gmail.com

Nadia Miga-Orczykowska, Stefan Wyszyński Provincial Specialist Hospital in Lublin, Aleja Kraśnicka 100, 20-718 Lublin, Poland
https://orcid.org/0000-0002-0551-6159, nadmig98@gmail.com

Paulina Lemieszek, Stefan Wyszyński Provincial Specialist Hospital in Lublin, Aleja Kraśnicka 100, 20-718 Lublin, Poland
https://orcid.org/0009-0001-6648-7283, paulina.lemieszek13@gmail.com

Ilona Jasiuk, Independent Public Clinical Hospital No. 1 in Lublin, Stanisława Staszica 16, 20-400 Lublin, Poland
https://orcid.org/0009-0009-8544-3276, ilona.jasiuk@gmail.com

Martyna Pustelniak, Provincial Combined Hospital in Kielce, Grunwaldzka 45, 25-736 Kielce, Poland
https://orcid.org/0009-0000-5606-0385, martyna.pustelniak@onet.pl

Justyna Wójtowicz, Stefan Wyszyński Provincial Specialist Hospital in Lublin, Aleja Krasnicka 100, 20-718 Lublin, Poland
https://orcid.org/0009-0006-6079-9637, wojtowicz.justtyna@gmail.com

Katarzyna Krukar, Provincial Combined Hospital in Kielce, Grunwaldzka 45, 25-736 Kielce, Poland
https://orcid.org/0009-0001-5544-8027, kasiakrukar3@interia.pl

Katarzyna Rudnicka, Stefan Wyszyński Provincial Specialist Hospital in Lublin, Aleja Kraśnicka 100, 20-718 Lublin, Poland
https://orcid.org/0009-0005-6815-6276, katarzyna.rudnicka95@gmail.com

Ewa Łukaszewska, VOXEL NZOZ MCD, Paderewskiego 5, 37-100 Łańcut, Poland
https://orcid.org/0009-0000-6065-7213, lukaszewska.ewapaulina@gmail.com

Klaudia Kister, 1st Clinic of Psychiatry, Psychotherapy and Early Intervention, Medical University of Lublin, 20-079 Lublin, Poland
https://orcid.org/0000-0003-2058-5395, klaudia2178@gmail.com

Abstract

Introduction and purpose: Actinic keratosis (AK) is a common dermatological condition that primarily affects fair-skinned individuals due to cumulative ultraviolet light exposure, potentially leading to squamous cell carcinoma (SCC). AK therapy is divided into two main branches: lesion-directed therapy (cryotherapy, lasers, and surgical methods) and field cancerization-directed therapy (photodynamic therapy and topical agents). Unfortunately, the occurrence of local skin reactions (LSRs) and the therapy duration counted in weeks disrupt patient compliance. This study aims to review the clinical trials concerning the efficacy, safety, and adverse effects of tirbanibulin, a novel promising treatment for AK, which led to its approval and therapeutic development.

Materials and methods: Literature available in PubMed and GoogleScholar databases were reviewed using the following keywords: actinic keratosis; actinic keratosis treatment; tirbanibulin.

Results: Tirbanibulin's mechanism involves inducing apoptosis by inhibiting microtubule polymerization, which distinguishes it from other treatments that often cause significant inflammation. Clinical trials demonstrate its high efficacy in clearing AK lesions with a favorable safety profile, leading to regulatory approval. The ease of use and short therapy duration (5 days) ensure patient compliance and satisfaction with the treatment.
Conclusion: Further longitudinal studies are necessary to confirm the long-term benefits and positioning of tirbanibulin in AK therapy. Raising public awareness about AK and the importance of early treatment with effective options like tirbanibulin is crucial for improving public health outcomes.

Keywords: actinic keratosis; actinic keratosis treatment; tirbanibulin

Introduction

Actinic keratosis (AK), also referred to as solar keratoses, is one of the most common dermatological complaints in fair-skinned individuals, that represents the cumulative ultraviolet light damage of epidermal keratinocytes.[1] That precancerous skin lesion is also considered as chronic and recurring in situ skin neoplasia, with a possible transformation into invasive squamous cell carcinoma (SCC).[2] AK usually occurs on face, scalp, arms and legs – the parts of the body which are the most affected by the sun.[1]

Etiopathogenesis and epidemiology

Actinic keratosis prevalence ranges from 11% to 60% in Caucasian individuals above 40 years[3] and it is estimated that nearly 60% of this age group with predispositions have been diagnosed with at least one AK lesion.[4] In the United Kingdom, 15-23% of the population has AK lesions, and among the white population over 50 years old, this percentage reaches

37.5%.[5,6] Moreover, individuals over the age of 80 are six times more likely to develop AKs when compared to those between the ages of 50 and 59.[7]

Long-term exposure to UV radiation is the main risk factor for the development of AK due to the impairment of cell repair mechanisms in keratinocytes.[8] UVB radiation causes the formation of thymidine dimers in DNA and mutations in the telomerase gene, while UVA induces DNA mutations through photo-oxidative stress.[9] Additionally, alterations in the p53 gene, and its signaling pathways can lead to uncontrolled proliferation of dysplastic keratinocytes, resulting in the formation of AK lesions.[10]

The risk of developing AK is also increased by age over 45, male gender, Fitzpatrick skin phototype I-II including light hair and eye color, freckles on the face or arms, a positive history of other types of non-melanoma skin cancer, prior sunburns, HPV infection, and immunosuppression. Furthermore, regular sunscreen use and a previous history of atopic conditions reduce the likelihood of AK development.[2,11]

The clinical significance of AK arises from patient discomfort, cosmetic appearance, and most importantly, the risk of progression to invasive SCC.[12] Malignant transformation occurs in 0.025% to 16% of cases, with increased risk in individuals with multiple AK lesions (more than five).[4]

Diagnosis

Although clinical symptoms of actinic keratosis may vary, they typically present as reddish, sometimes brownish, discrete, localized patches with accompanying thickening and scaling. The lesions may feel rough, dry, scaly, or crusted. Usually, AKs occur singly or are scattered, but in later stages, they may merge into larger plaque-like formations with subclinical changes in the area, also known as field cancerization. Actinic keratosis can be clinically challenging to distinguish from other benign skin conditions, such as lichenoid keratosis and other benign keratotic lesions. Most commonly, it progresses without symptoms, but occasionally it can also present with itching, pain, erosions, or even bleeding. Typically, the diagnosis of AK is made based on clinical examination by a doctor and dermoscopic evaluation of the skin, focusing on the previously mentioned clinical features. Dermoscopy demonstrates a sensitivity of 98.7% and specificity of 95% for diagnosing AK. During the assessment, a characteristic pattern called the "strawberry pattern" is often observed, consisting of scaling

(86.7%), follicular openings (83.1%), erythematous network (79.9%), and linear, wavy vessels (71.2%).[2,13,14] Histopathological confirmation is not routinely performed.[13]

Treatment

So far, clear and specific risk factors indicating the development of malignancy from AK have not been established. Moreover, spontaneous remission can be observed in up to 60% of cases.[15] Nevertheless, based on literature review, the estimated annual risk of malignancy for each individual lesion ranges from 0.03% to 20%, with over 60% of SCC diagnoses being associated with preceding AK lesions.[15–17] All these factors have led to a lack of consensus regarding which lesions should be treated. However, based on studies by Schmitz et al. and Fernandez-Figueras et al., there is an increasing trend to move away from the watch-and-wait approach.[18–20] Schmitz et al. even state that due to the unpredictability of which AK lesions are likely to become malignant, all of them should be treated[19] - both visible clinical changes and invisible subclinical changes, known as field cancerization, which is the entire area affected by AK lesions.[21]

The main objectives of treating actinic keratosis are to reduce the risk of developing invasive SCC, eliminate both visible and hidden AK lesions, and prolong the period without disease. Additionally, secondary goals include minimizing the side effects of treatments, and enhancing the patient's overall quality of life.[22]

The latest guidelines from the American Academy of Dermatology (AAD) emphasize sun protection measures for treating AK, including avoiding sun exposure, wearing protective clothing, and using broad-spectrum sunscreen creams.[23]

Treatment of AK divides into two main branches: targeted therapy aimed at specific AK lesions and field-directed therapy aimed at multiple clinical lesions and the underlying field cancerization.[4] The first category includes cryotherapy, laser therapy, surgery, and scraping. The second category encompasses photodynamic therapy (PDT), 5-fluorouracil (5-FU), oral retinoids, diclofenac, chemical peels, imiquimod, and tirbanibulin.[24] Until 2020, ingenol mebutate (IM) was also used; however, it has been withdrawn by the European Medicines Agency.[25] Unfortunetly, these treatments can cause local reactions such as pain, irritation, erosions, ulcerations, and permanent skin changes like pigmentation and scarring. Furthermore, most of those medications require administration over weeks or months, some of them twice a day, which may decrease patient adherence and compromise the success of the therapy.[21,26]

The selection of AK treatment should consider factors pertaining to the lesion itself (number, location, histology), the patient (age, adherence, immune status), and the therapy (duration, side effects, efficacy). In conclusion, it should be individualized. Better compliance is often shown with treatments that have simpler and shorter treatment cycles than those with longer cycles, which appears more suitable for patients for whom convenience and adherence may be challenging.[21] In recent years, clinicians have favored tirbanibulin as a treatment for AK. In this review, we will outline its mechanism of action, the path to its approval, and future research directions for this promising substance, with a specific focus on its utility in AK.

Tirbanibulin

Mechanism of action

The new synthetic chemical compound that has demonstrated strong anti-proliferative and anti-tumor activity in vitro and in vivo is tirbanibulin. This substance induces cell cycle arrest and ultimately leads to cell death through apoptosis. This is explained by tirbanibulin's ability to reversibly bind to the colchicine-binding site on β-tubulin, thereby inhibiting microtubule (MT) polymerization.[27,28] However, it is possible that this substance binds to a novel binding site on the αβ-tubulin heterodimer.[28] Immunofluorescence staining has demonstrated that tirbanibulin effectively disrupts the microtubule network by directly inhibiting tubulin in immortalized CCD-1106 KERTr keratinocyte cells. Furthermore, tirbanibulin induced complete cell cycle arrest at the G2/M growth interface in HeLa cells, leading to apoptosis, as evidenced by positive annexin V cell staining.[27] Additionally, immunoblot analysis revealed activation of both intrinsic and extrinsic apoptotic programmed cel death pathways - tirbanibulin led to hyperphosphorylation of Bcl-2, cleavage of caspases 8 and 9, activation of caspase 3, and subsequent cleavage of poly(ADP-ribose) polymerase (PARP).[29] Compared to other MT inhibitors, tirbanibulin exhibits very high affinity and specificity for tubulin. The drug's low toxicity and reversibility of cellular effects have been attributed to its complete reversibility of tubulin polymerization inhibition, which is concentration-dependent.[27] The effectiveness of tirbanibulin was evaluated in vivo using mouse xenograft models of breast cancer (MDA-MB-231 cells) and mucinous ovarian cancer (RMUG-S and RMUG-L cells), where it demonstrated delayed tumor growth, reduced expression of the proliferation marker Ki67, and increased apoptotic cell count. Moreover, in a murine model of

human prostate cancer (PC-3MM2GL cells), tirbanibulin showed inhibition of both primary tumor growth and metastasis.[29,30]

The family of nine non-receptor tyrosine kinases (SFK)[31] actively participate in angiogenesis and vascular endothelial growth factor (VEGF) signaling.[32] Increased expression of the tyrosine kinase Src has been noticed in both AK and SCC, indicating its role in keratinocyte migration and invasion of squamous cell carcinoma of the skin.[33] According to research, tirbanibulin reduces the levels of phospho-Src and its substrates in mouse cancer cells, disrupting SFK signaling.[34] However, it seems that this effect is indirect and results from affecting the microtubule network, which disturbs various cellular signaling pathways.[22] Additionally, tirbanibulin appears to decrease the expression of HPV oncoproteins through the Src-MEK pathway, as detected in the tested HeLa cells with integrated HPV 18 genome.[35]

The preclinical study indicated that the highest dose of tirbanibulin caused a minor elevation in the pro-inflammatory cytokine IL-8, whereas 5-fluorouracil led to a moderate increase in TNF-α and IL-8. Furthermore, there was a notable rise in IL-1α, which serves as a marker for cell death.[36] Consequently, the use of tirbanibulin was expected to be associated less frequently with intensified skin reactions compared to 5-fluorouracil.[29]

Clinical trials

Phase I

A Phase I study is an open-label, single-center, proof-of-concept study involving 30 individuals aged ≥ 18 years with AK lesions on the forearms treated with 1% tirbanibulin ointment once daily in four cohorts. Cohort 1, with 4-8 AK lesions, received 50 mg/day over an area of 25 cm^2, and Cohort 2, with 8-16 AK lesions, received 200 mg/day over an area of 100 cm^2, both groups for 3 days. Cohorts 3 and 4 had the same conditions, but the treatment lasted for 5 days. Observations were conducted up to day 45, assessing complete and partial clearance of AK. A reduction in the number of AK lesions was observed in all cohorts. Cohorts 1–4 demonstrated complete AK clearance rates of 25%, 0%, 50%, and 12.5%, respectively.[37]

Phase II

In the Phase II study, which was an open-label, uncontrolled, multicenter trial involving 168 individuals with clinically typical AK on the scalp or face, participants were divided into two equal cohorts. The aim of the study was to discover the best dosing regimen. Both cohorts

of 84 individuals each received 1% tirbanibulin ointment once daily on an area of 25 cm² of skin. The first cohort used the ointment for 5 days, and the second for 3 days. Patients were evaluated on day 57 – complete clearance of AK lesions was observed in 43% of individuals in the 5-day cohort (specifically, 52% of patients with facial lesions and 33% with scalp lesions) and in 32% of individuals in the 3-day cohort. The first cohort used the ointment for 5 days, and the second for 3 days. Patients were evaluated on day 57 – complete clearance of AK lesions was observed in 43% of individuals in the 5-day cohort (specifically, 52% of patients with facial lesions and 33% with scalp lesions) and in 32% of individuals in the 3-day cohort. A 12-month follow-up period from day 57 of the study was used to assess recurrences in patients with 100% clearance of lesions – in the 5-day cohort, recurrences were 57%, while in the 3-day cohort, they were 70%. Consequently, the optimal duration for the ointment application was determined to be 5 days.[38,39]

Phase III

The Phase III study consisted of two identical multicenter, double-blind, placebo-controlled trials, each involving 351 individuals aged ≥ 18 years with AK lesions on the scalp or face. Patients with 4-8 visible AK lesions in an area of 25 cm² were to apply either 1% tirbanibulin ointment or a vehicle ointment once daily for 5 days, depending on their random assignment to the study or control group. On day 57, complete clearance (the primary endpoint) and partial clearance (the secondary endpoint) were assessed in both trials. In the first trial, complete clearance occurred in 44% of those using tirbanibulin compared to 5% in the placebo group, and in the second trial, 54% compared to 13%. Combined data from both trials showed complete clearance in 49% of the tirbanibulin group versus 9% of the placebo group. Partial clearance also showed a significantly higher percentage in the tirbanibulin group compared to placebo – 68% versus 16% in the first trial and 76% versus 20% in the second trial. Combined data reported partial clearance in 72% of the tirbanibulin group versus 18% in the placebo group. Considering the recurrent nature of actinic keratosis on sun-damaged skin, recurrence of symptoms was expected. With conventional treatment, this risk ranges from 20% to 96%. Using the Kaplan-Meier method, the risk of recurrence with tirbanibulin therapy was estimated at 47%, and the appearance of both recurrent and new AK lesions was estimated at 73% after 12 months in patients achieving complete treatment response. The risk of full remission was estimated at 27%.[1,40] Post hoc analysis revealed that tirbanibulin had equal efficacy in clearing AK lesions across various patient subgroups categorized by Fitzpatrick skin type, BMI, or

previous treatment for AK lesions. However, the clearance of lesions from facial skin was more pronounced than from the scalp.[41] This demonstrates the potential for using this substance both as a second-line treatment option and as a first-line treatment.[42]

Safety and tolerability

Studies in healthy individuals have shown that 1% tirbanibulin ointment does not cause contact sensitization, phototoxic reactions, or photoallergic reactions on the skin.[43] Additionally, in all phases of the studies involving the use of tirbanibulin, local skin reactions (LSRs) were most commonly mild to moderate in severity.[1,37] The most frequently reported LSRs were erythema (93% of participants) and scaling (82% of participants). Other LSRs reported by patients included crusting, swelling, peeling, blisters or pustules, and ulceration or erosions.[1] It should be noted that severe LSRs occurred in < 10% of patients, with severe erythema reported in 6% of patients. LSRs typically appeared at the beginning of treatment, peaked at eight days, and then decreased within a month.[44] Post hoc analysis of the Phase III study demonstrated that complete clearance of AK with 1% tirbanibulin ointment was associated with mild to moderate local skin reactions (LSRs), with 70.2% of patients achieving a composite LSR score ≤ 5 (on a scale of 0-18). The small number of participants who achieved clearance with higher composite scores suggests that more aggressive skin reactions were not necessary to achieve complete clearance of AK.[45,46] Furthermore, no significant differences were observed in the occurrence of LSRs between the population previously treated with other therapies and the population where tirbanibulin was used as first-line treatment.[42]

No participants were withdrawn from the clinical trials due to adverse events (AEs) or local skin reactions (LSRs), and the incidence of AEs in the group using tirbanibulin ointment was similar to those using vehicle ointment (33% vs 32% in the first Phase III trial and 38% vs 39% in the second Phase III trial). Most reported AEs were mild, with itching and pain at the application site being the most common, which typically resolved spontaneously.[1]

In physical examinations, laboratory tests, and electrocardiograms, no clinically significant adverse effects of tirbanibulin were observed.[1] However, this medication can cause irritation around the eyes, so patients should take care when applying this substance in that area.[47] Current data indicate that extremely high doses of tirbanibulin can cause birth defects in rats and rabbits. However, there is no data regarding the safety of this medication during pregnancy in humans.[8]

Approval and recommendations

Tirbanibulin 1% ointment was first approved by the U.S. Food and Drug Administration (FDA) in December 2020 for the 5-day topical treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (Olsen grade I) on the face and scalp in adults. The European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA) also approved this substance in 2021. In the same year, the American Academy of Dermatology published guidelines to assist in clinical decision-making regarding AK treatment.[23] A year later, a strong recommendation was issued to include the topical use of tirbanibulin in the recommended list of topical therapies for treating AK.[48]

According to the model, the content of one package containing 2.5 mg of tirbanibulin in 250 mg of ointment is applied to a 25 cm^2 area of the face and scalp skin, once daily for five consecutive days. In practice, however, the treated areas are significantly larger. In the report, the contents of one ointment package were evenly applied on the balding scalp, forehead, and two AK lesions on the patient's face, covering a total area of nearly 318 cm^2 as measured digitally—almost thirteen times larger than the standard application area.[49] It demonstrates the efficiency of the ointment available on the market and the ease of uniform self-application.

The success of tirbanibulin

Since its initial approval, tirbanibulin has garnered significant interest among scientists and clinicians, who are increasingly eager to understand its advantages and disadvantages in various therapeutic applications.

The open-label, parallel-group pharmacokinetics safety study of tirbanibulin ointment 1% by Yavel et al. confirmed significant resolution of AK lesions when applied to 25 cm^2 of the face or scalp in adults with AK, its safety profile, and patient tolerance. All subjects had measurable but low serum concentrations of tirbanibulin. On the 5th day of ointment application, the mean maximum serum concentration was 0.26 ng/ml, demonstrating that tirbanibulin exhibits low systemic exposure even under maximum use conditions – serum concentrations below nanomolar levels.[50]

Heppt et al., in a meta-analysis comprising 46 studies, demonstrated that 1% tirbanibulin ointment was more effective in clearing AK lesions on the face and scalp after one treatment

cycle, within a treatment area of ≤25 cm², 8 weeks post-treatment cessation compared to 3% diclofenac. Its outcomes were comparable to those of 5% fluorouracil, in concentrations of 5%, 4%, and 0.5% combined with salicylic acid, as well as imiquimod at concentrations of 3.75% and 5%, ALA-PDT, MAL-PDT, and cryotherapy.[51]

The study by Dao et al.'s study emphasizes the advantage of tirbanibulin in terms of treatment duration (just 5 days) compared to 5% fluorouracil cream, 3% diclofenac gel, and 3.75% imiquimod cream. Additionally, they note that systemic adverse events (AEs) such as systemic vasculitis and necrosis observed with fluorouracil and imiquimod therapies for AK were not observed with tirbanibulin, highlighting its favorable safety profile.[8]

Dymond et al. evaluated the cost-effectiveness of using tirbanibulin compared to conventional AK therapies within the Scottish healthcare system. They deemed tirbanibulin to be a cost-effective treatment option with similar rates of AK lesion clearance but less severe LSRs and shorter treatment duration compared to 5% fluorouracil, 3% diclofenac sodium, and 5% imiquimod.[52]

The real-world study by Kirchberger et al. yielded very promising results. In this single-center study of patients aged ≥ 18 years with clinically typical AK lesions on the face and scalp, treatment with 1% tirbanibulin ointment was administered once daily for 5 days as per the label. After 4 weeks and subsequent follow-up visits, treatment efficacy was assessed using the Actinic Keratosis Area and Severity Index (AKASI) and digital dermatoscopy. Out of 33 analyzed patients, 30 were included in the analysis. The median AKASI score decreased from 5.6 (range: 1.4-11) before treatment to 1.2 (range: 0-7.4) after treatment. Complete clearance of lesions was observed in 47% of patients at the first follow-up visit and in 57% at the second. LSRs, with the most common being erythema (80%) and scaling (43%), resolved spontaneously without leaving lasting changes.[53] The results of this real-world study align with findings from two Phase III trials.[1]

The subsequent real-world study by Li Pomi et al. also confirms the effectiveness and favorable safety profile of tirbanibulin in treating AK. In this spontaneous open-label, prospective non-randomized study, 38 patients (28 men and 10 women) aged between 52 and 92 years were treated, collectively having 228 AK lesions. Complete clearance was observed in 51% of lesions, with partial clearance in 73%. Researchers emphasized excellent compliance and no treatment interruptions due to AEs.[54]

In addition to efficacy and safety profile, the single-center, prospective, observational study by Campione et al. also measured patient satisfaction with treatment. Tirbanibulin

ointment was applied on a 25 cm^2 area for 5 days in 30 participants with AKs on the face or scalp, with a follow-up period of 57 days. On the 57th day, 70% of patients showed complete clinical and dermatoscopic response. The most common local skin reactions (LSRs) were erythema and scaling, most of which occurred by day 8 and resolved without intervention. Treatment satisfaction was assessed using the TSQM 1.4 questionnaire (range 0-100), focusing on four aspects: convenience (score 97/100), side effects (94/100), effectiveness, and overall satisfaction (both around 80/100).[55] Additionally, in another study, patients rated their satisfaction with tirbanibulin treatment at 8.15 out of 10, with the highest ratings given for drug tolerance.[56]

Nazzaroo et al. conducted a multicenter retrospective study involving 15 dermatology departments in Italy, examining the efficacy and tolerability of tirbanibulin in a group of 250 patients. Post-treatment, the AKASI score was significantly lower across the entire population, with the percentage reduction in the AKASI score increasing with patient age. A satisfactory response, defined as partial and complete reduction in the number of AK lesions, was observed in almost 90% of cases, with a higher percentage of approximately 97% at the follow-up conducted 8 weeks later. The AKASI reduction was also significant in patients with Olsen grade II and III lesions (from 5.3 ± 2.8 to 1.6 ± 1.6; $P < 0.001$) and in patients with AK on the trunk or limbs (from 7.0 ± 1.3 to 2.0 ± 1.6; $P = 0.018$), where satisfactory responses appeared in nearly 90% of cases in both groups. This study, in addition to confirming the efficacy and tolerability of tirbanibulin, also offers hope for its future application in higher Olsen grades and in hard-to-reach areas.[57]

Another study confirming the validity of using 1% tirbanibulin ointment is the PROAK study by Schlesinger et al. The authors analyzed the clinical outcomes of nearly 300 patients with AK on the face or scalp in the USA, assessing the quality of life using Skindex-16, as well as effectiveness (Investigator Global Assessment), safety, and tolerability at weeks 8 and 24. The IGA was achieved by 71.9% of patients by week 24, with a similar percentage (73.8%) noted at week 8, indicating stable treatment efficacy over the longer term. The most frequently reported LSRs were mild or moderate erythema and flaking or scaling (less than 50%)[58], which is consistent with the results of previous studies.[1]

Although the phase I clinical trials were conducted on forearms[37], most studies on tirbanibulin focus on the area of the face and scalp, which has been approved as the official indication for the use of this drug.[59] In a retrospective case review study by Iglesias-Puzas et al., researchers aimed to demonstrate the functionality of tirbanibulin in treating AKs on the

upper limbs. Data from 17 patients with AK were analyzed across 22 treatment cycles (45% of AKs on the backs of hands, the rest on the arms and forearms). On day 60, complete clearance of lesions was observed in 45% of patients, and partial clearance in 82%. No differences in treatment efficacy were noted regarding the location or severity of AKs. LSRs were reported in 8 patients, most of which were mild. The safety profile of tirbanibulin for treating AKs on the upper limbs was found to be better than that for the approved indication, likely due to the stronger barrier function of the skin on the limbs, which reduces the tendency for LSRs in this area.[60]

In a phase I maximal-use trial by DuBois et al., the authors investigated the plasma pharmacokinetics, safety, and tolerability of tirbanibulin ointment 1% applied to a 100 cm^2 area, which is four times larger than in previous studies. 28 patients applied tirbanibulin once daily for a 5-day treatment course. On the last day, the mean maximum plasma concentration was 1.06 ng/mL. Systemic exposure was approximately 4 times higher than in the pharmacokinetic study with a 25 cm^2 treatment area, which is consistent with the increase in the treated area.[61] Another recently published study conducted on a 100 cm^2 area was a phase 3, multicenter, open-label study by Bhatia et al. In addition to safety and tolerability, the authors also evaluated the efficacy of tirbanibulin ointment 1% on 105 patients with AK on the face and scalp.[62] The results of both mentioned studies were consistent with earlier pivotal studies conducted on smaller areas.[1]

One cannot fail to notice another advantage of tirbanibulin, which is its desirable side effect on the area of application of the ointment on chronically photodamaged skin. This substance significantly slows down skin aging in these areas, exhibiting rejuvenating effects on texture, skin brightening, and reducing lentigines.[63]

Future directions

Tirbanibulin continues to be successful in clinical research. Currently, several post-approval clinical studies are ongoing to evaluate the impact of this substance in treating AK. One of them (NCT05387525) is a phase IV, multi-center, randomized, evaluator-blinded, active-controlled study aimed at assessing the likelihood of SCC confirmed by biopsy in the treatment area over a 3-year study period using tirbanibulin ointment 1%. Another phase IV study (NCT05900258) is investigating the efficacy of the drug on UV-damaged skin adjacent to AK lesions, while a phase 3 study (NCT06135415) is focusing on areas of 25-100 cm^2 of

skin. The objective of the upcoming study (EudraCT number: 2022–001251-16) is to evaluate the impact of tirbanibulin on patients' well-being. Tirbanibulin is also being investigated for its potential in treating BCC (NCT06112522). Studies conducted in Taiwan are exploring the use of 1% tirbanibulin ointment in treating plaque-type psoriasis, yielding promising results.[64]

Several case reports have described the efficacy of tirbanibulin in treating various dermatological conditions, including Bowen's disease[65], reccurence of superficial BCC[66], and recalcitrant viral warts.[67] It has also been used to eliminate periungual squamous cell carcinoma in a patient who failed treatment with 5% imiquimod and monthly cryotherapy.[68] Additionally, in a series of cases, 6 out of 7 lesions of SCC or SCCIS were eradicated using tirbanibulin 1% ointment following biopsy.[69] These cases suggest the potential consideration of this substance as a non-surgical treatment option for SCC. Furthermore, they indicate the potential development of tirbanibulin-based compounds as promising anticancer agents.[70]

Conclusion

Solar keratosis (actinic keratosis, AK) is a common skin condition that can potentially progress to squamous cell carcinoma (SCC). It is essential to raise awareness among both patients and non-dermatologist physicians for early diagnosis and treatment, thereby avoiding the need for more aggressive therapies for malignant tumors. Emphasis should also be placed on prevention strategies, such as using sunscreen and avoiding excessive sun exposure.

Tirbanibulin is a promising new drug with a notably favorable safety profile compared to previously available therapies. Its mechanism of action involves inducing apoptosis rather than necrosis of cells, which significantly reduces inflammation. Convenient dosing - once daily for only five consecutive days - and higher tolerance result in better patient compliance and satisfaction, with long-term effective outcomes. Additionally, the drug offers aesthetic benefits.

Longitudinal studies are needed to assess the long-term safety and efficacy of tirbanibulin, including monitoring for potential side effects and understanding the durability of treatment outcomes over extended periods. More comparative studies with other existing treatments for AK and related conditions will help to position tirbanibulin within the therapeutic landscape. Currently, 1% tirbanibulin ointment is approved only for topical use on the face and scalp for Olsen grade I AK lesions. However, results from future clinical trials may expand its applications, not only in dermatological conditions but also in oncology.

Disclosure

Authors' contributions

Conceptualization: Ilona Sajkiewicz, Nadia Miga-Orczykowska;

Methodology: Paulina Lemieszek, Ilona Jasiuk;

Software: Ilona Jasiuk, Martyna Pustelniak, Katarzyna Krukar;

Check: Katarzyna Krukar, Ewa Łukaszewska;

Formal Analysis: Ewa Łukaszewska, Klaudia Kister;

Investigation: Martyna Pustelniak, Ewa Łukaszewska;

Resources: Justyna Wójtowicz, Martyna Pustelniak, Klaudia Kister;

Data Curation: Klaudia Kister, Katarzyna Rudnicka;

Writing-rough preparation: Nadia Miga-Orczykowska, Justyna Wójtowicz, Katarzyna Rudnicka;

Writing-review and editing: Ilona Sajkiewicz, Paulina Lemieszek, Ilona Jasiuk;

Visualization: Justyna Wójtowicz, Katarzyna Krukar;

Project Administration: Ilona Sajkiewicz, Nadia Miga-Orczykowska;

Supervision: Ilona Sajkiewicz, Paulina Lemieszek.

All authors have read and agreed with the published version of the manuscript.

Funding Statement

The study did not receive special funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Acknowledgments

Not applicable.

Conflict of Interest Statement

The authors of the paper report no conflicts of interest.

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