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ORIGINAL ARTICLE

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Tirbanibulin 1% Ointment: The Mechanism of Action of a Novel Topical Therapy for Actinic Keratosis

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ABSTRACT

Actinic keratosis (AK) is a common, precancerous skin lesion that may progress to squamous cell carcinoma (SCC). Traditional topical therapies for AKs often require long treatment durations. These therapies may also cause significant local skin reactions that can reduce patient adherence. Tirbanibulin, a first-in-class topical agent for AKs on the face and scalp, was approved by the US Food and Drug Administration (FDA) in 2020. Tirbanibulin serves as a promising alternative with a shorter treatment duration of five days.

Unlike other topical AK therapies, tirbanibulin targets microtubules in keratinocytes. The agent inhibits tubulin polymerization, disrupts the microtubule network, and induces cell cycle arrest. These cellular effects may be reversible, reducing tirbanibulin's toxicity profile. Tirbanibulin has also demonstrated antiproliferative activity with the potential to selectively target highly proliferative keratinocytes, contributing to its antitumorigenic effects. In addition, studies suggest that tirbanibulin may induce apoptosis and interfere with the activity of Src, a tyrosine kinase that can contribute to the progression of AKs and SCCs.

Tirbanibulin's shorter treatment duration and favorable safety profile make it an appealing choice in AK management. In clinical studies, tirbanibulin 1% ointment was well-tolerated and demonstrated significant efficacy in clearing AK lesions in areas up to 100 cm^2 on the face and scalp. Tirbanibulin's novel mechanism of action introduces a new, exciting option for the field treatment of AKs.

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INTRODUCTION

Epidemiology

Actinic keratosis (AK) is a premalignant skin lesion that may result from prolonged ultraviolet (UV) damage.[1] AKs are common worldwide with an estimated global prevalence rate of 14%.[1] AKs are often characterized as hyperkeratotic papules or plaques with a rough surface or overlying scale on an erythematous base.[2–4] These skin lesions often appear on sun-exposed areas and are more common among males, those of advanced age, those with Fitzpatrick skin type I or II, and those who are immunosuppressed.[1,4] If left untreated, AKs may progress to invasive squamous cell carcinoma (SCC).[2,4]

Pathogenesis

Histologically, AKs demonstrate epidermal hyperplasia and varying degrees of cellular atypia.[2] The atypia can resemble SCC in situ but without full-thickness epidermal involvement.[2] The cellular changes that are present in both AKs and SCCs may be indicative of their mutual pathogenesis.[2] AK development commonly begins with DNA damage in the basal layer of the epidermis.[2,5] Affected keratinocytes often contain DNA mutations that have been classically associated with UVB-related damage (eg, C to T and CC to TT).[2,5] The mutations have also been associated with oxidative stress from UVA-mediated production of reactive oxygen species or the intrinsic aging of cells.[2] The DNA mutations found in AKs particularly involve the *TP53* gene, which encodes for the p53 protein that plays a critical role in tumor suppression.[5] The *TP53* mutations contribute to keratinocyte dysplasia, ultimately resulting in AK development on the epidermal surface.[2,5] In the research of AK progression to SCC, Src kinases have been of particular interest, as increased expression of these nonreceptor tyrosine kinases has been found in both AKs and SCCs.[6,7] Studies suggest that increased Src signaling may play an important role in the alteration of hemidesmosomes and migration of keratinocytes necessary for SCC progression and invasion.[6,7]

Treatment Overview

The potential for AKs to progress to SCC has been well-established.[4] However, a clinical method to definitively identify which AK lesions may progress to SCC is yet to be determined.[4] As a result, dermatologists have recommended that all AKs, including both clinically visible and subclinical lesions, be treated.[4] Recommendations to treat subclinical lesions stem from concerns regarding field cancerization, which refers to the presence of genetically altered cells in the areas surrounding AK lesions.[8] Although these surrounding areas may not present with clinical signs or symptoms suggestive of carcinogenesis, they may still contain genetic mutations that increase their risk for AK development.[4,8]

AK management options include lesion-directed and field-directed therapies. Lesion-directed therapies include liquid nitrogen cryosurgery, manual or surgical removal, and ablative lasers.[2,4] These therapies are often used to target clinically visible AKs in patients with few or isolated lesions and are performed by the clinician.[2,4] Field-directed therapies, such as photodynamic therapy (PDT) and topical agents, may be used in place of or in addition to lesion-directed therapies.[2,4] Field-directed therapies are often used to target both clinically visible and subclinical lesions in patients with multiple AKs.[2,4] Furthermore, field-directed therapies may help to reduce the risk of new AK development and recurrence.[2,8] Although PDT is conducted by clinicians, topical agents may be self-administered by the patient.[2,4]

Traditional Topical Therapies

Most topical therapies for AKs induce cell necrosis or apoptosis in rapidly proliferating keratinocytes.[4] Topical 5-fluorouracil (5-FU) disrupts DNA replication in the S phase and promotes the release of proinflammatory cytokines and cell necrosis.[4,6] Similarly, ingenol mebutate also induces inflammation and necrosis of atypical keratinocytes.[2,4] However, safety data reviewed by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee found an increased incidence of skin cancer in patients treated with ingenol mebutate compared to imiquimod after three years.[2] As a result, ingenol mebutate was removed from the US market in 2020.

Apoptosis-inducing agents include imiquimod and diclofenac.[4] Imiquimod primarily functions as a toll-like receptor 7 agonist and can stimulate the immune system.[6] The agent enhances cytokine activity levels and modifies the patient's immune response to identify and target tumor antigens in atypical keratinocytes.[4,6] On the other hand, the nonsteroidal antiinflammatory drug (NSAID) diclofenac functions by inhibiting cyclooxygenase-2 (COX-2) and preventing the formation of prostaglandins.[4] However, the use of diclofenac is not recommended as strongly as 5-FU and imiquimod due to the medication's black box warning for cardiovascular and gastrointestinal side effects, similar to other NSAIDs.[2]

Although 5-FU, imiquimod, and diclofenac may serve as potential therapy options for AKs, they often require several weeks of treatment.[6] Previous studies have found that therapies with longer dosing regimens may be associated with lower patient adherence.[4] In addition, 5-FU, imiquimod, and diclofenac have been found to induce local skin reactions (LSRs), such as erythema, pruritus, crusting, erosions, and ulcerations, at treated sites.[4,6] Imiquimod, in particular, has also been associated with systemic, influenza-like symptoms.[2] These adverse effects may decrease patient adherence even further.[2,4] The long dosing regimens and adverse effects associated with 5-FU, imiquimod, and diclofenac have created the need for an effective, well-tolerated topical agent with a shorter treatment duration.

Tirbanibulin

In December 2020, the FDA approved tirbanibulin, a first-in-class, topical treatment for AKs on the scalp or face.[9] Unlike previous topical agents, tirbanibulin 1% ointment only requires once-daily application for five consecutive days.[9] Although tirbanibulin was originally approved for use on an area up to 25 cm^2, the FDA expanded the treatment field to up to 100 cm^2 in June 2024.[10]

Mechanism of Action

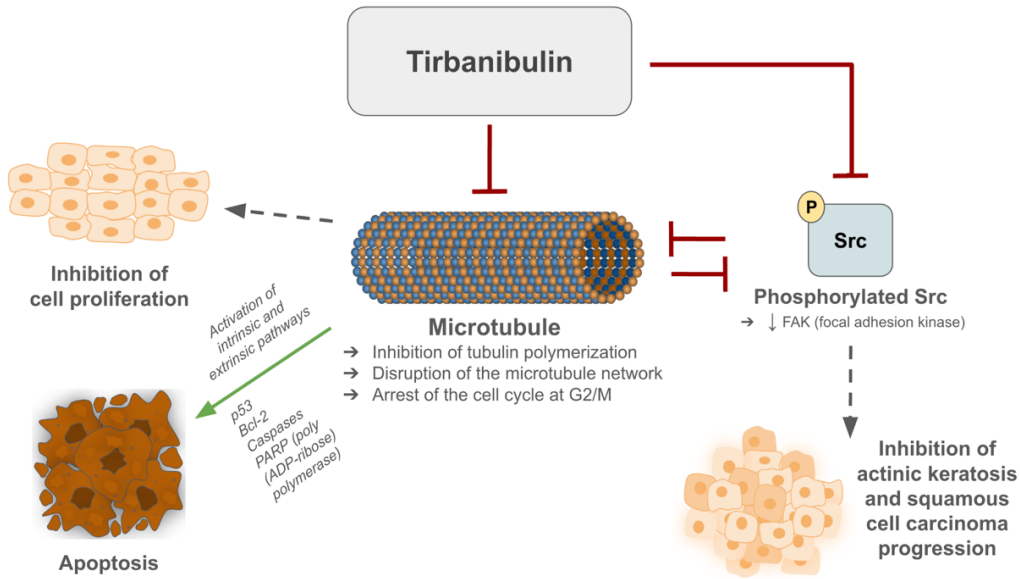
Several studies have focused on clarifying the mechanism of action of tirbanibulin (Figure 1). Research has found that tirbanibulin inhibits microtubules and exhibits antiproliferative and proapoptotic effects.[6,7] Additionally, tirbanibulin may interfere with Src kinase signaling, reducing AK and SCC progression.[6,7]

Microtubule Inhibition

Microtubules have demonstrated a high susceptibility to modulation by many existing chemotherapies.[6] During mitosis, microtubules are essential to the formation of the mitotic spindle that functions during the metaphase-anaphase transition.[6] Disruption of this stage may lead to cell cycle arrest and apoptosis.[6]

Microtubules consist of tubulin heterodimers, which are formed by α- and β-tubulin monomers.[6] Using liquid chromatography with tandem mass spectrometry, the in vitro ATNXUS-KX01-001 study found both α- and β-tubulin to be targets of tirbanibulin in colon cancer HT-29 cells.[6] These findings were further supported by results from photoaffinity labeling assays with purified tubulin and competitive binding

FIGURE 1. Tirbanibulin's proposed mechanism of action in actinic keratosis treatment.[6,7] Tirbanibulin binds to microtubules and inhibits tubulin polymerization, disrupts the microtubule network, and arrests the cell cycle at growth phase 2/mitosis (G2/M). Tirbanibulin may also inhibit cell proliferation and induce cellular apoptosis through both intrinsic and extrinsic pathways involving hyperphosphorylation of Bcl-2, cleavage of caspases 8 and 9, activation of caspase 3, and cleavage of poly (ADP-ribose) polymerase (PARP). Increased expression of p53 may augment proapoptotic effects. Additionally, tirbanibulin may interfere with Src signaling, decreasing expression of its downstream targets such as focal adhesion kinase (FAK). The inhibition of FAK may disrupt the microtubule network, while the inhibition of microtubules may suppress FAK activity. Ultimately, tirbanibulin's interference with Src signaling may inhibit actinic keratosis and squamous cell carcinoma progression.



assays with known tubulin-binding drugs, such as colchicine, vincristine, docetaxel, guanosine diphosphate (GDP), and guanosine triphosphate (GTP).[6] In another study examining tirbanibulin's binding site, competition experiments revealed a lack of competition between a tirbanibulin analogue and tubulin-binding drugs, suggesting that tirbanibulin may bind to a novel site on tubulin.[11] In contrast, other biochemical experiments suggest that tirbanibulin binds to β-tubulin on the colchicine-binding site.[12] These findings were further supported by a crystal structure and electron density map created of the tubulin-tirbanibulin complex.[12] However, unlike colchicine, tirbanibulin was found to bind to tubulin in a reversible rather than an irreversible manner.[12] Given the varied findings from previous experiments, additional research to confirm tirbanibulin's binding site is needed.

Studies to examine tirbanibulin's effects on microtubules have found that tirbanibulin inhibits tubulin polymerization, disrupts the microtubule network, and arrests the cell cycle at growth phase 2/mitosis (G2/M).[6,7,11,12] In the ATNXUS-KX01-001 study, a tubulin polymerization assay was performed to examine the cellular effects of purified tubulin, paclitaxel (an agent that promotes tubulin polymerization), and nocodazole (an agent that inhibits tubulin polymerization).[6] Tirbanibulin was found to inhibit tubulin polymerization in a manner similar to that of nocodazole.[6] Another study examining the effects of tirbanibulin in HeLa cells found that tirbanibulin inhibits tubulin polymerization in a manner similar to that of colchicine and vinblastine (other agents that inhibit tubulin polymerization).[12] Moreover, tirbanibulin's disruption of the microtubule network has been demonstrated in various cell lines, including human immortalized keratinocytes (CCD-1106 KERTr).[6,7] A previous study found that tirbanibulin disrupts the microtubule network in a concentration-dependent manner, and 30 minutes after tirbanibulin was washed out of the cell culture, filamentous tubulin structures were even restored.[11] Similarly, tirbanibulin's arrest of the cell cycle has also been found to occur in a reversible manner.[6,7,12] Flow cytometry of CCD-1106 KERTr cells incubated with tirbanibulin demonstrated complete G2/M cell cycle arrest.[6,7] However, a mitotic block reversibility assay of HeLa cells treated with tirbanibulin showed the G2/M cell cycle arrest to be reversible.[12] The reversibility of tirbanibulin's cellular effects, as demonstrated in these studies, may potentially explain its low toxicity shown in clinical trials.[12]

Antiproliferative Activity

Tirbanibulin has been shown to exhibit antiproliferative activity in several cancer cell lines, including SCC.[6,7] A cell growth experiment with CCD-1106 KERTr cells compared the effects of tirbanibulin on slower-growing cells in growth factor-reduced medium versus faster-growing cells in complete medium.[6,7] After keratinocyte cultures were incubated with tirbanibulin for 72 hours, tirbanibulin was found to inhibit cell growth and induce cell death more effectively in the fast-growing cells.[6,7] These results suggest that tirbanibulin may selectively target highly proliferative cells.[6] Additionally, in vivo, tirbanibulin was able to slow tumor growth in mouse xenograft models.[7,13] Antiproliferative activity was also demonstrated through decreased expression of the Ki-67 proliferation marker and increased levels of apoptotic cells as detected through TUNEL assay.[7,13]

Proapoptotic Effects

Flow cytometry analysis has shown that tirbanibulin may induce early apoptosis, as indicated by positive annexin V staining, and late apoptosis, as indicated by positive 7-aminoactinomycin D staining.[7] Immunoblot analyses suggest that tirbanibulin may activate both the intrinsic and extrinsic apoptosis signaling cascades through hyperphosphorylation of Bcl-2, cleavage of caspases 8 and 9, activation of caspase 3, and cleavage of poly (ADP-ribose) polymerase (PARP).[7] In vivo studies of tirbanibulin in mouse xenograft models have also demonstrated similar proapoptotic effects.[7,13]

Moreover, previous research has revealed that tirbanibulin may increase the expression of the tumor suppressor, p53.[11] p53 has been shown to localize on microtubules, and in response to DNA damage, translocate to the nucleus via the microtubule network.[14] In a previous study, treatment with microtubule-targeting agents led to the accumulation of p53 in the nucleus and activation of p53's downstream targets, including caspase-3 activation and PARP cleavage.[15] These findings suggest that through microtubules, tirbanibulin may contribute to the nuclear retention of p53 and augment apoptotic cell death. Given that mutations in the *TP53* gene have been identified in both AKs and SCCs,[5] tirbanibulin's potential to modulate p53 may be of therapeutic significance.

CCD-1106 KERTr cells incubated for 24 hours with tirbanibulin have also demonstrated significantly increased levels of interleukin (IL)-1α, a marker of cell death.[6,7] However, keratinocytes incubated with tirbanibulin released less tumor necrosis factor (TNF)-α and IL-8 compared to keratinocytes incubated with 5-FU.[6,7] TNF-α and IL-8 are proinflammatory cytokines that can contribute to the development of severe LSRs, as seen with AK therapies such as 5-FU.[6,7] These results suggest that tirbanibulin may induce cell death, but with a weaker response of inflammatory cytokines known to induce severe LSRs.[6,7] Because tirbanibulin primarily functions through apoptosis, which is associated with less inflammation than necrosis, LSRs may be milder, as shown in clinical studies.[6,7]

Src Kinase Inhibition

Phosphorylation of Src tyrosine kinase has been shown to promote cellular invasion and metastasis of various tumors[12] and may contribute to the progression of AKs to SCCs by inducing hemidesmosome alterations and cell migration.[6,7] However, tirbanibulin has been found to reduce levels of phosphorylated Src and its downstream targets such as focal adhesion kinase (FAK).[13] Tirbanibulin may inhibit Src through indirect mechanisms, with studies highlighting an intricate relationship between Src signaling and microtubules.[7] While Src downstream targets such as FAK play a role in stabilizing microtubules,[16,17] microtubules have also been shown to play a role in facilitating Src signaling.[18] Consequently, while inhibition of FAK may disrupt the microtubule network,[17] the inhibition of microtubules may also suppress FAK activity.[18] These complexities highlight the need for further research to clarify the mechanism through which tirbanibulin primarily exerts its effects.

Summary of Clinical Trials

The efficacy and safety of tirbanibulin 1% ointment for AK treatment have been demonstrated in phase 1 and phase 2 clinical trials.[19,20] Once-daily application of tirbanibulin 1% ointment to a 25 cm^2 area of the face or scalp with AK lesions led to complete AK clearance at day 57 for 32% of participants treated with a three-day course and 43% of participants treated with a five-day course.[19] A subsequent phase 3 study included two double-blind trials that were identically designed.[21] The first trial resulted in complete AK clearance in 44% of patients in the tirbanibulin group and 5% of patients in the control group.[21] The second trial resulted in complete AK clearance in 54% of patients in the tirbanibulin group and 13% of patients in the control group.[21] Partial AK clearance was also seen in a significantly higher percentage of patients in the tirbanibulin groups than in the control groups.[21] A phase 3 study examining tirbanibulin use over a 100 cm^2 area, rather than a 25 cm^2 area, found that the average number of AKs decreased from 7.7 AKs at baseline to 1.8 AKs at day 57.[22] The average reduction in lesion count was 77.8%, demonstrating tirbanibulin's efficacy.[22] In addition, phase 1, 2, and 3 trials have all shown a favorable safety profile, with the most common adverse events being mild or moderate LSRs, such as erythema, flaking, scaling, pruritus, and pain.[19–23] Importantly, there were no reports of serious adverse events, deaths, or discontinuations related to tirbanibulin use.[19–23]

Pharmacokinetics

A previous study examined the absorption of tirbanibulin 1% ointment used for AKs in a 25 cm^2 area of the face or scalp.[19] Results demonstrated minimal absorption after three or five days of consecutive treatment.[19] In fact, the plasma concentration of tirbanibulin was below the lower limit of quantification of 0.1 ng/mL in most collected samples, and the maximum individual plasma concentration did not exceed 2 ng/mL.[19] A phase 1 maximal use study also examined tirbanibulin use over a contiguous 25 cm^2 area of the face or scalp. After a five-day course, the mean maximum plasma concentration was 0.26 ng/mL.[23] For use over a contiguous area of 100 cm^2, another phase 1 maximal use study revealed a mean maximum plasma concentration of 1.06 ng/mL after five days.[20] These findings were consistent with the four-fold increase in treated area from 25 cm^2 to 100 cm^2.[20] Furthermore, topical application to the face rather than the scalp resulted in a higher exposure to tirbanibulin and its metabolites.[20] However, overall systemic levels of tirbanibulin remained low, which may explain the lack of systemic adverse effects observed in clinical studies.[20]

CONCLUSION

Tirbanibulin 1% ointment represents a novel, first-in-class topical therapy for AKs. Tirbanibulin's mechanism of action targets microtubules, inhibiting tubulin polymerization, disrupting the microtubule network, and arresting the cell cycle. Unlike some of the traditional topical agents for AKs, tirbanibulin's reversible effects on microtubules help to reduce its toxicity profile while still achieving effective lesion clearance. In addition, tirbanibulin's antiproliferative activity, proapoptotic effects, and inhibition of Src kinase signaling further contribute to its anti-tumorigenic properties.

Although tirbanibulin's efficacy in AK clearance has been demonstrated in clinical studies, cost may be a barrier to widespread use.[9] However, compared to traditional topical therapies, tirbanibulin provides a shorter treatment duration and favorable safety profile, potentially improving patient adherence. These benefits may still make tirbanibulin a compelling option for patients and healthcare providers. To further establish tirbanibulin's role in AK treatment, long-term studies on its safety and efficacy are needed.[9]

Overall, tirbanibulin's novel mechanism of action offers an effective, well-tolerated treatment option for field-directed therapy in AK management.

DISCLOSURES

Alyssa M. Roberts BS has no conflicts of interest to disclose.

Leon Kircik MD has served on as an investigator, consultant, speaker, and/or advisory board member for Abbott Laboratories, Abbvie, Ablynx, Aclaris, Acambis, Allergan, Inc., Almirall, Amgen, Inc., Anacor Pharmaceuticals, Anaptys, Arcutis, Arena, Assos Pharma, Astellas Pharma US, Inc., Asubio, Bausch Health, Berlex Laboratories, Biogen-Idec, Biolife, BioMimetix, Biopelle, BMS, Boehringer-Ingleheim, Breckinridge Pharma, Cassiopea, Centocor, Inc., Cellceutix, Cipher, Coherus, Colbar, Combinatrix, Connectics Corporation, Coria, Dermavant, Dermira, Dermik Laboratories, Dow Pharmaceutical Sciences, Inc., Dr. Reddy's Lab, Dusa, Embil Pharmaceuticals, Eli Lilly, EOS, Exeltis, Ferndale Laboratories, Inc., Foamix, Ferrer, Galderma, Genentech, Inc., GlaxoSmithKline, PLC, Glenmark, Health Point, LTD, Idera, Incyte, Intendis, Innocutis, Innovail, Isdin, Johnson & Johnson, Kyowakirin, Laboratory Skin Care Inc., Leo, L'Oreal, 3M, Maruho, Medical International Technologies, Merck, Medicis Pharmaceutical Corp., Merz, Nano Bio, Nektar, Nimbus, Novartis AG, Noven Pharmaceuticals, Nucryst Pharmaceuticals Corp, Obagi, Onset, OrthoNeutrogena, PediaPharma, Pfizer, Promius, PuraCap, PharmaDerm, QLT, Inc, Quinnova, Quatrix, Rapt, Regeneron, Sanofi, Serono, SkinMedica, Inc., Stiefel Laboratories, Inc., Sun Pharma, Taro, TolerRx, Triax, UCB, Valeant Pharmaceuticals Intl., Ventyx, Warner-Chilcott, XenoPort, and ZAGE.

Mark Lebwohl MD has served as a consultant for Aditum Bio, Almirall, Altrubio, Anaptysbio, Apogee Therapeutics, Arcutis, Arena Pharmaceuticals, Aristea Therapeutics, Arrive Technologies, AstraZeneca, Atomwise, Avotres Therapeutics, Biomx, Boehringer Ingelheim, Brickell Biotech, Bristol-Myers-Squibb, Cara Therapeutics, Castle Biosciences, CorEvitas, Corrona, Dermavant Sciences, Dr. Reddy's Laboratories, EPI, Evelo Biosciences, Evommune Inc., Facilitation of International Dermatology Education, Forte Biosciences, Foundation For Research and Education in Dermatology, Galderma Laboratories, L.P., Galderma Laboratories, L.P., Helsinn Therapeutics, Hexima Ltd, LEO Pharma AS, Meiji Seika Pharma, Mindera, Pfizer, Seanergy, STRATA Skin Sciences, Inc, Sun Pharmaceutical Industries Inc, Takeda Pharmaceutical Company, Trevi, Verrica, and Vial.

April W. Armstrong MD MPH has served as a research investigator, scientific advisor, and/or speaker to AbbVie, Amgen, Almirall, Arcutis, ASLAN, Beiersdorf, BI, BMS, EPI, Incyte, Leo, UCB, Janssen, Lilly, Novartis, Ortho, Sun, Dermavant, Dermira, Sanofi, Takeda, Regeneron, and Pfizer.

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