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Klisyri® (tirbanibulin): Itching for an answer to actinic keratosis

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Actinic keratosis (AK), also known as solar keratosis, is a common precancerous skin growth or lesion usually associated with chronic exposure to ultraviolet (UV) radiation.[1] It is the second most common diagnosis by dermatologists in the United States with around 40 million Americans developing actinic keratoses annually.[1] Actinic keratosis is an intraepidermal malignant neoplasm with proliferation of atypical keratoses which is caused by UV-B radiation promoting thymidine dimer formation in RNA and DNA.[2] This mutates the telomerase gene in tumor suppressor gene P53 causing proliferation of damaged keratinocytes, ultimately creating neoplastic cells and the consequent visual skin anomaly that is presented with AK. The genetic mutation appears to be causally linked to the earliest phase of skin cancer and is considered an early squamous cell carcinoma (SCC).[2]

Actinic keratosis presents as a defined reddish to reddish-brown scaly or keratotic macules or papules with a diffuse erythematous base about one centimeter or less in diameter.[2] The texture of the lesion is compared to sandpaper. Risk factors for AK include advanced age, male gender, Fitzpatrick skin phototypes I and II, UV exposure, immunosuppression, previous history of AKs or skin cancer, and genetic diseases like xeroderma pigmentosus, Blood syndrome, or Rothmund-Thomson syndrome.[3]

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The most affected areas include the face, ears, neck, scalp, extensor surface of the extremities, and lower lip; consequent symptoms include itching, burning or splinter-like sensation (although some may be asymptomatic).[4] Actinic keratosis is diagnosed by dermatologists either clinically or via dermoscopy (the examination of skin with a hand-held dermatoscope to visualize subsurface skin structures normally not visible to the naked eye) and is classified into grades 1, 2 and 3. Grade 1 AK presents as a red pattern and discrete white scales. Grade 2 AKs present with an erythematous background with white to yellow keratotic, enlarged follicular openings. Grade 3 AK exhibits enlarged follicular openings with keratotic plugs over a white to yellow background or marked hyperkeratosis which are seen as white-yellow structureless areas. The sensitivity and specificity of dermoscopy is 98% and 95% respectively.[4]

If left untreated, AKs may progress into invasive SCC which can destroy nearby tissues and spread to other organs. There is a ten-year incidence rate of progression to SCC of 10% without treatment, which can ultimately metastasize and rarely cause death.[3] Fortunately, there is a broad selection of therapies currently available for treatment including lesion-directed or procedural treatments like cryotherapy, laser therapy, surgery, curettage.3 Additionally, more field-directed or medical treatments may also be used such as 5-fluorouracil (5-FU), diclofenac 3% gel, chemical peeling, imiquimod and photodynamic therapy (PDT).[3,5] These therapies share the same goals to clinically eradicate evident and subclinical lesions, prevent their evolution to SCC and reduce relapses.[3] As there is not currently a gold standard for treatment, considerations should account for density, clinical manifestation of the lesion, tolerability and cost of treatment, age, immune system activity and compliance or adherence.[3] The International League of Dermatological Societies in cooperation with the European Dermatology Forum have created evidence- and consensus-based guidelines for treatment of actinic keratosis which highlight certain treatments under different circumstances.[5] The available therapies each have notable advantages and disadvantages. Lesion-directed therapies are rapid procedural techniques but may require anesthesia or cause inflammation and scarring.[3] Field-directed therapies may generally have longer-term response and produce overall positive cosmetic results, but adverse drug reactions may present during or after treatment.[3] With appropriate clinical judgment and a wide array of options, it is best to individualize therapy on a case-by-case basis.

On December 14th, 2020, an ointment known as tirbanibulin was approved by the Food and Drug Administration (FDA) for the indication of treating actinic keratosis.[6]

Clinical Pharmacology

Tirbanibulin is a novel microtubule inhibitor in which the dual mechanism of action is not fully understood for the topical treatment of AKs.[7] However, it was developed as a synthetic in-

hibitor for both tubulin polymerization and the signaling of Src kinase.[8] It induces p53 expression, arrest of cellular division at interphase Gap 2 and mitosis resulting in apoptosis through stimulation of caspase-3 and poly (adenosine diphosphate-ribose) polymerase cleavage.[8] It has been demonstrated in vitro to inhibit growth of primary human keratinocytes as well as melanoma cell lines.[9,10] Tirbanibulin targets a novel binding site for both mechanisms of action and is currently being further studied for psoriasis and other skin conditions.[8]

Pharmacokinetics

Tirbanibulin is a small molecule available as a topical ointment. It is 88% bound to plasma proteins independent of concentrations ranging 0.01 to 10 mcg/mL.[7] From a pharmacogenomic standpoint, in vitro studies suggest tirbanibulin is metabolized primarily through CYP3A4, and to a lesser extent, by CYP2C8.[10] Other associations may include CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, multidrug and toxin extrusion (MATE1 and MATE2-K), organic anion transporting polypeptide (OATP1B1 and OATP1B3), organic cation transporter (OCT1 and OCT2).[11] The resulting two inactive metabolites are KX2-5036 and KX2-5163.[11] The rate of systemic absorption was negligible according to the Phase II trial by Kempers et al. as they found less than 0.5 ng/mL or undetectable plasma concentrations using validated liquid chromatography and tandem mass spectrometry. A summary of pharmacokinetic parameters of tirbanibulin can be found at **Table 1**.

Table 1 | Route-Specific Topical Tirbanibulin Pharmacokinetics[7]

Absorption	
T_{max}[A]	7 hours
Distribution	
Protein Binding	88%
Metabolism	
Primary	CYP3A4
Secondary	CYP2C9
Elimination	
No Data Available	

[A]Time to maximum concentration

Clinical Trials

Tirbanibulin was approved based on two identical Phase III trials: NCT03285490 and NCT03285477. The phase I and II trials NCT02337205 and NCT02838628 were published as one article that demonstrated initial efficacy and safety in treating individuals with AK lesions with limited adverse reactions. Subsequently, the phase III trials were able to demonstrate further efficacy and safety with a larger cohort. Refer to **Table 2** for a summary of outcomes from the phase III trials.

Phase I and II trials: NCT02337205 and NCT0283862811

The phase I trial by Kempers, et al. was an open-label, proof-of-concept, single-center study targeting the adult population (≥18 years) with typical AK on the forearm.[8] A study population of 30 patients were placed into sequential cohorts of 4:10:8:8 where the respective cohorts each received different treatments: (1) tirbanibulin ointment 1% 50 mg/day daily for three days over a 25 cm2 treatment area with 4-8 AK lesions, (2) 200 mg/day daily for three days over 100 cm² treatment area with 8-16 AK lesions, (3) same treatment dose as cohort 1 over five days, (4) same treatment dose as cohort 2 over five days. The follow up period after treatment was 45 days. Although one participant withdrew on the second day, 29 out of 30 participants completed the study. The outcome of complete AK clearance after 45 days for the cohorts 1-4 are 25% (n=1), 0% (n=0), 50% (n=4) and 12.5% (n=1) respectively. Safety outcomes demonstrated the following: no treatment-emergent adverse events (TEAEs) that led to withdrawal, no deaths or serious adverse events, and no clinically significant changes in laboratory tests, vital signs, physical exams, or electrocardiograms. Application-site symptoms were primarily transient mild pruritus, and less commonly, stinging/burning sensations—both resolving without treatment.[8]

The phase II trial by Kempers, et al. was an open-label, uncontrolled, multicenter study in adults (≥18 years) targeting typical AK on the face or scalp.[8] The goal of this study was to establish a dose and regimen to further evaluate in a phase III study. Participants received tirbanibulin 1% ointment daily for three or five days (cohorts 1 and 2) over a 25 cm2 treatment area with 4-8 AK lesions at about 50 mg/day per application. Response assessment occurred at day 57 and recurrence follow-up at 12 months after day 57 for those with 100% clearance. A total of 168 participants completed the treatment with complete compliance. At day 57, with 43% (n=36) of participants achieving complete AK clearance in the five-day cohort and 33% (n=27) in the three-day cohort at day 57 follow-up. All 63 participants (in both arms) with 100% clearance at day 57 received the 12-month follow up with results showing 57% recurrence rate (95% CI, 47-73) in the five-day cohort and 70% recurrence rate (95% CI, 51-87) in the 3-day cohort. Most recurrences were within 6 months after day 57 of treatment. Safety outcomes were similar to the phase I trial as all participants completed the treatment and follow-up with no deaths, serious adverse events, or discontinuations due to treatment. Plasma concentrations were undetectable or <0.5 ng/mL. The recurrence follow-up showed no treatment-related adverse events or skin cancer in the treatment area.[11] The more efficacious five-day regimen was selected to be evaluated in the phase III trial.

Phase III trials: NCT03285490 and NCT032854779

Two identical phase III trials by Blauvelt et al., were created as multicenter (at 62 study sites in the United States), double-blind, parallel-group, vehicle-controlled trials targeting an eligible adult population (≥18 years) with clinically typical 4-8 AK lesions on the face or scalp within a contiguous 25 cm² area.[10] A computerized code generated a 1:1 ratio to randomize participants for receiving either tirbanibulin 1% ointment or vehicle ointment (placebo) with a 2:1 ratio for targeting face to scalp treatment areas. Key exclusion criteria included presence of atypical, hypertrophic, recalcitrant, or rapidly changing actinic keratoses, open wounds, or suspected skin cancers proximal to the treatment area, previous tirbanibulin treatment, and previous use of therapies on the treatment area within two weeks.

The active treatment group received tirbanibulin 1% ointment while the control group received placebo vehicle applied to the entire 25 cm² area once daily for five consecutive days. At each daily assessment during the treatment period of days one to five, safety criteria and lesion count were followed by the same investigator for each participant. For the duration of the study, only tirbanibulin or placebo can be used in the study area. If outside the study area, only lesion-directed treatments and procedures

may be used.

The primary efficacy outcome was percentage of patients with 100% clearance of all lesions within the application area at day 57. The secondary efficacy outcome was percentage of participants with partial clearance (≥75% reduction in number of AK lesions) within the application area at day 57. Those with 100% clearance of AK at day 57 received a follow-up in 12 months to assess recurrence and safety. For safety endpoints, signs of local reactions (erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, or erosions/ulcerations) were independently recorded from adverse events and followed a 4-point scale with absent, mild, moderate, severe for scores 0-3 respectively. A composite score (0-18) was calculated as a sum of the scores for each individual sign of local reaction.

A total of 702 patients (351 per trial) were enrolled with approximately equal distribution to each treatment group. The baseline characteristics for each group in both trials were similar with a majority being white males with a Fitzpatrick skin type of I and II and a median of six lesions. For the primary efficacy outcome at day 57 in trial 1 (NCT03285490), 77 of 175 (44%) participants in the tirbanibulin group and 8 of 176 (5%) in the placebo vehicle group achieved 100% lesion clearance (95% confidence interval [CI], 32 to 47; P<0.001); in trial 2 (NCT03285477), 97 of 178 (54%) and 22 of 173 (13%) achieved 100% lesion clearance in the tirbanibulin and placebo vehicle group respectively (95% CI, 33 to 51; P<0.001). Both were statistically significant for the outcome. For the secondary efficacy outcome at day 57, in trial 1, partial clearance occurred in 119 of 175 (68%) in the tirbanibulin group and 29 of 176 (16%) in the vehicle group (95% CI, 43 to 60; P<0.001). For trial 2, 136 of 178 (76%) and 34 of 173 (20%) achieved partial clearance in the tirbanibulin and placebo vehicle group, respectively. A summary of pooled data from both identical trials showed 100% clearance for 174 of 353 (49%) in the tirbanibulin group and 30 of 349 (9%) in the vehicle group (95% CI, 35 to 47); partial clearance was 255 of 353 (72%) in the tirbanibulin group and 63 of 349 (18%) in the vehicle group (95% CI, 48 to 60).

For the one-year follow up, 174 participants had complete clearance and 124 of 174 (71%) had one or more lesions develop within the application area. A total of 72 of 124 (58%) had recurrent lesions and 52 of 124 (42%) had new lesions distinct from baseline. From the Kaplan-Meier estimate at year 1, 27% of participants sustained complete clearance, 47% having recurrence of previously cleared lesions and 73% having incidence of any new or recurrent lesions within the application area. The incidence of recurrence with conventional treatment ranges from 20 to 96%.

Safety outcomes demonstrated that the most common local reactions present were erythema (91% across all of participants in the study) and flaking/scaling (82%); comparatively, crusting, swelling, vesiculation/pustulation and erosion/ulceration were far less frequent. Considering baseline local reactions, moderate erythema was more common in those receiving tirbanibulin in 223 of 353 participants (63%) versus vehicle ointment in 20 of 349 participants (6%). The trend demonstrated greater number patients with moderate local skin reactions in the treatment over placebo group. Mean local-reaction composite scores in those receiving tirbanibulin increased by day 8 to a maximum of 4.0 and 4.3 in trials 1 and 2 respectively; at day 15, these values approximately doubled; at day 29, these values were either at or below baseline value (0.6 in both trials 1 and 2). Local reactions spontaneously resolved and incidences at day 57 of hypopigmentation, hyperpigmentation and scarring was 14%, 16%, and 7% respectively from a baseline of 12%, 10%, and 5% respectively.

The local reactions were assessed separately from adverse events. Application site reactions not including the LSR criteria were considered adverse events. No serious adverse events or discontinuations occurred that were related to the treatment regimen for each group for both trials. About 33% and 32% of participants in trial 1 had adverse events in the tirbanibulin and placebo vehicle group, respectively. In the same order, 38% and 39% of participants had adverse events in trial 2, respectively. Most adverse events were mild, with application-site pruritus and pain being most common and. B both resolving spontaneously. Other common adverse events (in >2% of participants) were upper respiratory tract infection, viral upper respiratory tract infection and skin abrasion without substantial differences between the groups in each trial. No clinically significant changes in electrocardiograms, laboratory findings, physical exams or vital signs were observed.[10]

Adverse Effects and Precautions

The most common adverse reactions (≥2% incidence) were local skin reactions, application- site pruritus and, and application-site pain..[7,10] Tirbanibulin was generally well-tolerated with limited systemic side effects. Local skin reactions may include erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, erosion/ulceration). A summary of the adverse reaction data from the phase III studies can be found at **Table 3**. Precautions should be taken to avoid the transfer of tirbanibulin into the eyes or periocular area during and after applications due to potential eye irritation.[7]

Table 2 | Primary and secondary Outcomes of Tirbanibulin Phase III Trials[10]

Trial	Outcomes	Intervention	Results no/no. total (%)	Difference % (95% CI[a])
NCT03285490	100% or complete clearance of lesions	Tirbanibulin 1% Ointment 50 mg/day once daily x 5 days	77/175 (44)	40 (32-47)
		Placebo	8/176 (5)	
	≥75% or partial clearance of lesions	Tirbanibulin 1% Ointment 50 mg/day once daily x 5 days	119/175 (68)	52 (43-60)
		Placebo	29/176 (16)	
NCT03285477	100% or complete clearance of lesions	Tirbanibulin 1% Ointment 50 mg/day once daily x 5 days	97/178 (54)	42 (33-51)
		Placebo	22/173 (13)	
	≥75% or partial clearance of lesions	Tirbanibulin 1% Ointment 50 mg/day once daily x 5 days	29/176 (16)	57 (48-65)
		Placebo	34/173 (20)	

[A]95% Confidence Interval

Drug Interactions

No clinical studies evaluating the drug interaction potential of tirbanibulin have been conducted.[7] As it is first-in-class with a novel mechanism of action, extrapolation from class-effect data cannot be made. There is potential for interaction due to metabolism by CYP3A4 and CYP2C8, however the extent of metabolism has not been established to draw conclusions due to the low systemic absorption.

Dosage and Administration

Tirbanibulin is currently available for topical use only as a 1% ointment with a white to off-white color from a single-dose packet containing 2.5 mg tirbanibulin in 250 mg of tirbanibulin ointment.[7] To administer tirbanibulin, apply enough of the medication to evenly cover up to a 25 cm^2 treatment field on either the face or scalp once daily for five consecutive days with the single-dose packet per application.

Hands should be washed immediately with soap and water while avoiding washing or touching the treated area for about eight hours after application. No renal or hepatic considerations for dose adjustment must be made with tirbanibulin. No studies have been performed in humans to establish safety in pregnant women, lactation, or pediatric population or demonstrate potential induction of carcinogenesis.

Cost

There is no generic available commercially.[7] The KLISYRI® (brand medication for tirbanibulin) will costs about $980 to $1040 per carton of five packets of 1% tirbanibulin ointment based on GoodRx prices.[12] Insurance coverage has not been disclosed at this time.

Clinical Implications

The phase I trial helped set parameters for the following phase II and III trials that ultimately showed efficacy and safety in the use of tirbanibulin in patients with AK lesions and brought tirbanibulin to the market through the Food and Drug Administration. For the phase II and III, the method for selecting cohorts with inclusion/exclusion criteria were appropriate to reveal the efficacy of tirbanibulin as they made sure to exclude confounders that may complicate assessment of the lesions (such as pre-existing skin cancer). Low drop-out numbers and disclosure of reasons for inability to assess specific participants are provided and explained in the studies, showing transparency by the investigators.

The authors of the phase I and II trials adequately designed their studies and acknowledged the limited size of their cohorts. A limitation for the phase I study was having four different treatment groups with small number of participants per arm which created seemingly large differences when assessing the differences in lesion clearance between treatment groups. Fortunately, similar results were obtained in the subsequent phase II and III studies to show a trend that tirbanibulin is efficacious. With tolerability in mind, perhaps a future study exploring a regimen extending past five days could be created based on the trends seen in the phase I study establishing the superiority of five days over three days of treatment.

The data from the phase III trials is strongly indicative that the treatment with tirbanibulin is efficacious compared to a placebo with significant differences favoring tirbanibulin in partial and complete clearance of lesions in both the treatment and placebo arms. The study duration of 57 days was not explained anywhere in the study and was perhaps a parameter followed for consistency across the phase II and III trials. The 12-month follow-up interval in those with complete clearance of lesions provided a long-term perspective in recurrence rates in which patients could not use other non-procedural therapies until assessment. The recurrence rate at one year in other therapies range from about 17 to 65%, so tirbanibulin from the phase III study falls into this range at about 58%.[13] Additional assessment of safety with a scoring tool for common local reactions detailed the severity of reactions. The investigators treated local skin reactions differently than adverse events and application site reactions which were not specified. This could cause confusion when trying to assess adverse events overall. The protocol for assessing this could have been more defined. They also did not provide statistical significance in the differences between LSR severities for both pooled placebo and treatment cohorts. The clearance results they provided may indirectly compare to other field-directed therapies which report complete clearance range of 31 to 48% of patients in treatment arm versus 3 to 17% of patients who received vehicle placebo.9 Overall, the investigators in the phase III trials adequately demonstrated the superiority of tirbanibulin 1% ointment once daily for 5 days over placebo for treatment of actinic keratosis at 2 months with statistical significance in both complete and partial clearance of lesions.

Further research should be done to provide a direct comparison between tirbanibulin and other field-directed therapies, where differences in adverse effects or recurrence rates may play a large role in deciding the optimal therapy. If tirbanibulin becomes more established in clinical practice with effectiveness, researchers may be eager to appropriately design a randomized comparison with well-established treatments for AK (as Jansen, et al. designed their 2019 trial comparing four established treatments for AK).[14] Unfortunately, no reasonable comparison with the tirbanibulin phase III trials can be made at this time with respect to current treatments due to novelty of tirbanibulin (first-in-class), trial aspects or methodology, and population differences. There is still a need for more detailed and robust clinical practice guidelines to be established and updated to provide a more transparent direction for healthcare in treating such a prevalent lesion. In 2015, a journal article published by Kirby, et al. established that, although there may be many published guidelines for AK, there is still a need for quality clinical practice guidelines sufficient for clinical use based on the Appraisal of Guidelines for Research and Evaluation (AGREE II).[15] At the time, the Cancer Council of Australia/Australian Cancer Network guideline was the only of seven clinical practice guidelines included in the study to include a systematic review, evidence rating for recommendations, and reports of conflicts of interest and funding sources.[15]

The only bias acknowledged was the potential for recogniz-

Table 3 | Adverse Effects Pooled from Phase III Trials[10]

Adverse Effect	Incidence
Application Site Pruritis	9%
Application Site Pain	10%
Upper Respiratory Tract Infection	4%
Viral Upper Respiratory Tract Infection	3%
Skin Abrasion	2%

ing placebo versus tirbanibulin treatment with evident local reactions occurring in the treatment arm. However, it is not unreasonable to overlook this potential bias due to the nature of this study being unable to mask such obvious adverse effects. On the contrary, those local reactions in the treatment arm may bolster the safety outcomes. Other limitations not acknowledged may be the method used by the investigators to assess clearance. With the lack of a dermatoscope, subjectivity by dermatologists involved in the protocol may heavily influence results with defining who achieved the primary outcome.

Using the concluding data provided by the phase III trial, tirbanibulin is a promising medication when looking to treat AK. All reactions were generally well-tolerated and did not result in the cease of treatment or dropping out from the study. Those who did have reactions or adverse effects, also had spontaneous resolution of those reactions without adjunctive treatment.

One important consideration from a consumer-perspective will be the cost of the medication. More limitations exist for obtaining Klisyri® compared to other options that have generics available. It will be important to establish plans for getting this ointment into the hands of patients at a reasonable cost through discounts, coupons, or patient assistant programs.

Tirbanibulin does not currently have an established place in therapy and is not currently considered a first-line treatment option for AK. As it is a novel medication, more studies need to be completed to determine the advantages and disadvantages of tirbanibulin over existing treatment options or in combination with existing therapies.

Conclusion

Klisyri® (tirbanibulin) is a first-in-class microtubule inhibitor approved by the FDA in December 2020 for the treatment of actinic keratosis located on the face or scalp in adults. There is no current standard of therapy for treating AK and much is left to clinical and non-clinical considerations. More studies need to be published in order to understand the benefits of tirbanibulin over other existing therapies.

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Drug Updates: New Indications and Dosage Forms April 2021

Trodelvy® (sacituzumab govitecan-hziy) Injection
Label Revision: Treatment for adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease
New Indication: Treatment of metastatic urothelial cancer

Xolair® (omalizumab) Subcutaneous Injection
New Dose Form: Pre-filled syringe for self-injection approved across all indications

Ragwitek® (ragweed pollen allergen extract) Sublingual
Patient Population Altered: Use as Immunotherapy for Children and Adolescents With Short Ragweed Pollen-Induced Allergic Rhinitis With or Without Conjunctivitis

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New Indication: Combination with Chemotherapy for Patients with Advanced or Metastatic Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma Regardless of PD-L1 Expression Status

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