Actinic Keratosis Today

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ABSTRACT

Actinic keratosis (AK) is a frequent precancerous skin lesion that mostly affects chronically sun-exposed areas. Chronic sun damage leads to various mutations in onco-suppressor and oncogenic genes which cause an uncontrolled proliferation of atypical keratinocytes. Untreated AKs may evolve in cutaneous squamous cell carcinoma (cSCC), with the consequent need for dermato-surgical excision or even for systemic immuno-therapy in case of invasive/metastatic cSCCs. Epidemiology data on AK prevalence are various, however, the literature unanimously reports an increasing prevalence due to the aging of the population. Clinically AKs appear as a scaly, erythematous macule or papule or hyperkeratotic plaque. Management of AKs and the field of cancerization is important to avoid the natural evolution into squamous cell carcinomas (SCCs). Both physical and topical treatments are approved for managing AKs. Patient compliance with topical regimens is usually low due to the length of the posology and frequent skin adverse events. A recently approved tirbanibulin-based ointment, showed potential for inhibiting cell proliferation and blocking SRC-kinases, implicated in the progression of AKs in SCCs. The advantage of this new treatment is the practical posology, with a daily application for 5 consecutive days on AKs of the face-scalp area. Local skin reactions are usually mild and do not require treatment discontinuation. The short course of this new therapy and its excellent tolerance massively increased patient compliance. This article reviews what is currently known about this new therapy from its mechanism of action to clinical trial outcomes regarding safety, effectiveness, and patient adherence to the treatment.
Introduction

Actinic keratoses (or solar keratoses) are the clinical manifestation of a common, chronic disease of the skin of adults [1], which develops in areas exposed to sunlight [2]. Risk factors for the development of actinic keratoses and SCC are I-II phototypes according to Fitzpatrick’s scale, male sex, age, and immunodepression [3-5]. The incidence of AKs is likely underestimated, as they are not recorded routinely in cancer registries. Unsurprisingly, the prevalence of AKs shows an increase in its trend [3]. AKs represent one of the most common conditions diagnosed and treated by dermatologists in the United States (US), where currently up to 12% of individuals have AKs [6]. A Rotterdam prevalence study of >2,000 Dutch men and women, with a mean age of 72 years, found AK in 49% of men and 28% of women [7]. In Galway, South Wales and Merseyside (UK), 19-24% of individuals aged >60 had at least one AK. Over 30% of those attending a dermatology clinic (mean age of attendance 61 years) in Austria had AK. Up to 60% of Australians over the age of 40 have AKs [8,9].

Histologically, AKs are characterized by epidermal hyperplasia and by variable degrees of keratinocyte atypia, which can involve all layers of the epidermis, as in the in-situ forms of squamous cell carcinoma [10]. Indeed, AKs are considered by some to be a precursor of SCC [11,12] by others an initial and superficial form [13,14]. The histopathological similarities between AKs and squamous cell carcinoma reflect their same pathogenesis, a multi-stage process caused by somatic mutations induced by the carcinogenic action of ultraviolet (UV) radiation. These critically affect the tumor suppressor TP53 gene, which has mutations with UV signature (e.g., pyrimidine dimers) in almost 90% of AK specimens [7,15-19] Although on histological examination up to 90% of invasive cutaneous squamous cell carcinomas arise contiguously or in continuity with AKs [17,20,21], prospective evaluation of AKs over time demonstrates a low rate of transformation to invasive squamous cell carcinoma, with less than one invasive squamous cell carcinoma for every 1000 AKs in a year [22]. In a US study, 0.6% of patients developed invasive squamous cell carcinoma in the same anatomical site as the actinic keratosis within the first year, rising to 2.57% at 4 years [21]. Rather than referring to the anatomical regions affected by the keratoses actinic keratoses, the risk of developing squamous cell carcinoma can be attributed more correctly to the subject suffering from actinic keratoses, with a risk of invasive squamous cell carcinoma which increases proportionally to the number of actinic keratoses [23] and which is estimated at 10% in 10 years for an average patient with 7-8 actinic keratoses [1,21,24].

A clinical categorization method for AK grading based on the total thickness of different lesions was proposed by Olsen et al [25]. Grade 1 lesions are hardly tangible, Grade 2 lesions are rather thick, and Grade 3 lesions are very thick and hyperkeratotic according to this system. This clinical classifying system is often used to set patient inclusion criteria in randomized clinical trials of AK treatments.

The concept of the field of cancerization was proposed by Slaugther in 1953 [28] and was applied to squamous cell carcinomas of the oral cavity, although Willis in his seminal article in 1944 first hypothesized that the proliferation of keratinocytes can occur multifocally in the epidermis [28]. From a pathological point of view, field of cancerization could currently be defined as one or more areas of epithelial and stromal tissue characterized by genetic and epigenetic abnormalities, some of which are also present in cancer, even in the absence of histopathological alterations. In this perspective, the concept of field cancerization has diagnostic and prognostic implications, especially when considering that “healthy” perilesional skin surrounding clinically evident, multiple AKs could indeed be treated treatment of AKs, since therapy of AKs should be directed not only to visible lesions but also to the field of cancerization from which they originate. For practical purposes, however, a univocal consensus on the criteria required to clinically identify and treat the cutaneous field of cancerization is still lacking and it was defined in a recent review [26-29] as multifocal clinical atypia, characterized
by AKs and/or squamous cell carcinoma in situ (SC-Cis) with or without invasive cSCC, occurring in a field exposed to chronic UVR.

Sunscreens and protective clothing, together with adequate sun-exposure education, are crucial in managing patients with AKs; however, they are often insufficient to treat existing lesions [30,31]. Currently, available therapies for AKs are divided into field-directed treatments and lesion-directed treatments [31,32]. The latter mostly include physical treatments, of which cryotherapy is probably the most widely used technique [33]. Lesion-directed therapies, however, do not impact the field of cancerization, leaving invisible AKs that might arise in the future. Moreover, they are usually painful and can lead to melanocyte necrosis with consequent hypo- or hyperpigmentation and cosmetic concerns [34]. A summary of the characteristics, efficacy, and mechanism of action of topical treatments are shown in Table 1.

**Table 1. Comparative Treatment Efficacy and Safety of Face-Scalp Typical Actinic Keratosis Approved in Europe [24]**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>Duration of Treatment</th>
<th>Complete Clearance Rates at the end of the standard duration treatment Or (95% CI)</th>
<th>Rate of Discontinuation Due to Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryosurgery</td>
<td>Physical destruction of the affected tissue</td>
<td>Once</td>
<td>13.4 (6.2-30.3)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Tirbanibulin 1% ointment</td>
<td>Inhibits microtubule assembly and inhibits Scr kinase</td>
<td>5 consecutive days</td>
<td>11.1 (6.2-20.9)</td>
<td>0%</td>
</tr>
<tr>
<td>5-fluorouracil (FU) 0.5% + salicylate 10%</td>
<td>5-FU acts as a pyrimidine analogue, while salicylate has a keratolytic effect</td>
<td>Up to 12 consecutive weeks</td>
<td>7.6 (4.6-13.5)</td>
<td>1.9%-9.1%</td>
</tr>
<tr>
<td>Diclofenac 3% gel</td>
<td>Inhibits cyclooxygenases, and thus prostaglandin E2 production</td>
<td>Up to 12 consecutive weeks</td>
<td>2.9 (1.9-4.3)</td>
<td>2.1%-12.3%</td>
</tr>
<tr>
<td>Imiquimod 3.75% cream</td>
<td>Activates innate immune system</td>
<td>2 weeks, followed by a 2-week stop, followed by another 2 weeks cycle</td>
<td>8.5 (3.5-22.4)</td>
<td>0-1.6%</td>
</tr>
<tr>
<td>PDT with aminolevulinate (ALA)</td>
<td>The combined activity of a photosensitizer (ALA) and a specific wavelength cause the formation of free radicals</td>
<td>2 outpatient accesses</td>
<td>24.1 (10.9-52.8)</td>
<td>0.6%</td>
</tr>
<tr>
<td>PDT with methyl aminolevulinate (MAL)</td>
<td>The combined activity of a photosensitizer (MLA) and a specific wavelength cause the formation of free radicals</td>
<td>2 outpatient accesses</td>
<td>11.7 (6.0-21.9)</td>
<td>1.1%</td>
</tr>
<tr>
<td>5-Fluorouracil (FU) 4%</td>
<td>5-FU acts as a pyrimidine analogue</td>
<td>Up to 4 weeks</td>
<td>30.3 (9.1-144.7)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>5-Fluorouracil (FU) 5%</td>
<td>5-FU acts as a pyrimidine analogue</td>
<td>Up to 4 weeks</td>
<td>35.0 (10.2-164.4)</td>
<td>0%</td>
</tr>
</tbody>
</table>
**Tirbanibulin**

In 2020 and 2021 respectively, tirbanibulin 1% ointment has been approved by Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of Olsen grade 1 AKs of the scalp and the face [35]. Tirbanibulin has a short course of application, just 5 consecutive days on an area of a maximum of 25 cm². Furthermore, the rate of skin adverse events is very low, with a vast majority of just mild irritative reactions. For these characteristics, tirbanibulin represents a new effective, safe, and practical option for addressing the problem of patient compliance in AKs management.

This article reviews what is currently known about tirbanibulin, from its mechanism of action to clinical trial outcomes and preliminary real-life reports regarding safety, effectiveness, and patient adherence to the treatment.

**Mechanism of Action**

Tirbanibulin is a new synthetic drug that targets α and β tubulin, like other antitumoral drugs including vinca alkaloids, taxanes, colchicine, and docetaxel. In immunofluorescence, studies mechanism is concentration dependent on both in in-vitro tumoral lines and murine tumor tissues [36-38]. Immortalized keratinocytes incubation with tirbanibulin has proven to cause the arrest of the end of the interphase of phase growth 2 and mitosis when the assembly of microtubules allows for the migration of genetic material to opposite poles of the cell [36-38]. Of note, the good tolerability of this drug could be attributable to the reversibility of its effect [38].

Alongside the above, preclinical studies have proven tirbanibulin to have a pro-apoptotic effect in both in-vitro and murine models by activating both intrinsic and extrinsic pathways such as Bel-2 hyperphosphorylation, and caspase-mediated mechanisms [36,37,39]. Not only does tirbanibulin show an antiproliferative and pro-apoptotic effect [38], but some evidence also [39,40] suggests that it plays a role in the rapid decrease of phosphorated Scr tyrosine kinase, which plays a role in the alterations of hemidesmosomes necessary to the progression to a cSCC [41,42]. Certain medications used to treat AK, such as 5-fluorouracil, can produce localized skin responses by causing the release of proinflammatory cytokines such as tumor necrosis factor TNF α and interleukin IL 8. A preclinical investigation described the potential effects of tirbanibulin on the release of pro-inflammatory cytokines during a 24-hour incubation period of CCD-1106 KERT keratinocytes. The findings demonstrated that whereas 5-fluorouracil generated a substantial rise in TNF α and IL-8, tirbanibulin incubation only slightly increased IL-8 at the highest dosage. Furthermore, IL-1, an indicator of cell death, was significantly higher in tirbanibulin-treated cells than in control (DMSO) and 5-fluorouracil. These findings imply that 5-fluorouracil is more likely to trigger a robust proinflammatory cytokine response than tirbanibulin, which could minimize the severity of local skin responses [41].

**Phase 1 Trials**

The Phase 1 trial [44] was an open-label single-center study. The enrolled patients had clinically typical AKs, and their age had to be ≥18. Thirty participants were enrolled in 4 successive cohorts. Cohort 1 was treated in a 25 cm² area with 4-8 AKs with tirbanibulin ointment 1% applied once a day for 3 consecutive days. Cohort 2 was treated in a 100 cm² area with 8-16 AKs with tirbanibulin 200 mg once a day for 3 consecutive days. Cohorts 3 and 4 resembled cohorts 1 and 2 at baseline, except the treatment was carried on for 5 consecutive days. The results were evaluated in terms of lesion count reduction, which was classified as complete if 100% and partial if ≥75%. Each cohort was followed on days 10, 17, 31, and through day 45. Only 1 patient withdrew his consent, while the rest (n=29) completed the treatment and the follow-up.

Complete clearance was achieved in participants by rates of 25% in Cohort 1, 0% in Cohort 2, 50% in Cohort 3, and 12.5% in Cohort 4, while partial clearance was respectively 50%, 30%, 63%, and
50%. Data regarding effectiveness are summarized in Table 2.

Regarding safety, the only adverse effects reported were mild local skin reactions, mostly in cohorts 3 and 4 including itching, erythema, and stinging or burning sensation, which did not lead to the discontinuation of the treatment and that self-resolved. No contact sensitization, phototoxic, or photoallergic effects were reported (Table 3).

**Phase 2 Trials**

The phase 2 trial [44] was aimed at open-label, uncontrolled dose regimen-finding multicentric (16 centers) in which patients (n=168) aged at least 18 years were sequentially enrolled in 2 cohorts, each consisting of 84 patients.

In both cohorts, the treated area was 25 cm², with 4-8 clinically typical AKs on the scalp, face, and/or neck area. The daily dose of tirbanibulin, applied as a 1% ointment once a day, was around 50 mg/day, however, group 1 underwent the treatment for 3 consecutive days, while group 2 was for 5 consecutive days. The results were evaluated in terms of lesion count reduction, which was classified as complete if 100% and partial if ≥75%. Each cohort was evaluated on days 8, 15, 29, and 57.

Both cohorts showed a significant reduction in the lesion count by day 57, however, it was superior in those patients who used tirbanibulin for 5 days. Complete clearance was achieved by 43% (95% confidence interval [CI]: 32%, 0.54%) in the 5-day group vs 32% (95% CI: 22%, 43%) in the 3-day group while a ≥75% clearance was achieved by 56% (95% CI: 45%, 67%) and 52% (41%, 63%) respectively. Data regarding effectiveness is summarized in Table 1.

Furthermore, all the patients who achieved complete clearance (n=63) were included in a further 12-month follow-up to evaluate the rate of recurrence. Consistent with the data above, the recurrence rate was lower in the 5-day cohort (57% [95% CI: 41%, 73%]) when compared to the 3-day cohort (70% [95% CI: 51%, 87%]).

One hundred percent of patients completed the treatment and the follow-up. No severe adverse effects (SAEs) or discontinuation of the therapy due to adverse effects were reported, and 7% (n=12) of the patients reported adverse effects, with a slightly higher occurrence in the 5-day cohort (11%, n=9) vs

### Table 2. Actinic Keratosis Clearance Rates* Through Phase 1, 2 and 3 [44,45]

<table>
<thead>
<tr>
<th></th>
<th>100% clearance</th>
<th>≥75% clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (n)</td>
<td>% (n)</td>
</tr>
<tr>
<td><strong>Phase 1 Trial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort 1: 50 mg once daily for 3 days &gt;25 cm² (n=4)</td>
<td>1 (25%)</td>
<td>2 (50%)</td>
</tr>
<tr>
<td>Cohort 2: 200 mg once daily for 3 days &gt;100 cm² (n=10)</td>
<td>0 (0%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Cohort 3: 200 mg once daily for 5 days &gt;25 cm² (n=8)</td>
<td>4 (50%)</td>
<td>5 (60%)</td>
</tr>
<tr>
<td>Cohort 4: 200 mg once daily for 5 days &gt;25 cm² (n=8)</td>
<td>1 (12.5%)</td>
<td>4 (63%)</td>
</tr>
<tr>
<td><strong>Phase 2 study</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-day cohort: 50 mg once-daily for 5 days over 25 cm² (n=84)</td>
<td>36 (43%)</td>
<td>47 (56%)</td>
</tr>
<tr>
<td>5-day cohort: 50 mg once-daily for 3 days over 25 cm² (n=84)</td>
<td>27 (32%)</td>
<td>44 (52%)</td>
</tr>
<tr>
<td><strong>Phase 3 study</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tirbanibulin group (n=353)</td>
<td>174 (49%)</td>
<td>255 (72%)</td>
</tr>
<tr>
<td>Vehicle (n=349)</td>
<td>30 (9%)</td>
<td>63 (18%)</td>
</tr>
</tbody>
</table>

*Clearance rates were either classified as complete (100%) or partial (≥75%) at day 45. Data of cohorts 1-4 are summarized above.

#Clearance rates were either classified as complete (100%) or partial (≥75%) at day 57. Data from 3- and 5-day cohorts are summarized above.

°Clearance rates were either classified as complete (100%) or partial (≥75%) at day 57. Clearance was assessed for both tirbanibulin and vehicle (placebo) cohorts. The percentage difference between the 2 groups is shown. Data are from intention-to-treat analysis.
the 3-day cohort (4%, n=3). However, these effects were mostly mild lysosomal stress responses (LSRs), which never required discontinuation of the treatment or further interventions, and that were self-resolved (Table 3).

**Phase 3 Trials**

Phase 3 trials [45], conducted in the United States, were multicentric (62 centers), randomized, double-blind, parallel-group, vehicle-controlled (placebo trials). Patients were eligible for enrollment if they had 4-8 clinically typical AKs within a contiguous area of 25 cm² in the face-scalp area and were aged ≥18 years. The patients (n=702) were divided into 2 identical-sized groups (n=301, each) and were randomly assigned to receive a vehicle ointment or tirbanibulin 1% ointment with a 1:1 ratio. Enrollment, however, was controlled to achieve, within each trial, a 2:1 facial: scalp treated area ratio. Patients were evaluated at baseline and day 57. Primary and secondary outcomes were respectively complete clearance or incomplete lesion count reduction at day 57. These patients were re-evaluated after 12 months to assess the recurrence rate.

In trial 1 complete clearance occurred in 44% of patients (n=77) treated with tirbanibulin vs the placebo group 5% (n=8). Similar results were reported in trial 2 with 54% (n=97) vs 13% (n=22). Overall, a complete clearance was achieved by 49% (n=174) of the tirbanibulin group vs 9% (n=30) of the controls, with a difference of 41% (95% CI: 35%, 47%). Results were consistent with regards to the partial clearance outcome: across the 2 trials, a ≥75% clearance was obtained by 72% (n=255) of the tirbanibulin group vs 18% (n=63) of the vehicle, with a difference of 54% (95% CI: 48%, 60%) (Table 2).

No SAEs or discontinuation due to AEs occurred. The only AEs that occurred at a significantly higher rate in the tirbanibulin group vs placebo were LSRs, the most common of which were erythema (91%) and flaking or scaling (82%). Pain in the application site and pruritus were much less common. All the adverse effects were mild to moderate and resolved without the need for further treatment.

**Real-World Studies**

A real-world study that showed the real effectiveness of tirbanibulin in a real clinical contest was published by Kirchberger et al [46]. It was a single-center study of adult patients with AK of face and scalp treated with tirbanibulin ointment 1% applied daily for 5 consecutive days on the same lesion or field. The results of treatment were assessed 4 weeks after the beginning of administration of tirbanibulin plus optional assessments later in time. The effectiveness of tirbanibulin over the AKs was measured before

| Table 3. Treatment-Related Adverse Effects* Through Phases 1, 2, and 3. [44,45] |
|---------------------------------|-----------------|-----------------|
| **Phase 1 study**              | Mild n (%)      | Severe n (%)    |
| Cohort 1: 50 mg once daily for 3 days >25 cm² (n=4) | 0               | 0               |
| Cohort 2: 200 mg once daily for 3 days >100 cm² (n=4) | 0               | 0               |
| Cohort 3: 200 mg once daily for 5 days >25 cm² (n=4) | 0               | 0               |
| Cohort 4: 200 mg once daily for 5 days >25 cm² (n=4) | 0               | 0               |
| **Phase 2 study**              |                 |                 |
| 5-day cohort: 50 mg once daily for 5 days >25 cm² (n=84) | 9 (11)          | 0               |
| 5-day cohort: once daily for 3 days >25 cm² (n=84) | 3 (4)           | 0               |
| **Phase 3 study, intention-to-treat** |           |                 |
| Tirbanibulin                   | 124 (35)        | 0               |
| Vehicle                        | 124 (36)        | 0               |

*Adverse events are classified as mild (no need to discontinue the treatment) and severe (need to discontinue the treatment). Of note, most adverse events were treatment-related mild.
and after the treatment with a specific score, the actinic keratosis area and severity index (AKASI), and with digital dermoscopy. A group of 33 patients was eligible for the study design and treated but only 30 were analyzed because 3 were lost to follow-up. The results of this study showed that before treatment, the median AKASI score was 5.6 (1.4–11), after treatment it was 1.2 (0–7.4) (p < 0.0001), and at a second follow-up after a mean of 3.7 months was 0.6 (0-1.4). At the first and second follow-ups, 47 percent of patients (n = 14) and 57 percent of patients (n = 13) had complete clearance, as indicated by AKASI scores less than 1. Local adverse events occur between 2 and 10 days from the beginning of the treatment, with a median onset at the seventh day and a mean resolution time of 5 days. The most common local reaction reported is erythema (80%, n=26) followed by scaling and flaking (43%, n= 13%) and by pustulation ad pruritus (7%, n = 2). Six patients (20%) did not report any local adverse event. Every local reaction ended on its own, without any aftereffects. Another real-world experience involved 30 patients with AKs on their faces or scalp in a single-center, prospective, observational trial in which tirbanibulin ointment was applied to a 25 cm² area for five days in a row. To evaluate the drug’s safety profile, effectiveness, and patient satisfaction, they were monitored for a minimum of 57 days. Six local skin response (LSR) symptoms were assessed and their intensity was rated as mild, moderate, or severe. These signs are erythema, scaling, crusting, swelling, blisters/pustules, and erosions/ulcerations. Dermatoscopically and clinically, the efficacy was assessed. The Medication Treatment Satisfaction Questionnaire (TSQM 1.4) was used to measure treatment satisfaction. The majority of LSRs, which included swelling (3.3%), scaling (30%), and erythema (83.3%), appeared on day 8 but went away on their own. Morphologic response was observed in 70% of the patients on day 57.[47]. To evaluate the efficacy and safety of tirbanibulin 1% ointment, a spontaneous open-label, prospective non-randomized study focused on the treatment of 228 AKs in 38 consecutive patients—28 males (73%) and 10 females (26%), aged between 52 and 92 years (mean age: 72 ± 8.92 years). Of the lesions that were reported, 51% had total clearance and 73% had partial clearance. There was no treatment termination owing to the occurrence of adverse events, and an outstanding tolerability profile and high compliance rate were noted.[48]

Discussion

Tirbanibulin is approved by the FDA and EMA in the formulation of 1% ointment for treating grade I AKs (according to Olsen’s grading) of the head and the neck in a contiguous area of no more than 25 cm². The application cycle must be of 5 consecutive days [35,49]. Since this drug has been marketed very recently, studies on compliance, efficacy, and cost-effectiveness compared to other approved treatments are still lacking.

A recent systematic review [24] of several phases 2 and 3 randomized controlled trials (RCTs) showed how tirbanibulin proved comparable effectiveness in lesion count reduction and complete clearance of the lesions when compared to both physical and topical FC-directed treatments. Odds ratio (OR), for complete clearance, with their respective 95% confidence interval, assessed at 8 weeks after baseline were: cryosurgery 13.4 (6.2-30.3); diclofenac 3% 2.9 (1.9-4.3); fluorouracil 0.5% + salicylic acid 7.6 (4.6-13.5); fluorouracil 4% 30.3 (9.1-144.7); fluorouracil 5% 35.0 (10.2-164.4); imiquimod 3.75% 8.5 (3.5-22.4); imiquimod 5% 17.9 (9.1-36.6); ingenol mebutate 0.015% 12.5 (8.1-19.9); photodynamic therapy with aminolevulinic acid 24.1 (10.9-52.8); photodynamic therapy with methyl aminolevulinate 11.7 (6.0-21.9); tirbanibulin 1% 11.1 (6.2-20.9).

Longer duration of topical therapy has repeatedly been shown to lower patient adherence to the therapy, leading to worse outcomes in real life [2,51]. This data is coherent with a recent systematic encompassing 14 studies and over 4,000 patients of patient-reported outcomes evaluating topic therapies for treating AKs, which improved significantly in both shorter-duration treatments [51]. Even though tirbanibulin was not directly evaluated in
that systematic review, it is suggested that its 5-day course treatment would lead to high compliance and adherence to the treatment, in line with findings of Phases 1, 2, and 3 of the random controlled trials.

The safety of the drug is supported by the lack of significant changes in the clinical examination as well as in blood chemistry, urine, physical examination, and instrumental tests (ECG, blood pressure) in phase 1 and 2 trials [44] and by phase 3 trials [45]. This new drug, thus, not only seems to bring higher compliance but is very well tolerated. It has been proposed that the safety of tirbanibulin might be due to the reversibility of its mechanism of action [50].

Another review [35] investigated the most common application-site side effects, noting that they were mild LSRs: erythema (91%) scaling or flaking (82%), and much more rarely pain or itching at the application site. Consistently to the previous review, no severe AEs were reported, all AEs were resolved, and did not affect the adherence to therapy. All of these data from different trials are comparable with the local adverse events reported in real-life studies demonstrating the real safety of this treatment [59]. Moreover, a recent group of phase 1 studies in healthy volunteers [54] demonstrated that tirbanibulin ointment 1% had no sensitization or phototoxic or photoallergic potential connected with the treatment and supported the safety of this topical medication. Unsurprisingly, compliance to topical treatments seems to be related to both the length of the treatments and their tolerability profile [52,53]. One crucial point was that in the reviews [44,45,49,50] tirbanibulin showed the lowest discontinuation rate with a compliance percentage of up to 100%. This is likely due to the well-tolerated profile of the drug and its easy administration regimen.

Incidentally, anecdotal experience from these two studies proves that the antitumoral effects above make tirbanibulin a potential candidate for future treatment of skin carcinomas, especially basocellular and squamocellular carcinomas even though it is not approved yet for these indications [55,56].

In patients with AK, a new Phase 1 trial assessed the safety and systemic exposure of tirbanibulin ointment 1% when applied under maximal usage settings, i.e., 350 mg once day for five days in a row to 100 cm2 of the face or balding scalp having eight or more AK lesions. The majority of TEAEs were mild, with application site reactions being the most common treatment-related TEAEs, similar to other topical AK treatments [57].

Finally, given the great effectiveness and safety of this medication, new sites for possible application over the approved face and scalp start to be reported. As shown in this case review study [58] tirbanibulin 1% ointment demonstrated efficacy for the treatment of grade I and II AKs of upper arms with approximately 45% of complete clearance after a single cycle of therapy. Following the profile of safeness described for the face and scalp also for the upper extremities, tirbanibulin showed a significative level of tolerability and adherence to treatment thanks to its proapoptotic effect which reduces the inflammatory necrosis typical of the other medications prescribed for AKs.

**Conclusions**

Considering the short-term course of application, the low rate of local cutaneous side effects, and the efficacy profile, tirbanibulin represents a safe, effective, and practical option for managing grade I face and scalp AKs. In particular, tirbanibulin seems to raise patient adherence rates to topical AKs therapies. Furthermore, tirbanibulin shows potential benefits also on more advanced AKs or AKs located in other anatomical areas. Head-to-head studies comparing the efficacy of different therapeutical options with tirbanibulin are required to further understand the best positioning of this drug in a real-life setting.

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Clinical and Dermoscopic Diagnosis of Actinic Keratosis

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ABSTRACT Actinic keratosis (AK) is one of the most frequent tumors of the skin; the diagnosis is basically clinical although in some cases it may be difficult to distinguish it from other keratinocytic or even melanocytic neoplasms when it presents in pigmented form. Over the years several clinical classifications and scores to objectify the burden of disease have been created. In this review the most frequent scores and classification systems are summarized along with dermoscopic criteria that allow diagnosis with greater sensitivity and specificity.
Introduction

Actinic keratosis (AK) is the most common keratinocyte skin cancer (KC) mainly caused by chronic sun damage; over 80% of AKs arise on chronically sun exposed areas such as face, scalp, neck, forearms and hands [1,2]. In fact, the most important risk factors for the development of AKs is ultraviolet (UV) exposure, notably UVB rays, augmented by the length of exposure and a lighter skin phototype [3]. Rates of transformation of AKs into squamous cell carcinoma (SCC) vary from 0.0015% to 16% but no specific criteria have been linked to the risk of progression, therefore the treatment of AK is mandatory for all forms detected during the visit [4]. Studies demonstrated two pathways for the development of a SCC: a direct one, from AK stage I into SCC and another with a progressive model (from AK stage I to AK stage III and then transformation into SCC) [5]. As development of invasive AK directly from the cancer field cannot be ruled out, the ideal treatment should be able to eradicate AK lesions and reverse the underlying field cancerization [6].

The diagnosis of AK is based on the clinical and dermatoscopic features; the combination of clinical and dermatoscopic characteristics helped physicians to elaborate algorithms and systems of classification useful not only for the diagnosis but also for choosing the correct therapy and for monitoring the response to the treatment. The aim of this systematic review is to summarize the clinical and dermatoscopic clues for the diagnosis of AKs, including clinical classification systems.

Materials and Methods

We searched the literature for studies published in the last 20 years between 2004 and 2024, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched PubMed database using the term actinic keratosis in combination with the following terms: dermoscopic and/or dermatoscopic features, clinical features, classification, dermoscopic and/or dermatoscopic criteria. Eligibility was restricted to studies with more than thirty cases described. Reviews, meta-analyses, cohort studies, case series were eligible for inclusion. Only articles in English were selected. Letters and case reports without statistically relevant data were excluded from the analysis. Other potentially relevant articles were identified by manually checking the references of the included literature. The last search was run on 26th January 2023. Two investigators independently selected relevant articles according to predefined inclusion and exclusion criteria, as described above. Disagreements were solved by discussion, with a prior arrangement that any unsettled discrepancy would be determined by a third author.

Clinical Diagnosis of AKs: Olsen Classification

AK is clinically characterized by a squamous and erythematos macula or plaque; the degree of hyperkeratosis and symptomatology is variable. In fact, it can be asymptomatic, itchy and sometimes painful [7]. The first clinical classification of AKs is based on a three-stage model; the Olsen classification is based on the distinction of AKs into three stages: grade I in which the AK is a small erythematous macula, not very visible and more easily appreciated on palpation; grade II with greater hyperkeratosis and erythema, whereby the lesion is easily diagnosed with the naked eye and also easily appreciated; otherwise grade III is characterized by the maximum of hyperkeratosis and the diagnosis is immediate [8]. This classification has been among the most widely adopted in both clinical practice and scientific studies but has as a major limitation: it does not evaluate the entire skin area but defines only the grade of individual observable keratosis. Moreover, based on a 3-stage model, it seems to be a progressive model up to the most severe degree of keratosis with higher risk of transformation into iSCC. As other studies have shown, this is not true because even grade I AKs can evolve directly into iSCC, thus necessitating treatment of all forms.
The aim of the original Olsen classification (elaborated in 1991) was not to establish a clinical classification of AKs but to evaluate the response of AKs to masoprocol; the original classification had as a main clue the grade of hyperkeratosis, explaining why it has three grades. No predictive values are associated with this classification, no correlation has been found between Olsen grade and rate of progression and Olsen grade do not correlate with histology (i.e Rowert-Huber classification). Finally, Olsen classification addressed only single lesions, not considering AKs as components of field of cancerization (FC) [8,9]. For all these reasons, according to some authors, its use should be dismissed.

Dermatoscopic Features of AKs

Non Pigmented AK

The dermatoscope is certainly the quickest and most user-friendly tool for diagnosing AKs. They were first described by Zlaudek et al in 2006 with the identification of four main dermatoscopic features: a pattern characterized by erythema surrounding hair follicles to form a “pseudonetwork,” yellowish-white scales; fine linear wavy vessels with a perifollicular distribution and follicles with yellowish keratotic plugs surrounded or not by a with halo. These features combined form a typical pattern, which later became famous over the years for ease of recognition, termed the “strawberry pattern” [10]. This pattern is, however, more characteristic of lesions located on the face. Reinehr et al. have described how the most frequent dermatoscopic features of non-facial actinic keratoses are represented by opaque white scales and erythema for non-pigmented lesions, and homogeneous brown pigmentation for pigmented ones [11]. Rosettes, described as structures characterized by four white dots arranged like a 4-leaf clover visible under polarized light in actinic keratoses (AK) and squamous cell carcinomas (SCC), are actually quite nonspecific since they can also be identified in basal cell carcinomas (BCC), melanomas, and non-lesional photodamaged skin [12,13]. Dermatoscopy has also proven to be a valuable tool for the clinical and post-treatment follow-up of such lesions [14–17].

Pigmented AK

Since the initial use of dermatoscopy in diagnosing AKs, it has been challenging to accurately identify pigmented AKs (pAKs), particularly when differentiating them from lentigo melanoma (LM) in cases of diagnostic uncertainty. In a 2005 study on two cases of pigmented actinic keratoses (pAK), Zlaudek et al. asserted that although dermatoscopy could be helpful in some instances, the principle that the diagnosis of a pigmented lesion cannot rely on a single criterion meant that histopathology remained the gold standard for diagnosing these lesions [18].

The same conclusion was reached in a subsequent study by Akay et al. on 89 facial pigmented skin lesions, including 67 pAK, aiming to define the dermatoscopic criteria that distinguish them from LM. The study identified up to eleven different dermatoscopic features in pAK, such as grey dots, annular-granular patterns, rhomboidal structures, and pseudonetworks [19]. Subsequently, Lallas et al. studied 144 facial pigmented skin lesions, including 70 LM) and 56 pAK, to determine if the limitations of dermatoscopy in differentiating these two types of lesions were due to previous studies focusing exclusively on pigmented criteria without considering other possible characteristics. The results of their study indeed showed that features such as scales, red colors, and white circles were significantly associated with pAKs, whereas grey rhomboids, non-prominent follicles, and intense pigmentation were linked with LM (Figure 1) [20]. The most recently described criterion in the literature, useful for the differential diagnosis between pAK and LM, is the “inter grey halo,” as characterized by Nascimento et al. 21. This feature is described as a homogeneous circular structure, either gray-blue or beige, which on one side surrounds the hair follicle and on the other forms the inner contour of the pigmented pseudonetwork. Histologically, this structure corresponds to an inverted cone of epidermis spared by the follicular keratin plug and the anaplastic, hyperpigmented epidermis of the pseudonetwork.
Bowenoid AK

Bowenoid actinic keratosis (AK) is a histological subtype of AK characterized by single-cell keratinization and full-layer atypia that does not involve the cutaneous adnexa [22]. Dermatoscopically, it is distinguished by regularly distributed glomerular vessels on the surface of the lesion, unlike Bowen’s disease, where the vessels are typically arranged in clusters (Figure 1) [23].

Figure 1. Male kidney transplant patient presenting with a pinkish frontal macular lesion (A) dermatoscopically characterized by glomerular vessels evenly distributed over the surface (B) and corresponding to a Bowenoid AK on histopathology. Seventy-nine-year-old male with a pigmented hyperkeratotic patch of the left frontal region (C) characterized dermatoscopically by pigmented pseudonetwork, dilated yellowish-white follicular ostium, rosettes, and sharp margins (D) and corresponding to a pigmented AK on histopathology.

Dermatoscopy Signs of Invasiveness in AK

In 2012, based on Olsen’s clinical classification, the dermatoscopic features of nonpigmented AKs were analyzed to assess whether there were typical and/or pathognomonic criteria related to grades. It was shown that grade I AK showed mostly the erythematous pseudonetwork and white scales, grade II are characterized by the “strawberry” pattern while grade III are associated mostly with marked

Table 1. Clinical classification systems of AK

<table>
<thead>
<tr>
<th>Grades/Scores</th>
<th>Olsen classification</th>
<th>AKASI score</th>
<th>AK-FAS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis of FC</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Analysis of sun damage</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Analysis Hyperkeratosis</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Areas considered in the analysis</td>
<td>Lesion-based classification</td>
<td>Scalp and face</td>
<td>Scalp and face</td>
</tr>
</tbody>
</table>

FC: field of cancerization.
hyperkeratosis and follicular keratin plugs [24]. [Table 2]

The most interesting finding was to have observed more hyperkeratosis dermatoscopically in the higher grades (II and III) which then reached the maximum presence in in situ squamous cell carcinoma (iSCC) [25]. Another criterion that aids in the diagnosis and assessment of progression, along with those previously mentioned, is the red starburst pattern. This pattern is characterized by the presence of peripheral radial lines or vessels in the context of typical actinic keratosis (AK) criteria. It is indicative of progression to invasive squamous cell carcinoma (iSCC) [24]. Papageorgiou et al. published a study evaluating the presence of dermatoscopic criteria indicative of early invasion, capable of differentiating between early SCC and AK. Conducted on 45 AK cases and 50 early SCC cases, the study highlighted that the predictive criteria for early SCC are dotted/glomerular vessels, hairpin vessels, and white structureless areas, while an erythematous background was identified as a negative predictor (Figure 2) [26,27].

<table>
<thead>
<tr>
<th>Grade of AK</th>
<th>Dermoscopic feature</th>
<th>Histological correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Red pseudonetwork</td>
<td>Atypical keratinocytes localized in the third of the epidermis</td>
</tr>
<tr>
<td>II</td>
<td>Strawberry pattern</td>
<td>Atypical keratinocytes in the lower two-thirds of the epidermis</td>
</tr>
<tr>
<td>III</td>
<td>Yellow-White scales and follicular keratin plugs</td>
<td>Atypia throughout the epidermis</td>
</tr>
</tbody>
</table>

Figure 2. A 41-year-old male with an erythematous and hyperkeratotic macular lesion of the left malar region (A) dermatoscopically characterized by erythematous pseudonetwork, white scales, and (B) dilated follicular ostium corresponding to an AK on histology. Sixty-four-year-old male with an erythematous and hyperkeratotic maculo-papular lesion of the left malar region (C) characterized dermatoscopically by erythematous pseudonetwork and dilated follicular ostium at the periphery associated with a central white structureless area (D) corresponding histologically to an SCC.
AK in other Non-Invasive imagine Techniques

Optical Coherence Tomography (OCT)

OCT operates as a noninvasive, in vivo imaging method utilizing interferometry principles. It employs infrared light for imaging, achieving an axial and lateral resolution around 15 micrometers, with a penetration depth between 500 and 1000 micrometers. This method allows for the visualization of skin layers, adnexal structures, and blood vessels, but it does not provide cellular details [28]. Several studies have described the morphological characteristics of actinic keratoses (AK) in Optical Coherence Tomography (OCT), including: disruption of the dermo-epidermal junction (DEJ), epidermal thickening, hyperkeratosis, white streaks and dots, rapid attenuation of light, lower penetration depth, and a dark band in the stratum corneum [29–33]. The most predictive features described in the majority of published papers include architectural disarray, characterized by a complete or partial absence of the dermo-epidermal junction (DEJ); white streaks and dots, which histologically correspond to particularly dense areas of hyperkeratosis; epidermal thickening; and pronounced hyperkeratosis. The latter characteristic is not specific to actinic keratoses (AK) as it can also be found in other lesions and may compromise the quality of the images due to artifacts. These artifacts create shadows that obscure underlying portions of the tissue [29]. The basement membrane cannot be distinguished with this technique, making it difficult to reliably determine early tumor invasion. The practical utility of Optical Coherence Tomography (OCT) for actinic keratoses (AK) also lies in its ability to non-invasively monitor the outcomes and effectiveness of various therapeutic approaches available for this condition, offering additional possibilities and information beyond what is possible with dermatoscopy alone. In this regard, numerous studies have been published on the use of OCT to evaluate the results of therapies such as ingenol mebutate [34,35], hybrid fractional ablative and nonablative laser resurfacing [36], daylight photodynamic therapy after tailored pretreatment with ablative fractional laser or microdermabrasion [37], cryosurgery [38], imiquimod [39], tirbanibulin [40], and fluorouracil [41]. Furthermore, this method is useful in the identification of both clinical and subclinical actinic keratoses, thereby serving as an important tool for precisely defining the field of cancerization in patients with significant photodamage [42].

Line-Field Confocal Optical Coherence Tomography (LC-OCT)

Line-field confocal optical coherence tomography (LC-OCT) is a non-invasive optical imaging method that produces real-time vertical, horizontal, and three-dimensional section images. These images are comparable to traditional histology images and offer cellular resolution, with a penetration depth of approximately 500 micrometers [43]. This technique can identify diverse skin structures and assess various conditions, such as the presence of atypical epidermal cells, the integrity of the dermo-epidermal junction in the vertical plane, the uniformity of the keratinocyte pattern, and the presence of dendritic cells in the horizontal plane. Cinotti and colleagues employed LC-OCT to identify and analyze key patterns in AK and SCC, aiming to distinguish specific criteria that could differentiate between these conditions. Notable features common to both AK and SCC included hyperkeratosis, acanthosis, parakeratosis, erosion/ulceration, disrupted epithelial architecture, dyskeratotic keratinocytes, crowded cell nuclei, abnormal nuclei, tumor budding, and expanded blood vessels. Among these, dyskeratotic keratinocytes, atypical nuclei, and disorganized epithelial architecture were particularly significant indicators [44]. Just as with OCT and RCM, excessive hyperkeratosis can lead to artifacts characterized by heightened reflectivity in the upper portions and reduced image quality in the lower portions of lesions marked by this criterion. Greater lesion thickness, disrupted epidermal architecture, and non-outlined DEJ could assist instead in differentiating SCC from actinic keratosis AK [44]. Ruini and colleagues have shown that evaluating AK with LC-OCT can non-invasively replicate the PRO
histological classification, exhibiting strong correlation and interobserver agreement. As a result, this method facilitates the assessment of AK’s progression risk without requiring an invasive biopsy [45]. A study by Daxenberger et al. investigated the use of an artificial intelligence (AI) algorithm on LC-OCT images for diagnosing and grading AK. The performance of the AI algorithm was compared with that of a group of experts, demonstrating high concordance. Consequently, this suggests the potential to enhance the accuracy of diagnoses and improve the management of patients with this condition in clinical practice [46]. Numerous studies have been reported in the literature on the use of LC-OCT for monitoring AK after treatments such as cryotherapy [47] and irbanibulin [48].

Reflectance Confocal Microscopy (RCM)

Reflectance confocal microscopy (RCM) is a non-invasive imaging technique that enables the visualization of skin in the horizontal plane with cellular-level resolution. The imaging depth of RCM extends approximately 200-300 micrometers, reaching down to the papillary dermis [49]. The primary features of AK as observed through RCM include hyperkeratosis with parakeratosis at the level of the stratum corneum and an irregular honeycombed pattern in the spinous-granular layers. Given that this technique provides images on a horizontal plane, it does not enable the assessment of the vertical invasion depth of these lesions [50]. Pellacani and colleagues reported a high concordance rate and strong interobserver correlation in the grading of keratinocyte atypia in AK when evaluated using RCM compared to histopathological examination [51]. Specifically, grade 1 actinic keratosis (AK) displays focal areas of atypical honeycombed patterns mixed with areas of normal honeycomb at the spinous layer level. Grade 2 AK shows widespread keratinocyte atypia across both the spinous and granular layers, featuring keratinocytes of various shapes and sizes. Grade 3 AK is characterized by a markedly atypical honeycombed pattern described as disarranged. Keratinocyte pleomorphism increases proportionally with the AK grade [51,52]. Moscarella et al. outlined the principal features of pAK using RCM. These features include hyperkeratosis with parakeratosis, atypical honeycombed pattern, increased epidermal thickness, intraepidermal dendritic cells, and bright, small dermal papillae with enlarged interpapillary spaces. Notably, these observations were made in the absence of any features indicative of melanocytic lesions [53]. A confounding factor is the presence of intraepidermal dendritic cells, as this feature can also be observed in melanomas, making it challenging to differentiate between the two conditions based solely on this characteristic. Another diagnostic challenge associated with RCM involves distinguishing between AK and SCC. Due to the limited penetration depth of RCM, it is difficult to assess deeper structures, which restricts the available information for accurate differentiation between these conditions. Currently, the distinction between AK and SCC relies on the extent of keratinocyte atypia and epidermal disarray, which appears widespread and full-thickness in SCC, but tends to be more localized and focal in AK [54,55]. RCM has also been used for the post-treatment follow-up of AK treated with various modalities such as fluorouracil [56], imiquimod [57], ingenol mebutate [58], shave biopsy [59], photodynamic therapy [60], daylight photodynamic therapy [61], and cryotherapy [62].

Field-Cancerization Based Classifications: AKASI and AK-FAS Score

To evaluate not only the single AKs but the whole skin surrounding them, in 2017 the AKASI (AK Area and Severity Index) score was developed [63]. To calculate AKASI, four regions should be considered in the analysis: scalp, forehead, left face and right face. Within each region, according to the area affected by AKs, a score ranging from 1 (1-9% affected area) to 6 (90-100% affected area) is assigned. Other features considered are the distribution, erythema and thickness of AKs with a scale ranging from 0 (none) to 4 (maximum). Combining the area and the signs scores, a score ranging from 0 (no AKs) to 18 (most severe degree) is obtained.
With this system, a global look on the affected area is achieved, quantifying the characteristics of sun damaged regions and obtaining an objective score for monitoring the efficacy of a treatment prescribed. This classification has a major limitation the restriction of the score only for the head, for this reason it cannot be used for AKs located in other areas, such as hands, forearms or chest.

Also, in 2017 another score was developed, named AK-FAS (Actinic Keratosis Field Assessment Scale), to assess the severity of AKs [64].

This score is based on three criteria: hyperkeratosis, sun damage and AK area. Depending on percentage of area affected by AKs, a score from 0 (0% area affected) to IV (<50% area involved) is assigned. The scale has been validated on photographs of twelve patients and the validation of the AK-FAS showed good reproducibility, helping to standardize AK diagnosis, making it relevant to routine clinical practice but also for clinical trials and studies.

How to Improve Classification of AKs in Clinical Trials and Studies

Considering the limitations of each classification and the low rate of reproducibility of some of them it seems inevitable to have classifications that cannot be compared with each other and with different analyzed characteristics. As already suggested by other authors, it would be necessary to always analyze the presence or absence of the field of cancerization and to evaluate the extent of the area of AKs [65].

Otherwise, focusing only on individual lesions does not allow the assessment of the disease burden and does not allow the evaluation of the response to treatments accurately.

Olsen’s classification, despite the limitations already mentioned, remains the most widely used but should be unused especially in scientific studies. Furthermore, Olsen’s classification has no predictive value for the development of SCC, unlike AKASI score, which has been associated with the incidence of iSCC. The use of AKASI in clinical trials would also allow the same score to be used during clinical practice to compare data with those in the literature. This method already appears to be in use for other dermatologic conditions such as psoriasis in which the PASI score is used both in research and during daily practice.

Conclusions

AKs are the most frequent tumors diagnosed during daily dermatological practice; their diagnosis is usually made by clinical evaluation, but in some cases the clinical aspect is not sufficient for a diagnosis of certainty. Dermatoscopy, already defined a silent revolution in dermatology because of its ease of use and being an inexpensive method [66], adds more specificity to the diagnosis through visualization of typical criteria, such as red pseudonetwork, the presence of large and white follicles, strawberry pattern and whitish scales. Several diseases in fact have a clinical presentation that can mimic AK: for example, irritated flat seborrheic keratosis, superficial basal cell carcinoma, lentigo melanoma, or even inflammatory pathologies such as psoriasis or cutaneous sarcoidosis [67]. The presence of dermatoscopic criteria helps to direct the diagnostic and the therapeutic process. Despite its easy use, the biggest limitation that can be observed in the classification systems previously described in this paper such as AKASI and AK-FAS, is the disregard of dermatoscopic parameters in classifications based on scores that only clinically evaluate AKs and the field of cancerization. It would be preferable in the future to integrate noninvasive diagnostics into the classifications systems in order to obtain objective and reproducible data based on a non-expensive and user-friendly diagnostic method.

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Epidemiology and Risk Factors of Actinic Keratosis. What is New for The Management for Sun-Damaged Skin

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Key words: actinic keratosis, skin cancer, prevention, non-invasive imaging, PRO score


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Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Actinic keratosis (AK) is considered a chronic skin disease mostly caused by long-term exposure to UV radiation and other risk factors such as immunosuppression, leading to an individual susceptibility for skin cancer manifestation. The treatment of AK is laborious and costly, and the incidence of skin cancer is forecasted to double until the year 2030 in an aging society.

Risk factors in AK for malignant transformation in cutaneous squamous cell carcinoma (cSCC) are not fully understood, but studies suggest that histological features, such as atypia in the basal epidermal third and basal proliferation (PRO score) in AK play a pivotal role for development of malignancy. As the clinical appearance of AK does not correlate with the risk for malignancy, guidelines suggest treating every single AK lesion upon diagnosis. Skin imaging techniques, such as line-field confocal optical coherence tomography (LC-OCT) can help to provide an individual holistic follow-up for AK lesions by non-invasive visualization of atypia and basal proliferation. A follow-up for patients with AK may be critical for treatment success in terms of strengthening therapy adherence. When AK presents therapy refractory, cSCC manifests in nearly 30% of the cases after several years. Patients with AK suffering from field cancerization and immunosuppression are susceptible for a severe course of disease including metastasis and high mortality rates. Those vulnerable subgroups benefit from close skin cancer screening, early adequate treatment and chemoprevention, such as niacinamide or acitretin.

Skin cancer prevention is substantial. Primary prevention should include chemical and physical UV-light protection and avoidance of indoor tanning. Secondary prevention is essential in high-risk populations, such as fair skin type elderly men and STORs. Tertiary prevention should comprise adequate treatment strategies to prevent therapy resistance, reoccurrence and cSCC, especially when field cancerization and immunosuppression are present.
Introduction – Epidemiology

Actinic keratosis (AK) is characterized by the presence of atypical keratinocytes within the epidermal skin layer and is considered an in-situ neoplasia of the skin and a progenitor of cutaneous squamous cell cancer (cSCC) [1]. AK usually manifest on body areas, such as the face, scalp, head and neck area, hands, and forearms, being exposed to long-term ultraviolet (UV) radiation (UVR) over several years, usually decades. UVR and especially UV-B radiation (UVBR) causes damage to the skin and its keratinocytes at several stages of cell regulation and homeostasis, underlined by a complex interplay of local immunosuppression, skin inflammation, oxidative stress and DNA alteration. Clinically, AK is characterized by erythema and scaling. AK may appear erosive or may be accompanied by itching, but usually elderly patients do not consider these lesions as harmful, as AK progress or even regress slowly over time. The estimated prevalence of AK in the group of individuals being 60 years of age and older is 4.6-14.57% [2]. Moreover, the male population is affected at a higher rate of 3.5% compared to females (1.5%) [3]. Patients suffering from multiple AK, face a cumulative lifetime risk of 6-10% for malignant transformation into cSCC and the annual risk for malignant development for a single AK lesion ranges from 0.03-20% [4-6]. Furthermore, in up to 85% of cases of treated AK, recurrence or manifestation of new lesions can be observed after a one-year follow up, making AK a chronic and recurring disease [7]. The aging society and the high rate of recurrence may partly explain, why the treatment of AK is considered a laborious and costly task, placing an estimated financial burden on the US healthcare system of nearly $1-1.68 billion annually [8, 9]. These spendings cover the evaluation of almost 10 million patients for actinic skin damaged, annually [8]. Respectively, the costs for treatment of AK and cSCC reached an enormous amount of $4.59 billion for the year 2013 and accounted for more than 15% of health care spendings related to skin disease treatment [8]. However, treatment of cSCC remains significantly more costly per year than treatment of AK ($791 vs. $143) [10]. This burden may increase in an aging society and is supported by the fact that the incidence of cSCC has partly quadrupled in the last 30 years among the population in Germany [11]. Moreover, for the year 2030, Leiter et al. predict that, the incidence rate of NMSC will double again, with a continuous long-term trend in increasing incidence [12]. The estimated age-standardized incidence rates are 230 for males and 180-200/100,000 cases for females per annum in the year 2030 [12]. The chronic course of AK disease, including spontaneous regression, but also progression from sun damaged actinic skin, has influence on the quality of life (QoL) in several aspects, including fear about cSCC manifestation, cosmesis and clinical symptoms [13]. As AK is considered a chronic disease, QoL scores of those patients are comparable to scores of patients suffering from other chronic skin conditions, such as atopic dermatitis and psoriasis and are remarkably lower compared to patients without AK [13-15]. Interestingly, the number of AK correlates inversely with the QoL scores of patients and may cause a high sense of affliction in patients with multiple AK, field cancerization (FC) or recurring disease [13, 14, 16, 17]. Moreover, disease burden regarding lower QoL scores is significantly higher in female patients and patients younger than 60 years of age [18, 19]. For the reasons named, the complex management of AK, placing an immense financial burden on health care providers and psychological stress on diseased individuals, requires improved strategies for AK and cSCC prevention as well as adequate treatment strategies. This section will discuss the identification of possible risk factors in AK for early adequate therapy referral, as well as insights into recent approaches for therapy monitoring. Especially the quantification of objectifiable treatment response parameters may become substantial, as detection of non-responding lesions and reduction of malignant transformation in AK should remain primary goals in the handling of AK.
Pathogenesis of AK and Histological Risk Factors for Development of cSCC

The development of AK and the progression into invasive cSCC is multifactorial and is driven by a variety of endogenous and exogenous factors. Sunlight, and especially UVRB, was identified as a carcinogen for its ability to mutate TP53 [20, 21]. On gene level, TP53 functions as a tumor suppressor gene in the human genome, which controls various cell cycle mechanisms and is of importance in the regulation of cell proliferation and induction of apoptosis in mutated cells [21, 22]. Additionally, UVB irradiation of the skin initiates production of pro-inflammatory cytokines in keratinocytes, those include IL-1, IL-6, IL-8, interferon gamma (IFN-γ), granulocyte colony-stimulating factor (C-GSF), macrophage inflammatory protein (MIP-β) and tumor necrosis factor alpha (TNF-α) [23]. Together with other neuro- and vasoactive mediators this inflammation causes “sunburn” within 24 hours of exposure [24]. UVR is reported to cause formation of reactive oxygen species (ROS) in the skin, such as hydroxide peroxide and other hydroxyl radicals [25]. As DNA nucleotides targeted by ROS are highly susceptible to mutagenesis, a well-characterized nucleotide mispairing found in DNA of sun damaged skin is the change of G/C pair into an A/T pair [26]. NADPH-dependent DNA repair mechanism play a pivotal role in keratinocytes to reverse free radical damage in DNA to avoid oxidative mutagenesis eventually. Typically, mutations of TP53 are predominantly found in human cancer tissue, including cSCC, where mutations of TP53 are found in approximately 50% of the cases [21, 27, 28]. When the mechanism of DNA repair is absent due to mutation, the immunosuppressive mechanism of action of UVR, and especially UVAR, which already comes into play after the first ten days of sun exposure, mediated through DNA damage in the form of cyclobutene pyrimidine dimers (CPDs), leads the sequel AK development and progression to cSCC [24, 29, 30]. TP53 mutations found in UVB-induced skin patches of mice were like mutations in cSCC, suggesting that these patch lesions are precursors of cSCC [31]. A characteristic UVBR induced mutation in the TP53 gene is the transition of cytidine to thymidine, leading to a loss of function of the TP53 gene product [32]. Beside TP53, other additional mutations in the genome are considered to increase the risk of atypia in cSCC or stimulate uncontrolled cell proliferation. Mutations in the KNSTRN oncogene are reported to drive progression towards cell atypia [33]. On protein level, KNSTRN translates into a kinetochore-associated protein responsible for mitotic chromosome segregation during anaphase in the cell cycle. Mutations in this gene, caused by substitution of the genome bases cytosine for adenine and induced by UVR, lead to cell aneuploidy and enhanced tumor genesis [32, 33]. The mutation was observed in 19% of cSCC and in 13% of AK, contrary this mutation was never found in healthy skin [32].

The resulting uncontrolled cell cycle finally leads to keratinocyte cell atypia and dysplasia, which can initially be observed in the basal layers of the epidermis [34]. Beside genomic mutations found in AK, other co-factors seem to stimulate the malignant transformation of AK. It is estimated that in up to 35% of the cases of cancer manifestation, viral infections play a co-stimulatory role in carcinogenesis of cSCC [35]. For the skin, HPV DNA is found in forms of non-melanoma skin cancer (NMSC), such as basal cell carcinoma (BCC) and cSCC, but also in AK and healthy skin. For people under immunosuppression HPV DNA is found in 80% of NMSC. Still, its causal role in the pathogenesis for NMSC is poorly understood. It is assumed that HPV skin infection acts co-stimulatory in the pathogeneses of AK, but it is not considered to be a co-carcinogen for malignant transformation into NMSC [32]. Since AK is considered an in-situ SCC, the proliferation of atypical keratinocytes is limited to the epidermis, while the dermo-epidermal junction (DEJ) remains intact. From the evaluation of histological specimen of cSCC and adjacent AK tissue, Fernandez-Figueras et al. suggested two major pathways of malignant transformation from AK to cSCC [36]. The classic pathway describes the stepwise evolution of cSCC.
from atypia in the lowest third of the epidermis (AK I) evolving to atypia in the middle (AK II) and finally upper third of the epidermis (AK III), according to the previously proposed atypia grading by Röwert-Huber [34, 36]. At the final stage of the disease, invasive proliferation is defined by loss of DEJ integrity and invasive infiltration of atypical keratinocytes into the dermis. Beside the classic pathway, it was found that AK I can even directly progress into cSCC, without stagewise atypia evolution, especially when AK I grows in close contact to adnexal tissue [36]. Beside atypia, Schmitz et al. [37] identified distinct basal growth patterns in AK to be suggestive for cSCC development. Those basal growth patterns, found in histological sections, can be subsumed under the so-called PRO score, which grades the basal growth pattern in AK on a tier grading system (PRO I-III) [37]. For PRO I, the epidermal layer is flat and no protrusions in the dermis can be observed. For PRO II, the DEJ appears undulated and slight protrusion into the dermis can be appreciated. PRO III AK lesions are considered to be high proliferative, as protrusions found in those lesions reach a deep, cone-like penetration into the dermis. The DEJ remains still intact [37]. In 2019, Schmitz et al. histologically investigated the epidermis adjacent to samples of cSCC [38]. The epidermal layers were assessed for keratinocyte atypia (Röwert-Huber, AK I-III) and the basal growth pattern (PRO I-III). The majority (39.4%) of cSCC harbored PRO III in the adjacent epidermis, followed by PRO II (31.9%) and PRO I (25.7%) [38]. Also, basal proliferation of atypical keratinocytes (AK I) was found in more than 50% of the evaluated adjacent AK lesions [38]. The finding of AK I, being predominantly associated with cSCC was determined in accordance with the study of Fernandez-Figueras et al., who reported that cSCC often emerges from atypia (AK I) in the lower third of the epidermis [36, 38]. When AK I advances along adnexal structures this might even further facilitate the development of cSCC from AK I lesions [36].

The clinical Olsen classification, and both histological classifications (PRO score and Röwert-Huber) have in common to provide a possible grading to the malignant potential of AK. However, the clinical value of these classifications is debated and critically discussed in the literature. Recent studies imply that the clinical Olsen score is not sufficient to predict the potential of malignant transformation alone [11, 36, 39]. In a study conducted by Schmitz et al. in 2016, it was proven that the clinical appearance of AK, graded by the Olsen scale, did not correlate with the extent of keratinocyte atypia underneath, measured using the Röwert-Huber scale [39]. Only in 53.8% lesions, a matching clinical and histological classification was found, with the majority (83.1%) being Olsen II and AK II [39]. Another study found that the expression of the mutated TP53 gene in AK, tended to increase with a higher rate of keratinocyte dysplasia, but no significant level was reached [28]. Moreover, in AK no significant correlation was found between TP53 expression, the extent of dysplasia in the epidermis and the clinical thickness as well as thickness of the stratum corneum (SC) [28]. From these findings, Heerfordt et al. [28] supported the suggestion by Schmitz et al. [39] that the clinical appearance of AK is not a sufficient and reliable predictor of malignant transformation in AK. In contrast, Bakshi et al. were able to show that the mutational status of TP53 and its increased level of protein expression was found in clinical apparent AK, sun-exposed skin, cSCC and BCC, while significantly lower levels were found in regressive AK [40]. It was found that a progressive increase in nuclear TP53 staining was associated with a progress from actinically damaged skin to AK to cSCC eventually [40]. From these findings they concluded that TP53 may be a good biomarker of AK progression towards invasiveness [40]. The progression from AK to cSCC appears to be a complex process of interactions between the named co-carcinogenic factors. Their underlying mechanism are still insufficiently understood and thus subject to controversially discussion in the available literature. With these assumptions, Schmitz et al. suggest to use clinical and histological features, found in AK lesions, to predict the risk of malignant transformation in AK [32].
From these controversies, the latest S3-guideline for AK and SCC does not give any advice on risk factors for malignancy in AK [11]. Moreover, no predictive value for the risk of malignant transformation can be assumed by the clinical appearance of AK [11]. Still, the reported findings imply that the downward proliferation and basal atypia in AK are two major factors for discrimination of high-risk AK. Unfortunately, they cannot be assessed by clinical appearance and are not routinely evaluated in the follow-up of AK, due to invasiveness of skin biopsy [36, 39]. Hence, no long-term follow-up data of AK exists, reporting and documenting distinct ongoing changes in cellular morphology and epidermal architecture in the pathway of malignant transformation. Beside these histopathological features in AK, which may contribute to malignant transformation, Schmitz et al. [41] identified painfulness and refractory of therapy in AK as clinical warning sign for malignant transformation, as those therapy-resistant AK have an underlying histology of high-grade atypia (AK III) and high basal proliferation rates (PRO III).

Beside intrinsic risk factors for the development of AK, extrinsic factors such as intake of photosensitizing cardiovascular drugs seem to affect the likeliness of AK development. Studies report exposure to angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors and calcium channel blockers [42]. Moreover, the intake of antiplatelet agents was identified as an independent risk factor for AK development [43].

Risk Factors for Development of AK and cSCC – Immunosuppression

Solid organ transplant recipients (STORs) under immunosuppression face a significant risk of developing NMSC during their lifetime. 80% of transplant recipient develop AK during their lifetime, with up to 30% of them suffering from more than five AK lesions [44, 45]. Although, immunosuppression is associated with the likelihood of HPV colonization, immunosuppression alone, significantly correlates with the development NMSC, depending on its prescription duration [32]. While for a period of two years under immunosuppression, the reported incidence of NMSC is 5%, it significantly increases over time and reaches up to 60% in patients, being under immunosuppression for a period of at least 20 years [32]. Studies report a median of eight years after transplantation for NMSC to manifest, while transplant recipients older than 60 years of age seem to develop NMSC already after three to five years of transplantation [46, 47]. Patients under immunosuppression also face a ten times increased risk to develop a second cSCC when field cancerization (FC) is present [48, 49]. In a renal transplant cohort, 7% of recipients with AK developed cSCC, while recipients with FC developed cSCC in 15% of the cases. The authors concluded a correlation between risk of SCC development and the skin area suffering from AK, such as FC [50]. Studies found that, manifestation of BCC is predominantly observed after initiation of immunosuppression and the risk follows a linear trend, but for cSCC the risk even develops exponentially [51]. For immunosuppressed patients, the ratio of cSCC vs. BCC occurrence is 4:1 and therefore inverse proportionally to the ratio observed in immunocompetent patients [32]. According to Schmitz et al. this may partly be explained by the higher observed progression rate of up to 30% from AK to SCC in immunodeficient patients [32]. Recent follow-up data from the year 2022 for a Finnish cohort of organ-transplanted patients, who were retrospectively evaluated for the last 30 years, revealed that NMSC was found predominantly in 53% of all observed cancer manifestations [52]. Moreover, NMSC was found to be the leading cause for tumor-associated mortality in kidney transplanted patients in the Australian and New Zealand based population [53]. In general, patients under immunosuppression are reported to suffer from a more aggressive course of disease, coming along with higher rates of malignant infiltration, such as perineural spreading, high risk of recurrence (up to 13,4%), metastasis (5-8%) and higher rates of mortality [49, 54-57]. Moreover, NMSC manifests multifocal and eruptive. Similarly, patients with chronic lymphatic leukemia have a 5- to 8.6-fold higher risk to suffer from cSCC, compared to
immunocompetent patients [58-60]. In this patient population, cSCC occurs with significantly higher rates of poor outcome such as metastasis, recurrence, or tumor related death [61-64].

For the reasons named, STORs profit from close therapy monitoring and disease management to control and prevent development of NMSC in the first place, or to provide mechanism of control for secondary and tertiary prophylaxis. In terms of management of immunosuppressive medication in STORs, mammalian target of rapamycin (mTOR) inhibitors should be implemented as the preferred immunosuppressive medication of choice [65]. Unlike immunosuppressive drugs such as cyclosporine, azathioprin or high dose corticosteroids, mTOR inhibitors prevent multiple mechanisms involved in carcinogenesis, such as angiogenesis, cell expansion and cell survival [66-68]. Moreover, mTOR inhibitors block the HPV related induction of mTOR pathway and therefore act as antivirals, by inhibiting growth of HPV-16-immortalised keratinocytes [66-69]. Other strategies should include, early treatment of premalignant and malignant lesions, by non-invasive and invasive means, but should also comprise prophylactic approaches, such as photoprotection, reduction of immunosuppression, use of mTOR and chemoprophylaxis. Retinoids, such as acitretin, a synthetic vitamin A substitute, seem to provide a favorable approach for prophylaxis of NMSC in this population, due to their positive effects on cell cycle control [70]. These include stimulation of cellular differentiation and induction of apoptosis, beside immunomodulatory aspects, cellular proliferation, and keratinization [70]. Another favorable attribute of acitretin is the inhibition of ornithine decarboxylase, the initial rate-limiting enzyme in the polyamine biosynthetic pathway, being responsible for elevated levels of polyamines found in highly proliferating tumor cells [70, 71]. Several studies report a reduction of cSCC incidence in cohorts under chemoprophylaxis with acitretin for at least three to five years and report ‘rebound effect’ with rapid increases in cSCC incidence after discontinuation of acitretin, but beneficial long-term effects are not fully studied to this date [72-75]. Still the named favorable aspects of acitretin find recognition in a consensus-based recommendation on the prevention of cSCC from the year 2021, advocating for the beneficial use of acitretin as chemoprophylaxis in STORs, who either develop a single high-risk cutaneous cSCC after multiple low-risk cSCCs, or more than ten low-risk cSCCs per year [76].

### Challenges in AK Treatment – Field Cancerization

Patients suffering from actinic FC are at the highest risk to develop multiple NMSC during their lifetime usually being associated with poor outcomes [77]. The concept of FC was first described in 1953 by Slaughter et al. [78], examining more than 700 tissue samples of oropharyngeal carcinoma. In a predominant number of the reported cases, the unsuspicuous appearing surrounding tissue harbored pathologically relevant cell atypia, leading to a substantial number of second tumor manifestation in the subsequent [78]. On cellular level, FC correlates with the clonal expansion of a mutant cell clone, spreading in tumor adjacent tissue and being susceptible for malignant transformation [79]. While FC was found in several tumor types, such as head and neck, breast and cervix, skin tissue is especially vulnerable to develop cell atypia, due to a chronic UVR stimulus on sun-exposed body areas such as scalp, forearms, and dorsum of the hand [79]. Still, there is no standardized definition of FC implemented to this date. Vague definition describes FC as an anatomical area suffering from AK or skin adjacent to AK showing at least two clinical markers of chronic actinic sun exposure, such as telangiectasia, skin atrophy, pigmentation disorder or hyperkeratosis [80]. It remains unclear, whether FC can be assumed without clinical appearance of AK, or not [80]. While, AK and FC are currently not considered distinct diagnosis from each other, presence of FC is associated with development of a poor disease-related outcome compared to presence of several discrete AK [81]. The lack of understanding FC correctly and treating FC and multiple AK equally, may lead to undertreatment of FC patients...
and poor outcomes eventually [81]. Studies found that the risk for development of cSCC correlates with the number of AK present. Even immunocompetent patients have a 5.7-fold increased risk for cSCC manifestation, when more than 15 Aks are present on the head and neck area [82]. Willenbrink et al. [81] presume, that regarding FC, patients face an even higher risk, due to the confluent nature of AK and the wide field of premalignant atypical keratinocytes, prone to malignant transformation.

Risk factors for developing FC are similar to those of AK and cSCC and can be narrowed down to duration of UVR exposure, age, fair skin type, male sex and immunosuppression [81]. For age, a 4-fold increased risk of AK development is reported for the age group of 61 to 70 year of age. The same increased risk is reported for male sex in the German population [83, 84]. In males the prevalence of extensive sun damage (minimum of ten AK) is three times more present compared to females [85]. In terms of body site, the single strongest risk factor for development of ten AK is reported to be scalp baldness in males [85]. Willenbrink et al. [81] experienced the highest risk for the occurrence of FC in immunosuppressed patients, such as STORs. This assumption is backed by evidence reporting a prevalence of 17% of FC in STOR cohorts [81]. As patients suffering from FC may develop cSCC more likely, the development of multiple cSCC during a patient’s lifetime is clearly associated with a significant worsening of disease burden in terms of aggressive disease progress. It is reported that patients suffering from more than ten cSCC have a 3.8-4.2 times increased risk for nodal metastasis and diseases recurrence, compared to patients with a single cSCC [77].

Prevention of AK and cSCC

For the US American population, trends regarding the protective behavior of sun light exposure seem to have increased among adults, throughout 2010 to 2020 [86]. McKenzie et al. [86] reported that sun-protective behaviors significantly improved through the reported time period, not only for the use of sunscreen but also in regard to seeking shade, avoiding sun and sun burns, and by wearing physical UV-light protection, such as long-sleeved shirts and hats.

In terms of primary prevention of skin cancer, the focus lies on educational programs, risk assessment models for individuals, the use of sunscreen and legislative regulation [87]. As 80-90% of skin cancer seems to be associated with exposure to UV-radiation, sun protective behavior is promoted and appears to be essential [88, 89]. Educational programs seem to account for the most widely studied primary prevention strategy [87]. Those programs seem to be especially effective in terms of awareness and knowledge of sun protective behavior, when targeting minors in primary and secondary schools, compared to adults [90, 91]. The use of educational images is reported to be effective in terms of sun protective behavior, knowledge and for self-examination in terms of melanoma [92-94]. Other strategies, such as using reminders via text messages and email to strengthen sun protective behavior, lack evidence and studies report controversial results. While Finch et al. [95] found that electronic text reminders lead to a reduction in sunburns, the data was not unambiguous to interpret as the number of sunburns was self-reported. Other studies do not report any evidence for text message reminders [96]. Beside schools, the occupational setting appears to be a critical targeting point for the implementation of skin cancer awareness and protection, as behavior towards UV-light exposures differs tremendously between outdoor workers [97]. Education on skin cancer prevention at the workplace is reported to be effective in terms of sun protective behavior, using sunscreen to reduce the number of sunburns eventually [98, 99].

Although studies report imprecise results between the use of sunscreen and the risk of developing melanoma, Waldman et al.[100] report the beneficial use of sunscreen to reduce the manifestation of AK, SCC and less clear also for BCC. The use of indoor tanning modalities is rightly criticized to promote skin cancer development. A large meta-analysis conducted by Wehner et al. [101], evaluating more
than 9000 cases of skin cancer, found the population attributable risk fraction for cSCC to be 8.2% and 3.7% for BCC in the US population. These numbers are estimated to account for more than 170,000 annual cases of NMSC related to indoor tanning in the US alone [101]. The presented numbers were published in the year 2012. Since then, only a handful of countries have implemented policies to fully ban tanning beds, such as Australia and Brazil [102]. In Austria, Belgium, France, Germany, Portugal, Spain, and the United Kingdom, only bans for minors under the age of 18 exist [102]. Data from the US shows that, while indoor tanning prevalence decreased significantly among all US adults from 2007 to 2018 (10% vs. 4%), frequent indoor tanning was still common in 2018 with nearly 25% of respondents reporting the use of indoor tanning 25 times or more per year [103].

Multiple studies have been conducted, investigating this underlying pathway in vitro. Still clinical studies additionally suggest the beneficial use of niacinamide in skin cancer prevention [106, 109]. Park et al. [104] were able to show by microarray studies on in vivo irradiated human skin, that UV-induced cellular ATP loss was reduced by substitution of niacinamide but did not affect ROS formation or keratinocyte apoptosis. Chen et al. [110] were able to show in a double-blinded, randomized, controlled trial, including 386 immunocompetent Australians with a history of least two NMSCs, that the intake of 500 mg of niacinamide twice daily, significantly lowered the incidence of NMSC by 23% versus the placebo. For cSCC, a reduction by 30% was observed [110]. Interestingly also the number of AK lesions was significantly lower by 13% after 12 months of follow-up [110]. In a recent systemic review conducted by Mainville et al. [111] five trials were identified, reporting a significant reduction for cSCC and BCC for patients with untreated AK and previous manifestation of BCC and cSCC [110, 112-115].

For AK, the current knowledge remains heterogeneous. Mainville et al. [111] could not identify a beneficial use for the prevention of AK evaluating three trials [110, 112, 113]. Although, the level of evidence for AK was estimated very low because of study inconsistency and imprecision [111]. Based on these findings, recent recommendations published in the Journal of the American Academy of Dermatology in the years 2018 and 2020, emphasize the beneficial use of oral niacinamide 500 mg twice daily in patients with a field cancerization or more than one previous manifestation of SCC [116, 117]. For STORs the use of niacinamide did not provide any beneficial use over the placebo [118]. In this vulnerable group, the use of acitretin is recommended for skin cancer prevention [76], see above. As most of the studies present results on tertiary prophylaxis of skin cancer, further studies should focus on chemoprevention of AK [111]. The intake of niacinamide appears to be safe and well tolerated, but for high

Oral Drugs for Skin Cancer Prevention

Beside topical ointment, several systemic agents have been investigated for its use and effectiveness in the secondary prevention of AK development. Chemoprophylaxis of AK can be implemented to prevent the occurrence or reoccurrence of new AK lesions.

Niacinamide

Niacinamide is the water-soluble derivate of vitamin B3, a key-coenzyme in the generation of ADP on cellular level, by its role for the formation of NAD+ complex. Atypical keratinocytes in AK are reported to produce significant lower levels of ADP, which is physiologically required as a source for intracellular energy production in terms of providing functioning DNA strand repair mechanism [104]. This loss of mechanism is reported to reduce the effectiveness of DNA repair and promotes development of cSCC [105, 106]. Niacinamide also reduces UV radiation induced skin inflammation by significant downregulation of IL-6, IL-10, MCP-1 and TNF-α mRNA expression, in vitro [107]. Additionally, oral and topical Nicotinamide have shown to be immune protective against UVBR and UVAR [108, 109].
doses exceeding 3 g/d reversible hepatotoxicity is reported [110, 116, 119, 120].

The Role of Vitamin D in AK and its Possible Preventive use

The role of vitamin D in the development of NMSC is discussed controversially in the available literature and is not fully understood to date. Yet, vitamin D is attributed with skin cancer protective abilities. Vitamin D contributes to retain cell homeostasis, by mediating and promoting apoptosis and antiproliferative effects in melanocytes and keratinocytes in vitro [121]. Moreover, vitamin D acts protective in sun damaged skin, by reducing cyclobutene pyrimidine dimers and by inducing the formation of antioxidants such as metallothionein in vitro [122-125]. Vitamin D a true prohormone comes in two major configurations, namely cholecalciferol (D₃) and ergocalciferol (D₂). Both forms can be substituted by dietary intake while the larger amounts of vitamin D₃ are endogenously produced by photochemical modification of 7-dehydrocholesterol in the skin upon UVBR stimulus [121].

Vitamin D production in the skin largely depends on the distribution of melanin, as melanin absorbs and scatters UVBR, leading to effective conversion of 7-dehydrocholesterol into vitamin D derivates [126]. The amount of endogenous synthesized vitamin D₃ also largely depends on several independent aspects related to sun exposure, such as cumulative exposure time, amount of sun-exposed skin, age, skin phototype and body mass index [127]. While vitamin D is formed by UVBR stimulus in the skin, the dilemma in understanding the definite role of vitamin D in prevention and development of skin cancer lies in the complex interplay of UVBR as a key driver of skin cancer development, but also being the activator of vitamin D synthesis. Different hypothesis on vitamin D levels related to skin type exist. Assumptions are made that individuals with the fairest phototypes suffer from the lowest vitamin D levels due to minimum sun exposure, given their photosensitivity [128]. The hypothesis for skin pigmentation evolution proposes that progressive skin depigmentation was critical for our ancestors to ensure sufficient vitamin D production through UVBR, when migrating to areas with reduced sunlight [129].

Although fair-skinned individuals seem to produce higher levels of vitamin D, they are susceptible to skin cancer due to lower tanning ability and greater sunburn response [130, 131]. However, Bonilla et al.[126] found that fairer-skinned children with higher pigmentation score values had increased vitamin D levels, while applying more sun protective measures. They concluded that sun protection does not eradicate the positive effect on vitamin D production in less pigmented skin [126].

The challenge seems to identify the ideal balance between generating enough vitamin D while limiting skin damage caused by UVBR, but to this date no data exists identifying the optimal dose of daily vitamin D intake, to reduce skin cancer eventually. Inconsistent findings exist regarding the amount of sun exposure and vitamin D supplementation for skin cancer prevention [132]. Yet, several studies report, 25-hydroxyvitamin D (25(OH)D), the circulating form of vitamin D, being associated with skin cancer development risk and therefore may function as a biomarker to reflect long-term sun exposure and predict the risk of NMSC also in AK patients [133-138].

Current knowledge on the chemoprotective role of vitamin D remains to be discussed. Sutedja et al. evaluated a total of 18 studies on this topic, including 11 in vivo studies, with five of them being either randomized controlled trials or interventional studies [139]. Evaluating the study of Passarelli et al., the oral intake of 1000 IU/day of vitamin D alone or in combination with calcium was reported to be protective for cSCC development [139, 140]. Rosenberg et al. evaluated the efficacy of topical application of 5-fluorouracil (5-FU) in combination with calcipotriol 0.005% (low-calcemic vitamin D analog) over a course of 4 days, implemented as an immunotherapy for AK on the scalp and face skin to prevent cSCC development [141]. Over the course of three years, 5-FU + calcipotriol were effective in reducing the incidence of cSCC significantly,
compared to only 5-FU, while for BCC no difference was reported [141]. Rosenberg et al. also found that the treated skin harbored significantly more tissue-resident memory T-cells compared to the control (5-FU) [141]. In analogy, Cunningham et al. demonstrated that application of 5-FU combined with calcipotriol led to a robust and sustainable CD4+ T-cell response against atypical premalignant keratinocytes in AK, induced by upregulation of thymic stromal lymphopoietin cytokine in keratinocytes by calcipotriol, which is also reported for treatment of psoriatic lesions [142-144]. A similar positive effect was found for the oral pretreatment of AK using vitamin D3 10,000 IU daily for 5 or 14 days, followed by blue light photodynamic therapy (30 minutes; 20 J/cm²) [145]. In the control group with no vitamin D3 supplementation, individuals with 25(OH)D deficiency (< 31 ng/dL) had a clearance rate of 40.9% ± 42%, while in patients with normal 25(OH)D levels a clearance was found in 62.6% ± 14.2% of the cases. For high-dose vitamin D3 supplementation a significantly improved lesion clearance was found in 72.5% ± 13.6% cases [145].

Discussion – Management and Monitoring of Actinic Keratosis and Prevention of cSCC

Further research is needed to fully understand the effect of AK treatment on cSCC risk and outcomes of cSCC. A longitudinal cohort study conducted by Madani et al. [146] evaluated the risk of cSCC development for more than 200,000 AK patients vs. a control without AK for a period of ten years (2009-2020). After ten years, the cumulative incidence of cSCC reached 17.1% for AK patients vs. 5.7% for the control, with the number of AK being associated with the incidence of cSCC [146]. Interestingly, individuals being diagnosed with AK under 49 years of age, were nearly 7 times more likely to be diagnosed with cSCC than those without AK [146]. Therefore, early detection of AK may be critical, but the role of screenings for NMSC is not well understood to date. While for the detection of melanoma, schemes such as the “ABCD” rule exist and validation data in terms of sensitivity and specificity is available, the detection rate of NMSC in skin cancer screenings is not well documented [147, 148]. Often cancer registries even lack reliable epidemiologic data, because NMSC is common and usually curable and is therefore not monitored precisely [147]. A holistic review conducted by Henrikson et al. [149] found that routine clinician skin examination in terms of skin cancer screening, is not associated with higher detection rates of NMSC, skin cancer precursor lesions and melanoma compared to lesion-directed examination. Moreover, the included studies did not report NMSC mortality by stage at detection [149].

In terms of harms related to skin cancer screenings, little evidence exists for negative effects on psychological harms or cosmetic concerns. In a German study population 7% of taken shave biopsies were rated with poor cosmetic outcome at six months of follow-up and after a period of eight months after skin cancer examination, the patient’s wellbeing in terms of anxiety disorders and depression did not differ significantly from the normal range [149]. The insufficient evidence for screening reinforces the need for primary prevention of NMSC and monitoring of AK appears to be substantial in the follow-up of AK.

Especially, patients suffering from FC and/ or immunosuppression are vulnerable populations benefiting from close skin cancer screening and implementation of aggressive and early adequate therapy [81, 116]. For these patients, acitretin chemoprophylaxis should be implemented [76]. But also, when AK presents therapy refractory and additional treatment is required the risk for cSCC development increases dramatically up to 33.5% for a 4-year risk assessment [150]. Although, when AK is treated sufficiently, the risk of cSCC occurrence within the field of treatment is 2.2 to 5.8% over a course of four years, depending on the topical ointment applied [150]. These numbers imply that patients may benefit from a close follow-up for close AK lesion monitoring. This assumption may even be validated as studies suggest that the appliance of topical therapy often lacks adequate implementation by patients, as they are often not well informed about the specific
topical intervention regime [151]. For a cross-sectional cohort of 113 patients, Koch et al. [151] found a concerning non-adherence rate of 46.9% to the implemented topical AK treatment. Only 30.9% of the patients used the administered therapy in accordance with the product characteristics [151]. Patients, who did not adhere with the medical product guidelines were significantly less informed about the product and adjusted application timeframe and therapy frequency independently [151]. Recent literature suggests that some patient groups suffering from AK are not well informed about the condition of AK. Elderly patients (over 77 years of age) and those suffering from more than seven lesions were identified at high risk for not seeking treatment due to intrinsic and extrinsic motivation deficits [152]. But also, patients who never had AK related treatment and those suffering from only one to three AK lesions are more likely to expect a one-time treatment, indicating that they may not yet be aware that AK is considered a chronic condition, which usually requires multiple treatment modalities and lifelong surveillance [152].

Regularly patient visits may be a useful opportunity to inform patients about AK and to reinforce the patients’ therapy adherence as one of the main goals in the patient’s motivation for AK treatment is the prevention of malignant transformation [152]. Moreover, patients are strengthened in their will to treat AK, when it is recommended by the physician [152].

However, monitoring of FC and AK only by measuring lesion counts can be cumbersome and studies have shown that this approach is imprecise and impracticable, due to the sometimes-difficult identification of subclinical AK and confluent transition of AK [153]. Tools such as the actinic keratosis field assessment scale (AK-FAS) or the actinic keratosis area and severity index (AKASI) have in common to characterize and objectivize the extent of AK or FC. The AKASI evaluates the percentage of the head area affected by AK and graded by the severities of distribution, erythema and thickness and higher scores are associated with the incidence of SCC according to Schmitz et al. [154]. Another tool for the evaluation of sun damaged skin regarding the extent of AK and FC located at the face and scalp area is the AK-FAS scale [155]. AK-FAS takes total affected skin area, hyperkeratosis and aspects of sun damage into account, but was also evaluated from standardized clinical photographs so far and was not tested in the clinical setting [155]. Willenbrink et al. [81] concluded that both grading systems (AKASI and AK-FAS) are partly impractical in the clinical setting, because the assessment is time-consuming and laborious. Another disadvantage of both scoring systems may be the negligence of in situ cSCC and invasive cSCC within the sun damaged area [81]. Therefore Willenbrink et al. [81] assumed that those assessment tools are prone to fail for risk stratification towards SCC progression, as both tools were not validated in large prospective study cohorts.

When AK is present on the skin, non-invasive imaging techniques may provide a substantial benefit for risk assessment and monitoring of AK. Using skin imaging techniques allows non-invasive assessment of independent risk factors in AK such as PRO score and atypia score. Since the introduction of line-field confocal optical coherence tomography (LC-OCT) to the field of dermatology, numerous studies investigated its use in clinical dermatology to visualize benign and malignant skin lesions. LC-OCT images were found to strongly correlate with conventional histopathological images [156]. Further, Ruini et al. found that non-invasive real-time evaluation of the dermo-epidermal junction (DEJ) and subsequent PRO score quantification is possible, using LC-OCT [157, 158]. The non-invasive diagnosis of AK, using LC-OCT, can be made in analogy to AK features in histological sections with a focus on keratinocyte morphology and epidermis architecture (Figure 1) [1]. By the definition of AK, being an intraepidermal neoplasia, the integrity of the DEJ must be contained throughout the whole suspicious lesion under surveillance. The diagnosis of AK can be made by visualization of hyper- and parakeratosis, as well as epidermal thickening and the notion of atypical, basal and suprabasal keratinocytes of heterogenous size. Also, basal proliferation may be
features such as ulceration and keratin plugs may underline the diagnosis of sSCC [158-160].

Beside using non-invasive imaging for identifying AK, AI integration tools are able to characterize AK by objectifiable features, such as PRO score and atypia to provide a grading to AK [Figure 2].

### Figure 1. Diagnosis of AK using LC-OCT.

AK lesion on the forehead of a patient. Stratum corneum (SC) presents hyper-/parakeratosis (white arrows), while the epidermis harbors keratinocytes which are heterogeneous in size (white circle). The epidermis shows beginning basal proliferation (white asterisk), so PRO II can be assumed. In the papillary dermis dilated vessels are present. Based on the named features the clinician can be guided in making the diagnosis of AK using LC-OCT. (LC-OCT, deepLive™, DAMAE Medical, Paris, France; image size: 1.2 x 0.5 mm², lateral and axial resolution: 1.1 x 1.3 µm).

### Figure 2. AI-generated evaluation of AK features in LC-OCT.

AK lesion on the forehead of a patient. White arrows show the surface of stratum corneum (SC) and the viable epidermis (VE) detected by the skin segmentation algorithm. The red arrow shows the detected intact DEJ. Epidermal protrusions are found and indicated by the white circle. Keratinocytes colored in red show high atypia within the epidermis. The following parameters were detected by the implemented algorithms: SC thickness: 24.2 µm, VE thickness: 108.7 µm, DEJ undulation: 33%, KN atypia: 0.61. From this AK lesion, prevalence of atypia in 2/3 of the epidermal layer and PRO II can be assumed (SC= stratum corneum, VE= viable epidermis, KN= keratinocyte nuclei, DEJ= dermo-epidermal junction; LC-OCT, deepLive™, DAMAE Medical, Paris, France).
and an inadequate therapy response was therefore assumed. By the means of non-invasive imaging this lesion was identified as therapy non-responder, while clinically therapy associated inflammation and lesion clearing was assumed over the follow-up to some extent. These findings highlight the additional valuable input of non-invasive imaging as it allows to underline the clinical assumption of therapy refractory by objective parameters such as presence of atypia and therefore should be used as an automated tool for therapy monitoring of AK, as suggested by Fishman et al. [163].

The treatment and monitoring of AK remains a laborious task. The primary goal needs to be prevention or at least the early detection of cSCC. A follow-up for AK may be helpful to strengthen patient adherence to therapy and LC-OCT may add value to a non-invasive follow-up for AK by visualization of epidermal recovery processes and the evaluation of its objective parameters such as SC/epidermal thickness, DEJ undulation (PRO score) and keratinocyte atypia. This allows a more comprehensive follow-up of AK rather than considering clinical lesion aspects only. Moreover, lesions non-responding to the implemented therapy can be identified and can subsequently be referred to an adequate treatment regime early on.

**Short Summary**

- AK are considered a chronic skin disease and reflect long-term exposure to UV radiation, coming with an individual susceptibility for skin cancer manifestation.
- Risk factors in AK for development of cSCC are not fully understood, but studies suggest that atypia and basal proliferation in AK play a pivotal role for malignant transformation.
- Skin imaging can help to facilitate individual risk assessment of AK lesions by non-invasive visualization of atypia and basal proliferation.
- Guidelines suggest treating every single AK lesion independently from severity of clinical appearance. Patients with AK may benefit from a close follow-up to strengthen therapy adherence.
• Patients with AK and field cancerization and/or immunosuppression are highly vulnerable subgroups who benefit from close skin cancer screening, early adequate treatment, and chemoprevention.

• Skin cancer prevention is substantial. Primary prevention should include chemical and physical UV-light protection and avoidance of indoor tanning. Secondary prevention is essential in high-risk populations, such as fair skin type elderly men and STORs. Tertiary prevention should comprise adequate treatment strategies to prevent therapy resistance, reoccurrence and cSCC development, especially when field cancerization and immunosuppression are present.

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