Clinical Management of Actinic Keratosis: Review and Update

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ABSTRACT

Actinic keratosis is commonly seen in dermatology clinics. Age and chronic sun exposure are the essential risk factors for its pathogenesis. It is regarded as a premalignant lesion; hence, aggressive treatment is warranted. Abundant research has been published about overall management, however, extensive knowledge about actinic keratosis prevention, the cost, safety profile, and mechanisms of the existing therapeutics are pivotal in optimal clinical care. In this review article, we hereby present several commonly used approaches in office settings and the current guidelines. Finally, we will discuss the limitations of the available clinical evidence.

INTRODUCTION

Actinic keratosis (AK), also known as senile keratosis or solar keratosis, was first described by Dubreuilh in 1826.¹ Later in 1958, Pinkus renamed this lesion as actinic keratoses.¹ ² AK literally means thickened, scaly growth caused by electromagnetic radiation.³ It commonly presents as ill-bordered macules, papules or plaques, maybe covered with dry scales or showing varying degree of hyperkeratosis. The color of AK ranges from pink to erythematous to brownish, in cases of pigmented AK. AK frequently locates at the sun exposed area, and sometimes, they are better pinpointed by palpation than visualization.⁴ In majority of the cases, AK are asymptomatic albeit some patients may report burning or pruritus sensation.¹ ⁵ The key risk factor for developing AK is cumulative sun exposure.⁶ An epidemiology study in Turkey with 54,786 patients from outpatient dermatology clinic found that the AK prevalence was 4.61% for patients between 60 and 69 years old, 9.38% for patients between 70 and 79 years old, and 14.57% for patients ≥80 years old. AK prevalence was 2.50% across all age groups.⁵ The author concluded that AK prevalence was higher in patients >60 years of age and most commonly in patients >80 years of age. Furthermore, AK was more prevalent in males and in patients with Fitzpatrick skin types 2 and 3.⁵ Another epidemiology study in Netherlands examined various risk factors and revealed that male sex, the age of 70 years or older, Glogau scale 3 and 4, and the tendency to develop sunburn were significantly associated with the development AK.²

On dermoscopic examination, non-pigmented facial AKs typically manifests as a “strawberry pattern” which entails an erythematous vessel pseudo network, prominent follicular openings, and a surrounding white halo.⁴ A few histological and clinical subtypes of AK were described in the literature, for instance, hypertrophic,
atrophic, AK with cutaneous horn, pigmented, actinic cheilitis, acantholytic, and hyperplastic. A common histological feature is atypical keratinocytic proliferation confined in the epidermis. It is regarded as the spectrum along the continuum to squamous cell carcinoma (SCC). Although the rate for individual AK to progress into SCC is low, but 82.4% of SCCs were developed from AK directly or from tissue that is adjacent to AK lesions. AK is principally caused by sun exposure, or ultraviolet B (UV-B) radiation (wavelength 290–320 nanometer). Particularly, UV-B induces the formation of thymine dimer in DNA structures which leads to mutations in the telomerase gene and p53 gene, the tumor suppressor gene. Telomerase is the key enzyme to regulate cellular death. Increase in telomerase activity delays the programmed cell death and keeps cells immortal or keep proliferating unstoppably. Neoplastic keratinocytes, which are seen in over 90% of invasive SCC, are also frequently present in AKs. P53 gene is located on chromosome 17p13 and normally arrest the cell cycle and allow the repair of damaged DNA. Dysregulation of p53 pathways results in the uncontrolled growth and proliferation of damaged keratinocytes, and potentially neoplastic cells. This is suggested to be an early phase in SCC carcinogenesis, so that cancer can start to prosper and progress.

A prospective large population study in California followed patients with and without AK (served as the control group) for 10 years and found the annual risk of acquiring SCC for AK group was 1.92% compared to 0.83% for the control group. At the final 10 years end of study time point, the incidence of SCC was 17.1% in AK group while the incidence of SCC was 5.7% among control patients. With that being said, the early detection and treatment, patient education, and sun protection are critical for the overall management as well as efforts to decrease the healthcare burden. In this article, we herein present some approaches to prevent and manage AK based on the available literature and our own clinical experience.

**PREVENTION**

Inarguably, sun protection is the most paramount approach to prevent not only AK but skin cancers as well. This conclusion was well established by several clinical trials. The American Academy of Dermatology (AAD) website recommends patients avoid tanning beds and protect themselves by applying broad spectrum sunscreen daily with a SPF (sun protection factor) of 30 or higher. It also emphasizes the cruciality of routine self-body skin check and dermatologist visits.

Studies have further investigated topical chemoprevention for AK. A randomized, placebo-controlled trial with 283 individuals showed that topical application of 5-fluorouracil at the face and ears resulted 41% fewer new lesions at 24 months compared to placebo group. A similar study was reported with over 900 participants. Patients were instructed to apply either 5% fluorouracil cream or placebo on the face or ears twice daily for up to 4 weeks. The treatment group had fewer non-hypertrophic AK lesions at 6-month and 42-month follow-up visits. Reciprocally, the number of hypertrophic AK didn’t differ significantly in both groups at 42-month. A pooled analysis of two trials compared long term efficacy of imiquimod 5% cream and diclofenac 3% gel. The investigators observed superior result with imiquimod, 5% cream in multiple parameters, less percentage of histological changes to grade III AK or even SCC, greater time for neoplastic changes to occur, less proportion with malignant transformation into invasive SCC, and lower AK recurrence rate.
AK is often recognized as a field disease rather than a single clinically apparent lesion. The theory, field cancerization, contemplates that the skin proximal to AK lesions also carries a higher risk of malignancy due to shared chronic solar radiation. Therefore, field treatments are commonly applied. It not only tackles the clinically perceptible lesions, but also the subclinical ones that may potentially progress into AK or even SCC. Cryotherapy is commonly used when there are only a handful of visible or palpable lesions. Field treatment targets a certain anatomical region, including topical imiquimod, 5-fluorouracil (5FU), and photodynamic therapy (PDT). The commonly used monotherapies are listed in Table 1. The treatment regimen for United States Food and Drug Administration (FDA) approved field therapies were listed in Figure 1.

Single Lesion

**Liquid Nitrogen Cryotherapy**

Cryotherapy, the mainstay treatment for AK, is fast, inexpensive and can be easily done in the office setting. Either direct spray or probe may be used to deliver liquid nitrogen. The freezing time ranges from 5 to 10 seconds, and the “ice ball” should extend at least 1 millimeter beyond the clinical margin of AK. Depending on the degree of hyperkeratosis, multiple freeze-thaw cycles may be required. Cryotherapy causes local tissue damage and heals by secondary intention. With that being said, cryotherapy often leads to transient patient discomfort. Other side effects may be seen in certain individuals, for instance, hypopigmentation, scaring, and prolong wound healing, thus, patient education and wound care instructions need to be provided for desired clinical outcomes.

**Field Treatment**

*Imiquimod*

Imiquimod is an immune response modifier that belongs to the imidazoquinolines drug class and upregulates several key cytokines. It binds to the Toll-like receptor 7 and releases interferon-alpha, which leads to activation of the T helper type 1 (Th1) response. It has both anti-viral and anti-tumoral effects. In sum, imiquimod comes with three different concentrations and is only approved for immunocompetent individuals. The efficacy and the safety profile of imiquimod was well illustrated in several randomized Phase III clinical trials and meta-analyses. The most common side effects were treatment site reactions, such as erythema, ulceration, blistering, erosion, edema and influenza like symptoms. Many of the side effects were well tolerated and short-lived. Interestingly, case study has tried to apply 5% cream imiquimod on human skin to an area over 300 square centimeters (cm²), suggesting a more efficient use of this medication.

*Tirbanibulin*

Tirbanibulin works by inhibiting tubulin polymerization and upregulating p53 expression. It also arrests rapidly dividing cells at the interphase Gap 2 and mitosis, subsequently induces apoptosis. In 2020, FDA licensed topical tirbanibulin 1% ointment as a field treatment of AK to up 25 cm² contiguous area of the face or scalp. The clinical data of tirbanibulin was found on two...
Figure 1. FDA-approved, topical field therapies and total applications
**Table 1.** Commonly used monotherapies for single AK or field treatment (5-FU: 5 fluorouracil; ALA: 5-aminolevulinic acid; FDA: Food and Drug Administration; MOA: mechanism of action, PDT: photodynamic therapy; RCT: randomized clinical trials, SE: side effects)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MOA</th>
<th>Side Effects</th>
<th>Clinical evidence</th>
<th>FDA indication</th>
<th>Treatment regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single lesion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Liquid Nitrogen Cryotherapy</td>
<td>Damage the tissue and re-epithelialize</td>
<td>Patient discomfort, hypopigmentation, scarring, and prolong wound healing.</td>
<td>Few meta-analysis and systematic review</td>
<td>Not available information</td>
<td>Freeze the clinically visible AK for 5-10 seconds per cycle. and the “ice ball” should extend at least 1 millimeter beyond the margin of AK. Multiple freeze-thaw cycles may be required for thick lesions. Wound care instruction will be provided to the patient.</td>
</tr>
<tr>
<td>Field treatment</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imiquimod 2.5% cream</td>
<td>Upregulate immune response</td>
<td>Treatment site reactions (erythema, ulceration, pruritus, blistering, erosion, edema), influenza like symptoms</td>
<td>several Phase III RCTs and meta-analysis.</td>
<td>AK on the face or scalp in immunocompetent adults</td>
<td>Once per day overnight for about 8 hours X 2 weeks -&gt; 2 weeks of treatment free period -&gt; 2 weeks of treatment.</td>
</tr>
<tr>
<td>Imiquimod 3.75% cream</td>
<td></td>
<td></td>
<td></td>
<td>AK on the face or scalp in immunocompetent adults</td>
<td>Once per day overnight for about 8 hours X 2 weeks -&gt; 2 weeks of treatment free period -&gt; 2 weeks of treatment.</td>
</tr>
<tr>
<td>Imiquimod 5% cream</td>
<td></td>
<td></td>
<td></td>
<td>Non-hyperkeratotic, non-hypertrophic AK on the face or scalp in immunocompetent adults</td>
<td>One application/day, 2-times/week X 16 weeks, maximum area of 25 cm² per application</td>
</tr>
<tr>
<td>5-FU (varying concentration from 0.5% to 5%) cream or solution</td>
<td>Inhibiting DNA and RNA replication and increase expression of p53</td>
<td>Treatment site reactions</td>
<td>several Phase III RCTs and meta-analysis.</td>
<td>Topical treatment of multiple AK</td>
<td>Apply cream or solution twice daily for 2-4 weeks.</td>
</tr>
<tr>
<td>Conventional PDT (10% 5-aminolevulinic acid/methyl aminolevulinate + red light/blue light)</td>
<td>Photosensitizer is activated by light source and generates reactive oxygen species (ROS), which causes selective cellular damage</td>
<td>Treatment site reactions, itchy, edema, post-inflammatory pigment changes.</td>
<td>Multiple RCTs</td>
<td>10% ALA gel + red light: single or field AK on the scalp and face</td>
<td>Photosensitizer application -&gt; incubation time of several hours -&gt; exposure to light source. Patients are educated for sun protection for several days after PDT.</td>
</tr>
<tr>
<td>BF-200 ALA PDT</td>
<td>Stabilize ALA and increase epidermal penetration.</td>
<td></td>
<td>Multiple Phase III RCTs</td>
<td>Europe: facial and non-facial AK United States: mild-moderate AK on face/scalp</td>
<td></td>
</tr>
<tr>
<td>Day Light PDT (DL-PDT)</td>
<td>Same as conventional PDT</td>
<td>Less pain and inflammation than conventional PDT</td>
<td>Multiple RCTs</td>
<td>Not available</td>
<td>Photosensitizer and sunscreen without physical</td>
</tr>
</tbody>
</table>
blocker were applied topically—outdoor for 2 hours—stay indoor for the rest of the day.

<table>
<thead>
<tr>
<th>Topical diclofenac 3% in 2.5% hyaluronic acid (DFC/HA)</th>
<th>Inhibits the cyclooxygenase-1 and cyclooxygenase-2 and decreases arachidonic acid (AA) byproduct</th>
<th>Pruritus, contact dermatitis, dry skin. Milder inflammatory response than 5-FU.</th>
<th>Several Phase III RCTs and meta-analysis</th>
<th>AK</th>
<th>Topically apply twice/day for 60-90 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingenol Mebutate (IMB) (0.015% gel and 0.05% gel)</td>
<td>Disruption of plasma membrane and mitochondria. It also triggers cytotoxic reaction</td>
<td>Pain, hypopigmentation.</td>
<td>Several Phase III RCTs</td>
<td>United States: AK</td>
<td>0.015% gel: once daily 3 days on face or scalp 0.05% gel: once daily for 2 days on the truck or extremities. Treatment area should be less or equal to 25 cm²</td>
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Two post-hoc analyses of the two Phase III tirbanibulin trials were reported. One compiled the LSR score from baseline to day 57 in 174 patients in the treatment group who achieved CC. 26.5% of patients (46 out of 174) had LSR ≤3 and 70.2% patients had LSR ≤5. The conclusion further supported that tirbanibulin is well tolerated by study patients. Another one examined several factors and found AK on the face and fewer lesions at baseline were indicator for treatment success whereas Fitzpatrick skin type, body-mass index (BMI), and prior AK therapies were not associated to desired clinical outcome. Overall, the advantage of tirbanibulin is relatively short treatment course and the ease to apply the medication at home, and high patient compliance, however, the price may be a concern.

**5-Fluorouracil (5-FU)**

Systemic fluorouracil has been used to cure various malignancies for decades. Its underlying mechanism involves inhibiting...
thymidylate synthetase and other key steps in DNA and RNA replication, as well as increasing the expression of p53. Capecitabine is an oral prodrug converted to fluorouracil via a 3-step enzymatic process, ultimately by thymidine phosphorylase, an enzyme often overexpressed in cancerous cells. 15 high-risk solid organ transplant recipients (≥2 new non-melanoma skin cancers in the past 6 months or ≥10 new AKs in the past 12 months) received low dose oral capecitabine (1g/m² twice daily for 14 days and off treatment for 7 days per 21 days treatment cycle). Their mean incidence rate of AKs was 4.77 per month before treatment and 2.32 per month during treatment. Topical fluorouracil comes with varying doses and vehicles. The most common side effects were local inflammatory reactions, such as erythema, blistering, erosions.

Photodynamic therapy (PDT)

The protocol of PDT starts with topically applying a photosensitizer, typically 5-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL) over the treatment area, proceed by an incubation period of several hours, and finally exposing to a light source. The photosensitizer has a high affinity for rapidly proliferating cells and pilosebaceous units. It acts as a prodrug and is converted to reactive oxygen species (ROS) when exposing to light with appropriate wavelength (470-700 nm), finally causes cytotoxic damages.

Although the efficacy, safety profile, and excellent cosmetic result of PDT were demonstrated in multiple randomized clinical trials, the reported protocols were non-uniformed, with heterogeneities in length of incubation period, photosensitizer concentrations, setting of the illuminator, whether an assistive laser was used, and etc. Classically, 10% ALA gel and red light illuminator was approved by the FDA. A split face of 40 patients with 4-8 AK lesions underwent application of either 10% or 20% ALA gel followed by 1000 second blue light illumination revealed both regimens were equally effectively, but the 20% ALA gel application had a more robust local inflammatory reaction. The most common side effects of PDT were treatment site pain, inflammation, and burning, especially after sunlight exposure. Many innovative PDT approaches aimed to mitigate treatment related pain. Martin documented a novel PDT intervention on the face that consisted of a 15 minutes incubation period of ALA followed by 60 minutes of blue light. This novel intervention also had an equivalent efficacy with the conventional PDT with minimal pain and discomfort. Similarly, another split face/scalp study compared conventional ALA PDT protocol (incubate for 1 hour and blue light for 1000 second) versus modified protocol (blue light immediately following ALA application). Consequently, all patients in the modified protocol group reported significantly less pain than the control group and the efficacy were similar in both groups. Another evolutionary modality is the daylight PDT (DL-PDT). A photosensitizer, typically ALA, as well as a sunscreen without physical blocker of ultraviolet light (titanium oxide or zinc oxide) were applied topically followed by exposing the patient to sunlight for two hours. Afterwards, patients are instructed to remove the excessive photosensitizer and stay indoors for the rest of the day. DL-PDT can be done anytime of the year in countries that are south to latitude 45° north, which encompasses most of Europe and the United States, South America, and Australia. Optional outdoor temperature should be more than 10°C, otherwise, it would be too cold for the elderly patients. Besides almost pain free, other advantage of DL-PDT are the
affordability and simplicity to perform in office setting. Several studies had proved that DL-PDT are equally efficacious with conventional PDT. One of the drawbacks of DL-PDT is the uncontrollability of natural weather, alternative light emitting sources, such as lamp illuminator, were also discussed to solve this problem.

Another creative modification is the nano-sized emulsion integrated 7.8% ALA gel, namely BF-200 ALA, that stabilizes the ALA molecule and augments epidermal penetration. It is marketed for AK in facial and non-facial regions in Europe. Conversely, it is only authorized for managing AK on the face in the United States.

**Topical Diclofenac (DFC)**

Topical diclofenac is a non-steroidal anti-inflammatory drug (NSAID), which inhibits the cyclooxygenase-1 and cyclooxygenase-2 and decreasing arachidonic acid (AA) byproduct. The AA byproduct are thought be to the culprit of tumorigenesis. A bilateral comparison study of DFC and 5-FU showed that DFC had a milder inflammatory reaction despite longer treatment course.

**Ingenol mebutate (IMB)**

IMB incites local necrosis via disruption of the mitochondria and cellular plasma membrane. It also trigger cytotoxic reactions to specific tumor cells. It is only authorized to use in the United States, but not in European countries due to reported higher risk of non-melanoma skin cancer (NMSC) in IMB compared to imiquimod cream during the post-marketing surveillance.

**Comparison of Various Treatment Options**

Direct comparison of distinct modalities is scarce. A prospective trial in Netherlands aimed to evaluate the efficacy of four field treatments (5% 5-FU cream, 5% imiquimod cream, MAL PDT, and 0.015% IMB gel) for AK enrolled 624 patients who were randomly treated with either approach. At the 1-year end of treatment, the success rates were: 5-FU (74.7%), imiquimod (53.9%), MAL PDT (37.7%), and IMB (28.9%). The treatment compliance rates were: IMB (98.7%), MAL PDT (96.8%), 5-FU (88.7%), and imiquimod (88.2%). Good to excellent aesthetic outcome rates were: MAL PDT (96.6%), IMB (95.1%), 5-FU (90.3%), and imiquimod (89.7%).

A few meta-analyses and systematic literature review have compared the relative efficacy of the existing options. The first one, published in 2012, convinced that PDT is superior to cryotherapy in terms of efficacy and cosmetic results when targeting a single lesion. Additionally, DFC, 5-FU, imiquimod, and IMB were equally efficacious in managing AK field.

In 2013, Gupta and colleagues ranked the following approaches from highest to lowest based on reported clearance rates: 5-FU, ALA PDT (which is equivalent to imiquimod, IMB, and MAL PDT), cryotherapy, DFC/Hyaluronic acid, and finally placebo. Conversely, other factors needs to be evaluated when judging the most suitable option for the patient.

Another meta-analysis published in 2014 examined 10 modalities and concluded that treatments with the relatively highest efficacy were: BF-200 ALA PDT, followed by imiquimod 5% for 16-week, ALA PDT, and 5-FU 0.5%.

A retrospective chart review scrutinized the rate of invasive SCC incidences after more than 1 year of initial AK field treatment. The study emphasized that imiquimod was
equivalent to 5-FU in preventing SCC development; both therapeutics were superior to ALA PDT. However, this study didn’t account for the treatment compliance and anatomical location. For patients who had multiple regimens for their AK, the investigators assigned them based on the first treatment they have received which may potentially neglected issues such as treatment crossover.\textsuperscript{10}

**CONSENSUS GUIDELINES**

A consensus was reached among several international experts in 2015 regarding clinical diagnosis and management of AK. In this consensus, patients were classified into four categories: I. 1-5 clinical AK lesions per field; II. 6 or more AK lesions per field; III. 6 or more AK lesions with the addition of chronic actinic damage and hyperkeratosis per field; and finally, IV. immunocompromised patients with any degree of AK severity. First, sun protection is recommended for all patients. Secondly, cryotherapy is strongly recommended for single AKs (category I). 0.5% 5-FU, 3.75% imiquimod, IMB (0.015% gel and 0.05% gel), ALA PDT, and MAL PDT were strongly recommended for patients in category II and III. For patients in category IV, none of the approaches was highly recommended. Cryotherapy, curettage, 5% 5-FU, 5% imiquimod, ALA PDT, MAL PDT were weakly recommended depending on case-to-case scenario.\textsuperscript{56}

The most recent AAD AK diagnosis and management guidelines strongly recommended sun protection, 5-FU, imiquimod, cryotherapy, and tirbanibulin, which benefits clearly outweigh the risks. Remarkably, the experts firmly believed that the actual therapeutic effect of tirbanibulin was close to the reported therapeutic effect.

Other options, DFC, ALA red light PDT, ALA blue light PDT, DL PDT should be employed in certain conditions as the benefits finely balance with risks.\textsuperscript{57}

**LIMITATIONS**

The limitations of the available clinical evidence were the meager of long-term follow up data and effective armamentarium for immunocompromised patients and non-facial AK. We necessitate more research in those aspects to further assist our management and comprehension of AK, and even SCC.

**CONCLUSION**

Actinic keratosis usually occurs at sun-exposed areas. Although the risk for individual AK progressing into SCC is low, the majority of SCC arise from AK. Its pathogenesis involves the UV-B induced thymine dimer formation, mutation of tumor suppressor genes, disruption of cell cycle, and finally, the proliferation of neoplastic keratinocytes. Treatment of AK can be categorized by single lesion or field treatment. The theory of field cancerization suggests that skin tissue proximal AK lesions also have a higher risk of progression, thus, field treatments are more commonly used. Sun protection is crucial for all patients. Liquid nitrogen cryotherapy is the mainstay treatment for single AK, while PDT, topical imiquimod, and fluorouracil are commonly used as field treatment. Tirbanibulin, recently approved by the FDA, was endorsed as a highly effective option per consensus guidelines. Ultimately, more studies concerning long term recurrence rate, suitable approaches for immunocompromised patients and non-facial AK are mandated.
Conflict of Interest Disclosures: HH & DKB: None
BB: Biofrontera, Advisory Board & Investigator; SUN Pharmaceuticals, Inc Advisory Board & Consultant; LEO Pharma, US Speaker, Advisory Board & Investigator; Almirall LLC, Consultant, Speaker; PHD Biosciences, Consultant

Funding: None

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