CLINICAL MANAGEMENT RECOMMENDATION

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.[7]

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.[3] [8] A common histological feature is atypical keratinocytic proliferation confined in the epidermis.[3] It is regarded as the spectrum along the continuum to squamous cell carcinoma (SCC).[9] 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.[10] 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.[11] [12] 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.[12] 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.[6] 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.[13] [14] 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.[15]

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.[16] 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.[17] 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.[18]

CLINICAL MANAGEMENT

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.[19] 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.[20] 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.[21] 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.[21]

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.[22] [23] 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.[24] [25] [26] [27] [23] The most common side effects were treatment site reactions, such as erythema, ulceration, blistering, erosion, edema and influenza like symptoms.[4] [28] 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 (cm^2), suggesting a more efficient use of this medication.[29]

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.[30] In 2020, FDA licensed topical tirbanibulin 1% ointment as a field treatment of AK to up 25 cm^2 contiguous area of the face or scalp.[31] The clinical data of tirbanibulin was found on two

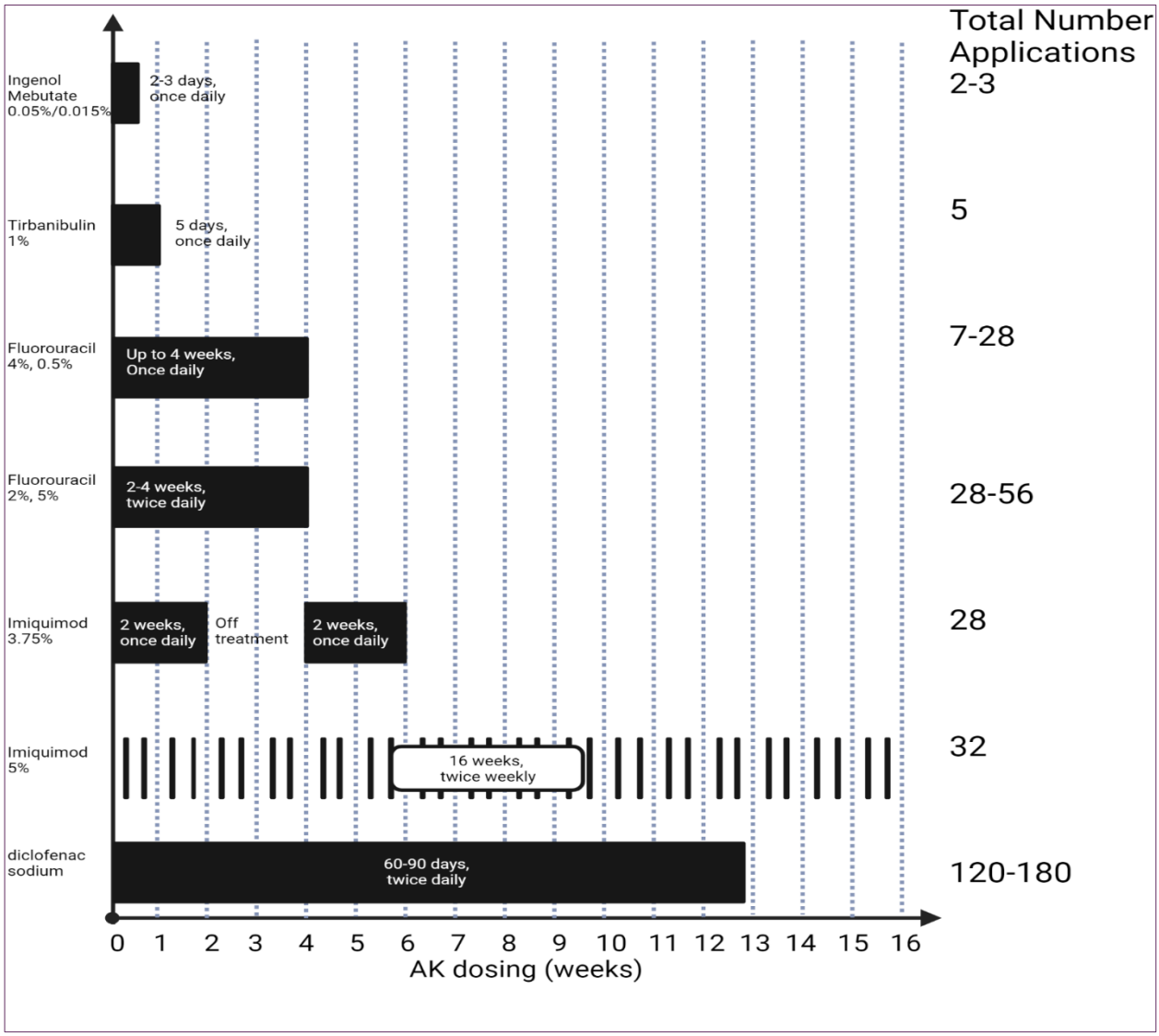

Figure 1. FDA-approved, topical field therapies and total applications

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,)[4 21 22 30 34 37 48 46 51]

Treatment	MOA	Side Effects	Clinical evidence	FDA indication	Treatment regimen
Single lesion					
Liquid Nitrogen Cryotherapy	Damage the tissue and re-epithelialize	Patient discomfort, hypopigmentation, scarring, and prolong wound healing.	Few meta-analysis and systematic review	Not available information	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.
Field treatment					
imiquimod 2.5% cream	Upregulate immune response	Treatment site reactions (erythema, ulceration, pruritus, blistering, erosion, edema), influenza like symptoms	several Phase III RCTs and meta-analysis.	AK on the face or scalp in immunocompetent adults	Once per day overnight for about 8 hours X 2 weeks --> 2 weeks of treatment free period --> 2 weeks of treatment.
imiquimod 3.75% cream				AK on the face or scalp in immunocompetent adults	Once per day overnight for about 8 hours X 2 weeks --> 2 weeks of treatment free period --> 2 weeks of treatment.
Imiquimod 5% cream				non-hyperkeratotic, non-hypertrophic AK on the face or scalp in immunocompetent adults	One application/day, 2times/week X 16 weeks, maximum area of 25 cm^2 per application
5-FU (varying concentration from 0.5% to 5%) cream or solution	inhibiting DNA and RNA replication and increase expression of p53	Treatment site reactions	several Phase III RCTs and meta-analysis.	Topical treatment of multiple AK	Apply cream or solution twice daily for 2-4 weeks.
Conventional PDT (10% 5-aminolevulinic acid/methyl aminolevulinate + red light/blue light)	Photosensitizer is activated by light source and generates reactive oxygen species (ROS), which causes selective cellular damage	Treatment site reactions, itchy, edema, post-inflammatory pigment changes.	Multiple RCTs	10% ALA gel + red light: single or field AK on the scalp and face	Photosensitizer application -> incubation time of several hours -> exposure to light source. Patients are educated for sun protection for several days after PDT.
BF-200 ALA PDT	Stabilize ALA and increase epidermal penetration.		Multiple Phase III RCTs	Europe: facial and non-facial AK United States: mild-moderate AK on face/scalp	
Day Light PDT (DL-PDT)	Same as conventional PDT	Less pain and inflammation than conventional PDT	Multiple RCTs	Not available	Photosensitizer and sunscreen without physical

					blocker were applied topically->outdoor for 2 hours-> stay indoor for the rest of the day.
Tirbanibulin 1% ointment	Inhibit tubulin polymerization and upregulate P53 expression	Treatment site reactions, pain, pruritus	Two identically-designed, phase III RCTs	AK to up 25 cm^2 contiguous area of the face or scalp	One packet (2.5 mg tirbanibulin in 250 mg) once /day for 5 consecutive days
Topical diclofenac 3% in 2.5% hyaluronic acid (DFC/HA)	Inhibits the cyclooxygenase-1 and cyclooxygenase-2 and decreases arachidonic acid (AA) byproduct	Pruritus, contact dermatitis, dry skin. Milder inflammatory response than 5-FU.	Several Phase III RCTs and meta-analysis	AK	Topically apply twice/day for 60-90 days
Ingenol Mebutate (IMB) (0.015% gel and 0.05% gel)	Disruption of plasma membrane and mitochondria. It also triggers cytotoxic reaction	Pain, hypopigmentation.	Several Phase III RCTs	United States: AK	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 cm^2

identically-designed phase III randomized clinical trials. In these trials, LSR(local skin reaction) scores were recorded from baseline to day 57.[30] The LSR score composed of six components: erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration. Each parameter was evaluated by a 0-3 scoring system, the sum of all parameters was calculated as the LSR score. Significantly higher complete clearance (CC, 100% reduction in lesion counts at day 57) and partial clearance rate (75% reduction in lesion counts at day 57) were observed in the treatment group than placebo group. The patients who achieved CC also had a recurrence rate of 47% at 1 year follow up. The most common adverse effects were treatment site pain and pruritus, which regressed spontaneously. No one had exited the study due to any adverse event.[30] Nevertheless, case studies have demonstrated successful topical application of more than 25 cm^2 on human skin, potentially making tirbanibulin more cost-effective.[31]

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.[32] 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.[33] 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.[34] Its underlying mechanism involves inhibiting

thymidylate synthetase and other key steps in DNA and RNA replication, as well as increasing the expression of p53.[34] 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/m^2 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.[35] Topical fluorouracil comes with varying doses and vehicles. The most common side effects were local inflammatory reactions, such as erythema, blistering, erosions.[36]

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.[37] [38]

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.[39]

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.[40] 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.[41] 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.[42] Several studies had proved that DL-PDT are equally efficacious with conventional PDT. [43] [44] One of the drawback of DL-PDT is the uncontrollability of natural weather, alternative light emitting sources, such as lamp illuminator, were also discussed to solve this problem.[45]

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.[46] [47]

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.[48] A bilateral comparison study of DFC and 5-FU showed that DFC had a milder inflammatory reaction despite longer treatment course.[49]

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.[50] [51] 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.[52]

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%).[53]

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.[24]

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.[54] 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%.[55]

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.[10]

CONCENSUS 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.[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.[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.

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References:

1. Reinehr CPH, Bakos RM. Actinic keratoses: review of clinical, dermoscopic, and therapeutic aspects. *An Bras Dermatol*. 2019;94(6):637-657.
2. Schmitt JV, Miot HA. Actinic keratosis: a clinical and epidemiological revision. *An Bras Dermatol*. 2012;87(3):425-434.
3. Cockerell CJ. Histopathology of incipient intraepidermal squamous cell carcinoma ("actinic keratosis"). *J Am Acad Dermatol*. 2000;42(1, Part 2):S11-S17.
4. Marques E, Chen TM. Actinic Keratosis. In: *StatPearls*. StatPearls Publishing; 2022.
5. Yaldiz M. Prevalence of actinic keratosis in patients attending the dermatology outpatient clinic. *Medicine* . 2019;98(28):e16465.
6. Madani S, Marwaha S, Dusendang JR, et al. Ten-Year Follow-up of Persons With Sun-Damaged Skin Associated With Subsequent Development of Cutaneous Squamous Cell Carcinoma. *JAMA Dermatol*. 2021;157(5):559-565.
7. Flohil SC, van der Leest RJT, Dowlatshahi EA, Hofman A, de Vries E, Nijsten T. Prevalence of actinic keratosis and its risk factors in the general population: the Rotterdam Study. *J Invest Dermatol*. 2013;133(8):1971-1978.
8. Banerjee S, Kaunelis D. *Imiquimod for the Treatment of Actinic Keratosis: A Review of Clinical Effectiveness and Cost-Effectiveness*. Canadian Agency for Drugs and Technologies in Health; 2018.
9. Filosa A, Filosa G. Actinic keratosis and squamous cell carcinoma: clinical and pathological features. *G Ital Dermatol Venereol*. 2015;150(4):379-384.
10. Cheng B, Veerabagu S, Miller CJ, et al. A comparison of invasive squamous cell carcinoma greater than 1 year after treatment with 5-Fluorouracil, Imiquimod, or Photodynamic Therapy with Aminolevulinic Acid. *Journal of the American Academy of Dermatology*. Published online 2022. doi:10.1016/j.jaad.2022.05.051
11. Jp. Bickers DR. Moy RL. Actinic keratoses. *J Am Acad Dermatol*.
12. Roewert-Huber J, Stockfleth E, Kerl H. Pathology and pathobiology of actinic (solar) keratosis - an update. *British Journal of Dermatology*. 2007;157:18-20. doi:10.1111/j.1365-2133.2007.08267.x
13. Thompson SC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. *N Engl J Med*. 1993;329(16):1147-1151.
14. Naylor MF, Boyd A, Smith DW, Cameron GS, Hubbard D, Neldner KH. High sun protection factor sunscreens in the suppression of actinic neoplasia. *Arch Dermatol*. 1995;131(2):170-175.
15. Actinic keratosis: Self-care. Accessed May 28, 2022. https://www.aad.org/public/diseases/skin-cancer/actinic-keratosis-self-care
16. Walker JL, Siegel JA, Sachar M, et al. 5-Fluorouracil for Actinic Keratosis Treatment and Chemoprevention: A Randomized Controlled Trial. *J Invest Dermatol*. 2017;137(6):1367-1370.
17. Pomerantz H, Hogan D, Eilers D, et al. Long-term Efficacy of Topical Fluorouracil Cream, 5%, for Treating Actinic Keratosis. *JAMA Dermatology*. 2015;151(9):952. doi:10.1001/jamadermatol.2015.0502
18. Gollnick H, Dirschka T, Ostendorf R, Kerl H, Kunstfeld R. Long-term clinical outcomes of imiquimod 5% cream vs. diclofenac 3% gel for actinic keratosis on the face or scalp: a pooled analysis of two randomized controlled trials. *J Eur Acad Dermatol Venereol*. 2020;34(1):82-89.
19. Jetter N, Chandan N, Wang S, Tsoukas M. Field Cancerization Therapies for Management of Actinic Keratosis: A Narrative Review. *Am J Clin Dermatol*. 2018;19(4):543-557.
20. Goldenberg G, Perl M. Actinic keratosis: update on field therapy. *J Clin Aesthet Dermatol*. 2014;7(10):28-31.
21. Prohaska J, Jan AH. Cryotherapy. In: *StatPearls*. StatPearls Publishing; 2022.
22. Nanda J, Bermudez R. Imiquimod. In: *StatPearls*. StatPearls Publishing; 2021.
23. Caperton C, Berman B. Safety, efficacy, and patient acceptability of imiquimod for topical treatment of actinic keratoses. *Clin Cosmet Investig Dermatol*. 2011;4:35-40.
24. Gupta AK, Paquet M, Villanueva E, Brintnell W. Interventions for actinic keratoses. *Cochrane Database of Systematic Reviews*. Published online 2012.

doi:10.1002/14651858.cd004415.pub2
25. Lebwohl M, Dinehart S, Whiting D, et al. Imiquimod 5% cream for the treatment of actinic keratosis: results from two phase III, randomized, double-blind, parallel group, vehicle-controlled trials. *Journal of the American Academy of Dermatology*. 2004;50(5):714-721. doi:10.1016/j.jaad.2003.12.010
26. Szeimies RM, Gerritsen MJP, Gupta G, et al. Imiquimod 5% cream for the treatment of actinic keratosis: results from a phase III, randomized, double-blind, vehicle-controlled, clinical trial with histology. *J Am Acad Dermatol*. 2004;51(4):547-555.
27. Korman, Moy, Ling, Matheson. Dosing with 5% imiquimod cream 3 times per week for the treatment of actinic keratosis: results of two phase 3, randomized, double-blind, parallel-group, vehicle …. *Arch nat conserv landsc res*. https://jamanetwork.com/journals/jamadermatology/article-abstract/393884
28. Bhatia N. Local skin reactions and the onset of influenza-like signs and symptoms induced by imiquimod. *JAAD Int*. 2022;7:113-118.
29. Berman B, Ricotti CA Jr, Cazzaniga A, Davis SC. Determination of the area of skin capable of being covered by the application of 250 mg of 5% imiquimod cream. *Dermatol Surg*. 2004;30(5):784-786.
30. Blauvelt A, Kempers S, Lain E, et al. Phase 3 Trials of Tirbanibulin Ointment for Actinic Keratosis. *N Engl J Med*. 2021;384(6):512-520.
31. Dunn A, Han H, Gade A, Berman B. The Area Capable of Being Covered by the Application of 250mg of Tirbanibulin Ointment. *J Clin Aesthet Dermatol*. 2022;15(3):13-14.
32. Berman, Schlesinger, Bhatia. Complete clearance of actinic keratosis with tirbanibulin ointment 1% is not correlated with the severity of local skin reactions. *SKIN J Cutan Med*. https://scholar.archive.org/work/hwrh24otqbchrff6owyeeki7ey/access/wayback/https://jofskin.org/index.php/skin/article/download/1542/pdf
33. Berman, Gual, Grada, Fumero. Efficacy of tirbanibulin ointment 1% across different patient populations: pooled results from two Phase 3 studies. *SKIN J Cutan Med*. https://scholar.archive.org/work/b7co2q56sbdjdnygz447ibx4om/access/wayback/https://jofskin.org/index.php/skin/article/download/1544/pdf
34. Casale J, Patel P. Fluorouracil. In: *StatPearls*. StatPearls Publishing; 2022.
35. Schauder DM, Kim J, Nijhawan RI. Evaluation of the Use of Capecitabine for the Treatment and Prevention of Actinic Keratoses, Squamous Cell Carcinoma, and Basal Cell Carcinoma: A Systematic Review. *JAMA Dermatol*. 2020;156(10):1117-1124.
36. Gupta AK, Davey V, Mcphail H. Evaluation of the effectiveness of imiquimod and 5-fluorouracil for the treatment of actinic keratosis: Critical review and meta-analysis of efficacy studies. *J Cutan Med Surg*. 2005;9(5):209-214.
37. Wan MT, Lin JY. Current evidence and applications of photodynamic therapy in dermatology. *Clin Cosmet Investig Dermatol*. 2014;7:145-163.
38. Raizada K, Naik M. Photodynamic Therapy For The Eye. In: *StatPearls*. StatPearls Publishing; 2021.
39. Nestor MS, Berman B, Patel J, Lawson A. Safety and Efficacy of Aminolevulinic Acid 10% Topical Gel versus Aminolevulinic Acid 20% Topical Solution Followed by Blue-light Photodynamic Therapy for the Treatment of Actinic Keratosis on the Face and Scalp: A Randomized, Double-blind Study. *J Clin Aesthet Dermatol*. 2019;12(3):32-38.
40. Martin GM. In-office Painless Aminolevulinic Acid Photodynamic Therapy: A Proof of Concept Study and Clinical Experience in More Than 100 Patients. *J Clin Aesthet Dermatol*. 2016;9(2):19-26.
41. Kaw U, Ilyas M, Bullock T, et al. A regimen to minimize pain during blue light photodynamic therapy of actinic keratoses: Bilaterally controlled, randomized trial of simultaneous versus conventional illumination. *J Am Acad Dermatol*. 2020;82(4):862-868.
42. Wulf HC. Photodynamic Therapy in Daylight for Actinic Keratoses. *JAMA Dermatol*. 2016;152(6):631-632.
43. Rubel DM, Spelman L, Murrell DF, et al. Daylight photodynamic therapy with methyl aminolevulinate cream as a convenient, similarly effective, nearly painless alternative to conventional photodynamic therapy in actinic keratosis treatment: a randomized controlled trial. *Br J Dermatol*. 2014;171(5):1164-1171.
44. Lacour JP, Ulrich C, Gilaberte Y, et al. Daylight photodynamic therapy with methyl aminolevulinate cream is effective and nearly painless in treating actinic keratoses: a randomized, investigator-blinded, controlled, phase III study throughout Europe. *Journal of the European Academy of Dermatology and Venereology*. 2015;29(12):2342-2348. doi:10.1111/jdv.13228
45. Kellner C, Bauriedl S, Hollstein S, Reinhold U. Simulated-daylight photodynamic therapy with BF-200 aminolaevulinic acid for actinic keratosis: assessment of the efficacy and

tolerability in a retrospective study. *Br J Dermatol*. 2015;172(4):1146-1148.
46. Ulrich M, Reinhold U, Dominicus R, Aschoff R, Szeimies RM, Dirschka T. Red light photodynamic therapy with BF-200 ALA showed superior efficacy in the treatment of actinic keratosis on the extremities, trunk, and neck in a vehicle-controlled phase III study. *J Am Acad Dermatol*. 2021;85(6):1510-1519.
47. Dirschka T, Radny P, Dominicus R, et al. Photodynamic therapy with BF-200 ALA for the treatment of actinic keratosis: results of a multicentre, randomized, observer-blind phase III study in comparison with a registered methyl-5-aminolaevulinate cream and placebo. *Br J Dermatol*. 2012;166(1):137-146.
48. Pirard D, Vereecken P, Mélot C, Heenen M. Three percent diclofenac in 2.5% hyaluronan gel in the treatment of actinic keratoses: a meta-analysis of the recent studies. *Arch Dermatol Res*. 2005;297(5):185-189.
49. Smith SR, Morhenn VB, Piacquadio DJ. Bilateral comparison of the efficacy and tolerability of 3% diclofenac sodium gel and 5% 5-fluorouracil cream in the treatment of actinic keratoses of the face and scalp. *J Drugs Dermatol*. 2006;5(2):156-159.
50. Lesiak A, Maćkowska A, Bednarski IA, et al. Ingenol mebutate treatment in actinic keratosis - clinical effectiveness and potential side effects. *Postepy Dermatol Alergol*. 2019;36(4):468-471.
51. Lebwohl M, Swanson N, Anderson LL, Melgaard A, Xu Z, Berman B. Ingenol mebutate gel for actinic keratosis. *N Engl J Med*. 2012;366(11):1010-1019.
52. Steeb T, Wessely A, Petzold A, et al. How to Assess the Efficacy of Interventions for Actinic Keratosis? A Review with a Focus on Long-Term Results. *J Clin Med Res*. 2021;10(20). doi:10.3390/jcm10204736
53. Jansen MHE, Kessels JPHM, Nelemans PJ, et al. Randomized Trial of Four Treatment Approaches for Actinic Keratosis. *N Engl J Med*. 2019;380(10):935-946.
54. Gupta AK, Paquet M. Network meta-analysis of the outcome “participant complete clearance” in nonimmunosuppressed participants of eight interventions for actinic keratosis: a follow-up on a Cochrane review. *Br J Dermatol*. 2013;169(2):250-259.
55. Vegter S, Tolley K. A network meta-analysis of the relative efficacy of treatments for actinic keratosis of the face or scalp in Europe. *PLoS One*. 2014;9(6):e96829.
56. Werner RN, Stockfleth E, Connolly SM, et al. Evidence- and consensus-based (S3) Guidelines for the Treatment of Actinic Keratosis - International League of Dermatological Societies in cooperation with the European Dermatology Forum - Short version. *Journal of the European Academy of Dermatology and Venereology*. 2015;29(11):2069-2079. doi:10.1111/jdv.13180
57. Eisen DB, Dellavalle RP, Frazer-Green L, Schlesinger TE, Shive M, Wu PA. Focused update to the Guidelines of Care for the Management of Actinic Keratosis: Executive Summary. *J Am Acad Dermatol*. Published online April 16, 2022. doi:10.1016/j.jaad.2022.04.013