Received: 23 June 2021 | Revised: 9 January 2022 | Accepted: 19 January 2022

DOI: 10.1002/der2.121

INVITED REVIEW

Dermatological Reviews WILEY

Update on diagnosis and treatment of actinic keratosis

Komal Agarwal MD[1] | Indrashis Podder MD, DNB[2] | Clay J. Cockerell MD[3,4] | Martin Kassir MD[5] | Stephan Grabbe MD[6] | Mohamad Goldust MD[6]

[1]Department of Dermatology, CNMC, Kolkata, India

[2]Department of Dermatology, Venereology and Leprosy, College of Medicine and Sagore Dutta Hospital, Kolkata, India

[3]Departments of Dermatology and Pathology, The University of Texas Southwestern Medical Center, Dallas, Texas, USA

[4]CockerellDermatopathology, Dallas, Texas, USA

[5]Worldwide Laser Institute, Dallas, Texas, USA

[6]Department of Dermatology, University Medical Center of the Johannes Gutenberg University, Mainz, Germany

Correspondence
Mohamad Goldust, Department of Dermatology, University Medical Center of the Johannes Gutenberg University, Mainz, Langenbeckstr. 1, D-55131 Mainz, Germany.
Email: mgoldust@uni-mainz.de

Abstract

Actinic keratosis (AK) is a relatively common skin condition occurring due to chronic sun-exposure, primarily affecting fair skin. Most dermatologists consider it an incipient malignancy due to its risk of full-blown malignant transformation to squamous cell carcinoma. However, the exact risk factors remain unknown, and thus its course cannot be predicted. Therefore, all cases of AK need early diagnosis and appropriate treatment to mitigate this risk. Over the years, several noninvasive diagnostic techniques such as dermoscopy, reflectance confocal microscopy, and newer treatment modalities (lesion-directed and field-directed) have been introduced with their own set of advantages and disadvantages. Notably, invasive skin biopsy with histopathology remains the gold-standard for diagnosis. Prevention is of paramount importance, highlighted by adequate sun-protection measures. This article reviews the diagnostic and treatment modalities of AK, with their latest updates, to optimize patient management.

KEYWORDS

actinic keratosis, diagnosis, latest, treatment, updates

1 | INTRODUCTION

Actinic keratosis (AK) is a commonly occurring, in situ evolving malignant neoplasm affecting the skin. It occurs due to chronic exposure to sunlight and is distributed on chronic sun-exposed areas like the face, scalp, neck, dorsum of hands, and forearms.[1]

AK has a high prevalence especially in countries with high ultraviolet light exposure such as Australia and is the third most common skin condition treated by dermatologists.[1,2] Various factors contribute to the development of AK, the most important being chronic ultraviolet (UV) radiation exposure. UVB exposure leads to formation of thymidine dimers that mutate the telomerase gene, whereas UVA causes indirect DNA mutation via photo-oxidation.[1] Other independent risk factors include male gender, age usually 7th decade, Fitzpatrick phototypes I and II, previous history of AKs or skin cancer, immunosuppression, and photosensitive genetic diseases like xeroderma pigmentosum and Bloom syndrome.[3]

AKs may have three different fates: regression, persistence, or progression toward squamous cell carcinoma (SCC).[4] The risk of AK progressing to SCC varies largely from 0.025% to 16%.[1,4] Patients with multiple AKs are at a higher risk of SCC, since the relative risk of SCC also increases with the number of AKs (1% for patients with five or fewer AK lesions and up to 20% for patients with more than 20 AK lesions).[5]

Abbreviations: AK, actinic keratosis; ALA, aminolevulinic acid; COX, cyclooxygenase; FU, fluorouracil; MAL, methyl ester of ALA; OCT, optical coherence tomography; PDT, photo dynamic therapy; RCM, reflectance confocal microscopy; SCC, squamous cell carcinoma; TCA, trichloroacetic acid.

2 | MATERIALS AND METHODS

We undertook a comprehensive English literature search across multiple databases including PubMed, SCOPUS, EMBASE, MEDLINE, and Cochrane using keywords (alone and in combination) and MeSH items such as "actinic keratosis," "diagnosis," "treatment," "dermoscopy," "recent updates" to obtain several relevant articles, priority being given to prospective randomized controlled trials. We scanned all the relevant articles in the English literature and summarized them to obtain the latest information about this condition to prepare the current article. We scanned the reference of selected articles for more relevant articles. Articles in other languages were excluded from our search.

2.1 | Diagnosis

The diagnosis of AK is mainly clinical but often there are multiple lesions with variable presentations. Both clinically apparent and subclinical AKs present on an area of chronic actinic damage thus, making clinical diagnosis difficult. Moreover, AKs may often be confused with seborrheic keratoses, Bowen disease, SCC, basal cell carcinoma, and discoid lupus erythematosus.[1] In such cases, several invasive and noninvasive diagnostic modalities may be utilized.

3 | CLINICAL DIAGNOSIS

AKs clinically present as single or multiple, ill-defined macule/papule/plaque lesions, pink to red-brown in color with dry, adherent scales. They are mostly located on the neck, face, ears, bald scalp, extensors of upper limbs, and lower lip.[4] The size of the lesion may vary from a few millimeters to a few centimeters.[4] They are usually asymptomatic but may be associated with itching, burning, bleeding, or tenderness. Larger, symptomatic lesions are at a higher risk of transformation to SCC.[1]

For better understanding, a clinical classification is used to grade AK into Grades I–III.[1,4,6] (Table 1).

Despite the above, the clinical diagnosis between Grade III AK and early invasive SCC may not always be possible and is subject to individual clinical interpretation.

Recently, Schmitz and colleagues have highlighted the importance of basal (downward) growth pattern of keratinocytes on histologic examination, as they do not correlate with the classical I–III grading system. They categorized the downward growth pattern under 3 heads-crowding (pro I), budding (pro II), and papillary sprouting (pro III), and opined that "downward or basal" proliferation of keratinocytes increases the risk of progression to SCC.[7] Another recent European study has considered basal proliferative AKs, along with atypical keratinocytes restricted to the lower third of epidermis to be more closely associated with invasive SCC, rather than full-thickness epidermal dysplasia.[8] Thus, it is of paramount importance to grade AKs according to the basal proliferation of keratinocytes (pro I, pro II, and pro III) in addition to the classical Grades I–III classification to evaluate their prognosis.

Even though clinical diagnosis has the advantage of being easy, inexpensive, and accessible, it is sometime insufficient alone to make the diagnosis and may often result in over or under diagnosis of AK.[4]

4 | ROLE OF DERMOSCOPY IN DIAGNOSIS

Dermoscopy, a recent introduction to the dermatologists' armamentarium, allows 6–100 fold magnification and visualization of skin structures with polarized light and it has proven to be a boon for dermatologists especially when dealing with potentially malignant lesions like AK.[4] It's a cheap, noninvasive and easily accessible diagnostic modality which may reduce the need for subsequent invasive procedures. The sensitivity and specificity of dermoscopy for nonpigmented AK is 98% and 95%, respectively.[1,4,9] The clinical grading (Grades I–III) of AK correspond to different dermoscopy patters[9] (Table 1).

Facial AKs are a diagnostic dilemma and are dermoscopically characterized by four patterns, as follows[9]:

- Erythema and pink-to-red "pseudo-network" surrounding the hair follicles,
- Surface scale white-to-yellow,
- Fine, linear-wavy blood vessels surrounding the hair follicles, and
- Yellowish keratotic plugs in the follicular openings with or without a whitish halo.

TABLE 1 Correlation of clinical grading of actinic keratosis, dermoscopy patterns, and reflectance confocal microscopy findings[1,4,7]

Grade	Clinically	Dermoscopy pattern	Reflectance confocal microscopy
Grade I	slightly palpable AKs (better felt than seen)	Red pseudo-network pattern and discrete white scales	Focal areas of atypical honeycombed pattern at the level of the stratum spinosum, intermingled with areas of typical honeycombed pattern.
Grade II	moderately thick AKs (easily felt and seen)	Erythematous background intermingled by white to yellow, keratotic, enlarged follicular openings (Strawberry pattern)	Keratinocytes present a marked atypia, with different cell sizes and shapes. Atypia of the keratinocytes is more diffuse, involving the stratum spinosum and granulosum.
Grade III	Very thick, hyperkeratotic AK	Enlarged follicular openings that are filled with keratotic plugs over a scaly and white- to yellow-structureless appearing background	Markedly atypical honeycombed pattern with areas of partial disruption of the normal epidermal layers, defined as a "disarranged pattern"

These features combined often produce a "strawberry appearance."[4,9]

Less frequently, AKs may be pigmented and dermoscopically demonstrate superficial brown network of brown, curved double lines surrounding enlarged, keratotic follicles of various sizes. Pigmented AKs on the face show a pseudo-network, the characteristicmeshes and holes help the diagnosis. Pigmented AK and lichenoid AK may often be confused with lentigo maligna due to overlapping dermoscopy findings like gray dots (annular granular pattern), pseudonetwork around the follicular openings and asymmetrical, pigmented follicular openings.[10] Further studies demonstrated presence of prominent follicles, scales and red color in favor of diagnosis of pigmented AK, whereas presence of intense pigmentation and gray rhomboidal lines pointing toward lentigo maligna.[4,10]

Dermoscopy may also help to predict the progression of AK to SCC when initial dotted or glomerular vessels become hairpin and linear vessels, indicating progression toward a more invasive growth.[9] Nonpolarized dermoscopy with fluid immersion is useful in such cases as it renders the keratin largely invisible, providing more information about vascular structures. Moreover, a central mass of keratin, ulceration, and red starburst pattern gives a clue toward a more aggressive lesion.[4]

5 | FLUORESCENT TECHNIQUES

The topical application of aminolevulinic acid (ALA) and the methyl ester of ALA (MAL) associated with photodynamic therapy does not only serve as a therapeutic modality but also helps in diagnosis. These topical photosensitizers are precursors of and converted to protoporphyrin IX (PpIX) in neoplastic cells. PpIX emits fluorescence, thus helping in the diagnosis of cutaneous lesions. This fluorescence helps to detect the otherwise occult areas of abnormal skin.[4,11] Various techniques can be used to detect the fluorescence, such as Wood's ultraviolet lamp which shows pink fluorescence in areas of activated PpIX, Fiber optic probe/point spectrofluorometry, and wide-field camera-based imaging.

6 | REFLECTANCE CONFOCAL MICROSCOPY (RCM)

RCM, a new diagnostic technique, provides resolution almost same as histology but it is an in-vivo, noninvasive technique. It works on the principle of reflection, scattering, and absorption of near-infrared light.[12] The major features of AK seen on RCM are: architectural irregularity, superficial disruption, and cellular pleomorphism at the level of spinous and granular layers. In addition, there is presence of scales, parakeratosis, honeycombed pattern of stratum spinosum and granulosum, and small irregular dermal papilla at the dermoepidermal junction. Dermoscopy and RCM findings could be correlated to various clinical gradings of AK (Table 1).[9]

Pigmented AK may show atypical honeycomb pattern with pleomorphic and atypical keratinocytes on RCM. The intradermal cells are stellate shaped, with short dendrites and no complex branching. In case of melanoma there is the presence of pagetoid, intraepidermal cells having dendritic or rounded shape (more specific for melanoma).[4]

A distinction between SCC and AK using RCM is quite challenging as in the case of hyperkeratotic lesions, stratum basale and dermoepidermal junction changes are not well visualized by RCM. A few differences may be noticed between SCC and AK on RCM. Extensive keratinocytic atypia involves the entire epidermis with nest-like structures and pleomorphic cells in dermis in SCC; focally disarranged, mildly atypical of normal keratinocytes in the stratum granulosum with no dermal pleomorphic cells are seen in AK.

The major disadvantages of RCM are the high cost and its inability to explore hyperkeratotic lesions and vertical invasion of lesions due to shallow penetrance.[4,12]

7 | OPTICAL COHERENCE TOMOGRAPHY (OCT)

OCT is an in vivo, noninvasive imaging technique based on the use of infrared light. The images are 2 dimensional and cross sectional, with an axial and lateral resolution of approximately 15 mm and a depth of up to 2 mm.[4] Layers of the skin, adnexa, and vessels can be detected, but the basement membrane, cellular and subcellular detail cannot be detected. On OCT, AKs are characterized by high surface reflection, white streak, dot, gray area corresponding to hyperkeratosis, low-signal band in the stratum corneum with point of disruption, and heterogeneous appearance in the epidermis or dermis.[4,13] Barton et al. reported a dark band in the stratum corneum with conventional OCT characteristic for AK with a sensitivity and specificity of 79% and 100%, respectively.[13] Other than conventional OCT, high-definition-OCT device is available which has better resolution and can provide vertical (slice-mode) and horizontal (en-face mode) imaging. The en-face mode of high definition-OCT imaging of AK can identify cellular and nuclear polymorphism.

To stratify the degrees of epidermal dysplasia, a three-tiered grading scale has been proposed by Cockerell et al. for AKs.[14] A good correlation has been noticed between the histopathological AK grading and high definition-OCT en face features, that is, atypical honeycomb pattern and/or disarranged epidermal pattern due to cellular pleomorphism.

Grade KIN-I: In early or subclinical lesions, a mild atypical honeycomb pattern is confined to the bottom third of the epidermis.

Grade KIN-II: Clinical AKs with atypical honeycomb pattern involving the lower two-thirds of the epidermis.

Grade-III: Full thickness disarranged epidermal pattern corresponding with the presence of dyskeratotic keratinocytes.

Recently, Ruini and colleagues have highlighted the role of OCT as a reliable in-vivo tool to assess downward proliferation of keratinocytes in AK (PRO-grading), with strong interobserver agreement and a good correlation with histopathology.[15]

8 | HISTOPATHOLOGICAL EXAMINATION

Histopathology remains the gold standard to confirm the diagnosis of AK. AK is characterized by focal keratinocytic atypia with architectural irregularity. The epidermis shows hyperkeratosis, parakeratosis, and irregular acanthosis. The basal keratinocytes are variable in size and shape, with altered cell polarity and nuclear atypia. The changes are focal and tend to spare hair follicles and if there is full-thickness epidermal atypia, it is relatively limited rather than being diffuse in fully developed SCC in situ. It is noteworthy, that the clinical classification of AK lesions do not accurately match the histological classification of the same. Thus, it is often not possible to draw conclusions regarding the histology of the lesions from their clinical appearance. This reinforces the fact that all AK lesions need to be treated as well as for field cancerization.

8.1 | Treatment

AKs are a risk factor for the development of SCC, but the fate and evolution of each lesion is quite unpredictable, thus necessitating early and prompt treatment of all AKs. The main aims of treating AK are eradication of evident and subclinical lesions, preventing their progression to SCC, and reducing the relapse rate.

The lack of a standard treatment protocol for AK leaves the treating dermatologist with different choices. Several factors need to be considered before choosing the appropriate modality such as density and clinical features of the lesion, cost of treatment, and clinico-demographic parameters of the patient such as age, immunity, comorbidities, and compliance.

Broadly, the treatment for AK can be divided into general measures and specific measures. The latter can be categorized under 2 heads- *lesion-directed* and *field-directed* therapies[1,16–22] (Table 2).

Lesion-directed treatments involve ablative procedures that remove atypical keratinocytes from the lesions, whereas, Field-directed treatment involves use of medications that target clinically visible as well as subclinical lesions within a field of chronic sun-damaged skin, that is, "field cancerization."[1]

9 | GENERAL MEASURES

As chronic sun-exposure (ultraviolet rays) form the backbone of AK pathogenesis, strict sun-protection measures from an early age are of paramount importance to prevent the occurrence of this disorder and its malignant transformation. Commonly employed sun-protection measures include regular use of sunscreens (at least SPF 30), umbrellas, full-sleeved clothing, sunglasses, and shade-seeking behavior. Another critical measure is providing adequate information about this disease and its consequences, along with its preventive strategies to the common public in simple language, using mass media such as television, radio, and educational programs.

9.1 | Specific measures

9.1.1 | Lesion directed therapy

Cryotherapy

Cryotherapy or cryosurgery is the preferred modality of treatment for patients with few lesions (1–6 lesions), or those who are non-compliant to topical therapy.

Liquid nitrogen is the preferred agent. It can be applied with a cotton tip applicator or a spray involving 1 mm area of the surrounding normal skin using a single freeze-thaw cycle between 5 and 40 s.[16] The response to cryosurgery depends on the duration of freezing and it is approximately 98%.[1] Pretreatment of the area with 5-FU or 3% diclofenac gel can increase the efficacy of cryotherapy.[1,16] Also, post cryotherapy application of 5% imiquimod helps in better removal and destruction of clinical/subclinical and total AKs.[17]

Cryotherapy has the advantage of being a rapid technique with good efficacy, not requiring anesthesia, or hospital admission. Minor adverse effects like erythema, pain, blistering, and hypochromia may be seen.

10 | LASER THERAPY

Laser therapy is one of the most effective treatment modalities available as it physically removes the lesion of AK. Additionally, there is resurfacing of skin, thus serving as a prophylaxis against future AK lesions. Commonly used lasers are ablative lasers like CO2 and erbium yttrium aluminum garnet that ablate the epidermis and superficial dermis, or non-ablative fractional lasers like erbium glass systems that create a controlled coagulation of tiny columns of skin, leaving the surrounding skin undamaged.[16,17]

The response rate to laser treatment is 90% in case of AKs with a recurrence rate of 10%–15% at 6 months.[1] Lasers can be combined with other topical treatments to improve the efficacy. The response rate of lasers and cryotherapy is almost similar (71.6% for cryotherapy vs. 65.3% for laser ablation) but the stability of patients at 1 year is more for cryotherapy as compared to lasers (66.8% for cryotherapy vs. 37% for laser ablation).[17,23]

Laser has the advantage of being a rapid and effective modality of treatment but restricted availability, high cost, and a steep learning curve serve as disadvantages.[18]

11 | CURETTAGE

Curettage is used for hyperkeratotic AK or lesions that are refractory to other treatments.[16] Post-curretage electrodessication may help with hemostasis and for defining the lesion margins.

It allows collection of sample for histopathological examination (HPE) but has the drawback of requiring anesthesia and risk of scarring.[17–19,23]

TABLE 2 Treatment options for actinic keratosis[1,16–24]

	Dose	Advantage	Disadvantage	Recurrence
Lesion-directed therapy				
Cryotherapy	Liquid nitrogen is applied with a cotton tip applicator or a spray involving 1 mm area of the surrounding normal skin using a single freeze-thaw cycle between 5 and 40 s.	Rapid technique, no anesthesia or hospital admission needed	Erythema, pain, blistering, hypopigmentation	The response to cryosurgery depends on the duration of freezing and it is approximately 98%.[1] Pretreatment of the area with 5-FU or 3% diclofenac gel can increase the efficacy of cryotherapy.[1,16]
Laser therapy	• CO_2 laser • Erbium yttrium aluminum garnet laser • Erbium glass laser	Rapid technique, no anesthesia or hospital admission needed	Expensive, higher learning curve, not available at all places, associated with pain, erythema, delayed healing	The response rate is 90% with a recurrence rate of 10%–15% at 6 months.[1] The response rate of lasers and cryotherapy is almost similar (71.6% for cryotherapy vs. 65.3% for laser ablation) but the stability of patients at 1 year is more for cryotherapy as compared to lasers (66.8% for cryotherapy vs. 37% for laser ablation).[17,23]
Curettage	1–2 sittings may be required	Rapid technique allows sample collection for HPE, works well for hyperkeratotic lesions	Requires anesthesia, risk of scarring, risk of reactivation of herpes simplex	Complete clearance rate is 31% and 47% after 2 and 3 months of follow up respectively. The recurrence rate at end of 1 year is 21%
Surgery	Excision or shave biopsy done in a single sitting	Rapid, single sitting procedure	Requires anesthesia, risk of scarring	
Field-directed therapy				
5-fluorouracil	5% 5-FU is applied twice a day for 4 weeks. Combination of 5FU with 10% salicylic acid can be used topically once daily for 12 weeks.	Easy, inexpensive	Erythema, burning, inflammation, pruritus, and erosions. Systemic toxicity like headache, insomnia, irritability, thrombocytopenia, leucocytosis, neurotoxicity is seen in patients with dihydropyrimidine dehydrogenase deficiency.	Recurrence rate of 54% at end of 1 year in those receiving 5% 5-FU
Diclofenac	3% gel applied topically twice daily for 2–3 months	Cheap, easy, and well-tolerated treatment modality.	Long duration of treatment, erythema, pruritus, dryness, hepatotoxicity, should be avoided in aspirin sensitive patients	Clearance rate of 58% after 1 month[1] and recurrence rate of 85% at end of 1 year
Imiquimod	Imiquimod 5% cream is used three times a week for 4 weeks. 3.75% cream is used once daily for 2 weeks, then 2 weeks gap and again application for 2 weeks (2-0-2).	Easily available, well-tolerated	erythema, weeping, erosions, pruritus, upper respiratory tract infections, influenza-like symptoms	85% clinical clearance of AK and a recurrence rate of 10% within 1 year.[21]

(Continues)

TABLE 2 (Continued)

	Dose	Advantage	Disadvantage	Recurrence
Ingenol mebutate *(has been withdrawn from market in 2020 due to increased concerns about skin cancers)*	0.015% gel applied once daily for 3 days for facial lesions. 0.05% gel applied once daily for 2 days for lesions on the body.	Shortest duration of treatment	Pain, pruritus, inflammation, infection, and systemic effects like periorbital edema, nasopharyngitis, and headache, keratoconjunctivitis.	50% recurrence at end of 1 year
Chemical peels	Trichloroacetic acid (TCA), alpha hydroxy acids, zinc chloride, or phenolic acid.	Rapid technique, easy, inexpensive, easily accessible	Erythema, inflammation, pigmentation, and scarring	The effectiveness of chemical peels in AK is 75%, with 25%–35% relapse rate within 1 year.[19,21]
Retinoids	Oral or topical	Prophylactic action	Erythema, photosensitivity, irritation, dryness, erosions, and so on. systemic retinoids may cause chelitis, keratitis, hepatotoxicity, mood instability, dyslipidemia.	More head-head studies specific to AK are needed with longer follow-up to comment on the recurrence rates.
Photodynamic therapy	5-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL)	No post treatment scarring or disfigurement.	Poor efficacy in immunocompromised patients and lesions on extremities. Side effects like burning, stinging, erythema.	Recurrence rate at 12 months of follow-up was 20% with ALA-PDT and 34% with MAL-PDT

12 | SURGERY

Excision or shave biopsy of lesions is indicated only when there is a high suspicion of SCC especially in hyperkeratotic lesions.[16,18,19]

Its time-consuming modality requires anesthesia and may result in scarring.

12.1 | Field directed therapy

12.1.1 | 5- fluorouracil (5FU)

5FU is a pyrimidine analog and acts by inhibition of thymidylate synthase and incorporation of 5-FU into RNA and DNA.[20] It is available in various topical formulations like 1% or 5% cream/solution, 2% solution, and 0.5% fluorouracil cream.

It can be used as a topical therapy for patients with multiple AK, 5% 5-FU is applied twice a day for 4 weeks. 0.5% 5-FU cream which uses microsponge delivery system, also shows similar effectiveness with lesser side effects.[1,20] Studies have been conducted using 0.5% 5-FU cream for 1, 2, and 4 weeks, there has been significant reduction in number of lesions and in the clearance of lesions and the efficacy continued to increase with subsequent weeks of therapy. Complete clearance rate at 8 weeks (4 weeks after the end of treatment) ranged from 58% to 96% in those receiving 5-FU 5% and 48% in those receiving 0.5%. Facial irritation was the main side effect which increased during the first 2 weeks and then showed no further increase during the 3rd and 4th week. 0.5% 5-FU over 5% 5-FU is a better therapeutic option because of once daily application, lower potential for irritation, and systemic absorption. Use of 0.5% 5-FU cream one week before cryosurgery reduces the number of lesions and risk of recurrence.[20] Combination treatment of 5FU with topical tretinoin can increase the efficacy.[1,20] Similarly, a combination of 5FU with a keratolytic like 10% salicylic acid can be used topically once daily for 12 weeks.[21,22]

It is an easy, inexpensive treatment but may be associated with side effects like erythema, burning, inflammation, pruritus, and erosions.[20] Systemic toxicity like headache, insomnia, irritability, thrombocytopenia, leucocytosis, neurotoxicity is seen in patients with dihydropyrimidine dehydrogenase deficiency. Not recommended in pregnant females as it may lead to birth defects and miscarriage.

13 | TOPICAL DICLOFENAC

Diclofenac is a nonsteroidal anti-inflammatory drug, that inhibits the activity of cyclooxygenase (COX), UV-induced pro-inflammatory cytokines, inhibits tumor cell proliferation and angiogenesis and induces metalloproteinases.[19,22] Thus, leading to keratolysis and collagen degradation. Diclofenac works as a treatment for AK as AK have an increased expression of COX-2 enzyme.[19–21]

It is available as a 3% gel in 2.5% sodium hyaluronate (hyaluronic acid as the vehicle ensures better penetration of diclofenac). It has to

be applied topically twice daily for 2–3 months and has a clearance rate of 58% after 1 month.[1,21]

It is a cheap, easy, and well-tolerated treatment modality. It should be avoided in aspirin-sensitive patients, long duration of treatment and side effects like erythema, pruritus, dryness are some of the drawbacks.

14 | IMIQUIMOD

Imiquimod is a synthetic immunomodulatory drug and is a toll-like-receptor-7 (TLR-7) agonist. It stimulates the release of tumor necrosis factor-alfa (TNF-a), interferon alpha and gamma (IFN-a and IFN-c), and interleukin-12 (IL12) thus, regulating the activation of macrophages, natural killer cells, dendritic cells, and cytotoxic T-cells.[1,20] It also plays a role in gene modulation and has antiviral and antitumoral potency.

Imiquimod is available as 2.5%, 3.75%, and 5% cream.[21] A number of penetration enhancers have been used to increase efficacy, the best ones being transethosomes.[20,21] Imiquimod 5% cream is used three times a week for 4 weeks, maximum area 25 sq. cm. on face or bald scalp. It has 85% clinical clearance of AK and a recurrence rate of 10% within 1 year.[21] The 3.75% cream formulation has better patient compliance due to easier dosing of once daily application for 2 weeks, then 2 weeks gap and again application for 2 weeks (2-0-2). It can be used for a larger surface area of up to 200 sq. cm. and works on both clinical and subclinical lesions on a wide area of cancerization. Imiquimod 2.5% cream is to be used using the similar protocol as for 3.75% cream. It is advised to apply imiquimod using the dorsum of the hand instead of fingertips (dorsum of left hand to apply to right cheek, so the cheek and dorsum of hand both are treated simultaneously) to avoid wasting the product. The maximum lesion count (sum of clinical and subclinical lesions) during treatment with imiquimod may be used to evaluate the effectiveness of treatment.[1]

Imiquimod is easy and accessible treatment option for AK but long-term therapy may be associated with side effects like erythema, weeping, erosions, pruritus, upper respiratory tract infections and influenza-like symptoms.[22] This modality provides the most cosmetically acceptable results.

15 | INGENOL MEBUTATE

Ingenolmebutate is a novel topical drug obtained from the latex sap of plant Euphorbia peplus. On topical application it uses P-glycoprotein drug transport to go through the stratum corneum and exerts action on the dermis and hypodermis. It acts via three different mechanisms[19]:

- Tumor ablation (rapid disruption of plasma membrane and mitochondrial swelling, leading to cell death due to primary necrosis)—by release of inflammatory cytokines.
- Neutrophil infiltration leading to acute inflammation.
- Last, tumor-reactive antibodies are induced and antibody-dependent neutrophil cytotoxicity eliminates residual cancer cells thus, preventing relapses.

Ingenolmebutate is a protein kinase C pathway activator and targets the sub-epidermal tumor vasculature. It slows cell proliferation, enhances differentiation of undifferentiated cells, induces cell cycle arrest, promotes apoptosis of caspases, phosphorylation of signaling molecules and increases stability of p53.[19,21,22]

Ingenolmebutate was approved by the US. FDA for treatment of non-hypertrophic/non-hyperkeratotic AK in 2012. It is available in a gel formulation of 0.015% for face and 0.05% for body. It has to be applied once daily for 2 consecutive days for body lesions and 3 consecutive days for lesions on the face. It has a very rapid action and requires only 2–3 days of treatment.[21]

Common side effects are application-site reactions like pain, pruritus, inflammation, infection, and systemic effects like periorbital edema, nasopharyngitis, and headache. Dryness, scabbing, and erythema resolve on its own in a month. Treatment of periocular area should be avoided due to risk of mild epithelial keratoconjunctivitis to severe.[21] Safety in pregnant females and children less than 18 years of age has not been established.

Notably, Ingenol Mebutate has been withdrawn from the market and its use has been suspended by the European Medicines Agency (EMA) over concerns of increased risk for skin malignancy, which outweighed its possible benefits, as on April 2020.[24]

16 | TIRBANIBULIN

Tirbanibulin is the newest topical treatment that has completed its phase 3 trial and was approved in the United States in 2020. The possible mechanism of action involves inhibition of tubulin polymerization and Src kinase signaling. The proposed dose is 1% ointment applied once daily for 5 days. It has shown encouraging results, with significantly improved responses when compared to placebo or vehicle formulation at 2 months. However, this molecule is limited by the development of transient local reactions like erythema, flaking and scaling.[25] A pooled-data analysis of two phase-3 trials revealed AK lesions in 73% of patients (recurrent or new), while 47% showed recurrence of lesions when followed-up at 1 year. Sustained AK clearance was observed in 27% of patients at 1-year follow-up. All patients had previously shown complete clearance of AK lesions after 57 days of treatment with Tribanibulin.[26] A recent review has also advocated tribanibulin as a safe and effective therapeutic option for AKs on the scalp and face with improved patient compliance due to its shorter treatment regimen.[27]

17 | CHEMICAL PEELS

Chemical peels are caustic agents applied on the skin surface to cause a controlled cell damage/death at a given depth. It has been used as one of the topical field-directed treatment for AK. The results depend on the chemical used, concentration, time of application, and thickness of the lesions. The commonly used agents are trichloroacetic acid (TCA), alpha hydroxy acids, zinc chloride, or phenolic acid.

The effectiveness of chemical peels in AK is 75%, with 25%–35% relapse rate within 1 year.[19,21] Combination treatment like 5FU with 70% glycolic acid or Jessner's peel has better efficacy than chemical peels alone.[1]

Chemical peels offer an easy, inexpensive, easily accessible treatment modality with minor drawbacks like erythema, inflammation, pigmentation, and scarring.

18 | TOPICAL AND ORAL RETINOIDS

Retinoids act in AK through their mechanism of action on pathway of oxidative stress and cell differentiation.[2] All trans retinoic acid (tretinoin) and retinaldehyde (derivative of vitamin A) has been used topically and orally, respectively in AK. Even though retinoids are never a first choice of treatment in AK they help decrease the number of damaged cells. Oral retinoids are preferred in patients with multiple lesions (more than 6), high-risk patients with genetic disorders like xeroderma pigmentosum and so on.[2]

Combination therapy of isotretinoin 20 mg orally with topical application of 5FU once daily is known as "turbo therapy" and has shown good efficacy.[2]

Side effects of topical retinoids include erythema, photosensitivity, irritation, dryness, erosions and so on. Systemic retinoids may cause chelitis, keratitis, hepatotoxicity, mood instability, dyslipidemia. Retinoids should be avoided in pregnancy.

19 | PHOTODYNAMIC THERAPY (PDT)

PDT is a local field-directed treatment of AK based on the principle of photosensitization, photochemical reactions and generation of reactive oxygen species leading to cell death.

The mechanism of action of PDT is as follows[1,21,22]:

- Application of topical photosensitizer compounds like 5-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL) for 3 h. These compounds are captures by premalignant lesions.
- Irradiation by wavelength of specific absorption spectrum leads to activation of photochemical mechanisms
- Release of prostaglandins and cytokines like PGE-2, IL-1, IL-2, TNF-a, and ROS.
- Necrosis or apoptosis of cells and vascular endothelial damage.

Daylight photodynamic therapy is often considered as a first-line treatment Grades I and II AK on face and scalp in immunocompetent patients.[1] A new modification, known as painless PDT employs application of MAL or ALA cream and exposure to daylight simultaneously to avoid pain. The cream is removed after 2 h of exposure. A chemical filter should be used to block the UV rays and avoid sunburn.

PDT is a suitable treatment option for multiple lesions on scalp and face. The efficacy of PDT is not satisfactory on the extremities due to lower temperature of the limbs. Incubation of ALA at higher temperature when used for extremities may help improve the efficacy.[1,18] Oral administration of Polypodium leucotomos along with PDT of scalp shows better efficacy and decreased rate of recurrence. The efficacy of PDT is poor in immunocompromised patients due to higher risk of treatment failure, recurrence, and development of cancerous lesions on treated areas dtriggered by ultraviolet rays or PDT used.[1] Overall, PDT has the advantage of leaving behind no post treatment scarring or disfigurement.

Despite several advantages of blue light PDT in AK, some patients experience a stinging pain during illumination, which may reduce its acceptance. Recently, Kaw et al. have proposed a new regimen for PDT to minimize this pain called 'simultaneous PDT' (blue light started immediately after topical 20% 5-ALA application to scalp and/or face, and continued for either 30, 45, or 60 min), as opposed to the conventional regimen (blue-light application after 1 h pre-incubation of topical 5-ALA).[28] A comparison of both regimens demonstrated the modified 'simultaneous' PDT regimen to be essentially painless with similar treatment efficacy to conventional regimen.

20 | PIROXICAM

Piroxicam is a nonselective nonsteroidal anti-inflammatory agent that blocks the activity of COX-1 and COX-2. 1% piroxicam gel was topically applied twice daily on AKs for 12 weeks. Changes were evaluated using AKESA (erythema, scale, and atrophy on a target lesion) scoring system.[29] There was regression of 48% lesions at the end of 12 weeks.[29] Minor side effects like pruritus, erythema, and xerosis were seen during the course of treatment. Hypertensive patients on thiazide diuretics are at higher risk of SCC and AK due to the photosensitizing property of thiazides. 0.8% topical piroxicam and sunscreen 50+ has been used as a combination therapy for AKs.[30] There was significant reduction in lesion count with the improvement of field cancerization.[30]

21 | CONCLUSION

AK is a relatively common pre-malignant skin lesion, which can progress to squamous cell carcinoma, although the risk cannot be predicted beforehand. Thus, early diagnosis and appropriate treatment should be our primary aim for all patients with AK. Besides, cosmetic disfigurement is also present, which seem to be the main reason for dermatologic consultation. Over the years several noninvasive diagnostic modalities have become popular ranging from dermoscopy to confocal microscopy. Dermoscopy is not as effective for AK compared to melanoma or basal cell carcinoma, while confocal microscopy is limited by its shallow penetrance. Thus, invasive histopathology remains the gold-standard diagnostic technique, especially in cases with high risk

for malignant transformation such as long-standing and large lesions. The selection of appropriate treatment modality depends on individual patients and their treating physician, as there is no current agreement on most effective therapy. Treatment strategies can be subdivided into two groups- lesion directed and field directed. Among the various modalities, 5-FU can be both preventive and therapeutic, while imiquimod and PDT provide the most cosmetically acceptable results. However, in lesional excision (surgical or ablative laser) remains the treatment of choice is there is evidence of malignant transformation. The role of preventive strategies like sun-protection and proper patient education cannot be overemphasized.

This review focused on the various diagnostic and treatment modalities available for this disease, along with their recent updates and individual characteristics. However, these authors propose further studies comparing these modalities with each other (head to head), to identify the most effective management strategy for such patients.

DISCLAIMER

We confirm that the manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met and that each author believes that the manuscript represents honest work.

ACKNOWLEDGMENTS

Open Access funding enabled and organized by Projekt DEAL.

AUTHOR CONTRIBUTIONS

Komal Agarwal: Writing and revising the manuscript. **Indrashis Podder, Clay J. Cockerell, Martin Kassir, Stephan Grabbe**: Review and revising the manuscript. **Mohamad Goldust**: Conception, writing, review, and revising the manuscript.

ORCID

Indrashis Podder https://orcid.org/0000-0002-9589-083X
Mohamad Goldust https://orcid.org/0000-0002-8646-1179

REFERENCES

1. Dianzani C, Conforti C, Giuffrida R, et al. Current therapies for actinic keratosis. *Int J Dermatol*. 2020;59:677-684.
2. Nashan D, Meiss F, Muller M. Therapeutic strategies for actinic keratoses—a systematic review. *Eur J Dermatol*. 2013;23:14-32.
3. Costa C, Scalvenzi M, Ayala F, Fabbrocini G, Monfrecola G. How to treat actinic keratosis? An update. *J Dermatol Case Rep*. 2015;9:29-35.
4. Casari A, Chester J, Pellacani G. Actinic keratosis and non-invasive diagnostic techniques: an update. *Biomedicines*. 2018;6:8.
5. Green A, Battistutta D. Incidence and determinants of skin cancer in a high-risk Australian population. *Int J Cancer*. 1990;46:356-361.
6. Rowert-Huber J, Patel MJ, Forschner T, et al. Actinic keratosis is an early in situ squamous cell carcinoma: a proposal for reclassification. *Br J Dermatol*. 2007;156(suppl 3):8-12.
7. Schmitz L, Gambichler T, Gupta G, et al. Actinic keratoses show variable histological basal growth patterns—a proposed classification adjustment. *J Eur Acad Dermatol Venereol*. 2018;32:745-751.
8. Schmitz L, Gambichler T, Kost C, Gupta G, Stücker M, Stockfleth E. Cutaneous squamous cell carcinomas are associated with basal proliferating actinic keratoses. *Br J Dermatol*. 2019;180:916-921.
9. Zalaudek I, Giacomel J, Argenziano G, et al. Dermatoscopy of facial nonpigmented actinic keratosis. *Br J Dermatol*. 2006;155:951-956.
10. Akay BN, Kocyigit P, Heper AO, Erdem C. Dermatoscopy of flat pigmented facial lesions: diagnostic challenge between pigmented actinic keratosis and lentigo maligna. *Br J Dermatol*. 2010;163:1212-1217.
11. Rollakanti KR, Kanick SC, Davis SC, Pogue BW, Maytin EV. Techniques for fluorescence detection of protoporphyrin IX in skin cancers associated with photodynamic therapy. *Photonics Lasers Med*. 2013;2:287-303.
12. Ulrich M, Maltusch A, Rius-Diaz F, et al. Clinical applicability of in vivo reflectance confocal microscopy for the diagnosis of actinic keratoses. *Dermatol Surg*. 2008;34:610-619.
13. Barton JK, Gossage KW, Xu W, et al. Investigating sun damaged skin and actinic keratosis with optical coherence tomography: a pilot study. *Technol Cancer Res Treat*. 2003;2:525-535.
14. Cockerell CJ, Wharton JR. New histopathological classification of actinic keratosis (incipient intraepidermal squamous cell carcinoma). *J Drugs Dermatol*. 2005;4:462-467.
15. Ruini C, Schuh S, Gust C, Hartmann D, French LE, Sattler EC. In-vivo LC-OCT Evaluation of the downward proliferation pattern of keratinocytes in actinic keratosis in comparison with histology: first impressions from a pilot study. *Cancers (Basel)*. 2021;13:2856.
16. Gold MH, Nestor MS. Current treatments of actinic keratosis. *J Drugs Dermatol*. 2006;5(suppl 2):17-25.
17. Werner RN, Jacobs A, Rosumeck S, Erdmann R, Sporbeck B, Nast A. methods and results report—evidence and consensus-based (s3) guidelines for the treatment of actinic keratosis—international league of dermatological societies in cooperation with the European dermatology forum. *J Eur Acad Dermatol Venereol*. 2015;29(11):e1-e66.
18. Zane C, Facchinetti E, Rossi MT, Specchia C, Ortel B, Calzavara-Pinton P. Italian expert consensus for the management of actinic keratosis in immunocompetent patients. *J Eur Acad Dermatol Venereol*. 2016;30(7):1077-1084.
19. Chetty P, Choi F, Mitchell T. Primary care review of actinic keratosis and its therapeutic options: a global perspective. *Dermatol Ther (Heidelb)*. 2015;5(1):19-35.
20. Berman B, Amini S. Pharmacotherapy of actinic keratosis: an update. *Expert OpinPharmacother*. 2012;13(13):1847-1871.
21. Samrao A, Cockerell CJ. Pharmacotherapeutic management of actinic keratosis: focus on newer topical agents. *Am J Clin Dermatol*. 2013;14(4):273-277.
22. Siegel JA, Korgavkar K, Weinstock MA. Current perspective on actinic keratosis: a review. *Br J Dermatol*. 2017;177:350-358.
23. Siegel JA, Korgavkar K, Weinstock MA. Cryotherapy is preferable to ablative CO_2 laser for the treatment of isolated actinic keratoses of the face and scalp: a randomized clinical trial. *Br J Dermatol*. 2014;170(5):1114-1121.
24. Heron CE, Feldman SR. Ingenol mebutate and the treatment of actinic keratosis. *J Drugs Dermatol*. 2021;20:102-104.
25. Blauvelt A, Kempers S, Lain E, et al. Phase 3 trials of tirbanibulin ointment for actinic keratosis. *N Engl J Med*. 2021;384:512-520.
26. Blauvelt A, Kempers S, Schlesinger T, et al. Tirbanibulin ointment 1% for actinic keratosis (AK): pooled data from two phase 3 studies. *SKIN J Cutan Med*. 2020;4:s121.
27. Dao DD, Sahni VN, Sahni DR, Balogh EA, Grada A, Feldman SR. 1% Tirbanibulin ointment for the treatment of actinic keratoses. *Ann Pharmacother*. 2021;76:10600280211031329.

28. 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;82:862-868.
29. Campione E, Diluvio L, Paternò EJ, Chimenti S. Topical treatment of actinic keratoses with piroxicam 1% gel: a preliminary open-label study utilizing a new clinical score. *Am J Clin Dermatol*. 2010;11(1):45-50.
30. Agozzino M, Russo T, Franceschini C, et al. Effects of topical piroxicam and sun filters in actinic keratosis evolution and field cancerization: a two-center, assessor-blinded, clinical, confocal microscopy and dermoscopy evaluation trial. *Curr Med Res Opin*. 2019;35(10):1785-1792.

How to cite this article: Agarwal K, Podder I, Cockerell CJ, Kassir M, Grabbe S, Goldust M.. Update on diagnosis and treatment of actinic keratosis. *Dermatological Reviews*. 2022;3:359-368. doi:10.1002/der2.121