


## Review

**Actinic keratosis – review for clinical practice**

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Conflict of interest: All authors have no conflict of interest to report.

Article updated on August 08, 2018, after first online publication on August 02, 2018: Acknowledgment section added.

doi: 10.1111/ijd.14147

**Introduction**

Actinic keratosis (AK) is clinically described as rough erythematous plaques that occur mainly on sun-damaged skin, such as the face, neck, and arms.<sup>1</sup> The term keratosis refers to the thickening of stratum corneum, and the term actinic, to its origin from sun exposure.<sup>2</sup> The lesions on the face have a flat aspect, while those in the upper limbs are usually thicker.<sup>2</sup>

AK has a worldwide prevalence of 11–25%. In the United States, prevalence varies from 11 to 26%, where the condition accounts for a third of dermatological consultations and the second most frequent diagnosis. In Australia, AKs affect 40–60% of adults over the age of 40. Prevalence is related to fair skin, age, and gender.<sup>3–5</sup>

Several studies have shown that individuals with Fitzpatrick skin types I and II are more likely to have AK. Individuals over

**Abstract**

Actinic keratosis (AK) is a lesion that arises as a result of excessive exposure to solar radiation and appearing predominantly on Fitzpatrick phototype I and II skin. Given that some AKs evolve into squamous cell carcinoma, these lesions are considered premalignant in nature, occurring mostly in elderly men and immunosuppressed individuals chronically exposed to ultraviolet (UV) radiation. There are several mechanisms for the formation of AKs; among them are oxidative stress, immunosuppression, inflammation, altered proliferation and dysregulation of cell growth, impaired apoptosis, mutagenesis, and human papillomavirus (HPV). Through the understanding of these mechanisms, several treatments have emerged. Among the options for AK treatment, the most commonly used include 5-fluorouracil (5-FU), cryotherapy, diclofenac, photodynamic therapy (PDT), imiquimod (IQ), retinoids, and ingenol mebutate (IM). There have been recent advances in the treatment options that have seen the emergent use of newer agents such as resiquimod, betulinic acid, piroxicam, and dobesilate. The combination between therapies has presented relevant results with intention to reduce duration of therapy and side effects. All AK cases must be treated because of their propensity to transform into malignancy and further complicate treatment. In addition to medical or surgical care, education about sun exposure prevention remains the best and most cost-effective method for AK prevention. The objective of this article is to conduct a literature review of the clinical presentation of AK including advances in treatment options available.

the age of 80 are six times more likely to develop AKs when compared to those between the ages of 50 and 59.<sup>6</sup> Other studies also show that the prevalence of AK is higher in men than in women, what may be attributed to increased sun exposure in men.<sup>1,2,7–10</sup> A study conducted in England reported an AK prevalence rate of 15.4% in men and 5.9% in women in their 40s.<sup>5</sup> When individuals above 70 years were observed, this rate increased to 34.1% and 18.2% in men and women, respectively. Similar findings were seen in Australia, with AK prevalence rates of 22% and 8% for men and women aged 30–39 years, respectively. At 60–69 years of age, the rates were 83% and 64%. According to Weber,<sup>11</sup> this discrepancy between genders has been attributed to difference in sun exposure. However, regardless of gender, individuals who are chronically exposed to solar radiation, such as workers and those active

outdoors, are at high risk of developing AK and subsequently skin cancer.<sup>3–5,12–16</sup>

The Brazilian population is primarily mixed; many are descendants from Portuguese, Italians, and Germans who migrated in the beginning of the 20th century and for decades worked in the fields. Those have, in general, low skin phototypes and were subjected to chronic sun exposure. In addition, the culture of outdoor leisure and sun exposure from tender ages is a constant.

### Malignancy of actinic keratosis

The potential to transform into squamous cell carcinomas (SCC), the second most common type of cancer of the skin, is of great concern.<sup>1,15–18</sup> In many cases, AKs are subclinical and disseminated; therefore, the term field cancerization is nowadays more appropriate to describe the lesions.<sup>19</sup> Though it has no mortality, it is an important target for research and treatment because of its high incidence and difficulty in establishing which lesions with precancerous potential will progress to malignancy.<sup>3,10,13,18–21</sup> The main etiological factor for SCC is the accumulation of UV damage. This risk is directly related to the number of actinic keratoses and time of appearance. Some studies show that in a 10-year period, about 16% of AKs can progress to invasive SCC. Pires<sup>3</sup> indicated that 59% of SCCs occur from the premalignant transformation of AK. Bowen's disease (BD) is defined as the presence of squamous cancerous cells *in situ* that manifest as a slowly eroding or enlarging erythematous plaque and is also considered to be a precursor to SCC.<sup>1,3,5,10,16</sup>

### Mechanism of possible transformation

The main causative agent of AK is UV radiation. Excessive exposure to UV A and B generates a cascade of structural damage to cells' DNA and membrane lipids, leading to a generation of overall inflammation.<sup>21–23</sup>

UVA rays (315–400 nm) constitute 95% of the solar radiation that reaches the surface of the Earth. They penetrate more deeply in the skin, being able to reach the dermis, and are responsible for tanning the skin through the activation of melanocytes in the epidermis. The damage caused by exposure to UVA rays also occurs indirectly through the production of free radicals. This may lead to premature aging. The damage occurs through the generation of Reactive Oxygen Species (ROS) such as the hydroxyl radical (OH), superoxide (O<sub>2</sub><sup>-</sup>), hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), and singlet oxygen (<sup>1</sup>O<sub>2</sub>). Once generated, ROS react with proteins, membrane lipids, saccharides, and DNA bases causing a reaction that deregulates the cellular processes generating biological responses, such as inflammation. Inflammation happens as a cascade of events characterized by infiltration of macrophages and neutrophils, increased production of prostaglandins, tumor necrosis factors, and interleukins that by its turn generates more ROS and triggers even further damage through a positive feedback loop. Direct DNA damage is mainly caused by hydroxyl radicals. It has been postulated that this is responsible for 60–70% of damage.<sup>9,21–24</sup>

UVB rays (280–315 nm) constitute 4–5% of the solar radiation that reaches humans and are able to penetrate to the basal layer of the epidermis. Although less penetrating and less abundant, the damage caused by UVB directly on the keratinocyte's DNA is quite significant. It acts by replacing cytosine and thymine bases causing mutations in the TP53 gene which is responsible for the production of the p53 protein, which prevents cell duplication in case of damage and promotes, among other biological effects, apoptosis.<sup>9,23,25</sup> In addition to direct damage to DNA, UVB radiation also promotes ROS production.

AK can also be observed in organ transplant patients who use immunosuppressants and in patients with HIV/AIDS. This group has a higher propensity to develop nonmelanoma skin cancer of high mortality rates, since there is a compromise of skin immune surveillance leading to an accelerated proliferation of dysplastic keratinocytes similar to those caused by solar radiation.<sup>1,9,26</sup>

Recently the human papillomavirus (HPV) has been associated with the formation of AK. The mechanism has not been very well understood, but it is believed that the virus' protein reduces levels of an apoptotic protein normally activated in keratinocytes as a protective measure when exposed to ultraviolet radiation.<sup>1,9</sup>

### Treatments

AK treatment is mostly based on destructive methods. They range from curettage, cryotherapy with liquid nitrogen, topical chemotherapeutics, and chemical peels.<sup>27</sup> Immunomodulators have also been used with a certain degree of success.<sup>28</sup> A number of studies support the efficacy of PDT in the treatment of localized or disseminated AKs.<sup>29,30</sup> PDT has similar results to traditional treatments and, like clinical treatments, allows cancerization field treatment where subclinical lesions may be present, as compared to surgery or cryotherapy that treat only visible lesions.<sup>31</sup> A study based on literature review that looked at the results of chemical treatments (diclofenac 3% in 2.5% of hyaluronic acid, 5-FU, IQ IM) compared to vehicle or placebo, concluded that the efficacy of all clinical treatments was similar but differed in their adverse effects and cosmetic results. IQ and PDT showed better cosmetic results than cryotherapy and 5-FU.<sup>32</sup>

The choice of treatment depends on clinical evaluation, taking into account the extent of the condition, the pros and cons of each method, and cost. When it comes to a public hospital that basically serves the low-income and under-resourced population, the treatment of AK and the cancerous field is a challenge. Under these circumstances, IQ is reserved for the most localized and resistant cases and PDT, by the cost, performed sporadically. Other low-cost resources such as diclofenac gel and retinoids are used for less complex cases of thin or grades I or II AK for 3–6 months, with variable results.

### 5-fluorouracil (5-FU)

5-FU is a topical and relatively cost-effective treatment. It is classified as an antineoplastic analogue to pyrimidine.<sup>1</sup> Its main mechanism of action is through the reduction in proliferation of

atypical cells and induction of apoptosis. This occurs through the reduction in thymidylate synthase, an enzyme that acts on DNA synthesis.<sup>4,9,33</sup> The antitumor effect is increased by the inflammation caused by the drug. On the other hand, this limits the patient's tolerability to the treatment thereby affecting compliance. If the inflammation is severe, topical steroids may be used to ameliorate the symptoms.<sup>33</sup> 5-FU concentrations of 1, 2, and 5% are recommended for the treatment of keratosis located on the hands, back, and forearms. For face and scalp, a 0.5% concentration is recommended.<sup>1,5,33</sup> The cream is usually applied twice a day for 2–4 weeks.<sup>1</sup> Clearance of the lesions occurs in approximately 62.5% of patients in complete adherence to the treatment, and recurrence rates are around 30%.<sup>9,34</sup> A 50% efficacy in AK control is observed in patients who underwent a treatment, with topical 5-FU for 4 weeks in repeated cycles every 4–6 months. For those, a previous treatment with electrocoagulation, cryosurgery, and chemical cauterization was conducted.

Treatment may be challenging because of the development of adverse events such as severe dermatitis that may be accompanied by wound infections, pruritus, burning, blistering, necrosis and erosions, pain, and ulceration. Scarring and photosensitivity can occur and is increased by sun exposure. Topical 5-FU should not be used to treat patients who suffer from other skin diseases, such as melasma or acne rosacea, or pregnant women, because of their teratogenic potential.<sup>5,9,33</sup> There have been reports of gastrointestinal and hematological toxicity in patients with severe deficiency in the major 5-FU degradation enzyme, dehydropyrimidine dehydrogenase (DPD).<sup>33</sup>

A new formulation combining 5-FU 0.5% and salicylic acid 10% is available in Europe and has demonstrated efficacy for the treatment of AK. The protocol for its use is once a day in an area of up to 25 cm<sup>2</sup> for 12 weeks. Side effects such as local inflammation and pruritus have been observed.<sup>17,35,36</sup>

### Diclofenac

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) and is usually used to suppress signs and symptoms of inflammation, as well as having antipyretic and analgesic properties. The mechanism of action is through the blockade of the enzyme cyclooxygenase 2 (COX-2). This enzyme promotes tumor growth, enhances cell proliferation, stimulates angiogenesis, and inhibits apoptosis.<sup>35</sup> Inhibition of the COX-2 pathway will result in reduced prostaglandin production. Prostaglandins suppress the immune system, stimulate cell proliferation, and promote invasion by cancer cells and angiogenesis, thus allowing tumor formation.<sup>9,38</sup> Diclofenac also decreases the formation of arachidonic acid metabolites. This inhibits apoptosis and increases the invasive capacity of tumor cells.<sup>4,39</sup>

The use of anti-inflammatory drugs in the treatment of AK arose from studies that revealed exacerbated expression of COX-2 in malignant and premalignant lesions. A high expression of COX-2 related to increased sensitivity to UV-induced

skin tumors has been observed.<sup>40</sup> Although the overall efficacy of 3% diclofenac gel is lower than that of other topical agents, it is considered to be a well-tolerated and well-compliant treatment representing a therapeutic alternative in patients who cannot tolerate the side effects of other topical agents, such as 5-FU or IQ.<sup>33</sup> The probability of adverse effects caused by a 3% diclofenac gel is reported to be 5%.<sup>41</sup>

A single formulation of 3% diclofenac gel and 2.5% hyaluronic acid is currently available. The recommended therapeutic regimen consists of applying the cream twice a day for 2–3 months, with a clearance rate of 40% and complete cure probability of 58%.<sup>41</sup> Adverse effects described include desquamation, pruritus, dry skin, localized edema, paresthesia, erythema, rashes, and less frequently, photosensitivity.<sup>37,42,43</sup>

### Retinoids

Topical retinoids have been used for over 30 years in the treatment of various skin conditions such as mild, moderate, and severe acne, melasma, photoaging, and actinic keratosis. The most commonly used topical retinoids are: tretinoin, adapalene, isotretinoin, tazarotene, retinol (and its esters), and retinaldehyde.<sup>15,44–48</sup>

Systemic retinoids are mostly administered in skin cancer chemoprevention. The most commonly used are: etretinate, acitretin, and isotretinoin. Comparing topical to systemic retinoids, the former cause less systemic toxicity, but local adverse effects may occur depending on the concentration of the drug. Oral retinoids are most commonly used in patients with a large number of keratosis and may be used in the prevention of developing SCC in certain populations, such as the immune suppressed.<sup>1,15</sup>

Oral isotretinoin may be used in a variety of doses, but the most common one is 20 mg/day for 3 weeks, and topical tretinoin is used at a concentration of 0.1% twice a day for 6 months. It is also possible to use a combination of low-dose oral isotretinoin (20 mg daily) and 5-FU topically twice daily. The purpose of this is to generate inflammation, which takes 2 weeks to appear and has a synergistic effect with the drugs.<sup>2,49,50,51</sup> With the combination of 5-FU and isotretinoin, one can obtain greater potential of apoptosis and inhibition of cellular proliferation. Comparing 5-FU monotherapy and its association with oral isotretinoin, we observed that the combination improved the results regarding the reduction in the number of AKs, prevention of the appearance of new lesions, and repair of the skin damaged by radiation.<sup>49,52</sup> The main obstacle in the use of this class of drugs is the side effects, such as erythema, peeling, burning and pruritus, xerosis, hair loss, dry skin and mucous membranes, and the need for intense protection from sunlight. Teratogenicity is the most serious adverse event, since exposure at any time during pregnancy poses a risk.<sup>15,20</sup>

Tretinoin, or retinoic acid, is a molecule derived from vitamin A. In 1962, Stuttgart first used retinoic acid for the treatment of AK. In the 1970–80s, a retinoid deficiency was associated with

epithelial cancer. Since then many studies have shown the efficacy of retinoids in the treatment of AK and in skin cancer prevention.<sup>1,15,55</sup> The effect of retinoic acid occurs through nuclear retinoid receptor mediation. There are two types of receptors: retinoic acid receptors (RARs) and retinoid X receptors (RXRs). Both have three subtypes,  $\alpha$ ,  $\beta$ , and  $\gamma$ , and each subtype has several isoforms. In the skin, RAR- $\gamma$  and RXR- $\alpha$  are the most active. In premalignant lesions, a low expression of these receptors and also of the RAR- $\beta$ 2 has been observed.<sup>49,53,54</sup> It is important to emphasize that premalignant lesions may present vitamin A deficiency because their reuptake is impaired. This causes the expression of the RAR- $\beta$ 2 receptor to be decreased since it is self-induced by retinoids. RAR- $\beta$ 2 receptor expression is restored by retinoid therapy, with normal and differential growth of the lesion cells being reconstituted, which correlates directly with clinical improvement and indicates the importance of retinoids in the treatment of carcinogenesis.<sup>49,54</sup> Table 1 summarizes the main retinoids used in the dermatological clinic, their sites of action, and cellular receptors.

### Imiquimod

IQ is a synthetic amine imidazoquinolone having a potent immune response modifying activity when used topically. It acts by binding to toll-like receptors (TLR) that detect pathogens' molecular patterns. TLRs play a key role in the activation of the innate and adaptive immune response. These receptors are located on the surface of dendritic cells, monocytes, macrophages, and Langerhans cells. Their activation by IQ induces apoptosis and leads to the release of cytokines and chemokines such as tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), interferon- $\gamma$  (IFN- $\gamma$ ), interleukins, and granulocyte-macrophage colony-stimulating factor (GM-CSF). The release of cytokines and chemokines causes an influx of inflammatory cells into the lesions and consequently its destruction mediated by innate response immune cells, such as natural killer (NK) cells, and adaptive response

**Table 1** Main retinoids used in the dermatological clinic, their sites of action, and most frequent pathologies for which they have action

Retinoid	Generation	RAR	Site of action	Uses
Isotretinoin	1	$\alpha$ , $\beta$ , $\gamma$	Topical/ systemic	AK, acne, aging
Tretinoin	1	$\alpha$ , $\beta$ , $\gamma$	Topical	AK, acne, aging
Adapalene	3	$\beta$ , $\gamma$	Topical	AK, acne
Etretinate	2	–	Systemic	AK, psoriasis
Acitretin	2	–	Systemic	AK, psoriasis
Tazarotene	3	$\beta$ , $\gamma$	Topical	Psoriasis, acne
Retinoaldehyde	1	–	Topical	AK, aging
Retinol	1	–	Topical	AK, aging, psoriasis

RAR, retinoic acid receptor; AK, actinic keratosis.<sup>15</sup>

cells, such as cytotoxic T lymphocytes. Therefore, the development of an inflammatory reaction predicts a good therapeutic efficacy.<sup>33,55,56</sup>

The characteristic properties of IQ have led to its use in several dermatological applications, including genital warts, AK, and superficial basal cell carcinoma. IQ has also been used in the treatment of cutaneous metastasis of breast cancer.<sup>55,56</sup>

The FDA has approved the use of IQ cream at 5, 3.75, and 2.5% concentrations for AK on the face and scalp.<sup>57</sup> For superficial basal cell carcinoma, the 5% cream is more suitable.<sup>33</sup> For the 2.5 and 3.75% cream, the protocol is to use it once a day for 2 weeks, followed by 2 weeks off and another 2 weeks of application.<sup>1,33,58,59</sup> The 5% formulation is indicated for topical use in immunocompetent adults with two applications for 16 weeks on an area up to 25 cm<sup>2</sup>. The 3.75% formulation has an advantage over the 5% one since it presents similar efficacy but with less degree of adverse events and a shorter time of use with the possibility of application on a larger area.<sup>56</sup> This formulation has yet a 35.6% probability of complete cure and recurrence rate after 12 months of 20.9%.<sup>41</sup> Reactions to IQ may occur beyond the application site and include pruritus, erosions, burning, erythema, peeling, vesicles, exudations, and crusts.<sup>33,56,58,60</sup>

### Ingenol mebutate

IM is a diterpene derived from a plant called *Euphorbia peplus*.<sup>61,62</sup> The mechanism of action is not fully understood, but *in vivo* and *in vitro* models suggest a dual mechanism of action; the induction of local cell death by disrupting the plasma membrane and the mitochondria of tumor cells and the production of proinflammatory cytokines leading to other neutrophilic inflammatory cell infiltration.<sup>63</sup>

The FDA-approved therapeutic regimens are 0.015% gel formulation once a day on the face and scalp for three consecutive days, or 0.05% gel formulation once daily on the body and extremities for two consecutive days.<sup>33,61</sup> IM (0.05% gel) applied once a day for two consecutive days has been shown to lead to clearance of lesions in 71% of the patients. A concentration of 0.015% gel applied to the face once a day for three consecutive days has also led to a complete response in 42.2–50% of the patients and partial response in 85%; a recurrence after 12 months occurred in a rate of 12.8%.<sup>41,64,65</sup> Although several topical therapies are approved for AK treatment, a major advantage of IM gel over other topical medications is the reduced number of doses required, providing similar or greater efficacy when compared with diclofenac gel (3%) or 16 weeks of treatment with IQ (5%).<sup>19,63,66</sup> Erythema, edema, peeling, crusting, pain, and/or superficial ulceration at the site of application have been described as possible adverse events. In general, the effects disappear spontaneously within 2 days for face and scalp and 4 days for body and extremities and the medication is well tolerated in general.<sup>33,61,67</sup>

### Photodynamic therapy

PDT is a clinically approved and minimally invasive procedure that relies on the reaction between a photosensitizing compound and a light source to produce reactive oxygen species (ROS). It has been used in the treatment of many premalignant, malignant, and inflammatory skin cancers including AK, basal cell carcinoma, BD, and cutaneous lymphoma.<sup>21,68</sup>

Among the most used photosensitizing compounds are 5-aminolevulinic acid (ALA) and its lipophilic derivative, methylaminolevulinate (MAL).<sup>69</sup> These accumulate preferentially in the cells of actinic keratosis, a phenomenon possibly related to several factors such as the altered cell permeability and decreased lymphatic drainage. Within the AK cells, the photosensitizers are converted to protoporphyrin IX that absorb light and lead to the generation of ROS thus resulting in damage to the microvasculature, induction of a local inflammatory reaction, and cell death.<sup>13,21,68,69</sup>

PDT has shown good results, since the treatment does not modify the integrity of the tissues. In addition, none of the clinically approved compounds accumulate in the nuclei of the cells, thereby reducing DNA damage. Adverse effects reported in the use of PDT include pain and photosensitization of the skin.<sup>68</sup>

There is no significant difference between MAL and ALA when it comes to efficacy, but ALA causes less pain during treatment.<sup>21</sup> When it comes to selectivity, it is noted that MAL is more selective for premalignant cells than ALA.<sup>69</sup> Zhao *et al.*<sup>21</sup> reported studies where greater efficacy of PDT was observed when compared with 5-FU.

### Cryotherapy

Cryotherapy is the freezing of the lesion by direct application of liquid nitrogen or eventually other cryogens using a cryospray, catheter, or swab with subsequent thawing. Between  $-40$  and  $-50$  °C, skin keratinocytes are destroyed and nitrogen continues to be applied until approximately  $-196$  °C for efficient extermination.<sup>1,18</sup> The treatment regimens used range from 5 to 15 seconds of application; however, for thick lesions it may take up to 30 seconds. The application must be made on and around each lesion. For complete eradication of AKs, it is important to achieve a margin of 2–4 mm freezing around the target lesion. Therefore, a determining factor in the success of the treatment will be the ability to visualize the lesion.<sup>1,18,70</sup>

Cryotherapy is an efficient destructive treatment of individual and discrete lesions. However, it has a limited effect on larger, thicker lesions on photo-injured areas. Patients with cold intolerance should also not be treated with cryotherapy.<sup>2,16</sup> Some of the effects that may appear during treatment are mild pain, erythema, and crusting that usually disappear up to 10 days after the procedure, as well as the possibility of hypopigmentation in individuals with dark skin. The procedure's advantage is its non-dependence on the patient's adherence. Its efficacy ranges from 75 to 99% and is directly related to the way the application is performed.<sup>18,70</sup>

Table 2 compiles the usual available drug treatments and provides a cost idea in Brazil for each of them.

### Emerging treatments

The search for new drugs to treat AK is related to the need for drugs that have better tolerance, greater efficacy, and greater safety than previous treatments. The development of newer treatments follows two approaches; one is the search for new drugs within the classes that are already used, and the other is the search for new classes of drugs.<sup>71</sup> This topic will address some of the treatments that are under investigation.

### Resiquimod

Resiquimod (RQ) is under investigation as a treatment to AKs. This is an IQ analogue that has the same mechanism of action but is 10–100 times more efficient.<sup>1,33,56</sup> RQ is available at the concentrations 0.01, 0.03, 0.06, or 0.1%. Good results were obtained with applications of 3 times a week for 4 weeks. There have been reports of 1% RQ applied twice a day for 90 days, resulting in complete regression of the AKs in 48% of the cases.<sup>43</sup>

### Piroxicam

Piroxicam is a benzothiazine nonsteroidal anti-inflammatory which acts by the same mechanism as diclofenac but is structurally different. It is a potent cyclooxygenase 1 (COX-1) inhibitor and suppresses important proteinases involved with tumor growth.

Studies indicate activity against AKs with fewer adverse effects. A study conducted using piroxicam 0.8% incorporated into topical products, such as sunscreens, and applied twice a day for 6 months resulted in significant improvement of AKs. Piroxicam seems to be more effective than other NSAIDs and has antioxidant and antiviral effects that could be relevant in AKs associated with HPV.<sup>33,39,72,73</sup>

### Dobesylate

Dobesylate is an endothelial stabilizing agent used to prevent diabetic retinopathy and varicose veins on legs. It inhibits vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF). FGF has a role in oncogenesis since it stimulates cell proliferation, invasion, and angiogenesis. FGF is upregulated in skin tumors. Formulations with 2.5 and 5% of dobesylate have been studied for AK and basal cell carcinoma treatment and have proven to be effective, safe, and well tolerated, but studies are still preliminary.<sup>33,42</sup>

### Astragalin

Astragalin is a kaempferol glycoside derivative extracted from the flowers of *Prunus. persica*. The extract is largely used in Asia for skin disorders, and it is shown to have a protective effect against UV-induced damages on skin. Specifically, Astragalin has shown to attenuate UVB-induced AK by suppressing

**Table 2** Main topical treatments used in clinical dermatology for actinic keratosis

Drug	Usual concentrations (%)	Cost	Appearance	Mechanism of action	Most frequent associations
5-fu	0, 5, 1, 2 and 5	+	Cream	Direct action on DNA synthesis and to a lesser degree on RNA.	–
Diclofenac	3	+	Gel or cream	It inhibits COXs, especially COX-2 by UVB radiation.	Hyaluronic acid 2.5%
Tretinoin, isotretinoin	0, 1–0.3	+	Gel or cream	Antiproliferative and anti-apoptotic properties.	–
Ingenol mebutate	0.015 and 0.05	+++	Gel	Induction of local cell death and the production of proinflammatory cytokines.	–
Imiquimod	2.5, 3.75 and 5	+++	Cream	Local immune response modifying activity	–

+++; high cost; ++, medium cost; +, low cost; 5-FU, 5-fluorouracil; COX, cyclooxygenase; UVB, ultraviolet B.<sup>9,32,60</sup>

an important pathway involved in AK formation, therefore being a promising natural therapeutic agent.<sup>74–76</sup>

### Daylight photodynamic therapy (DL-PDT)

In DL-PDT, the photosensitizer (MAL) applied on skin is activated by one single 2-hour exposure to daylight. It is an alternative to conventional PDT (c-PDT) that offers advantages of tolerability, treatment duration, and because it requires no artificial light source. Studies in literature demonstrated that DL-PDT is as effective as c-PDT but with less adverse effects such as pain, leading to greater adherence.<sup>77–80</sup>

### Conclusion

AK is still very prevalent among the elder population and should be treated individually and with a personalized strategy taking into consideration the number of lesions and their location. It is important to take into account subclinical lesions that may not be visible but may represent a risk. Thus, dermatologists must take the necessary time and use clear and direct language to ensure understanding of how to use the drugs and precautions needed during and after treatment. The need for sun protection during this time must be marked as well as the possibility of adverse effects such as inflammation and other signs.

In tropical countries, where solar incidence is high, many people are exposed daily to UV radiation, whether at work or in leisure activities. Education on the use of photoprotection methods as well as the dangers of sun exposure and its signs is imperative (more specifically for fair skin population). The use of broad spectrum sunscreen with an SPF of at least 30 in addition to UVA protection must be indicated throughout the skin recovery process along with other means of sun protection such as clothing and accessories. This may contribute in reducing new cases of AK and better quality of life.

All AK cases deserve attention, for it is initially a simple condition that can aggravate and cause great suffering and worsen a patient's quality of life. Education and prevention of sun exposure are still the best and cheapest actions that can be taken to

fight AK.<sup>10,14</sup> There is a need for more comparative studies of combination treatments that provide solid and clear information to assist the dermatologist in the choice of treatment.

The main issue to be addressed is the reduction in side effects, and this can be achieved by ameliorating the drug's efficacy and then decreasing treatment time and thus compliance.

### Acknowledgement

The authors are grateful to FAPESP (2015/02129-6) for financial support.

### References

- Dodds A, Chia A, Shumack S. Actinic keratosis: rationale and management. *Dermatol Ther* 2014; **4**: 11–31.
- Castro IA, Schutz LC, Capp E, et al. Ceratoses actínicas. *Revista HCPA Porto Alegre*. 2006; **26**: 66–72.
- Pires ACB. *Da queratoseactínica ao carcinoma espinocelular* [dissertação]. Porto (Portugal): Universidade do Porto, 2011: 33f.
- Segatto MM, Dornelles SIT, Silveira VB, et al. Comparative study of actinic keratosis treatment with 3% diclofenac sodium and 5% 5-fluorouracil. *An Bras Dermatol* 2013; **88**: 732–738.
- Chetty P, Choi F, Mitchell T. Primary care review of actinic keratosis and its therapeutic options: a global perspective. *Dermatol Ther* 2015; **5**: 19–35.
- SBD – Sociedade Brasileira de Dermatologia. *Classificação dos fototipos de pele*. Available from: <http://www.sbd.org.br/cuidados/por-que-as-pessoas-tem-tons-de-pele-diferentes/> (Accessed: 13 out. 2016).
- Rocha FP, Menezes AMB, Almeida Júnior HL, Tomasi E. Marcadores e fatores de risco para queratoseactínicas e carcinomas basocelulares: um estudo de caso-controle. *An Bras Dermatol* 2004; **79**: 441–54.
- Rosso JQD, Kircik L, Goldenberg G, et al. Comprehensive management of actinic keratosis: practical integration of available therapies with a review of a newer treatment approach. *J Clin Aesthet Dermatol* 2014; **9**: 2–12.
- Costa C, Scalvenzi M, Ayala F, et al. How to treat actinic keratosis? An update. *J Dermatol Case Rep* 2015; **9**: 29–35.
- INCA-Instituto Nacional de Câncer José Alencar Gomes da Silva. *Coordenação de Prevenção e Vigilância*. In: *Estimativa 2016: Incidência De Câncer No Brasil*. Rio de Janeiro: Ministry of Health, 2015: 122p.

- 11 Weber A (2009). *Comparative study between photodynamic therapy and topical imiquimod in actinic keratosis treatment* [thesis]. Federal University of Porto Alegre, Porto Alegre, Brazil.
- 12 Salasche SJ. Epidemiology of actinic keratosis and squamous cell carcinoma. *J Am Acad Dermatol* 2000; **42**: 4–7.
- 13 Spencer JM, Hazan C, Hsiung SH, et al. Therapeutic decision making in the therapy of actinic keratosis. *J Drugs Dermatol* 2005; **4**: 296–301.
- 14 Flor J, Davolos MR, Correa MA. Protetores solares. *Quim Nova* 2007; **30**: 153–158.
- 15 Ianhez M, Fleury Junior LF, Miot HA, et al. Retinoids for prevention and treatment of actinic keratosis. *An Bras Dermatol* 2013; **88**: 585–593.
- 16 Soini EJ, Hallinen T, Sokka AL, et al. Cost–utility of first-line actinic keratosis treatments in Finland. *Adv Ther* 2015; **32**: 455–476.
- 17 Stockfleth E, Kerl H, Zwingers T, et al. Low-dose 5-fluorouracil in combination with salicylic acid as a new lesion-directed option to treat topically actinic keratosis: histological and clinical study results. *Br J Dermatol* 2011; **165**: 1101–1108.
- 18 Oliveira MC, Trevisan F, Pinto CAL, et al. Histopathological analysis of the therapeutic response to cryotherapy with liquid nitrogen in patients with multiple actinic keratosis. *An Bras Dermatol* 2015; **90**: 384–389.
- 19 Stockfleth E, Harwood CA, Serra-Guillen C, et al. Phase IV head-to-head randomized controlled trial comparing ingenol mebutate 0.015% gel with diclofenac sodium 3% gel for the treatment of actinic keratosis on the face or scalp. *Br J Dermatol* 2018; **178**: 433–442.
- 20 Clouser MC, Roe DJ, Foote JA, et al. Effect of non-steroidal anti-inflammatory drugs on non-melanoma skin cancer incidence in the SKICAP-AK trial. *Pharmacoepidemiol Drug Saf* 2009; **18**: 276–283.
- 21 Zhao B, He Y. Recent advances in the prevention and treatment of skin cancer using photodynamic therapy. *Expert Rev Anticancer Ther* 2010; **10**: 1797–1809.
- 22 Freitas BJSA. *Possíveis marcadores de estresse oxidativo para câncer de pele não melanoma: efeito da suplementação de vitamina C, E e mineral zinco em indivíduos que tiveram câncer de pele não melanoma* [tese]. Campinas, SP: Universidade Estadual de Campinas, 2014: 211 p.
- 23 Svobodova A, Walterova D, Vostalova J. Ultraviolet light induced alteration to the skin. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2006; **150**: 25–38.
- 24 Barreiros ALB, David MJ. Estresse oxidativo: relação entre geração de espécies reativas e defesa do organismo. *Quim Nova* 2006; **29**: 113–123.
- 25 Martinez MAR, Francisco G, Cabral LS, et al. Genética molecular aplicada ao câncer cutâneo não melanoma. *An Bras Dermatol* 2006; **81**: 405–419.
- 26 Ulrich C, Hackenthal M, Ulrich M, et al. Treatment of multiple actinic keratosis with topical diclofenac 3% gel in organ transplant recipients: a series of six cases. *Br J Dermatol* 2007; **156**: 40–42.
- 27 Callen JP, Bickers DR, Moy RL. Actinic keratosis. *J Am Acad Dermatol* 1997; **36**: 650–653.
- 28 Berker D, McGregor JM, Hughes BR. Guidelines for the management of actinic keratosis. *Br J Dermatol* 2007; **156**: 222–230.
- 29 Chamberlain AJ, Kuruwa HA. Photodynamic therapy: is it a valuable treatment option for actinic keratosis? *Am J Clin Dermatol* 2003; **4**: 149–155.
- 30 Kennedy JC, Pottier RH, Pross DC. Photodynamic therapy with endogenous protoporphyrin IX: basic principles and present clinical experience. *J Photochem Photobiol* 1990; **6**: 143–148.
- 31 Shergill B, Zokaie S, Carr AJ. Non-adherence to topical treatments for actinic keratosis. *Dove Med Press* 2014; **8**: 35–41.
- 32 Gupta AK, Paquet M, Villanueva E, et al. Interventions for actinic keratosis (Review). *Cochrane Database Syst Rev* 2012; **12**.
- 33 Micali G, Lacarruba F, Nasca MR, et al. Topical pharmacotherapy for skin cancer: part I. Pharmacology. *J Am Acad Dermatol* 2014; **70**: 965.e1–965.e12.
- 34 Stockfleth E, Sibbring G, Alarcon I. New topical treatment options for actinic keratosis: a systematic review. *Acta Derm Venereol* 2016; **96**: 17–22.
- 35 Herranz P, Morton C, Dirschka T, et al. Low-dose 0.5% 5-fluorouracil/10% salicylic acid topical solution in the treatment of actinic keratosis. *J Cutan Med Surg* 2016; **20**: 555–561.
- 36 Nguyen HP, Rivers JK. Actikerall<sup>™</sup> (5 fluorouracil 0.5% and salicylic acid 10%) topical solution for patient directed treatment of actinic keratosis. *Skin Therapy Lett* 2016; **21**: 1–3.
- 37 Nelson CG. Diclofenac gel in the treatment of actinic keratosis. *Ther Clin Risk Manag* 2011; **7**: 207–211.
- 38 Campione E, Paternó EJ, Candi E, et al. The relevance of piroxicam for the prevention and treatment of nonmelanoma skin cancer and its precursors. *Drug Des Devel Ther* 2015; **9**: 5843–5850.
- 39 Thun MJ, Henley SJ, Patrono C. Nonsteroidal anti-inflammatory drugs as anticancer agents: mechanistic, pharmacologic, and clinical issues. *J Natl Cancer Inst* 2002; **94**: 252–266.
- 40 Smith EV, Grindlay DJ, Williams HC. What's new in acne? An analysis of systematic reviews published in 2009–2010. *Clin Exp Dermatol* 2011; **36**: 119–122.
- 41 Nisticò S, Del Duca E, Torchia V, et al. Cost-efficacy analysis of 3% diclofenac sodium, ingenol mebutate and 3.75% imiquimod in the treatment of actinic keratosis. *Int J Immunopathol Pharmacol* 2018; **32**: 1–8.
- 42 Cuevas P, Espinoza W, Pérez C, et al. Topical treatment of actinic keratosis with potassium dobesilate 5% cream. A preliminary open-label study. *Eur J Med Res* 2011; **16**: 67–70.
- 43 Micali G, Lacarruba F, Nasca MR, et al. Topical pharmacotherapy for skin cancer: part II. Clinical applications. *J Am Acad Dermatol* 2014; **70**: 979e1–979e12.
- 44 Nascimento C. Recidiva da acne após tratamento com isotretinoína oral: seguimento de cincoanos. *Surg Cosmet Dermatol* 2011; **3**: 188–191.
- 45 Baldwin HE, Nighland M, Kendall C, et al. 40 years of topical tretinoin use in review. *J Drugs Dermatol* 2013; **12**: 638–642.
- 46 Nast A, Bayerl C, Borelli C, Degitz K, Dirschka T, Erdmann R, Fluhr J, Gieler U, Hartwig R, Meigel EM, Möller S, Ochsendorf F, Podda M, Rabe T, Rzany B, Sammain A, Schink S, Zouboulis C, Gollnick H. S2k-leitlinie zurtherapie der akne [S2k guideline for therapy of acne]. *J Dtsch Dermatol Ges* 2010; **8**: 1–59.
- 47 Massa A, Massa A, Picoto A, et al. Avaliação e tratamento do doente com acne: parte 1. *Rev Port Clin Geral* 2011; **27**: 59–65.
- 48 Figueiredo A, Massa A, Picoto A, et al. Avaliação e tratamento do doente com acne – parte II: tratamento tópico, sistêmico e cirúrgico, tratamento da acne na grávida, algoritmo terapêutico. *Rev Port Clin Geral* 2011; **27**: 66–76.
- 49 Nickle SB, Peterson N, Peterson M. Updated physician's guide to the off-label uses of oral isotretinoin. *J Clin Aesthet Dermatol* 2014; **7**: 22–34.

- 50 Magalhães GM, Borges MFM, Queiroz ARC, et al. Double-blind randomized study of 5% and 10% retinoic acid peels in the treatment of melasma: clinical evaluation and impact on the quality of life. *Surg Cosmet Dermatol* 2011; **3**: 7–22.
- 51 Rendon M, Bneburg M, Arellano I, et al. Treatment of melasma. *J Am Acad Dermatol* 2006; **54**: 272–281.
- 52 Misiewicz J, Sendagorta E, Golebiowska A, et al. Topical treatment of multiple actinic keratosis of the face with arotinoid methyl sulf- one cream vs. tretinoin cream: a double blind comparative study. *J Am Acad Dermatol* 1991; **24**: 448–451.
- 53 Mukherjee S, Date A, Patravale V, et al. Retinoids in the treatment of skin aging: an overview of clinical efficacy and safety. *Clin Interv Aging* 2006; **1**: 327–348.
- 54 Xu X. Tumorsuppressive activity of retinoic acid receptor $\beta$  in cancer. *Cancer Lett* 2007; **253**: 14–24.
- 55 Torres A, Storey L, Anders M, et al. Immune-mediated changes in actinic keratosis following topical treatment with imiquimod 5% cream. *J Transl Med* 2007; **5**: 1–17.
- 56 Bubna AK. Imiquimod – its role in the treatment of cutaneous malignancies. *Indian J Pharmacol* 2015; **47**: 354–359.
- 57 NIH – NationalInstitutesof Health. *Imiquimod*. Available from: <https://aidsinfo.nih.gov/drugs/482/imiquimod/0/professiona>. (Accessed 13 out. 2016).
- 58 Goldenberg G, Linker RV, Singer G, et al. An investigator-initiated study to assess the safety and efficacy of imiquimod 3.75% cream when used after cryotherapy in the treatment of hypertrophic actinic keratosis on dorsal hands and forearms. *J Clin Aesthet Dermatol* 2013; **6**: 36–43.
- 59 FDA – Food and Drugs Administration. Draft Guidance on Imiquimod. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2010/020723s022lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020723s022lbl.pdf). (Accessed 13 out. 2016).
- 60 Kopera D, Kerl H. Visualization and treatment of subclinical actinic keratosis with topical imiquimod 5% cream: an observational study. *Biomed Res Int* 2014; **135916**: 1–5.
- 61 Berman B, Amini S, Valins W, et al. Pharmacotherapy of actinic keratosis. *Expert Opin Pharmacother* 2009; **10**: 3015–3031.
- 62 Le TT, Skak K, Schroder K, et al. IL-1 contributes to the anti-cancer efficacy of ingenol mebutate. *PLoS One* 2016; **11**: e0153975.
- 63 Garbe C, Basset-Seguín N, Poulin Y, et al. Efficacy and safety of follow-up field treatment of actinic keratosis with ingenol mebutate 0.015% gel: a randomized, controlled 12-month study. *Br J Dermatol* 2016; **174**: 505–513.
- 64 Berman B, Cohen DE, Amini S. What is the role of field-directed therapy in the treatment of actinic keratosis? Part 1: overview and investigational topical agents. *Cutis* 2012; **89**: 241–250.
- 65 AbdallaRstom AS, Paschoal FM, De Gales AP. Campo cancerizável: artigo de revisão. *Surg Cosmet Dermatol* 2014; **6**: 310–318.
- 66 Bobyr I, Campanati A, Consales V, et al. Efficacy, safety and tolerability of field treatment of actinic keratosis with ingenol mebutate 0.015% gel: a single center case series. *Springerplus* 2016; **14**: 1–7.
- 67 Rosen R, Marmur E, Anderson L, et al. A new, objective, quantitative scale for measuring local skin responses following topical actinic keratosis therapy with ingenol mebutate. *Dermatol Ther (Heidelb)* 2014; **4**: 207–219.
- 68 Agostinis P, Berg K, Cengel KA, et al. Photodynamic therapy of cancer: an update. *CA Cancer J Clin* 2011; **61**: 250–281.
- 69 Issa C, Manela-Azulay M. Terapíafotodinâmica: revisão da literatura e documentaçãoiconográfica. *An Bras Dermatol* 2010; **85**: 1–14.
- 70 Berlin JM. Current and emerging treatment strategies for the treatment of actinic keratosis. *Clin Cosmet Investig Dermatol* 2010; **3**: 119–126.
- 71 Madhunapantula S, Robertson GP. Chemoprevention of melanoma. *Adv Pharmacol* 2013; **65**: 361–398.
- 72 Babino G, Diluvio L, Bianchi L, et al. Long-term use of a new topical formulation containing piroxicam 0.8% and sunscreen: efficacy and tolerability on actinic keratosis. A proof of concept study. *Curr Med Res Opin* 2016; **32**: 1345.
- 73 Garofalo V, Ventura A, Mazzilli S, et al. Treatment of multiple actinic keratosis and field of cancerization with topical piroxicam 0.8% and sunscreen 50+ in organ transplant recipients: a series of 10 cases. *Case Rep Dermatol* 2017; **9**: 211–216.
- 74 Svobodová A, Psotová J, Walterová D. Natural phenolics in the prevention of UV-induced skin damage. A review. *Biomed Pap* 2003; **147**: 137–145.
- 75 Radice M, Manfredini S, Ziosi P, et al. Herbal extracts, lichens and biomolecules as natural photo-protection alternatives to synthetic UV filters. A systematic review. *Fitoterapia* 2016; **114**: 144–162.
- 76 Zhang J, Li N, Zhang K, et al. Astragalín attenuates UVB induced actinic keratosis formation. *Anticancer Agents Med Chem* 2017; <https://doi.org/10.2174/1871520618666171229190835>.
- 77 Grinblat B, Galimberti G, Chouela E, et al. Daylight-mediated photodynamic therapy for actinic damage in Latin America: consensus recommendations. *Photodermatol Photoimmunol Photomed* 2016; **32**: 81–87.
- 78 Calzavara-Pinton P, Zane C, Pacou M, et al. Bucher's indirect comparison of daylight photodynamic therapy with methyl aminolevulinat cream versus diclofenac plus hyaluronic acid gel for the treatment of multiple actinic keratosis. *Eur J Dermatol* 2016; **26**: 487–492.
- 79 Galvão LEG, Gonçalves HS, Botelho KP, et al. Daylight photodynamic therapy – experience and safety in treatment of actinic keratosis of the face and scalp in low latitude and high brightness region. *An Bras Dermatol* 2017; **92**: 142–144.
- 80 Galimberti GN. Daylight photodynamic therapy versus 5-fluoracil for the treatment of actinic keratosis: a case series. *Dermatol Ther (Heidelb)* 2018; **8**: 137–141.