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.

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. The term keratosis refers to the thickening of stratum corneum, and the term actinic, to its origin from sun exposure. The lesions on the face have a flat aspect, while those in the upper limbs are usually thicker.

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. Several studies have shown that individuals with Fitzpatrick skin types I and II are more likely to have AK. Individuals over the age of 80 are six times more likely to develop AKs when compared to those between the ages of 50 and 59. 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. A study conducted in England reported an AK prevalence rate of 15.4% in men and 5.9% in women in their 40s. 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, 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.

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. In many cases, AKs are subclinical and disseminated; therefore, the term field cancerization is nowadays more appropriate to describe the lesions. 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. The main etiologic 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 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.

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. 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$_2^-$), hydrogen peroxide (H$_2$O$_2$), and singlet oxygen (¹O$_2$). 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.

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. 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.

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.

Treatments

AK treatment is mostly based on destructive methods. They range from curettage, cryotherapy with liquid nitrogen, topical chemotherapeutics, and chemical peels. Immunomodulators have also been used with a certain degree of success. A number of studies support the efficacy of PDT in the treatment of localized or disseminated AKs. 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.

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.

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. 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. 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. 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. The cream is usually applied twice a day for 2–4 weeks. Clearance of the lesions occurs in approximately 62.5% of patients in complete adherence to the treatment, and recurrence rates are around 30%. 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 cautereization 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, blisters, 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. There have been reports of gastrointestinal and hematological toxicity in patients with severe deficiency in the major 5-FU degradation enzyme, dehydropyrimidine dehydrogenase (DPD).

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 cm² for 12 weeks. Side effects such as local inflammation and pruritus have been observed.

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. 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. Diclofenac also decreases the formation of arachidonic acid metabolites. This inhibits apoptosis and increases the invasive capacity of tumor cells.

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. 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. The probability of adverse effects caused by a 3% diclofenac gel is reported to be 5%. 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%. Adverse effects described include desquamation, pruritus, dry skin, localized edema, paresthesia, erythema, rashes, and less frequently, photosensitivity.

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.

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.

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. 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. 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.

Tretinoin, or retinoic acid, is a molecule derived from vitamin A. In 1962, Stutten 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. 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, α, β, and γ, and each subtype has several isoforms. In the skin, RAR-γ and RXR-α are the most active. In premalignant lesions, a low expression of these receptors and also of the RAR-β2 has been observed. 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-β2 receptor to be decreased since it is self-induced by retinoids. RAR-β2 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. 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.

The FDA has approved the use of IQ cream at 5, 3.75, and 2.5% concentrations for AK on the face and scalp. For superficial basal cell carcinoma, the 5% cream is more suitable. 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. The 5% formulation is indicated for topical use in immunocompetent adults with two applications for 16 weeks on an area up to 25 cm². 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. This formulation has yet a 35.6% probability of complete cure and recurrence rate after 12 months of 20.9%. Reactions to IQ may occur beyond the application site and include pruritus, erosions, burning, erythema, peeling, vesicles, exudations, and crusts.

**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 α (TNF-α), interferon-γ (IFN-γ), 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 cells, such as cytotoxic T lymphocytes. Therefore, the development of an inflammatory reaction predicts a good therapeutic efficacy.

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.

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. 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%. 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%). Erythema, edema, peeling, crusts, 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.

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

<table>
<thead>
<tr>
<th>Retinoid</th>
<th>Generation</th>
<th>RAR</th>
<th>Site of action</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isotretinoin</td>
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<td>α, β, γ</td>
<td>Topical/systemic</td>
<td>AK, acne, aging</td>
</tr>
<tr>
<td>Tretinoin</td>
<td>1</td>
<td>α, β, γ</td>
<td>Topical</td>
<td>AK, acne, aging</td>
</tr>
<tr>
<td>Adapalene</td>
<td>3</td>
<td>β, γ</td>
<td>Topical/ Systemic</td>
<td>AK, acne</td>
</tr>
<tr>
<td>Ertretinate</td>
<td>2</td>
<td>–</td>
<td>Systemic</td>
<td>AK, psoriasis</td>
</tr>
<tr>
<td>Acrasilene</td>
<td>2</td>
<td>–</td>
<td>Systemic</td>
<td>AK, psoriasis</td>
</tr>
<tr>
<td>Tazarotene</td>
<td>3</td>
<td>β, γ</td>
<td>Topical</td>
<td>Psoriasis, acne</td>
</tr>
<tr>
<td>Retinoaldehyde</td>
<td>1</td>
<td>–</td>
<td>Topical</td>
<td>AK, aging</td>
</tr>
<tr>
<td>Retinol</td>
<td>1</td>
<td>–</td>
<td>Topical</td>
<td>AK, aging, psoriasis</td>
</tr>
</tbody>
</table>

RAR, retinoic acid receptor; AK, actinic keratosis.
**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.1,21,68

Among the most used photosensitizing compounds are 5-aminolevulinic acid (ALA) and its lipophilic derivative, methylaminolevulinate (MAL).59 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.13,21,68,69

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.68

There is no significant difference between MAL and ALA when it comes to efficacy, but ALA causes less pain during treatment.21 When it comes to selectivity, it is noted that MAL is more selective for premalignant cells than ALA.69 Zhao et al.21 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.1,18 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.1,18,70

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.2,16 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.18,70

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.71 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.1,33,56 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.43

**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.33,39,72,73

**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.33,42

**Astragalin**

Astragalin is an 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...
an important pathway involved in AK formation, therefore being a promising natural therapeutic agent.74-76

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.77-80

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 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.

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Actinic keratosis – review for clinical practice