doi:10.36849/JDD.6704

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Classifying Actinic Keratosis: What the Reality of Everyday Clinical Practice Shows Us

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ABSTRACT

Difficulties faced by clinicians in routine clinical practice when selecting the appropriate treatment for patients with actinic keratosis (AK) include: the independent evaluation of AK lesions, the absence of a standardized definition of field cancerization (FC), and the lack of a reproducible classification to grade the entire AK-affected area. Moreover, to assess the severity of AK, most guidelines rely on lesion count, which is often not reproducible among specialists.

The present work has 2 main objectives: first, to review and highlight some of the issues clinicians tackle when classifying and monitoring AK lesions and the status of FC, looking in more detail at some of the most commonly used clinical scales for classifying AK lesions. Second, we pose questions that we encounter in daily clinical practice, and whose answers or comments help to deal with cases of AK, facilitating the work of clinicians: How should we approach AK diagnosis? How do the challenges of clinical studies on the evaluation of treatment efficacy translate into clinical practice? We review the literature on the clinical classifications and management of AK, and propose how to guide the diagnosis, management, and monitoring of patients with AK.

J Drugs Dermatol. 2022;21(8): 845-849. doi:10.36849/JDD.6704

INTRODUCTION

Actinic Keratosis and Field Cancerization Concepts

Actinic keratosis (AK) is clinically characterized as rough, scaly patches or spots on the skin with a variable degree of hyperkeratosis. AK is a chronic disease that usually affects skin areas that are long-term exposed to ultraviolet (UV) radiation from the sun,[1] such as the face or scalp. Its prevalence is high and is likely to rise in the coming years,[2,3] with an increasing incidence in the aging population.[4]

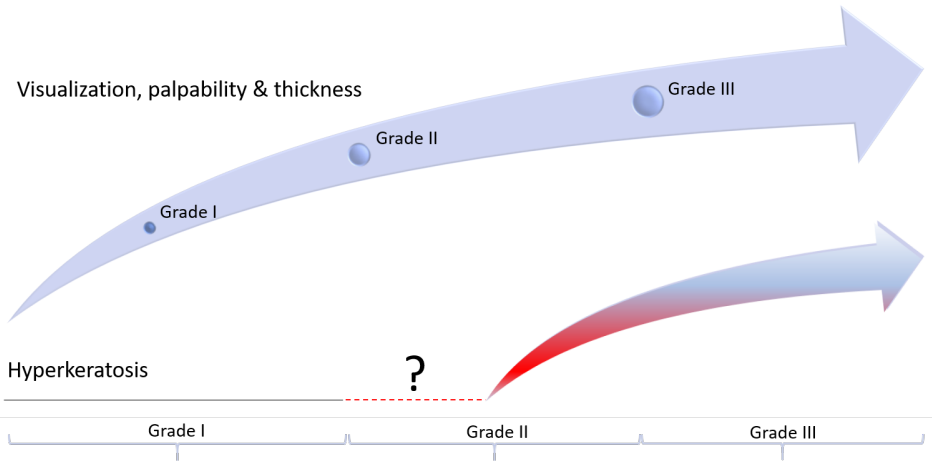
Histologically, AK demonstrates atypia of the basal layer of the epidermis, often associated with parakeratosis,[5] and usually coexists with surrounding non-visible lesions. However, the whole area is prone to the development of invasive skin cancers, a process known as 'field cancerization'.

Field cancerization has significant clinical consequences and therapeutic implications for AK, including the advantages of exploiting field treatments compared with lesion-directed ones. Moreover, this aspect deserves special attention because it implies that AK lesions should not be characterized by discrete stages.

The categorization of individual AK lesions often fails in its attempt to define unambiguous boundaries between their different evolutionary stages, such as the 3-stage Olsen's classification. This problem could be avoided by adopting a continuous dimensional approach that incorporates and analyzes more aspects of the disease (ie, lesion count, overall sun-damaged area, characteristics of all lesions globally in the context of the affected region), beyond individual lesion assessment. The same region may present AK lesions in different stages or even progressive AK. Three-dimensional staging leads to the problem that these stages can be misinterpreted as progression steps from grade I (mild) to grade III (severe). However, this is not the case when talking about hyperkeratosis – these are simply different grades of classification, descriptive stages, that should be not misjudged in terms of progression. Long-term sun exposure of the skin gives the diagnosis of AK a progressive and chronic character[6] that should be reflected in its categorization.

Moreover, an algorithm has been proposed that complements existing evidence-based guidelines to differentiate patients

FIGURE 1. Olsen's criteria in a continuous progressive line. This first classification of actinic keratosis (AK) lesions assumes that hyperkeratosis appears "suddenly" at some point during Olsen stage II. However, the inherent progressive nature of these lesions makes sudden or abrupt onset of hyperkeratosis unlikely. In grade II, there is the possibility of the absence or presence of hyperkeratosis (in red), which makes it difficult to distinguish between Olsen grade I and II patients; there may be an overlap between both types of patient.



according to their lesion pattern (scattered isolated lesions, lesions clustered in small areas, or large affected fields), without reference to the absolute numbers of lesions.[7]

Clinical Classifications for AK lesions: What They Give Us

Although several classification systems have been suggested for AK over the years, currently there is no gold standard in clinical practice to guide the therapeutic approach.[8,9]

Lesion-based assessment: Olsen – clinical classification of AK

The original Olsen classification emerged 30 years ago (1991) in the context of a clinical trial. The intention of Olsen et al was not to establish a clinical classification of AK per se, but to assess the efficacy and safety of masoprocol in the treatment of AK.[10] They created a global AK lesion scale of 1 to 3, based on the overall thickness of AK, and a 7-grade scale to assess the overall response to treatment.

In this regard, the classification presented shortcomings and limitations because it was based on imprecise terminology that was not intended for the objective classification of lesions.[10] Over the years, Olsen grades have been modified, describing AK lesions according to their thickness and degree of hyperkeratosis on clinical examination. Interestingly, however, in the first original publication of the Olsen group (1991) the term 'hyperkeratosis' was not even mentioned among the initial lesion criteria.[10] Although some guidelines base their treatment decisions for AK on this classification,[11,12] many others do not (ie, Spain,[13] Switzerland,[14] and Germany,[15] among others).

Given that clinicians want to prevent patients from developing AKs into invasive squamous cell carcinoma (iSCCs), a classification that determines the risk of AK lesions or the field progress is needed. However, the Olsen classification carries no predictive value. For this reason, and other key issues mentioned below, this classification should be dismissed.

First, the distinction between the absence or presence of hyperkeratosis in terms of palpation and visualization is unreliable and not standardized, as dermatologists do not consistently evaluate lesions.[18] This makes Olsen a rather imprecise, subjective classification, especially when distinguishing between stage I or II lesions (see Figure 1). Second, a three-dimensional scale is misleading, as it implies a fixed progressive escalation. Olsen intends a continuum of "increasingly dangerous" grade I to III lesions, while no correlation has been found between Olsen grade and rate of progression. Third, Olsen addresses only single lesions, although these are only a component of FC. In this respect, and as a fourth argument, interobserver agreement of Olsen grading and individual lesion counts are neither good nor consistent.[19–21] Finally, Olsen grades do not correlate with underlying histology (ie, Röwert-Huber classification).[22,23] Comparatively, both systems do not match accurately (54% of agreement);[23] and more than one-third of lesions clinically classified as Olsen grade III appear histologically as AK I. Both Olsen and Röwert-Huber classifications have shown limited use for clinical practice.[1,24,25] In fact, the risk of transformation of an individual AK lesion to iSCC cannot be predicted based on clinical or histological features.[26]

Field-based assessments: AKASI and AK-FAS

Until recently (2017) the severity of AK has been mainly evaluated by subjective assessment of patients. Thereafter, there have been attempts to globally view and objectify the classification of AK lesions.

Some approaches have tried to quantitatively assess the severity of AK across an affected area, namely the AK Area and Severity Index (AKASI) developed in 2017 and focused on the head.[24] This approach is based on other severity scoring systems in dermatology, the Psoriasis Area and Severity Index (PASI).

To calculate AKASI, 4 regions are first delimited, each assigned a weighting based on their relative size: scalp (40%), forehead (20%), left face (20%), and right face (20%). Within each region, the investigator calculates the percentage of the area affected by AK lesions, in a range from 1 (1%-9% affected area) to 6 (90%-100%). In parallel, the severity of 3 clinical signs of AK (distribution, erythema, and thickness) is assessed on a scale from 0 (none) to 4 (maximum). The area score and the sign scores are summed and multiplied by the area weight factor (eg, 20% = 0.2) to obtain an area total score. The 4 area scores are summed to obtain a total head score ranging from 0 (no AK) to 18 (most severe degree possible).

In our opinion, the AKASI fulfils the condition of taking a global look over the affected area because both the extent of AK and the severity of 3 clinical signs of AK are assessed within each area. This adds value to the classification as these aspects may also guide therapeutic decisions. It also attempts to quantify the characteristics of sun-damaged regions and it is not time-consuming, making it is easy to use in routine clinical practice. In addition, the affected area is already perceived as FC through sight and palpation.

Still, the decision to treat an area with FC will rely not only on AKASI, but also on medical assessment and patient characteristics such as medical history (ie, previous iSCCs, presence of immunosuppression). Other limitations are the restriction to head lesions only, and the determination of the percent extent of AK within each area in a subjective way.

Also in 2017, and shortly after AKASI, the Actinic Keratosis Field Assessment Scale (AK-FAS) was developed to assess the severity of AK.[27] This scale is outlined considering that most previous tools were established on counting AK lesions and were poorly reproducible. AK-FAS is based on 3 criteria: AK area, hyperkeratosis, and sun damage. AK area is the most important criterion in the scale and the key differentiator from previous tools.

Initially, the scale was validated on photographs of 12 patients and was based on a combination of the Olsen criteria and an assessment scale developed by the principal investigator. However, the proposed definitions were difficult to interpret consistently as many clinical presentations fell between grades. Therefore, the AK area was added, defined as the total skin surface affected by AK lesions (including non-visible, subclinical lesions) and expressed as a percentage of the total skin surface assessed. Depending on this percentage, a score from 0 (0% area affected) to IV (>50%) is assigned.

Originally, hyperkeratosis and sun damage in the area were labeled as either present or absent; but, again, preliminary testing showed that this label was subject to interpretation, leading to discrepancies during clinical assessment. In addition, sun damage was of little interest as it was invariably marked as "present". Therefore, in the current version of the scale, the AK area has been retained, and pre-defined criteria for presence/absence of hyperkeratosis and sun damage have been added.[27] The development path of this scale highlights the difficulty and inconsistency of AK-affected areas, especially regarding the presence or absence of hyperkeratosis.

Key endpoints for the management of AK: are the clinical trials endpoints consistent with those used in routine practice?

Whether available classifications help to adequately define AK lesions, both in routine clinical practice and in clinical trials when assessing treatment outcomes, is still unclear. Reynolds and colleagues[28] highlight in a recent consensus (including a final sample of 29 physician and patient stakeholders) the heterogeneity of safety and efficacy outcomes reported in clinical trials of AK treatments, which makes comparisons difficult. Accordingly, endpoints do not generally include the clinical classification systems, nor do they take into account aspects that defined some of their earlier versions (ie, presence/absence of hyperkeratosis).

Outcomes for lesion improvement newly defined in Reynolds work that were 'more similar' to those established in previous clinical classifications were the: clearance of AK lesions (without further specification), progression to SCC, and number of clinically apparent AK lesions. However, of these, only complete clearance of AK lesions and percentage of AK lesions removed were voted among the key outcomes. This is a major problem as the classification systems are not being used to assess the efficacy of AK treatments in clinical trials.

The lack of consistency between clinical trials and standard practice endpoints in AK has a clear recent example with tirbanibulin. This drug was approved by the U.S. Food and Drug Administration (FDA) in December 2020, and in July 2021 the European Medicines Agency (EMA) approved marketing authorization for Klisyri® (Almirall), intended as a 5-day medicinal product for the treatment of AK on the face or scalp.

It is interesting to note that while the FDA specifies that tirbanibulin 1% ointment is "indicated for the topical treatment of actinic keratosis of the face or scalp",[29] the EMA, on the other hand, opts for a different indication: "indicated for the field treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (Olsen grade 1) of the face or scalp in adults".[30,31] In

the latter case, patients who are at a particular stage of the lesions are mentioned, while in the former case there is no such specification. The Olsen grading was not used in the pivotal phase III studies for tirbanibulin[32] and deviates from the primary global endpoint used in these studies which were: complete clearance (100%) of AK lesions (no prespecified classification of lesion grade). In addition, lesions of patients participating in phase III could be established as Olsen I or II, depending on the classification considered. In this regard, patient photographs taken at baseline in tirbanibulin phase III trials suggested that there could be patients with a mixture of Olsen grade I and II lesions within the same treatment area (up to 25 cm^2).[32]

Situations such as this recent example should make us reconsider the endpoints used in clinical trials. These should preferably mirror those used in routine clinical practice, so the results of the research apply to this setting.

How to Deal with AK Daily Clinical Practice: Recommendations

Considering the abovementioned limitations and based on our clinical experience, we propose the following recommendations aiming to improve diagnosis, monitoring, and management of patients with AK.

Recommendation 1: To refocus clinical diagnosis, management, and monitoring endpoints toward an area-wide assessment rather than the assessment of individual AK lesions

Firstly, FC should be evaluated as a chronic disease with a high genetic mutational burden driven by radiation exposure from sunlight causing the development of future AKs or SCC. In clinical practice, dermatologists should assess the entire area affected by AK, rather than individual lesions, to optimize the treatment approach.[1,24] Treatment of FC, in general, has been reported to help reduce the recurrence of AK lesions,[12,33,34] and guidelines advocate field treatment,[11,12,14] but without much further specification on how to define and classify FC status.

There should be an increasing and systematic shift towards field characterization of AK lesions as the importance of FC is becoming more evident in clinical practice. It would be useful to establish a consensus to define a universal grading system for UV skin damage. In this sense, there is also a lack of a universal optimal management score system to assess the overall efficacy of treatment. In most AK clinical trials, a efficacy is assessed by the achievement of complete clearance; although many patients only reach partial but substantial improvement.

Thus, we believe that partial clearance including reduction of AK burden (number of lesions) and improvement of UV skin damage parameters (FC), would represent more appropriate clinical endpoints.

Recommendation 2: To abandon the Olsen classification to guide AK management

We still consider that there is no objective method for clinical classification of AK lesions that correlates with a reliable histopathological classification. The Olsen classification appears to be poorly reproducible and inconsistent among experts for assessing severity and correctly guiding treatment.[1] Moreover, this classification system is unreliable and inconsistent for routine application, with limited use in clinical practice.[1,8,25] In our opinion, this classification is characterized by low feasibility and might provide a false understanding of the underlying lesions in terms of their risk of progression. Therefore, the inadequacy of Olsen's classification in both clinical trials and clinical practice implies that this classification should no longer be used as a guide for AK management.

Recommendation 3: To introduce into clinical routine a global assessment scoring system to characterize field cancerization

Unlike the Olsen grading system, the AKASI system tries to take a global view of the affected area, assessing aspects such as distribution and erythema. Thus, the approach to the diagnosis and monitoring of AK should consider the routine use of AKASI to assess UV-damaged skin. Also, this classification could be used to stratify the risk for developing iSCC, as AKASI grade has been associated with the incidence of iSCC.[35] AKASI is simple and quick to perform, and therefore suitable for assessing disease severity in both clinical studies and daily practice.

Recommendation 4: To match efficacy endpoints between clinical trials and clinical practice

We recommend reviewing and standardizing, when possible, the endpoints for determining the clinical efficacy of treatment with respect to what is then assessed in routine clinical practice. Simultaneously, the use of treatments in daily practice should be contextualized with the type of endpoints assessed in clinical trials. This is observed in the study of psoriasis, another chronic skin disease (such as AKs and UV skin damage), where efficacy endpoints in clinical trials correspond to what is evaluated in clinical practice. That is, PASI is used both in daily routine[36,37] and in clinical trials[38,39] to measure disease severity, in order to adapt treatments accordingly.

Recommendation 5: To characterize actinic damage in actual practice

Actinic damage is not always specifically reported in medical records. We encourage to evaluate the following aspects to characterize actinic damage: pigmentation disorders, atrophy, telangiectasia, and sandpaper-like texture.

To sum up, despite the efforts made, it still seems necessary to try to establish changes in the main endpoints for assessing AK lesions and their underlying area, as well as in the evaluation of the efficacy of treatments, that can address the intrinsic limitation of the mismatch between clinical studies and actual practice (ie, using complete clearance as the main endpoint in clinical studies vs significant improvement in practice). We also suggest avoiding applying classifications such as the Olsen grading system, which do not improve routine clinical practice and appropriate treatment selection.

DISCLOSURES

LS and PB received honoraria from Almirall, Beiersdorf, Biofrontera, Galderma, Mylan, and Sanofi Genzyme. LS, PB and AB have participated in clinical advisory boards for Almirall. Almirall S.A. supported this work.

ACKNOWLEDGMENT

Editorial assistance and writing support were provided by Mònica Giménez PhD and Eva Mateu PhD ofTFS HealthScience.

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