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OPINION ARTICLE

Actinic Keratosis: New Concepts and Therapeutic Approaches for an Ancestral Condition☆

Queratosis actínica: un proceso ancestral, nuevos conceptos y enfoques terapéuticos

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As I write this contribution to Spain's most prestigious dermatology journal, it is clear I need not provide a description of actinic keratosis (AK), but I do feel that experience will allow me to reflect instructively and readably on the subject of how therapy has evolved over the years.

Ours is a Mediterranean country with a high incidence of AK. We enjoy many more days of bright sunlight, and 70% of our marvelous coastline offers attractive access to the sea. Because our peninsula was invaded by Celtic tribes from northern Europe over 5000 years ago, our population now includes many individuals with the light skin and eyes that tend to photoaging.

AK is among the classic clinical signs of that process, and after the age of 50 years nearly all Spaniards have—to one degree or another—lesions consistent with a diagnosis of solar keratosis. Today such lesions cannot be considered a mere cosmetic problem.

For many years AK was classified as a premalignant lesion. Cockerel[1] insisted in 2003, however, that we define the process in terms of histopathologic evidence. A grading system known by the acronym KIN—for keratinocytic intraepidermal neoplasia—was introduced. In this system, AK grades I through III are defined according to the degree of epidermal dysplasia and the risk of malignant transformation to invasive squamous cell carcinoma.

Since then, specialists have agreed to consider AKs to be true intraepidermal neoplasms, or neoplasms in situ.[2,3] It is estimated that from 5% to 20% of preexisting lesions, including subclinical ones, may progress and grow to become invasive squamous cell carcinoma.

Evidence led the drafters of the 2006 European Dermatology Forum guidelines to conclude that even though it is impossible to predict which AKs will undergo malignant transformation, these lesions have the potential to do so. For that reason, they concluded, AKs should be treated.''[4]

A Spanish adaptation of those guidelines was recently published in *Actas Dermo-sifiliográficas*.[5]

A more recent concept, field cancerization, involves subclinical lesions and mutated cells in sun-exposed areas. This concept addresses the risk of developing squamous cell carcinoma not merely on visible AKs but also throughout an entire field in which ongoing solar UV irradiation continues to act on subclinical lesions and mutated cells, generating further mutation and exercising an immunosuppressive effect. These processes have been well described and are fully understood today.[6,7]

I recall that the treatment for AK that prevailed for decades consisted of destroying a lesion by scraping and electrocoagulating it, potentially causing scars. Alternatively, a dermatologist might have applied dry ice, providing

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a primitive type of cryotherapy that in the light of recent advances seems of debatable value, at least for the purpose of treating all lesions.

The development of liquid nitrogen spray has provided a convenient way to reach the freezing point needed for cryotherapy. As the spray is easy to apply and gives more or less acceptable results, it has quickly become the most widely used procedure for treating individual AKs. This approach, though not new, is likely to continue to be the first choice for outpatient care of AK in Spain.

I also recall the introduction of 5-fluorouracil (5-FU) cream to treat field cancerization with very good results. A drawback was that this formulation caused a painful inflammatory and ulcerative reaction that could compromise patient adherence.

5-FU diminishes the proliferation of cells (especially those undergoing increased mitosis) through the action of its active ingredient, 5-fluorodeoxyuridine monophosphate. This antimetabolite is a pyrimidine analog that inhibits thymidylate synthetase, and also affects DNA synthesis and, to a lesser degree, RNA synthesis.

The combination of 5-FU cream and retinoic acid was an advance that provided better results more quickly.

5-FU continues to be an excellent treatment that can be used over extensive areas, and a recent meta-analysis ranked this cream as the most effective option.[8] Only intolerance limits its use.

A very interesting article published by a group at the Hospital Charité in Berlin compared clinical, histopathologic, and even immunohistochemical markers of the efficacy of 5-FU, imiquimod, and cryotherapy after 4 weeks of treatment.[9] 5-FU and imiquimod were equivalent from the clinical standpoint and both were superior to cryotherapy. The histologic findings were slightly better with imiquimod than with 5-FU, and again both were superior to cryotherapy.

Similarly, p-53 results were also better with imiquimod than with 5-FU in this study, and both these treatments were superior to cryotherapy; cosmetic outcomes were better with imiquimod than with either 5-FU or cryotherapy.[9]

A disadvantage for us in Spain is that 5-FU cream must be compounded by the pharmacist because a commercial form is unavailable here, but that situation that may soon change.

A recent multicenter observational study lasting a year and a half (the unpublished AKces study of 2009–2010 on burden of disease, personal communication) recorded the treatment prescribed and applied in the first 5 patients who sought care for multiple AKs in 67 hospital dermatology clinics throughout peninsular Spain. The following treatments were used: only imiquimod, 47.1%; cryotherapy, 33.5%; photodynamic therapy, 6.5%; and other treatments or combinations, 12.6%.

Returning to the useful concept of field cancerization, I recall that articles we would consider old today mentioned that the regression of incipient AKs can be achieved with the use of sunscreens. Trials are currently under way to determine whether sunscreens containing photolyase—an enzyme that can repair damaged DNA in keratinocytes—might be more effective, safer, and better tolerated in the treatment of field cancerization in patients with a predisposition to AK and nonmelanoma skin cancer.

Photodynamic therapy with application of aminolevulinic acid (ALA) before exposure to a light source was introduced in the United States; later, European dermatologists began to apply photodynamic therapy with methyl aminolevulinate. Both approaches have progressed, achieving good results, in spite of certain difficulties, such as the need for several time-consuming sessions and specific equipment. In some cases anesthesia (a regional block of the area to be treated) is needed to alleviate the intense pain some patients feel during irradiation.

The efficacy of photodynamic therapy, however, seems to be well demonstrated according to European practice guidelines.[10,11]

A 5-ALA formulation with nanoparticles recently entered the Spanish market. This agent seems to offer enhanced bioavailability and a more intense phototoxic effect on tumor cells.[12]

In 2007 I had the pleasure of serving as principal investigator for the multicenter European trial required to register the use of imiquimod 5% cream for treating AK.[13]

Imiquimod's mechanism of action is well understood: it induces innate and acquired immune responses that destroy abnormal cells throughout the area where it is applied.

The results of our trial showed complete clinical and histologic resolution in 55% of the treated area.[13] Clinical clearing of lesions in 83% of patients has been observed in another trial, however.[14]

The protocol initially proposed (2 cycles in 4 weeks) is difficult to follow if there is a strong inflammatory reaction, as the patient is reluctant to undergo the second cycle.

Another aspect of the initial proposal—limiting the size of the area treated to 25 cm^2—is not followed strictly in clinical practice. Larger areas than the limit specified in the prescribing information are commonly treated because the contents of a single-use packet will cover a slightly larger surface. It is important to remember that using more packets of imiquimod cream, however, can lead to flu-like symptoms in some patients due to the release of interferon and by other mechanisms.

Another product recently introduced for treating field cancerization combines diclofenac 3% and hyaluronic acid 2.5%. The patient applies the gel twice a day for 16 weeks, using approximately 4 g (maximum, 8 g).

The duration of this therapy makes it somewhat tedious, but it is usually well tolerated. In some patients, however, it can cause a certain degree of inflammation and even photosensitivity, a known side effect of various nonsteroidal anti-inflammatory drugs. The mechanism of action for this drug took time to unravel, although we can now say that inhibition of the cyclooxygenase-2 pathway and induction of apoptosis now seem to have been demonstrated.[15]

New drugs for treating this very common disease in Spain continue to appear. An example is 0.015%–0.05% ingenol mebutate gel. Evidence for this product's mechanism of action is lacking, although effects on the cell membrane of dysplastic keratinocytes and also on cell mitochondria have been described. Ingenol mebutate also induces an infiltrate, consisting of neutrophils and proinflammatory cytokines, with secondary cytotoxicity.

These actions have possible side effects, such as irritation and inflammation in the treated zone, but a great advantage of the ingenol mebutate gel is that it is applied for only 2

or 3 days.[16] However, the irritation can persist for several weeks and it is currently recommended to limit application to 25 cm^2. The duration of treatment efficacy has not been demonstrated by long-term follow-up studies.

A preparation combining 0.5% 5-FU and 10% salicylic acid, which is marketed in some European countries for treating individual lesions, seems to be very useful even for hyperkeratotic lesions.[17,18] This product may become available in Spain very soon.

A formulation we can look forward to seeing in Spain is the imiquimod 3.75% cream. Indicated for field cancerization, it is already being marketed in the United States and some countries in Europe. The treatment protocol calls for 2 short cycles of 2 weeks each, with a resting period of 2 weeks between them. This treatment clears lesions completely in 35% of patients and partially in 60%.[19,20] Studies of field-directed treatment with this product showed that the highest count of lesions that were initially clinically invisible, but that became detectable with application (the Lmax concept), did so at the beginning the 2-week cycle; additionally, the greatest effect was achieved by treating the entire affected zone.[21]

We have seen that AK—so commonplace in the population over the age of 50 years that it was considered of little importance a few years ago—is now being taken more seriously because our concept of the condition has changed. We now have a better understanding of photobiology and the cancerization process—both its induction and progression to nonmelanoma skin cancer—as well as a wide range of therapies that can cure these lesions to the degree a cure is possible.[22–29]

The dermatologist who is aware of the variety of treatments currently on hand can apply the knowledge in the interest of prevention—through relevant explanations about the use of sunscreens—or can treat lesions with a new arsenal of single or combined therapies. New approaches are available to target both individual hyperkeratotic AKs and field cancerization. Each option must be explained to the patient so that the greatest possible degree of adherence and the best curative outcome can be achieved.

Conflicts of Interest

The author declares that he has provided advisory or consultancy services for the following laboratories: MEDA, Leopharma, and Almirall.

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References

1. Cockerell CJ. Pathology and pathobiology of the actinic (solar) keratosis. Br J Dermatol. 2003;149 Suppl 66:34–6.
2. Ackermann AB, Mones JM. Solar (actinic) keratosis is squamous cell carcinoma. Br J Dermatol. 2006;155:9–22.
3. Rowert-Huber J, Patel MJ, Forschner T, Ulrich C, Eberle J, Kerl H, et al. Actinic keratosis is an early in situ squamous cell carcinoma: A proposal for reclassification. Br J Dermatol. 2007;156 Suppl 3:8–12.
4. Stockfleth E, Kerl H. Guidelines for the management of actinic keratoses. Eur J Dermatol. 2006;16:599–606.
5. Ferrándiz C, Fonseca-Capdevila E, García-Diez A, Guillén-Barona C, Belinchón-Romero I, Redondo-Bellón P, et al. Adaptación española de la guía europea para la evaluación y tratamiento de la queratosis actínica. Actas Dermosifiliogr. 2014;105:378–93.
6. Stockfleth E, Ferrandiz C, Grob JJ, Leigh I, Pehamberger H, Kerl H, European Skin Academy. Development of a treatment algorithm for actinic keratoses: A European Consensus. Eur J Dermatol. 2008;18:651–9.
7. Stockflet E, Ortonne JP, Alomar A. Actinic keratosis and field cancerisation. Eur J Dermatol. 2011;(Supp 21):1–12.
8. Gupta AK, Paquet M. Network meta-analysis of the outcome 'participant complete clearance' in nonimmunosuppressed participants of eight interventions for actinic keratosis: A follow-up on a Cochrane review. Br J Dermatol. 2013;169:250–9.
9. Krawtchenko N, Roewert-Huber J, Ulrich M, Mann I, Sterry W, Stockfleth E. A randomized study of topical 5% imiquimod vs topical 5-fluorouracil vs cryosurgery in immunocompetent patients with actinic keratoses: A comparison of clinical and histological outcomes including 1-year follow-up. Br J Dermatol. 2007;157:34–40.
10. Morton CA, Szeimies R-M, Sidoroff A, Braathen LR. European guidelines for topical photodynamic therapy part 1: Treatment delivery and current indications–actinic keratoses, Bowen's disease, basal cell carcinoma. JEADV. 2013;27:536–44.
11. Fernández Guarino M, Harto A, Sánchez-Ronco M, Pérez-García B, Marquet A, Jaén P. Estudio retrospectivo, descriptivo y observacional del tratamiento de queratosis actínicas múltiples con metilaminolevulinato tópico y luz roja: resultados en la práctica clínica y correlación con la imagen de fluorescencia. Actas Dermosifilogr. 2008;99:799–887.
12. Shi L, Wang X, Zhao F, Luan H, Tu Q, Huang Z, et al. In vitro evaluation of 5-aminolevulinic acid (ALA) loaded PLGA nanoparticles. Int J Nanomedicine. 2013;8:2669–76.
13. Alomar A, Bichel J, McRae S. Vehicle-controlled, randomized, double blind-study to assess safety and efficacy of imiquimod 5% cream applied once daily 3 days per week in one or two courses of treatment of actinic keratoses on the head. Br J Dermatol. 2007;157:133–41.
14. Stockflet E, Sterry W, Carey-Yard M, Bichel J. Multicentre, open label study using imiquimod 5% cream in one or two 4-week courses of treatment for multiple actinic keratoses on the head. Br J Dermatol. 2007;157 Suppl 2:41–6.
15. Martin GM, Stockfleth E. Diclofenac sodium 3% gel for the management of actinic keratosis: 10+ years of cumulative evidence of efficacy and safety. J Drugs Dermatol. 2012;11:600–8.
16. Lebwohl M, Swanson N, Anderson LL, Melgaard A, Xu Z, Berman B. Ingenol mebutate gel for actinic keratosis. N Engl J Med. 2012;366:15.
17. Stockfleth E, Kerl H, Zwingers T, Willers C. Low-dose 5-fluorouracil in combination with salicylic acid as a new lesion-directed option to treat topically actinic keratoses: Histological and clinical study results. Br J Dermatol. 2011;165:1101–8.
18. Stockfleth E, Zwingers T, Willers C. Recurrence rates and patient assessed outcomes of 0.5% 5-fluorouracil in combination with salicylic acid treating actinic keratoses. Eur J Dermatol. 2012;22:370–4.
19. Swanson N, Abramovits W, Berman B, Kulp J, Rigel DS, Levy S. Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: Results of two placebo-controlled studies of daily application to the face and balding scalp for two 2-week cycles. J Am Acad Dermatol. 2010;62:582–90.
20. Hanke CW, Swanson N, Bruce S, Berman B, Kulp J, Levy S. Complete clearance is sustained for at least 12 months after

treatment of actinic keratoses of the face or balding scalp via daily dosing with imiquimod 3.75% or 2.5% cream. J Drugs Dermatol. 2011;10:165–9.
21. Stockflet E, Gupta G, Peris K, Aractingii S, Dakovic R, Alomar A. Reduction in lesions from Lmax: A new concept for assessing efficacy of field-directed therapy for actinic keratosis. Results with imiquimod 3.75%. Eur J Dermatol. 2014;24:23–7.
22. Rosen T. Reexamination of field-directed therapy for actinic keratosis. Cutis. 2012;90:163–5.
23. Stockfleth E. The paradigm shift in treating actinic keratosis: A comprehensive strategy. J Drugs Dermatol. 2012;11:1462–7.
24. Ceilley RI, Jorizzo JL. Current issues in the management of actinic keratosis. J Am Acad Dermatol. 2013;68:28–38.
25. Rigel DS, Stein Gold LF. The importance of early diagnosis and treatment of actinic keratosis. J Am Acad Dermatol. 2013;68:20–7.
26. Rosen T, Lebwohl MG. Prevalence and awareness of actinic keratosis: Barriers and opportunities. J Am Acad Dermatol. 2013;68:2–9.
27. Berman B, Cockerell CJ. Pathobiology of actinic keratosis: Ultraviolet-dependent keratinocyte proliferation. J Am Acad Dermatol. 2013;68:10–9.
28. Spencer J. Understanding actinic keratosis: Epidemiology, biology, and management of the disease. J Am Acad Dermatol. 2013;68:1.
29. Esmann S, Jemec GB. Patients' perceptions of topical treatments of actinic keratosis. J Dermatol Treat. 2014;25:375–9.