UPDATE ON THE TREATMENT OF ACTINIC KERATOSIS

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Abstract: *Actinic keratoses (AKs) are skin lesions that result from chronic exposure to UV radiation and can progress to carcinomas, especially squamous cells carcinoma. We studied articles published between 2006 and 2016 and used the search engines: Pubmed, Medscape, Science direct and Wiley online library. We have synthesized treatment lines, new topical therapies, their efficacy and limitations. Imiquimod 2.5% and 3.75% respectively are part of first-line therapy with equivalent efficacy as IMI 5%, but with reduced adverse effects. Ingenol mebutate provides more than 90% adherence explained by the short duration of treatment. Regarding the healing rate and lesion recurrence, 5-FU / SA proved to be superior to both IMB and IMI. A new photosensitising substance that could remove the disadvantages of using ALA / MLA photodynamic therapy is indole-3-Acetic acid and, the first studies of the 0.015% IAA-PDT in liposomal gel confirm efficacy, tolerability and low cost. Piroxicam gel 1%, applied 2x /day for 3 months also had promising results. Due to the chronic evolution of actinic keratoses, regular dermatological control and repeating therapy when needed, reduces the number of AK cases, minimizes recurrence and reduces the risk of progression to squamous cells carcinoma.*

INTRODUCTION

Actinic keratoses (AKs) are by far the most common malignant skin lesions that develop on the sun-damaged skin as a result of chronic exposure to UV radiation. Clinically, they are characterized by brown or yellowish keratotic papules or plaques, flat or raised, which appear with predilection at the level of the cephalic extremity (face, ears, scalp, lips (actinic cheilitis)), the dorsal face of the hands and forearms as well as in other areas of the body frequently exposed to the sun. The cumulative harmful effect of sun rays associated with individual risk factors (older age, male gender, phototype I and II, exposure to carcinogens, chronic immunosuppressive therapy etc.) increases the risk of these precancerous lesions. Numerous epidemiological studies support us and confirm an increase in the prevalence of actinic keratoses in the Caucasian race.(1,2,3)

AKs are considered by many authors to be early stages of cutaneous carcinomas or spinocellular carcinomas in situ, and more recent articles have described actinic keratoses as squamous cell carcinoma in situ (SCCIS).(4) Thus, AKs are the precursors of invasive squamous cell carcinoma (SCCs), with the evidence that 60-65% of the total SCC can occur on an actinic lesion or in the immediate vicinity.(5)

Chronic exposure to UV radiation causes DNA damage and formation of cyclobutane-pyrimidine (CPD) dimers and other DNA photoproducers (6,4-pyrimidine-pyrimidone).(2) These DNA mutations result in p53 oncoprotein suppression leading to a clonal expansion of keratinocytes (due to the lack of basic keratinocyte response to UV-induced apoptosis) with the occurrence of AK and the subsequent development of SCC.(4)

The role of HPV infection in the occurrence of AK is attributed to the hyperexpression of viral oncoproteins E6 and E7 by infected keratinocytes.(4) A recent study reported that 63.8% of SCC showed keratinocytic intraepidermal neoplasia (KIN) in the lower 1/3 of the epidermis, and 77.9% of the cases showed KIN in their vicinity, suggesting the direct transformation of AK into squamous cell invasive carcinomas.(6)

Although the risk of progression of a "certain" actinic lesion in SCC cannot be predicted, however, the risk of AK transformation into an invasive spinocellular carcinoma was estimated at 0.60% at 1 year and 2.57% at 4 years.(7)

Given the special nature of these precancerous states, often with multifocal impairment, AK benefits from various therapeutic options that include two major treatment categories, by treating the entire field of cancerisation (field directed therapy) or by treating one single lesion (lesion directed therapy). Among the treatment methods, we mention the possibility of performing surgical exeresis, electrotherapy, cryotherapy, chemical peels, photodynamic therapy (PDT), and local therapies with: 5-fluorouracil (5-FU), diclofenac sodium 3% in hyaluronic acid gel, imiquimod IMI 5% (Aldara), and the latest local therapies include the combination of 5-FU 0.5% in salicylic acid 10% (Actikerall), ingenol mebutate (Picato), IMI 2.5% /3.75%, Piroxicam gel 1 %.

PDT using indole-3-Acetic acid as a photosensitizing product could also represent a possible treatment alternative with initial encouraging results, but studies and trials are needed to confirm efficacy and tolerability.

While 5-FU topical therapies, diclofenac sodium 3% and IMI 5% benefit from numerous studies to confirm their efficacy, new topical therapies such as ingenol mebutate IMI 2.5% and 3.75% and 0.5% respectively 5 -FU / SA are constantly subject to attention in an attempt to establish and compare both the benefits and possible adverse effects, both individually and in combination with other therapies.

PURPOSE

The aim of this study was to analyse and synthesize the therapeutic methods used in the treatment of AK, focusing on non-invasive methods (local topicals), as well as to insist on

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new local therapies to compare efficacy, indications and safety of their use in order to obtain complete healing, reduce recurrences as well as to limit morbidity and mortality associated with invasive SCC.

MATERIALS AND METHODS

We have reviewed literature articles published between 2006 and 2016 and used search engines such as Pubmed, Medscape, Science Direct and Wiley Online Library using keywords such as "New Therapies in AK", "AK Treatment Guide", "Efficacy of AK treatment", "Ingenol mebutate and AK". We have synthesized the new treatment lines, possible therapeutic combinations, recommendations, their efficacy and limitations.

RESULTS AND DISCUSSIONS

From all the published articles and studies that we have looked into regarding AK treatment, we found that the published data comparing the efficacy and tolerability of various topical therapies are limited and that there are few scientific approaches in the literature that allow a review of the entire therapeutic arsenal used in AK treatment.

By compiling a table, we synthesized the treatment variants most commonly used in AK management.

Table no. 1. Synthesis on the therapeutic management of actinic keratoses

KA management		
Isolated lesions, less in number		Multiple lesions "filed cancerisation"
Method to destroy the tumour tissue	Medical treatment	
Surgical exeresis	Diclofenac 3% in 2,5% hyaluronic acid	Diclofenac 3% in 2,5% hyaluronic acid
Cryotherapy	0,5% 5-FU/SA or 3,75%	Imiquimod 5% or 3,75%
Curettage with or without DTC	Imiquimod 5% or 3,75%	Imiquimod 5% or 3,75%
Laser CO2	Ingenol metabutate	PDT
	5-FU	
	PDT	

Ingenol metabutate (IMB) gel is a new topical therapy designed to treat AK. It acts through a double mechanism by inducing cell death from the lesion and by inducing an inflammatory response characterized by an immunocompetent cell infiltrate. Studies on IMB treatment have shown that short duration of treatment (3 days) ensures very high adherence (> 98%) compared to other topical therapies.(5,8)

In a multicentre randomized clinical trial conducted in 24 clinical sites in France and Italy involving 199 patients, the majority being previously treated, Pellacani et al compared efficacy, tolerability and patient satisfaction regarding AK treatment with ingenol mebutate gel in concentrations of 0.015% and 0.05% applied simultaneously or sequentially in 2 different areas of the body: face /scalp respectively trunk /extremities. Between March 2013 and October 2013, 101 patients were treated simultaneously for actinic lesions in the cephalic region as well as those on trunk or extremities with different concentrations (0.015% or 0.05%) of IMB and the remaining 98 patients received sequential treatment with IMB on face /scalp (0.015%) and trunk /extremities (0.05%).

The results evaluated on the 3rd day after first local application and at week 8 noted that no major differences were observed with regard to local skin reactions depending on the area of the treated body having a face /scalp score versus trunk /extremities, in day 3, of 10.6 vs 9.7, and the most common side effects were pruritus and local pain;(5) complete healing in the two patient groups evaluated at week 8 showed a percentage of 52.7% face /scalp versus 46.9% trunk /extremity score and the mean percentage reduction in AK was 83.4% vs 79.1%.(5) As a conclusion, the simultaneous and sequential treatment of actinic keratoses with ingenol mebutate showed efficacy and tolerability similar with an increased healing rate and reduction of AK number in the two areas of the body.

Also, 3 studies have followed the long-term efficacy of IMB gel over a 12-month period. Since only patients whose healing was complete after 8 weeks were included, the remaining patients whose healing was not complete may be considered at risk in the subsequent development of cutaneous carcinoma. Because economically, skin cancers are among the top 5 most expensive diagnostics (9), Elias et al published in March 2016 an article on cost-effectiveness /cost-benefit analysis comparing ingenol mebutate (Picato) with diclofenac 3% and IMI 5%.

For this purpose, a cohort study was conducted over a period of 5 years (mean age being 73 years) involving only individuals with actinic lesions at the begining of the study. Taking into account that these therapies have indications on certain topographic areas of the body, the study was divided into 3 groups comparing IMB with diclofenac 3% and IMI 5% for facial and scalp lesions, as well as IM with diclofenac 3% for actinic lesions localized on trunk and extremities. Secondly, the specific studies found in the literature were compared with the results of the cohort study. Over the course of the study, an adherence for IMB of nearly 90% and about 60% for the other 2 therapies was estimated. Experts say lack of adherence reduces the effectiveness of treatment by 50%.

At the end of the 5 years, IMB demonstrated greater efficacy than diclofenac 3%. At face and scalp level, it has been achieved a higher healing rate than Diclofenac 3% (0.192) with a better quality of life (QALY 0.011). Also, costs were significantly lower in patients treated with IM and therefore, saving per patient 297.60 € for the treatment of lesions on the scalp and face and 222.66 € for lesions on trunk and extremities.(9)

At the same time, IMB was more effective than IMI 5% based on a 0.032 healing rate and a 0.002 QALY. The total cost per patient was € 551.50 with IM and € 527.89 with IMI 5%.(9)

The conclusion of this study is that IMB is a therapy of real interest in terms of both efficiency and costs.

Another AK treatment line is Imiquimod (IMI) an immune response modulator that acts as a Toll-like 7 and 8 receptor antagonist and thus induces an increase in cytokine expression with antitumor activity (TNF-α, IFN G). It is also believed to facilitate apoptosis and has antiangiogenic activity. Stimulation of the immune response leads to a higher number of actinic lesions by revealing subclinical lesions.

While the effectiveness of 5% IMI in the treatment of KA has been proven in many multicentre studies, Stockfleth et al assessed whether using lower concentrations of IMI, a similar treatment efficiency will be achieved, but with less adverse effects.

2 placebo-controlled studies compared the IMI efficacy of 2.5% and 3.75% by treating actinic lesions in the face and scalp in 2-week cycles (2 weeks daily followed by 2 weeks pause followed by 2 more weeks of treatment daily). The results were similar in the two studies; the mean percent reduction was 25% for placebo, 72% for IMI 2.5% and 82% for IMI 3.75%. Moreover, the recurrence rate at 12 months was 33% for IMI 2.5% and 41% for IMI 3.75%.(10)

Reducing the duration of local treatment from 16 weeks (IMI 5%) to 6 weeks for the therapy with IMI 3.75%

offers a real advantage in terms of patient therapeutic compliance.(10,11) The combination of cryotherapy and IMI 3.75% was also evaluated. Daily local application of IMI 3.75% for a 2-week period after cryotherapy showed a 87% reduction in lesions and a full healing rate of 30% compared to placebo 3% and 50% respectively.(11)

Although no topical therapy provides 100% prevention of recurrences, IMI, by benefiting from the two concentrations (2.5% /3.75%) along with the IMI 5% brand, is part of the first line of topical therapy in the treatment of AK with evidence-based efficacy.

In May 2015, Simon et al published in the European Journal of Dermatology and Venerology, a prospectively randomized study on 66 patients (33 per arm) to compare the efficacy of 0.05% 5-FU to 10% salicylic acid versus cryotherapy in the treatment of hyperkeratosis AK. Before and after the treatment in each patient, a keratosis as specific as possible using a 3 mm punch was biopsied. Local treatment with 0.05% 5-FU / SA in the 33 patients consisted of daily application to each lesion for 6 weeks and the other 33 patients received a cryotherapy session on the first day followed by the 2nd session at an interval of 3 weeks if it is considered necessary to repeat the procedure.

Efficacy was assessed at 8 weeks after the end of the treatment for 0.05% 5-FU / SA and 14 weeks respectively 11 weeks after the first and second cryotherapy session, histological healing being obtained in 62.1% of patients treated with 0.05% 5-FU / SA and 41.9% of those treated with cryosurgery.(12) Of the patients who experienced complete clinical healing 14 weeks after the end of treatment, at the 6-month-check-up, a recurrence of lesions has been reported in 27.3% (3/11) of patients receiving 5-FU / SA vs. 50.0% (4/8) in patients treated with cryosurgery.(12) At the end of the study, it was shown that the group of patients treated with 5-FU /SA showed a much higher rate of histological healing than those treated with cryotherapy, a lower incidence of recurrence of lesions as well as good tolerability, being easily accepted by both the patient and the attending physician with satisfactory clinical and cosmetic results.

Furthermore, in a systematic review of the new therapeutic options in AK treatment published in 2016, Stockfleth et al compared the efficacy of 5-FU /SA, IMB and IMI 2.5% /3.75% both from the point of view of rate of healing and recurrence of lesions by analysing 11 publications regarding the 7 randomized clinical trials. The findings of this article were that, in terms of complete healing rate, 5-FU /SA remains superior to the other two topical therapies (55.4% vs 25-36.5% for IMB and 42.2% for IMI).(13) At the same time, the recurrence rate of lesions reported at 12 months after study completion was lower in patients treated with 5-FU /SA (32.7%) compared to patients treated with IMB in whom, the recurrence rate was of 53.9%.(13)

Photodynamic therapy (PDT) with aminolevulinic acid (ALA) /methyl aminolevulinic acid (MLA) is an effective therapy in treating multiple AKs with a high overall response rate, but whose use is hampered by major disadvantages: involves time consuming (4-6 h), high costs, pain in the treated area of the skin, which may take several hours).(14) These inconveniences reduce the feasibility and use of PDT in dermatological practice. For a good period of time, it was searched for that photosensitizer to reduce the negative aspects of the therapy, thus increasing the number of patients treated with PDT and implicitly, reducing the incidence of invasive SCC.

The ideal photosensitizer should be cheap, non-toxic, with stable molecules and with a short latency period between application and irradiation.

Indole-3-Acetic acid (IAA) largely fulfils these criteria. It is a phytohormone of the auxin family, with known clinical efficacy in the treatment of seborrheic dermatitis and acne vulgaris.(15) It is a low-cost molecule, easily extracted from plants, with thermal and chemical stability. It does not show spontaneous cytotoxicity, but it has cytotoxic antineoplastic properties after enzymatic activation by ***horseradish peroxidase*** (HRP). It is also activated by exposure to UV light.(15)

In 2016, a group of Italian researchers published a pilot study whose purpose was to evaluate the efficacy, tolerability and single cycle safety of a 0.015% IAA-PDT in liposomal gel for treating multiple AKs from the face and scalp. 12 previously untreated patients with a mean age of 77 years, mostly men were included. The number of non-hyperkeratosis AK per patient was 7.6 (+ - 2.5). A thin layer of IAA at 0.015% in liposomal gel was applied under occlusive dressing for 15 minutes on each area to be treated. Subsequently, the treated area was exposed to a green light source (520nm wavelength) of 9 J / cm2.

IAA accumulates in the target cells and absorbs the light with a specific wavelength. Energy is transferred to the intertissular oxygen, thus common oxygen reagents are resulting. They directly damage the cells by inducing necrosis and apoptosis, and also indirectly, by stimulating inflammation mediators.

The duration of the cycle was 4 weeks (1 session /week) and the assessment was done at 1 month and 3 months respectively. The first application did not reveal a significant reduction in AK number (6.7 + -3.1). After the first two applications, there was a significant reduction compared to the first session (4.5 + -3.3) while the last two did not bring significant additional results (4.0 + -3.4 and 4.2 + -4.0 respectively). At the end of the cycle (1 month later), efficacy was evaluated and 5 of the patients did not achieve a reduction in actinic lesions below 50% and were excluded from the study. At the 3-month follow-up, 25% (3/12) experienced complete remission of lesions and 25% (3/12) partial remission.(14)

All patients completed the study without complaining about local pain, pruritus or burning sensation, indicating excellent tolerability. Most patients showed local erythema at the end of the applications, well tolerated, which disappeared within minutes.

Although in terms of efficacy, the IAA-PDT at 0.015% in the liposomal gel appears to be inferior to MAL /ALA-PDT, the overall response rate at 3 months is 50% (3 complete remission, 3 partial remission).(14)

A recent meta-analysis of Vegter and Tolle compared the average healing rate for non-hyperkeratosis actinic lesions in the face and scalp, obtained from different therapies with IMI at 5% for 6 weeks, cryotherapy, Diclofenac 3%, and ingenol mebutate obtaining the following values: 45.1%, 44.1%, 35.4% and 43% respectively.(14) If we extrapolate these data, the efficacy of IAA-PDT seems to be close to that of current therapies of AK on the face and scalp. Based on the results of the study, the authors conclude that the IAA-PDT at 0.015% in the liposomal gel can be used on multiple AKs at face and scalp level with a very good safety profile. Moreover, these data suggest that IAA-PDT may have an important short-term effectiveness in reducing AK and is well tolerated by patients.
In the future, these data should be confirmed by larger randomized clinical trials to propose IAA-PDT as a possible alternative treatment for AK.

Based on the medical evidence on the efficacy of Diclofenac (COX 2 inhibitor) 3% in hyaluronic acid in treating

AK, Campione et al discussed for the first time Piroxicam 1% gel as a possible therapeutic option in the management of these lesions. Piroxicam is an inhibitor of cyclooxygenase 1 and 2 involved in the metabolism of arachidonic acid, used as an effective treatment in animal skin cancers.(16)

Its efficacy is secondary to the blockade of Cox-1 and Cox activity, 2 enzymes involved in tumorigenesis, which cause inhibition of apoptosis and immunosuppression.

In order to demonstrate the efficacy and tolerability of this therapy, a trial was conducted in which 10 patients (6 women and 4 men) were enrolled, with an average age of 72, presenting a total of 31 actinic lesions, keratosic, atrophic and verrucous forms located on the face and scalp, the back of the hands and lower limbs. Piroxicam 1% gel was applied twice /day for 3 months. During this time all patients have used sunscreen and have avoided sun exposure as much as possible. At the end of the 3 months of treatment, a complete remission of 15 of 31 AKs (48%) was observed. Clinical keratoses and verrucous forms presented the best therapeutic response. This can be correlated with the different stage in carcinogenesis of lesions, since patients with atrophic lesions have a longer duration of disease evolution.(16) Twelve of the 31 lesions (39%) showed a partial remission and 4 (13%) lesions remained clinically stable. This therapy can play an important part in the prevention of skin cancers, with a strong impact on public health.

Nashan et al say that there is no “best” therapeutic approach in AK management but, he has highlighted the fact that the new variants of topical therapies as well as the combination of existing therapies can lead to real progress in the treatment of this condition.(17)

CONCLUSIONS

The treatment of actinic keratoses must be performed as early as possible for the clinically evident lesions and for the treatment of subclinical keratoses by treating the cancer field, preferably. There are currently a number of therapeutic methods available to the clinician, some interventionist, others that can be performed in outpatients, adapted to the particular clinical forms of these precancerous lesions, recently considered as keratinocytic neoplastic intraepithelial lesions. The choice of these treatments should take into account the associated risk factors in patients’ pathology, being an important arsenal for the dermatologist in the management of actinic keratoses.

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