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ARTICLE

Ingenol mebutate for the treatment of actinic keratosis: effectiveness and safety in 246 patients treated in real-life clinical practice

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ABSTRACT

Introduction: The aim of the study was to evaluate the results on effectiveness and safety of topical treatment for actinic keratosis (AK) with ingenol mebutate gel (IMG) in real-life conditions and to perform an analysis of the factors that may influence the treatment outcomes.

Materials and methods: Retrospective study of patients with non-hyperkeratotic AK lesions prescribed with IMG in Spain according to clinical practice. Dermatologists reported the characteristics of patients and AK at baseline, and the findings observed up to 60 d after treatment.

Results and conclusions: A total of 260 treatments in 246 patients with a mean (SD) age 70.6 (10.4) years were reviewed. The number of clinically visible AK in the treated area decreased from 6.16 (3.02) to 1.22 (2.02) ($p < .001$) lesions with an average reduction of 84%. Univariate analysis showed higher reduction rates when IMG was applied in the face/scalp ($p = .026$), in women ($p = .041$), and in patients under 70 years of age ($p = .033$). According to multivariate analysis, advanced age was associated with worse clearance rates ($p = .038$). However, besides statistical significance, we can conclude that gender (female) and age (under 70 years-old) show a tendency to have better efficacy outcomes but without clinical relevance. Topical IMG was generally well tolerated and had positive cosmetic results after 60 d. Age influences on IMG effectiveness for AK and LSRs were correlated with higher effectiveness ratios.

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Actinic keratosis; topical therapy; ingenol mebutate gel; skin cancer

Introduction

Actinic keratosis (AK) is clinically defined as erythematous, scaly macules, papules, or plaques that can also present thick hyperkeratosis and occur as a result of the exposure to ultraviolet (UV) radiation (1). They are considered premalignant lesions with a small, but definite risk of transformation into squamous cell carcinoma (2).

Detectable lesions are often associated with field changes, where the surrounding skin is altered and subclinical lesions may be present. Thus, a field-directed therapy, such as topical treatment, should be preferred for the prevention of invasive cancer development (3).

Current approaches to the management of AK use both lesion-directed and field-directed therapies in search of a higher success of treatment. In all cases, total and permanent clearance of lesions is the primary goal of any intervention (4).

Ingenol mebutate gel (IMG) is a topical chemotherapeutic treatment derived from the sap of the plant *Euphorbia peplus*, a herb that has been used as an alternative therapy for several different skin lesions such as AK and skin cancers (5,6).

Preclinical investigations indicate that IMG is a pleiotropic effector that induces rapid and direct cell death and immune responses mediated by specific activation of protein kinase C (PKC), including neutrophil-mediated oxidative burst (7). IMG has also been examined in phase II–III studies as a promising new therapeutic option for AK and superficial basal cell carcinomas (8,9).

Due to its mechanism of action, the development of specific local skin responses (LSRs) such as erythema, ulcerations, and crusting (10) has been reported after the topical treatment with IMG. Evidence suggests that these LSRs tend to spontaneously resolve within 2–4 weeks after treatment, which is correlated with the initial severity shown within the affected skin field (11).

While the efficacy and safety of IMG has been well established in clinical trials (12), data regarding the effectiveness and safety of IMG in routine clinical practice is scarce (13). This study intends to evaluate the effectiveness and safety of the use of IMG on AK in real-life conditions and in a larger number of patients; which in turn will allow to perform an analysis of the factors that may influence the treatment outcomes and the establishment of a patient profile for the optimal selection of those patients that may benefit the most from IMG treatment.

Materials and methods

This was a retrospective study of all patients with clinically visible, non-hyperkeratotic AK lesions whom according to dermatologist criteria were prescribed with IMG between January and December of 2015, in a dermatology clinic in Granada and in the dermatology department of the Hospital Universitario Reina Sofía in Córdoba, both in Southern Spain.

Patients received a daily application of IMG 150 mcg/g during 3 d for lesions located on the face and/or scalp, while other locations were treated for 2 d with the 500 mcg/g formula. All data was extracted from clinical records, and the revision of pictures taken during each visit. It included data from baseline (prescription of IMG visit) and standard follow-up visits at 3–4 d, 15, 30, and 60 d after the end of treatment. Patients' profile included

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demographics (age, gender, etc.), fitzpatrick skin phototype, and dermatological history; including the presence and location of previous AK lesions and their treatments. A wash-out period for field-directed therapies of at least three months was needed as inclusion criteria.

Baseline AK in need for treatment included the location and *number of clinically evident lesions* in the areas intended to treat. Clinical outcome considered the estimated number of AK and clearance of the AK lesions as reported by the dermatologist throughout follow-up. *Complete clearance* was considered in cases where the reduction of clinically visible lesions corresponded to 'all previous AK' (100%). Meanwhile, *Partial clearance* was assigned when the total number of previous AK were reduced at least three quarters (>75%).

As previously described by Lebwohl et al. (14), treatment with IMG is frequently associated to the development of LSRs such as erythema, flaking/scaling, crusting, swelling, vesiculation/postulation, and erosion/ulceration. Therefore, these six signs were assessed throughout the study and scored with a standardized validated scale that ranged from 0 (no signs) to 4 (maximum severity) for each lesion, resulting in a possible total composite score ranging from 0 to 24. The study was conducted in accordance to the Declaration of Helsinki (Fortaleza, 2013) and Good Clinical Practices.

Statistical analysis

Descriptive statistics were applied on all registered variables. Categorical variables are presented as frequencies and proportions, while quantitative variables (continuous or ordinal) are presented as central tendency (average) and as dispersion measures (standard deviation and range).

Primary outcomes included the reduction in the number of AK lesions observed in each visit and the proportion of patients with complete and partial clearance of AK lesions, to measure IMG effectiveness; as well as the incidence and severity of LSRs to measure safety. The average composite and sign-specific LSR score throughout control visits were analyzed with Friedman's.

The sample was stratified based on its baseline characteristics, including gender, age (≤70 years vs. >70 years), history of skin cancer, fitzpatrick skin phototypes (I–II vs. III–IV), and location of the AK lesions treated with IMG (face/scalp vs. trunk/extremities) in order to compare the *mean LSR score for each visit* and the *percentages of reduction of clinically evident AK* 60 d after treatment (Mann–Whitney *U* test); these groups were also considered for comparison based on the *percentage of patients with complete or partial clearance* (Chi-square test). These results are presented as odds ratio (OR) along with confidence intervals at 95% (CI 95%). In addition, a multivariate analysis was performed to study the factors that may influence the complete elimination of clinically visible lesions. Studied factors were gender, age, skin phenotype, cutaneous history, treatment location, and LSRs at 3–4 d of follow-up. Significations (*p* values) below .05 were considered as statistically significant. All analyzes were performed with SPSS version 22.0® (SPSS Inc., Chicago, IL) for Windows.

Results

A total of 260 treatments in 246 patients with a mean (SD) age 70.6 (10.4) years (range 32–92 years) were reviewed. The sample comprised a majority of men (72.4%) with fitzpatrick phototypes II and III. More than half of patients (56.7%) had cutaneous history of skin cancer. Presence of AK was reported in several different locations, most frequently in the face. Field-directed therapies were the most used alternatives prior to participation in the study (114 from 153 patients (74.5%)) (Table 1).

Table 1. Sample characteristics.

Age	
≤70 years	120 (48.8%)
>70 years	126 (51.2%)
Gender	
Female	68 (27.6%)
Male	178 (72.4%)
Fitzpatrick skin phototype	
I	11 (4.5%)
II	116 (47.3%)
III	105 (42.9%)
IV	13 (5.3%)
Relevant dermatological history	
Skin cancer history	139 (56.7%)
Location of previous lesions	
Face	171 (69.5%)
Scalp	90 (36.6%)
Upper extremity	31 (12.6%)
Lower extremity	12 (4.9%)
Chest	10 (4.1%)
Back	2 (0.8%)
Previous treatments	
Topical *solution*	115 (46.7%)
Imiquimod	39 (33.9%)
Sodium diclofenac	43 (37.4%)
Trichloroacetic acid	50 (43.5%)
Surgical excision	80 (32.5%)
Cryosurgery	67 (27.2%)
Photodynamic therapy	27 (11.0%)

Table 2. Effectiveness of IMG treatment.

	Clearance							
	Complete		Partial			CI95%		
Factors	N	%	N	%	OR	Min	Max	*p* value
Women								
Yes	50	74.6	17	25.4	1.90	1.02	3.55	.042
No	113	60.8	73	39.2				
Location of AK								
Face/scalp	147	66.5	74	33.5	1.75	0.80	3.75	.156
Rest of the body	16	53.3	14	46.7				
Skin phototype								
I–II	85	65.4	45	34.6	1.10	0.66	1.85	.707
III–IV	77	63.1	45	36.9				
Age								
≤70 years	86	69.9	37	30.1	1.60	0.95	2.69	.076
>70 years	57	59.2	53	40.8				
History of skin cancer								
Yes	88	60.7	57	39.3	1.45	0.86	2.46	.165
No	74	69.2	33	30.8				

OR: Odds ratio.

Effectiveness of IMG treatment

Overall, the number of clinically visible AK in the treated area went down from 6.16 (3.02) (range: 1–18) to 1.22 (2.02) (range: 0–17) ($p < .001$) with an average reduction of 84% (23.5). At the final visit, 64.9% of treatments were associated with complete clearance, with a particularly higher frequency of this outcome in women. Additionally, those patients under 70 years old showed a non-significant trend to higher rates of complete clearance (Table 2).

Despite these findings, when the average reduction in the number of clinically visible AK was compared, some differences between groups of patients were identified (Figure 1). Thus, higher reduction rates of AK lesions were observed when

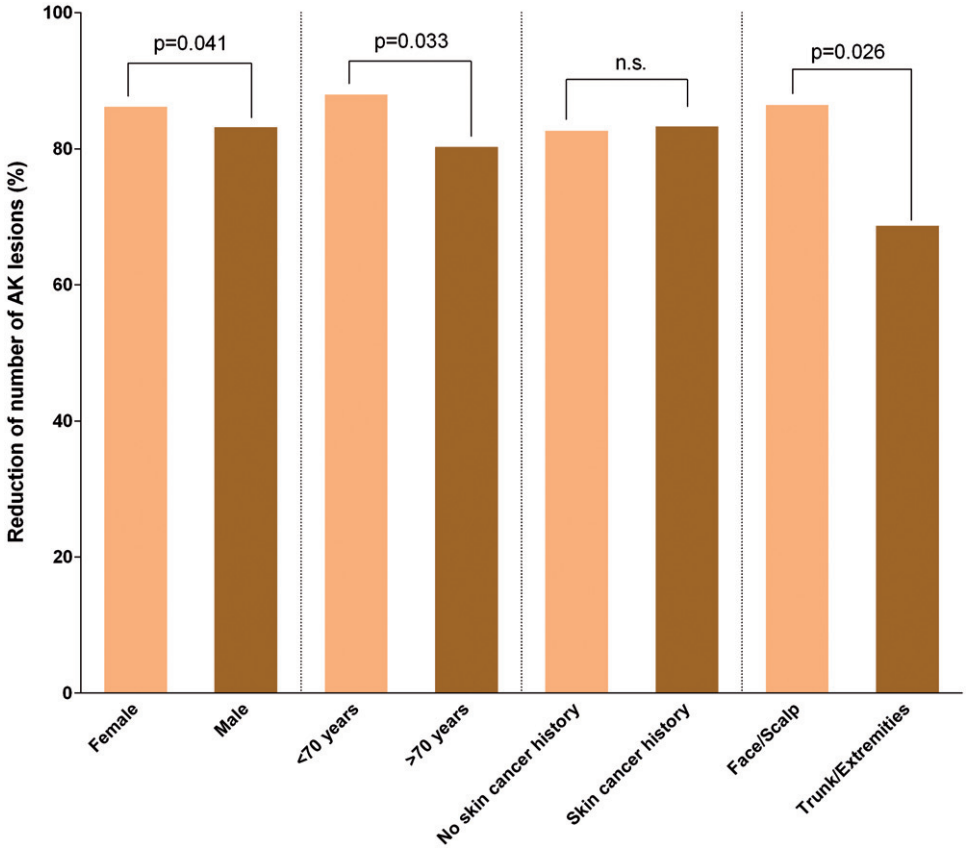

Figure 1. Differences between groups of patients and average reduction of AK. AK: actinic keratosis. *p* value: Mann–Whitney *U* test.

IMG was applied in the face/scalp ($p = .026$), in female patients ($p = .041$), and those patients younger than 70 years old ($p = .033$).

According to the results of multivariate analysis (data not shown), age was the strongest predictive factor for the treatment's effectiveness, since younger patients achieved higher clearance rates than older patients ($p = .038$). None of the other factors included in the multivariate analysis showed statistically significant results.

Local skin responses (LSRs)

Two hundred and fifty-two treatments were completed as intended, while five were suspended (due to LSRs). Regarding adverse reactions, 39% of patients reported various bothers or symptoms, of which pruritus (96.8%), and burning (41.9%) were the most frequently described.

The presence, in some degree, of LSRs was observed in 99% of cases. The severity of each reaction peaked within 3–4 d after completion of treatment in all cases. The composite LSR score was mostly comprised by erythema and flaking/scaling scores at first evaluation (Figure 2), and in each further scoring across control visits. The mean composite LSR score showed a significant trend to reduction throughout the follow-up visits (Table 3 and Figure 3).

Comparison of global LSR scores at their peak at 3–4 d after treatment revealed three factors that have significant influence over the presence of LSRs: treatment location, gender, and age. Regarding the location of AK treatment (therefore the concentration of IMG applied), the analysis showed that the face and scalp have statistically significant higher scores for *crusting*. In addition, some differences were found when other factors were considered for comparison: gender, for example, showed higher scores in women in all specific LSRs. Meanwhile, based on the classification of patients by age, those under 70 years old showed a higher score when evaluating the severity of erythema (Table 4); of note, cases with fitzpatrick skin phototype IV were the only group showing any sign of skin ulcer/erosion at the end of follow up (0.13 (0.52)).

Comparison of global LSR scores of each visit regarding effectiveness outcome showed a similar pattern between complete and partial clearance, but also showed a statistical significant higher LSR scores for patients with complete clearance from the peak of LSRs at 3–4 d visit until 30 d visit ($p < .05$); to finally become close at 60 d of follow-up (Figure 4).

Satisfaction and cosmetic outcomes

In general terms, patients' satisfaction with treatment was positive, with a 72.1% of patients reporting it as 'high.' Cosmetic outcomes ranged from good to excellent in 86.7% of the cases, with improvement on skin appearance for 214 patients (88.8%). Positive willingness to repeat IMG treatment was reported by 58.9% of patients, who would agree to receive IMG treatment again (data not shown).

Discussion

The need for treatment of AK as a known precursor of squamous cell carcinoma (SCC) has turned into a generalized approach in dermatological daily practice, particularly in face of an increasing incidence around the globe. In the European region, where fair skin phototypes (therefore, with higher risk of UV-damage) and older patients represent the majority of people demanding dermatological consultations, the intervention of factors that might

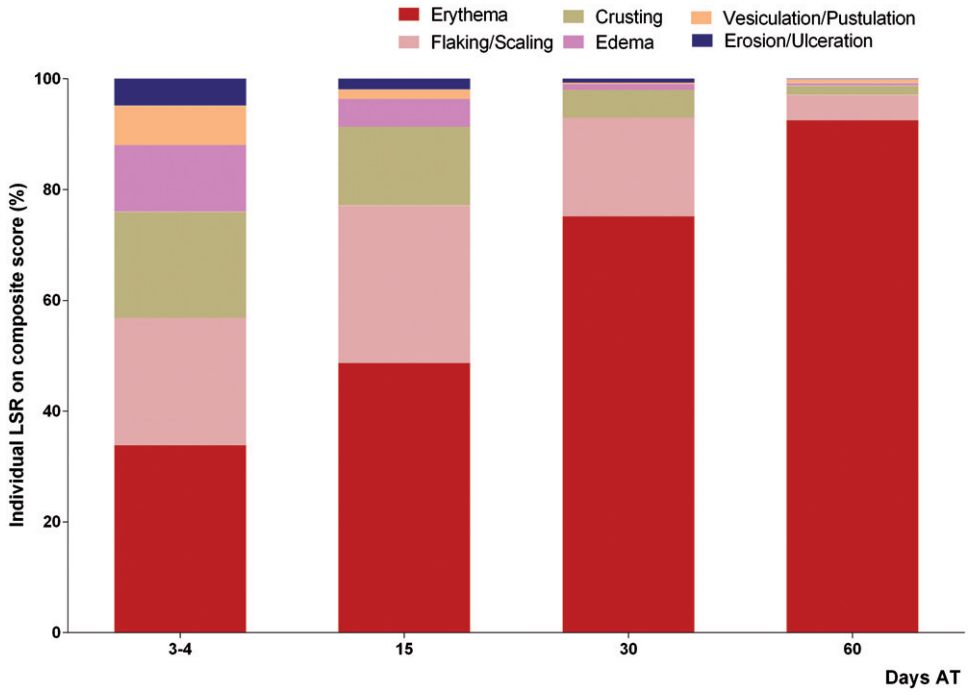

Figure 2. Weight of each LSR on the composite score across follow-up. LSR: local skin response; AT: after treatment.

Table 3. Severity of LSRs across study visits.

	Days after treatment				
	3–4 d	15 d	30 d	60 d	*p*
Total sample ($n = 257$)					
Mean (SD)	9.77 (5.05)	4.91 (4.46)	1.54 (2.19)	0.45 (1.02)	**<.001**
Range (min–max)	0–22	0–21	0–13	0–8	–
IMG 150 mcg/g (face and scalp; $n = 221$)					
Mean (SD)	9.93 (4.94)	5.15 (4.61)	1.62 (2.27)	0.46 (1.01)	**<.001**
Range (min–max)	1–22	0–21	0–13	0–8	–
IMG 500 mcg/g (trunk and extremities; $n = 31$)					
Mean (SD)	7.71 (5.09)	2.97 (2.40)	0.87 (1.12)	0.16 (0.45)	**<.001**
Range (min–max)	0–20	0–11	0–4	0–2	–

SD: standard deviation; min: minimum; max: maximum; *p* values: Friedman's test
Bold values indicate significant p values.

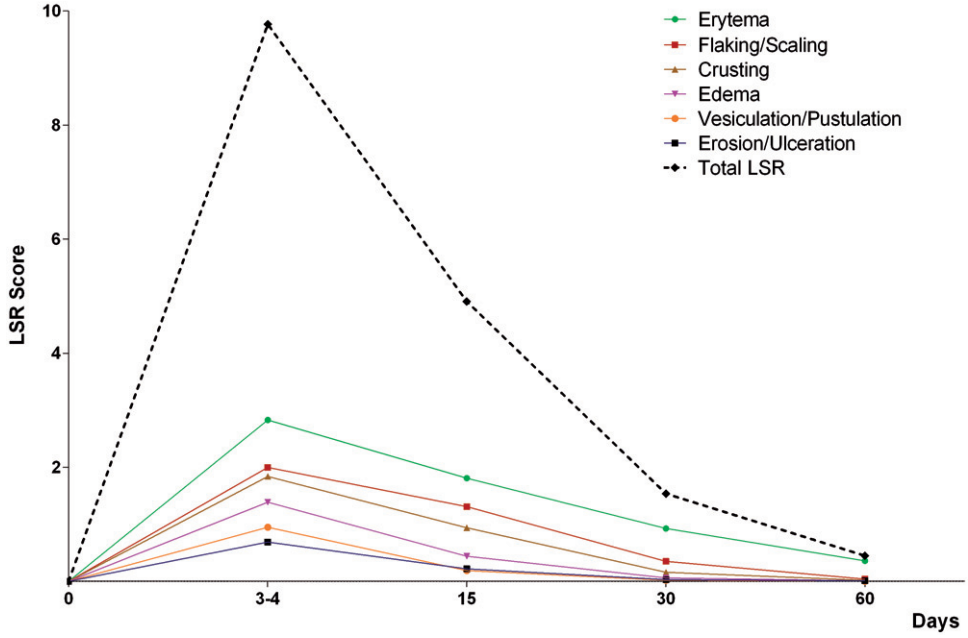

Figure 3. Evolution of the LSRs after IMG treatment. LSR: Local skin response; IMG: ingenol mebutate gel. $^{*}p < .001$ from visit to visit in all cases. *p* value: Friedman's test.

Table 4. LSR mean (SD) scores at 3–4 d after treatment.

	Treatment area			Gender			Age		
LSR	Face and scalp	Chest, back, and extremities	*p*	Female	Male	*p*	≤70 years	>70 years	*p*
Erythema	*n* = 223 2.87 (0.90)	*n* = 32 2.59 (1.07)	.203	*n* = 70 3.13 (0.98)	*n* = 187 2.73 (0.89)	**<.001**	*n* = 124 3.02 (0.84)	*n* = 133 2.67 (0.98)	**.002**
Flaking/scaling	*n* = 223 2.03 (0.96)	*n* = 32 1.81 (1.03)	.245	*n* = 70 2.23 (1.00)	*n* = 187 1.93 (0.95)	**.013**	*n* = 124 2.22 (0.87)	*n* = 133 1.81 (1.02)	**.001**
Crusting	*n* = 223 1.93 (1.10)	*n* = 32 1.25 (1.08)	**.001**	*n* = 70 2.24 (1.26)	*n* = 187 1.71 (1.03)	**.001**	*n* = 124 1.91 (1.08)	*n* = 133 1.80 (1.16)	.424
Edema	*n* = 223 1.46 (1.18)	*n* = 32 1.00 (1.19)	.590	*n* = 70 1.96 (1.23)	*n* = 187 1.20 (1.11)	**<.001**	*n* = 124 1.48 (1.21)	*n* = 133 1.33 (1.17)	.303
Vesiculation/Pustulation	*n* = 223 0.99 (1.17)	*n* = 32 0.75 (1.19)	.205	*n* = 70 1.54 (1.28)	*n* = 185 0.74 (1.06)	**<.001**	*n* = 124 1.07 (1.18)	*n* = 133 0.86 (1.17)	.096
Erosion/ulceration	*n* = 222 0.74 (1.04)	*n* = 32 0.44 (0.84)	.107	*n* = 70 1.19 (1.24)	*n* = 186 0.53 (0.87)	**<.001**	*n* = 124 0.85 (1.11)	*n* = 132 0.58 (0.93)	**.050**
Total	*n* = 223 10 (4.98)	*n* = 32 7.84 (5.07)	**.022**	*n* = 70 12.29 (5.91)	*n* = 187 8.83 (4.34)	**<.001**	*n* = 124 10.56 (5.06)	*n* = 133 9.04 (4.94)	**.013**

p values: Mann–Whitney *U* test.
Bold values indicate significant p values.

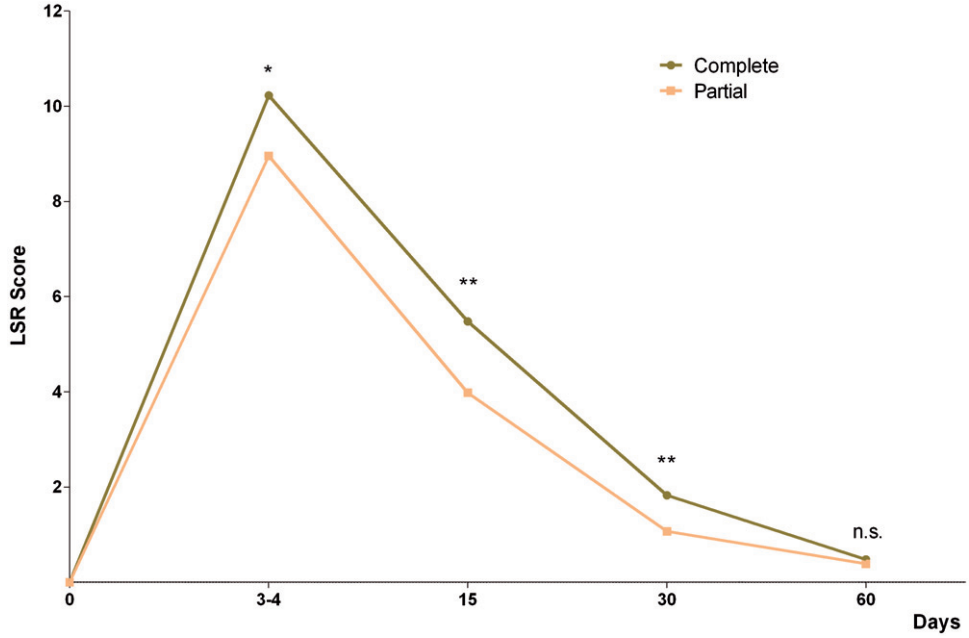

Figure 4. Relationship between the evolution of LSR score and clearance outcomes. $^{*}p < .05$; $^{**}p = .001$; ns: non-significant. *p* value: Mann–Whitney *U* test.

impact an effective reduction of morbidity due to skin cancer are of particular relevance.

These studies on AK therapy, along with investigations of other chronic dermatological diseases, have established several highly valued factors and the ideal characteristics of treatments in order to improve patient satisfaction and adherence. Cumulative experience on this subject suggests that, beyond the good effectiveness and/or high rates of clearance of lesions observed with most available options, the selection of treatment should consider the alternatives that could reduce the likelihood for re-treatment need, with lower frequencies of adverse events and ideally, allowing shorter treatment regimens and patient-friendly formulations.

IGM is a relatively recent topical field therapy with an increasing relevance among the topical drugs used for AK treatment. Its dual mechanism of action, that includes the specific-dysplastic cell's induction of necrosis and a neutrophil-mediated immunostimulant effect, allows targeting both clinically evident and subclinical AK through a shorter treatment (2–3 d); this feature also seems to reduce the impact of local effects, which, as observed in our patients, are mostly of mild severity and self-resolving. Furthermore, shorter duration of its application has shown to facilitate patients' adherence to treatment, compared with the low adherence rates observed with alternatives that are applied for longer periods (4).

The results presented here reinforce the positive effects of treatment with IMG with a relevant number of cases that achieved a complete clearance of the evident AK. Previous studies have reported rates of complete remission of lesions from 34.1 (14) to 71% (15) and 42.2% (14) with the two commercially available alternatives of IMG (500 and 150 mcg/g, respectively). It should be stated that in most cases, these rates of efficacy are based on the disappearance of visible lesions. Hence, no evaluation of the effects on sub-clinical actinic transformation has been considered in this study although it exists, as histological examinations confirm clinical clearance of AKs following treatment with 500 mcg/g IMG.

Also, our findings are particularly interesting, since they correspond to a study population for which IMG was prescribed, based on the dermatologist's criteria, as part of their routine clinical practice (16). In addition, some of the characteristics of the sample studied are also relevant since, as previously commented, around 57% of cases have had some type of skin cancer and almost 47% have been treated with topical formulations for AK lesions in the past.

Univariate analysis shows what could be considered as an association between location, gender, and age *versus* effectiveness after 60 d; since AK in face/scalp, in female and in younger patients more frequently presented complete clearance. However, once the multivariate test was performed, the 'gender effect' disappears and location and age seem to be the only factors with statistical association. Besides statistical significance, the association of younger patients with better efficacy outcomes does not seem to be relevant from the clinical point of view. Nevertheless, due to the retrospective nature of this analysis and the observational nature of these results, a long-term evaluation of the results should be contemplated for more conclusive associations.

Of note and overall patients, those with more severe LSRs at 3–4 d have shown a higher reduction on the number of AK. The mechanism of action of IMG has been subject of different studies from pre-clinical to randomized controlled trials, showing that IMG field-directed treatment induces rapid necrosis of the dysplastic keratinocytes through activation of the pro-apoptotic PKC (1) and a neutrophil-mediated antibody-dependent cellular cytotoxicity (ADCC) (17). This loss of the epidermis, followed by a rapid re-epithelization that has also been described, translates into a significant reduction in the number of mutant p53 patches in the newly formed epidermis, therefore, removing replication-competent mutant p53-expressing keratinocytes that give rise to these patches (18).

After this remodeling process, the development of LSRs such as erythema and flaking/scaling could be expectable, as it has been widely reported throughout all evidence on different concentrations of IMG (alone or combined with other therapies) (15,19,20). These, however, tend to resolve spontaneously and without clinically relevant sequelae, as shown in the 60 d AT evaluation where most of the severity did not reach a 0.5 score.

The data collected in our study on the use of IMG as part of the routine clinical practice for the treatment of AK, support the findings on effectiveness and safety of previous clinical trials. Furthermore, LSRs were correlated with higher effectiveness ratios. However, multicentric studies with a larger sample size are needed in order to better characterize the patient profile that might benefit most from this treatment.

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Disclosure statement

Rafael Salido Vallejo served as an investigator for LEO Pharma A/S, Almirall and Roche; he has received speaker honoraria for Almirall, LEO Pharma A/S, Galderma, Biofrontera and Abbvie; he has attended advisory boards for Almirall and LEO Pharma A/S.

Rosa Ortega del Olmo served as investigator for LEO Pharma A/S; she has received speaker honoraria for LEO Pharma A/S; she has attended advisory boards for LEO Pharma A/S.

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References

1. Samrao A, Cockerell CJ. Pharmacotherapeutic management of actinic keratosis: focus on newer topical agents. Am J Clin Dermatol. 2013;14:273–277.
2. Ratushny V, Gober MD, Hick R, et al. From keratinocyte to cancer: the pathogenesis and modeling of cutaneous squamous cell carcinoma. J Clin Invest. 2012;122:464–472.
3. Cantisani C, Paolino G, Corsetti P, et al. Evaluation of ingenol mebutate efficacy for the treatment of actinic keratosis with Antera 3D camera. Eur Rev Med Pharmacol Sci. 2015;19:92–97.
4. Berman B. New developments in the treatment of actinic keratosis: focus on ingenol mebutate gel. Clin Cosmet Investig Dermatol. 2012;5:111–122.
5. Weedon D, Chick J. Home treatment of basal cell carcinoma. Med J Aust. 1976;1:928.
6. Lebwohl M, Shumack S, Stein Gold L, et al. Long-term follow-up study of ingenol mebutate gel for the treatment of actinic keratoses. JAMA Dermatol. 2013;149:666–670.
7. Rosen RH, Gupta AK, Tyring SK. Dual mechanism of action of ingenol mebutate gel for topical treatment of actinic keratoses: rapid lesion necrosis followed by lesion-specific immune response. J Am Acad Dermatol. 2012;66:486–493.
8. Patel RV, Frankel A, Goldenberg G. An update on nonmelanoma skin cancer. J Clin Aesthet Dermatol. 2011;4:20–27.
9. Izzi S, Sorgi P, Piemonte P, et al. Successfully treated superficial basal cell carcinomas with ingenol mebutate 0.05% gel: report of twenty cases. Dermatol Ther. 2016;29:470–472.
10. McIntyre WJ, Downs MR, Bedwell SA. Treatment options for actinic keratoses. Am Fam Physician. 2007;76:667–671.
11. Jim On SC, Knudsen KM, Skov T, et al. Relationship between severity of the local skin reactions and the rate of local skin reaction resolution in patients treated with ingenol mebutate gel. Clin Cosmet Investig Dermatol. 2016;9:211–216.
12. Garbe C, Basset-Seguin 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.
13. Bettencourt MS. Use of ingenol mebutate gel for actinic keratosis in patients in a community dermatology practice. J Drugs Dermatol. 2014;13:269–273.
14. Lebwohl M, Swanson N, Anderson LL, et al. Ingenol mebutate gel for actinic keratosis. N Engl J Med. 2012;366:1010–1019.
15. Siller G, Gebauer K, Welburn P, et al. PEP005 (ingenol mebutate) gel, a novel agent for the treatment of actinic keratosis: results of a randomized, double-blind, vehicle-controlled, multicentre, phase IIa study. Australas J Dermatol. 2009;50:16–22.
16. Ricci F, Tambone S, Neri L, et al. Real-life efficacy and safety of ingenol mebutate for the treatment of actinic keratosis of the face and scalp: a single arm retrospective study. J Dermatolog Treat. 2016;27:525–530.
17. Alchin DR. Ingenol mebutate: a succinct review of a succinct therapy. Dermatol Ther (Heidelb). 2014;4:157–164.

18. Cozzi SJ, Ogbourne SM, James C, et al. Ingenol mebutate field-directed treatment of UVB-damaged skin reduces lesion formation and removes mutant p53 patches. J Invest Dermatol. 2012;132:1263–1271.
19. Anderson L, Schmieder GJ, Werschler WP, et al. Randomized, double-blind, double-dummy, vehicle-controlled study of ingenol mebutate gel 0.025% and 0.05% for actinic keratosis. J Am Acad Dermatol. 2009;60:934–943.
20. Goldenberg G, Berman B. Assessment of local skin reactions with a sequential regimen of cryosurgery followed by ingenol mebutate gel, 0.015%, in patients with actinic keratosis. Clin Cosmet Investig Dermatol. 2015;8:1–8.