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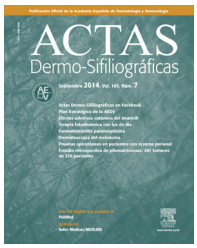

E- CASE REPORT

Clinical Response to Ingenol Mebutate in Patients With Actinic Keratoses☆

A. Batalla,* Á. Flórez, C. Feal, G. Peón, M.T. Abalde, L. Salgado-Boquete, C. de la Torre

Servicio de Dermatología, Centro de Especialidades de Mollabao, Xestión Integrada Pontevedra-Salnés, Pontevedra, Spain

KEYWORDS
Actinic keratosis;
Effectiveness;
Ingenol mebutate;
Treatment

Abstract Cryotherapy is the most common treatment for actinic keratosis, but its effect is limited to individual lesions. Several topical drugs, however, are available that, in addition to treating individual actinic keratoses, target field cancerization and thereby act on subclinical lesions. Examples are 5-fluorouracil, imiquimod, diclofenac, and ingenol mebutate. We report on 17 patients with actinic keratoses treated with ingenol mebutate and describe our findings on treatment effectiveness, adherence, and tolerance. Complete and partial response rates were 35% and 53%, respectively. Ninety-four percent of patients fully adhered to treatment and 18% developed severe local reactions. Ingenol mebutate is an effective treatment for actinic keratosis. Although it has a similar rate of local reactions to other treatments available for actinic keratosis, its short treatment regimen favors better adherence.

PALABRAS CLAVE
Queratosis actínica;
Efectividad;
Ingenol mebutato;
Tratamiento

Respuesta a ingenol mebutato en los pacientes con queratosis actínicas en la práctica clínica

Resumen La crioterapia es el tratamiento más frecuentemente utilizado para las queratosis actínicas, ejerciendo su efecto únicamente sobre lesiones individuales. Existen fármacos tópicos que tratan además el campo de cancerización, actuando sobre queratosis actínicas no clínicamente evidentes, entre los que se encuentran el 5-fluorouracilo, el imiquimod, el diclofenaco o el ingenol mebutato.

Presentamos 17 pacientes con queratosis actínicas tratados con ingenol mebutato y describimos las observaciones en relación con la efectividad, el cumplimiento terapéutico y la tolerancia del fármaco. Las tasas de respuesta completa y parcial fueron del 35% y del 53%, respectivamente. El cumplimiento fue correcto en un 94% de los casos. En el 18% de los pacientes existieron reacciones locales intensas.

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* Corresponding author.
E-mail address: anacebey@yahoo.es (A. Batalla).

El ingenol mebutato es efectivo para el tratamiento de las queratosis actínicas. Aunque presenta similar tasa de reacciones locales a los restantes tratamientos disponibles para esta indicación, su pauta corta de administración favorece el cumplimiento.

Introduction

Actinic keratoses (AK) are considered by most authors to be premalignant lesions that can progress to invasive squamous cell carcinoma.[1] In addition to lesion-directed therapies such as cryotherapy, the available treatment options for AK also include topical treatments that act on both the isolated—clinically visible—lesions and on the surrounding area of skin with chronic actinic damage and subclinical AK. Treatments include 5-fluorouracil, imiquimod (IMQ), diclofenac (DCF), and photodynamic therapy.[1,2]

Ingenol mebutate is a treatment indicated for AK that has only recently become available. It has been shown to be effective in the treatment of both individual lesions and the cancerization field, with treatment cycles of 3 consecutive days for the face and scalp and 2-day cycles for the trunk or limbs, achieving a complete cure rate of around 40%.[1] The main difference between ingenol mebutate and other field cancerization therapies is that the treatment cycle is shorter and adherence to the dosing schedule is easier.

Case Descriptions

We present a series of 17 patients treated with ingenol mebutate. Demographic and clinical characteristics were evaluated as well as treatment-related data (effectiveness, adherence to treatment, and tolerance) (Table 1). Effectiveness was evaluated at 2 months[2] and was classified as follows: complete response if no abnormalities were detected in the treated area (normal skin); partial response if the abnormalities had diminished but were still present to some degree, making a cycle of any other treatment necessary; and no response if the lesions were unchanged. The regimen prescribed was 3 doses for facial lesions and 2 doses if the site affected was on the body. Correct adherence to treatment was defined as the application by the patient of all the doses prescribed; if any dose was skipped, adherence was defined as partial. To assess tolerance, the patients were asked about localized irritation at the site of application using the terminology specified in the Summary of Product Characteristics (minimum, type I; mild, type II; moderate, type III; and severe, type IV).

The mean age of the group of patients treated was 76 years. Only 1 patient had a history of melanoma skin cancer, and 3 patients a history of non-melanoma skin cancer. None of the prior skin cancer lesions were located in the area treated with ingenol mebutate. Fourteen of the 17 patients (82%) had previously received treatment for AKs, mainly cryotherapy (76%), imiquimod (29%), or diclofenac (29%). The mean interval between the last prior treatment and application of ingenol mebutate was 20 months (median, 6 months). All the patients in the present study received treatment with ingenol mebutate for AK lesions on the face (76%; 13/17) or scalp (24%; 4/17). The response to treatment was complete in 35% (6/17) and partial in 53% (9/17). In 2 cases (12%), there was no response. Figure 1 shows a case of complete response to ingenol mebutate. Long-term follow-up was variable after the assessment of response at 2 months post-treatment. Table 1 shows the maximum follow-up period and the clinical outcome at the end of follow-up for the patients who presented a complete response (mean: 10 mo, median: 11 mo; complete remission in 67% of cases). Adherence was correct in 94% (16/17) of the patients. The only case in which there was partial compliance was due to a type IV local reaction after application of the first dose; the following 2 applications were not administered because of the severe symptoms associated with that reaction (Fig. 2). In addition to that case, 2 other patients had local type IV reactions (3/17 in total, 18%). The rates for type III and type I/II reactions were similar: 41% in both groups. No relationship was observed between the severity of the reaction and a better or worse response ($P = 0.4$; Fisher test). None of the patients reported cosmetic alterations or scarring in the treated area.

Discussion

In this case series of patients treated with ingenol mebutate in routine clinical practice, we observed a response rate of 88% (complete response, 35%; partial response, 53%), high adherence (94%), and frequent local skin reactions (minimal to mild, 41%; moderate to severe, 59%).

The response rates in this study were slightly lower than those reported in the literature (Table 2).[1] It has been observed that the success rate may be higher when ingenol mebutate is combined with other therapies (Table 2).[3]

It is difficult to perform a direct comparison of the different treatment options for AK due to the heterogeneity of the available studies.[4,5] Table 2 summarizes the results of studies which, based on the best scientific evidence, analyze the effectiveness of various interventions, including ingenol mebutate. In terms of effectiveness, ingenol mebutate is ranked midway between the most effective treatment (5-fluorouracil) and the least effective options (cryotherapy and diclofenac), achieving results comparable to treatments of intermediate effectiveness (photodynamic therapy and IMQ).[6,7] In the case of ingenol mebutate, relative effectiveness is influenced by the site of treatment, with higher rates of clearance for the head region, for which it has proved more effective than 5% IMQ.[6]

With respect to adherence to treatment, 94% of our patients completed treatment, a percentage similar to that reported by other authors.[1] Adherence to treatment with

Table 1 Patients Treated With Ingenol Mebutate.

Age	Sex	Past History of Skin Cancer		Previous Treatment	Time Since Last Treatment	Site	Adherence[a]	Tolerance[a] (Severity of Reaction)	Effectiveness[a]	Maximum Follow-up
		Melanoma	NMSC							
84	W	Yes (LM)	Yes (BCC)	None		Facial	Correct	III	Complete	17 months (No recurrence)
88	W	None	None	None		Facial	Correct	IV	Complete	12 months (no recurrence)
86	W	None	Yes (BCC)	Yes (CT, IMQ, 5-FU)	6 months (CT)	Facial	Correct	I/II	Partial	
82	W	None	None	Yes (CT, DCF)	6 months (CT)	Facial	Correct	III	Partial	
78	W	None	None	Yes (CT)	6 months (CT)	Facial	Correct	I/II	Partial	
64	M	None	None	Yes (CT, ELC, IMQ)	10 y (CT)	Scalp	Correct	III	Partial	
68	M	None	None	Yes (CT, DCF)	6 months (DCF)	Facial	Correct	I/II	Partial	
93	W	None	None	Yes (CT, IMQ)	6 months (CT)	Scalp	Correct	I	None	
86	M	None	None	None		Scalp	Correct	I	None	
80	W	None	None	Yes (CT, DIC)	8 months (DCF)	Facial	Correct	III	Partial	
77	M	None	None	Yes (CT, DCF, PDT)		Facial	Correct	I/II	Partial	
64	M	None	None	Yes (CT, IMQ)	7 months (CT)	Facial	Correct	III	Complete	10 months (no recurrence)
74	M	None	Yes (BCC, SCC)	Yes (CT, IMQ)	3 months (CT)	Scalp	Correct	I/II	Complete	5 months (relapse: 3 lesions)
81	W	None	None	Yes (CT)	8 months (CT)	Facial	Correct	III	Partial	
51	W	None	None	None		Facial	Partial	IV	Partial	
53	W	None	None	Yes (CT)	5 y (CT)	Facial	Correct	IV	Complete	11 months
89	W	None	None	Yes (CT, DCF)	3 months (DCF)	Facial	Correct	III	Complete	4 months (relapse: 1 lesion)

Abbreviations: 5-FU, 5-fluorouracil; BCC, basal cell carcinoma; CT, Cryotherapy; DCF, diclofenac; ELC, electrocoagulation; IMQ, imiquimod; LM, lentigo maligna; M, Man; NMSC, nonmelanoma skin cancer; PDT, photodynamic therapy; SCC, squamous cell carcinoma; W, woman.

[a] The definitions used to classify adherence, tolerability, and effectiveness are described in the text.

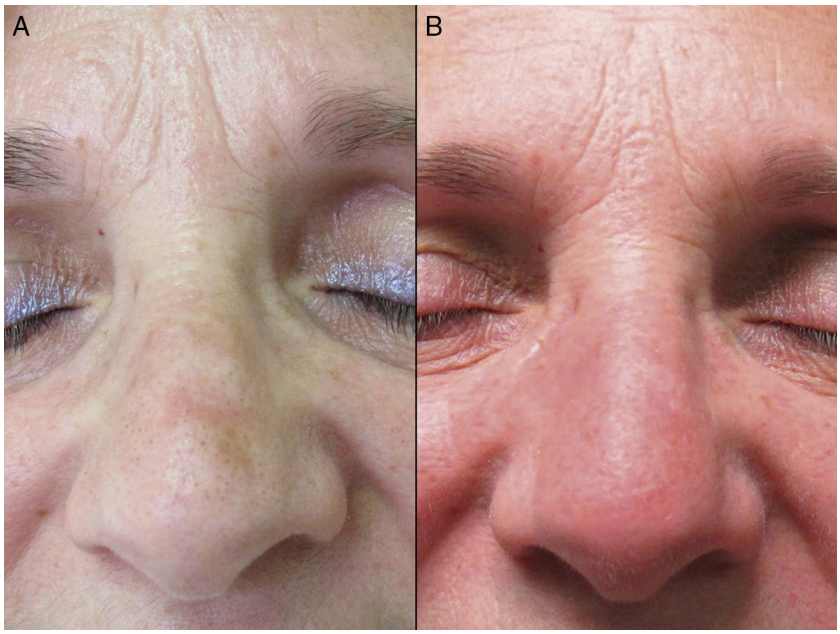

Figure 1 Complete response to ingenol mebutate. A, Actinic keratosis on the nasal pyramid. B, Complete response at 2 months.

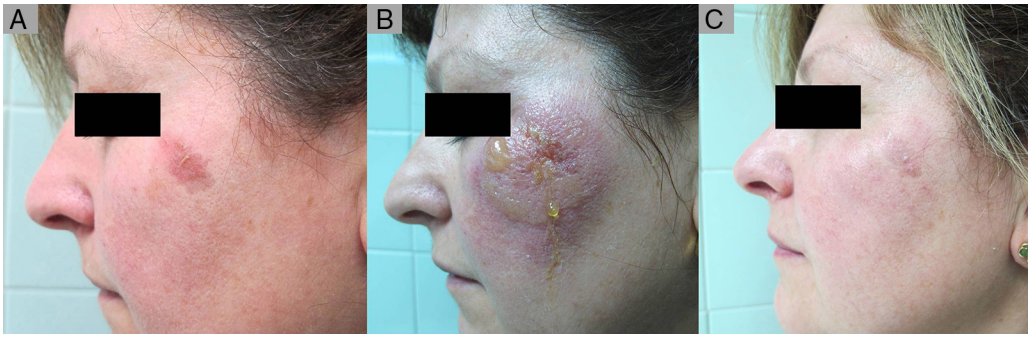

Figure 2 Partial Response to ingenol mebutate following treatment that was not completed due to a type IV local reaction. A, Non-hyperkeratotic actinic keratosis on the left malar. B, Type IV local reaction after administration of the first single dose of ingenol mebutate; the following 2 applications were not administered. C, Residual actinic keratosis. The patient required an additional session of cryotherapy.

ingenol mebutate is much higher than with other patient-applied topical therapies (Table 2),[8] a phenomenon that can be explained by the short treatment cycle required.[9]

Although localized skin reactions at the site of application of ingenol mebutate are common (>96%), these usually occur after the treatment cycle has been completed and do not, therefore, lead the patients to abandon treatment.[1] Local inflammatory reactions in the treated area are also common during the administration of the other topical treatments used to treat AK.[10]

The retrospective design of the present study has allowed us to describe the characteristics of treatment with ingenol mebutate in clinical practice. However, it also has several limitations. Since no histological analysis is available of the lesions in the treated area, the selection of non-hyperkeratotic or ''superficial'' AKs was necessarily subjective. This subjectivity may have given rise to minor differences in the severity of the treated area and could therefore have affected our results. In the absence of any exact count of the number of lesions at baseline, there was also a degree of subjectivity in the assessment of whether response was complete or partial. The early assessment of response to treatment (at 2 months) may also have positively influenced our results. Nonetheless, we considered 2 months to be the best moment for this evaluation because it allowed us to assess all the patients in the study at the same time point since the prescribing physicians followed the indications of the Summary of Product Characteristics with respect to the timing of follow-up. Finally, the small number of patients treated makes it difficult to compare our results with other studies.

Our conclusion is that ingenol mebutate is useful in the treatment of AKs and field cancerization, and that the dosage used favors adherence to treatment.

Table 2 Main Studies That Have Assessed Effectiveness, Adherence, and Localized Reactions in Actinic Keratosis.

Study	Characteristics	Intervention	Effectiveness
Lebwohl et al.[1]	Phase 3 RCT - Effectiveness on face and scalp: n = 547 (277 IM, 270 placebo) -Effectiveness on trunk and limbs = 458 (226 IM, 232 placebo)	IM vs placebo Objective: complete clearance rate (assessment at 57 days)	Complete clearance: AK on face and scalp: 42% AK on trunk and limbs: 34% Partial response (clearance $\geq$ 75%): AK on face and scalp: 64% AK on trunk and limbs: 49%
Berman et al.[3]	Phase 3 RCT n = 329	IM + CT vs CT Objectives: - Complete clearance rate at wk 11 - Effectiveness at 12 months	Complete clearance at wk 11 CT and IM: 61% CT: 49% Complete clearance at 12 months CT and IM: 55% CT: 40%
Vegter et al.[7]	Meta-analysis 25 RCTs n = 5562	Treatments for AK on face or scalp. Objective: to achieve complete clearance	ALA-PDT gel: 85.3% MAL-PDT: 65.9% ALA-PDT patch: 62% 5% IMQ 4-wk: 57.2% 0.5% 5-FU: 54.6% CT: 49.1% 5% IMQ 16-wk: 45.1% IM: 43% 3% DCF: 35.4% 3.75% IMQ 2- or 3-wk: 34.8% Placebo: 6.9%

Table 2 (*Continued*)

Study	Characteristics	Intervention	Effectiveness
Gupta and Paquet[6] (Cochrane review update)	Meta-analysis of 36 RCTs n = 6473 Data Collection: up till April 2012	Treatments for AK Objective: to achieve complete clearance	No clearance percentage specified. Treatments are shown in order of effectiveness
All Sites	Scalp Only		Overall
5% 5-FU >0.5%5-FU, ALA-PDT >5% IMQ > IM > MAL PDT > CT > DCF > placebo	5% 5-FU > 0.5%5-FU > IM > ALA-PDT > 5%IMQ > MAL-PDT > CT > placebo		5-FU > ALA-PDT≈5%IMQ ≈ IM≈MAL-PDT >CT > DCF
Study	Characteristics and Intervention		Local Adverse Effects
Lebwohl et al.[1]	See above		Local reactions: -AK, face and scalp: 98% Moderate-intense reactions in a ''minority'' of cases AK trunk and limbs: 96% 70% moderate to intense
Study	Characteristics	Intervention	Adherence
Lebwohl et al.[1] Shergill et al.[8]	See above Cross-sectional study n = 305 DCF, 5% 5-FU, 5% IMQ, 0.5% 5-FU	See above Objective: To identify adherence rate and factors conditioning adherence	>98% Percentage of non-adherence or abandonment[a] 88% Percentage of non-adherence by length of treatment 52% in treatments of 3-4 wks duration 69% in treatments of 6-8 wks duration 71% in treatments of 6-12 wks duration

Abbreviations: 5-FU, 5-fluorouracil; ALA, 5-aminolaevulinic acid; AK, actinic keratosis; CT, cryotherapy; DCF, diclofenac; IM, ingenol mebutate; IMQ, imiquimod; MAL, methyl aminolaevulinate; PDT, photodynamic therapy; RCT, randomized clinical trial.

[a] Non-adherence indicates not using the correct dosage and abandoment indicates not completing the treatment cycle.

Ethical Disclosures

Protection of human and animal subjects. The authors declare that the procedures followed adhered to the ethical guidelines of the responsible committee on human experimentation and comply with the Declaration of Helsinki of the World Medical Association.

Data confidentiality. The authors declare that they followed the protocols of their institution with respect to the publication of private patient data.

Right to privacy and informed consent. The authors obtained the informed consent of the patients and/or subjects referred to in this article. These documents are in the possession of the corresponding author.

Conflicts of Interest

Ana Batalla and Ángeles Flórez have received lecture fees from Leo-Pharma Spain for interventions on the topic of actinic keratosis.

The other authors declare that they have no conflicts of interest.

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