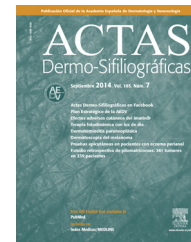




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## E- CASE REPORT

# Clinical Response to Ingenol Mebutate in Patients With Actinic Keratoses<sup>☆</sup>



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### KEYWORDS

Actinic keratosis;  
Effectiveness;  
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Treatment

### PALABRAS CLAVE

Queratosis actínica;  
Efectividad;  
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Tratamiento

**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.

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### 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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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.

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## Introduction

Actinic keratoses (AK) are considered by most authors to be premalignant lesions that can progress to invasive squamous cell carcinoma.<sup>1</sup> 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.<sup>1,2</sup>

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%.<sup>1</sup> 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<sup>2</sup> 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).<sup>1</sup> It has been observed that the success rate may be higher when ingenol mebutate is combined with other therapies (Table 2).<sup>3</sup>

It is difficult to perform a direct comparison of the different treatment options for AK due to the heterogeneity of the available studies.<sup>4,5</sup> 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).<sup>6,7</sup> 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.<sup>6</sup>

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

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