



# ACTAS Dermo-Sifiliográficas

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## RESIDENT'S FORUM

### RF-Herpes Zoster Triggered by Ingenol Mebutate Gel: First European Case Report<sup>☆</sup>



### FR-Aparición de herpes zoster secundario a la aplicación de ingenol mebutato en gel: comunicación del primer caso europeo

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#### KEYWORDS

Ingenol mebutate;  
Herpes zoster;  
Herpes simplex virus

#### PALABRAS CLAVE

Ingenol mebutato;  
Herpes zoster;  
Virus herpes simple

## Introduction

Actinic keratosis (AK) is a premalignant skin lesion that can progress to squamous cell carcinoma. Ingenol mebutate (IM) gel is a widely used topical treatment for the management of

nonhyperkeratotic AK. This gel has also been used off-label to treat actinic cheilitis.<sup>1</sup>

## Case Description

An 85-year-old Caucasian man with a history of hypertension and dyslipidemia was referred to our clinic for asymptomatic scaly lesions on the scalp that had appeared 5 years earlier. Physical examination revealed multiple erythematous, scaly plaques (0.5–1 cm) on the surface of the scalp containing little infiltrate. Because the lesions were clinically compatible with AK the patient was prescribed 0.015% IM gel, to be applied once per day for 3 consecutive days. One week after treatment, the patient developed a painful skin rash consisting of multiple vesicular lesions located predominantly in the left cervical area compatible with herpes zoster (HZ). The lesion distribution suggested involvement of branches C2–C4 of the cervical plexus. Polymerase chain reaction (PCR) confirmed a diagnosis of varicella-zoster virus (VZV). Brivudine (125 mg/d) was prescribed for 7 days. The HZ lesions resolved without complications. Based on the location and timing of the lesions, reactivation of VZV was attributed to treatment with IM. Consequently, the Spanish Pharmacovigilance System for Medicinal Products for Human Use (SEFV-H) was informed about this side effect.

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## Discussion

Adverse skin reactions to IM include erythema, post-inflammatory hyperpigmentation, and residual scars, all of which are likely related to local inflammation caused by IM. Erosive pustular dermatosis of the scalp,<sup>2</sup> bullous reactions,<sup>3</sup> and squamous cell carcinoma<sup>4</sup> have been associated with IM treatment. To date, no cases of VZV reactivation associated with IM treatment have been described in Europe.

In August 2015, following reports of 20 such cases in the United States in the post-marketing phase, the Food and Drug Administration (FDA) included HZ as a possible adverse effect of IM, and added this information to the summary of product characteristics (SmPC). However, this adverse effect has not been included in the SmPC for IM in Europe.

The total number of recorded cases is not entirely clear, as some reported cases may have been due to herpes simplex virus (HSV) reactivation. While HSV latency can be mediated by distinct mechanisms, one gene implicated in this process is the latency-associated transcription (LAT) gene. Certain stimuli that inhibit the expression of this gene, including hypoxia and cellular apoptosis induced by IM or other topical treatments for AK, can induce transcription and reactivation of viral genes in certain patients.<sup>5,6</sup>

Age and immune compromise are other known risk factors for VZV reactivation. Because patients with AK are generally over 60 years of age, the use of IM in this subgroup of patients could increase the risk of developing HZ.

## Conclusion

To date, there have been no other reports in Europe of VZV reactivation in immunocompetent patients treated with IM

gel. In cases in which a blistering reaction occurs after IM treatment, we believe it is important to perform a Tzank or PCR test, based on which an association with VZV or HSV can be ruled out. If VZV reactivation is confirmed, antiviral treatment should be started immediately to reduce the risk of late complications that can lead to high morbidity.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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