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Clinical Medicine Insights: Dermatology

Ingenol Mebutate

Nicole Basset-Seguin

Hôpital Saint Louis, Paris, France.

ABSTRACT: Actinic keratoses (AK) are frequent, sun-induced lesions. Ingenol mebutate (IE) is a newly launched treatment for AK which major advantages is a short term application (3 days for a 0.015% concentration for face and scalp and 2 days for 0.05% for other body sites). IE is a macrocyclic diterpene ester extracted from the sap of the plant *Euphorbia peplus*. Its mechanism of action associates induction of rapid cell death and recrutement of neutrophils via PKCδ activation. Placebo controlled studies reported a rate of complete clearance on the face and scalp of 42% with IE and 3.7% with placebo and of 34.1% versus 4.7% for trunk an extremities. Partial clearance (at least 75% improvement) was seen in 63.9% of patients, versus 7.4% with placebo for face and scalp and 49.1%, versus 6.9% for trunk and extremities. Local skin reactions, sometimes severe, can be observed as early as day 1, peak at day 4 and resume within 2 weeks. Long term studies have shown that about half the patients who have responded are still in remission after 12 months. A number of studies are on their way to look at comparative, combination or repeated strategies to optimize the management of AK.

KEYWORDS: ingenol mebutate, actinic keratosis, field cancerisation, in situ carcinoma

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CORRESPONDENCE: nicole.basset-seguin@sls.aphp.fr

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Introduction

Actinic keratoses (AK) are a common reason to consult a dermatologist, especially in fair-skinned elderly patients. In England it has been shown that while only 15% of men and 6% of women around 40 years old have AK, these rates increase to 34% in men and 18% in women above 70 years of age.[1]

The incidence of AK is higher in countries whose populations are more exposed to the sun; they are diagnosed in as many as 40% to 60% of people over 40 years in Australia.[2] A recent paper from the Netherlands showed that among 2061 individuals aged 45 years or older (mean age 72) given a full body inspection, prevalence was 49% in men and 28% in women.[3] Bald males were the most at risk.

AK are sun-induced lesions, presenting as thin or thicker keratotic and sometimes erythematous lesions on sun-exposed body sites (eg face, scalp, dorsum of the hands, arm, low neck, neck or legs). They can be limited in number or multiple, leading to the concept of field cancerization. This concept, in terms of AK, is defined as the presence of numerous subclinical lesions around the AK site, detectable at the molecular level by the presence of keratinocyte clones harboring p53 mutations.[4] Indeed, the major concern about AK is their potential to transform into squamous cell carcinoma (SCC). An individual AK may regress, persist, or progress to invasive SCC. AK is often considered an in situ carcinoma. The risk of transformation is not precisely evaluated as it ranges from 0.10% to 16%/year/patient.[5–7] The potential for progression over approximately six years was prospectively studied in a population at high risk for skin cancer. A total of 7784 AKs were identified on the face and ears in 169 participants. The risk of AK progression to primary SCC (invasive or in situ) was 0.60% at 1 year and 2.57% at 4 years.[8] The 10-year risk for invasive disease was estimated at 6% to 10% for a typical patient with sun-damaged skin and several AKs.[9] More

importantly, it has been shown that the majority (82.4%) of SCC in sun-exposed sites have developed from an AK.[10]

AK is a chronic condition and patients must be examined regularly to detect any sign of transformation of an AK into SCC. Therapy is often changed to improve results, and patient satisfaction, and adherence. Guidelines and expert reviews have been published to help physicians considering the various treatment options.[11–13]

Treatments are either lesion-directed, indicated in cases of isolated or sparse AK, or field-directed, suitable for cases of multiple AK. While destructive therapies such as cryotherapy (the most commonly used worldwide), photodynamic therapy (PDT), or laser are often chosen, pharmaceutical treatments such as imiquimod, diclofenac, or efudix are also often prescribed, as they do not necessitate any specific medical device, can be done by the patient and are suited for field cancerization treatment.

However, these pharmaceutical treatments need to by applied for long periods of time and can induce long-lasting, sometimes severe, local reactions, which are not always easily managed in elderly patients.

Ingenol mebutate is a new medical treatment recently developed and launched in many countries. Its main characteristics are its short duration of application (2 to 3 days) and two different concentrations, 0.015% for face and scalp and 0.05% for other body sites.

We will review in this paper what is known about ingenol mebutate, the molecule, its mechanisms of action and the results of the major clinical trials.

What is Ingenol Mebutate?

Ingenol mebutate (LEO PHARMA) is the active agent, a macrocyclic diterpene ester, in the sap of the plant *Euphorbia peplus*. This herb has been used as a traditional remedy for various dermatoses. The sap from the plant has been used as a purgative and as a treatment for warts, corns, waxy growths, asthma, catarrh, and cancers of the stomach, liver and uterus.[14,15] Its activity in human skin cancers is of particular interest here. Ingenol mebutate is extracted from large amounts of *Euphorbia peplus* (Figs. 1A and B). About 800 kg of plants is necessary to produce 1 g of active product.

The price of ingenol mebutate varies among countries, but should be close to that of imiquimod in most of them.

Mechanisms of Action of Ingenol Mebutate

The mechanism of action of ingenol mebutate is still not fully understood.

Ingenol mebutate seems to have two major mechanisms of action (Fig. 2):

1. The rapid and direct induction of cell death, by plasma membrane and mitochondrial disruption and necrotic cell death.[16] This cell death action involves multiple cell organelles, resulting in rapid disruption of the plasma membrane and mitochondrial swelling, followed by cell death of tumor cells in a cell-type and differentiation-dependent manner.[17] Ingenol mebutate causes calcium release from intracellular stores, rather than an influx of extracellular calcium.[17]
2. Induction of PKC δ, which activates endothelial cells. This allows them to support the recruitment of neutrophils, which have a cytotoxic function with a role in destroying tumors.[18]

In these ways, ingenol mebutate gel destroys epidermal cells within hours and induces attraction of neutrophils targeted to kill any residual dysplastic epidermal cells, important for preventing relapse. The two distinct and complementary

Figure 1A. Picture of *Euphorbia Peplus* plant.

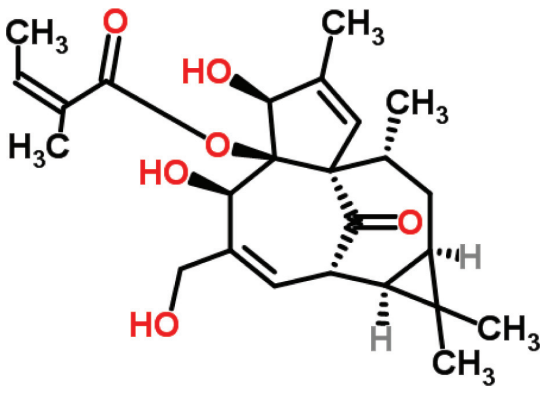

Figure 1B. Ingenol mebutate structure.

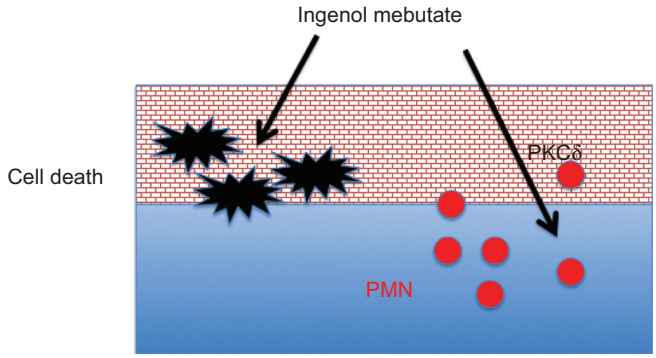

Figure 2. Schematic mechanism of action of ingenol mebutate. 1) direct cell death, and 2) recruitment of PMN through PKCδ activation.

mechanisms of action could explain why a short course of treatment with ingenol mebutate gel can be effective.[19]

Results of Major Clinical Studies

The results of four multicenter, randomized, double blind studies were recently published.[20,21] Randomly assigned patients with AK self-applied one of two different concentrations of ingenol mebutate or placebo (vehicle) to a contiguous 25 cm^2 field. The treatment was applied once daily for three days (face and scalp) or for two days (trunk and extremities). The primary outcome was complete clearance of the AK, assessed at 57 days.

The rate of complete clearance on the face and scalp was higher with ingenol mebutate than placebo (42.2% vs 3.7%, $P < 0.001$). Partial clearance (at least 75% improvement) was seen in 63.9% of patients, versus 7.4% with placebo. At day 57, half of the patients had an 83% or more reduction of lesion count. Local reactions peaked at day 4, rapidly decreasing by day 8, and were close to baseline at day 15.

For trunk and extremities, the rate of complete clearance was also higher with ingenol mebutate than with placebo (34.1% vs 4.7% $P < 0.007$). Partial clearance was 49.1% with ingenol mebutate, versus 6.9% with placebo. At day 57, half of the patients had a 75% or greater reduction of lesion count. Local skin reactions peaked between day 3 and 8, and then declined rapidly.

These results show that ingenol mebutate is a rapid and effective treatment for AK. Face and scalp lesions are more responsive than trunk and extremities, which is true for the majority of AK treatments. Local skin reactions can be seen as early as day 1 and peak around day 4. They include redness, scaling, crusting, pruritus, pain and periorbital edema. These reactions can be severe and patients must be informed about them. However, they are predictable, which helps to define the best time to prescribe the treatment according to the patient's preferred schedule. Few systemic reactions have been described (headache, nasopharyngitis).

Long-term results (12 months) for these patients have recently been published and showed that 46.1% (face and scalp) and 44% (trunk and extremities) of patients that were in complete remission remained in remission at month 12. Estimated time to recurrence were 365 days for AK of the face and scalp and 274 days for trunk and extremities.[22]

A recent paper reported the sequential use of cryosurgery followed after 3 weeks by treatment with ingenol mebutate or placebo. The short-term clearance rates (at 11 weeks) on the face or scalp were higher than with cryosurgery alone. Long-term results should be published in the near future.[23] These data suggest that the combination of these two treatments improves the clinical response observed with cryotherapy alone.

Additionally some indications of Euphorbia peplus for other non-melanoma skin cancers (ie Bowen, BCC and SCC) have been proposed.[24]

Recommendation of Use

Ingenol mebutate exists in two different concentrations and application schedules. On the face and scalp, ingenol mebutate (0.015%) must be applied for 3 consecutive days on a 25 cm^2 contiguous field. On the trunk and extremities, Ingenol mebutate (0.05%) must be an applied for 2 consecutive days on a 25 cm^2 contiguous field.

This 25 cm^2 field can be easily transcribed into an anatomical unit, as shown in Figure 3.

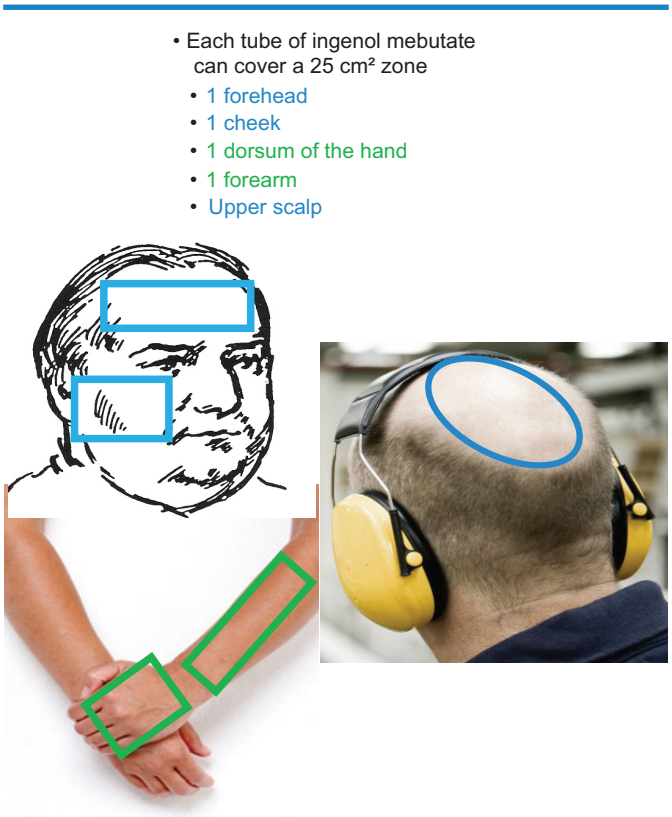

Figure 3. Anatomical sites corresponding to a 25 cm^2 surface.

No systemic passage has been observed, even when a larger surface was treated (100 cm^2). No photosensitivity nor photoallergy have been observed when combining ingenol mebutate application and UV radiation. However, because AK are sun induced and ingenol treatment provokes a local inflammation, photoprotective measures associated with the treatment are recommended.

Patients must be given clear information about local skin reactions, which can sometimes be severe. Only a few systemic symptoms have been reported and patients rarely complain of pain, even in cases of severe local reaction.

At the present time, no restriction of use in organ transplant patients has been specified.

Perspective

Several studies are being developed to answer further questions about ingenol mebutate:

- Can ingenol mebutate be reapplied in case of recurrence?
- How does ingenol mebutate compare to other pharmaceutical treatments?
- Can ingenol mebutate prevent the development of SCC?

A study looking at tolerability of ingenol mebutate compared to imiquimod is under development. Its major focus is the incidence of epidermoid carcinoma in the treated zone. What will be the long-term evaluation of the sequential use of cryotherapy and ingenol mebutate, for which short term results were so promising? What other combination of treatments, such as PDT and ingenol mebutate, could be evaluated?

Conclusion

Ingenol mebutate is a new treatment option for actinic keratoses. Its major advantages are good efficacy combined with a short treatment period, providing optimal treatment observance. Long-term efficacy is encouraging, and studies are being developed and conducted that will help physicians to better evaluate the value of ingenol mebutate compared to other available treatments.

Author Contributions

Conceived and designed the concept: NBS. Analyzed the data: NBS. Wrote the first draft of the manuscript: NBS. Made critical revisions and approved final version: NBS. All authors reviewed and approved of the final manuscript.

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