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REVIEW

Ingenol Mebutate: A Succinct Review of a Succinct Therapy

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ABSTRACT

Background: Ingenol mebutate is a newly approved topical field therapy for actinic keratosis (AK). It has a dual mechanism of action comprising of a rapid induction of necrosis that specifically targets dysplastic cells, as well as neutrophil-mediated immunostimulatory effects. Such a dual mechanism allows for this agent to clear AK lesions in as little as two to three daily applications, thus providing for improved treatment outcomes and patient satisfaction.

Review: Given that this is a new dermatologic therapy, this review summarizes the key literature surrounding this agent. This review covers the indications for use, mechanisms of action, method of administration, efficacy and safety profile and important drug interactions of ingenol mebutate.

Conclusions: Ingenol mebutate should be considered a highly relevant field therapy for AK and the prevention of progression to squamous cell carcinoma.

Keywords: Actinic keratosis; Dermatology; Field therapy; Ingenol mebutate; Ingenol 3-angelate; Picato; Solar keratosis; Squamous cell carcinoma

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INTRODUCTION

Actinic keratosis (AK) is an area of dysplastic epidermal keratinocytes that undergo transformation due to substantial ultraviolet (UV) exposure [1], and the distribution of these lesions reflects areas of the body that are most sun-exposed, namely the face, scalp and arms. Within these regions, numerous lesions are often found and premalignant cells are thought to exist within the normal skin alongside AK, so called 'field cancerization' [2]. The rate of transformation to squamous cell carcinoma (SCC) is low [3], however, the overall risk of skin cancer is increased in the presence of AK, therefore, warranting their detection and treatment.

Current treatment modalities available for AK comprise lesion-directed therapies such as cryotherapy and surgical excision, and the field-directed therapies, namely the topical agents 5-fluorouracil, diclofenac and imiquimod [4]. The advantage of field therapies is that they target both clinically apparent and subclinical lesions over a contiguous area of application [5]. Developed in Australia, ingenol mebutate (Picato®, LEO Pharma A/S, Ballerup, Denmark) is a promising new topical chemotherapeutic that is quickly gaining acceptance as an effective field therapy against AK [6]. Ingenol mebutate was approved for use in Australia in 2013. It is derived from the sap of the Euphorbia peplus plant, which has already been in widespread use as a traditional herbal remedy for various dermatological lesions [7]: Ingenol mebutate has been trialed for other skin lesions such as superficial basal cell carcinoma [8]. A key reason behind the increasing relevance of ingenol mebutate as a treatment for AK is that it is efficacious in the destruction of AK lesions after a period of as little as 2–3 days [9], compared with the current topical agents that are applied for weeks to months [10]. This shorter duration of application translates to a number of obvious clinical benefits; a shorter duration of adverse effects, should they occur, as well as improved patient adherence comparative to alternative treatments. Given the relative infancy of ingenol mebutate as a dermatologic therapy, this brief review aims to summarize the key points of this agent.

METHODS

A Medline search was performed in June 2014, utilizing the key words and search terms "Ingenol mebutate," "Picato," "Ingenol-3-angelate," "Actinic keratosis" and "Field therapy." Advanced search parameters included limiting the search to retrieving English language abstracts and publication dates were limited from 2000 to present, yielding 1,530 results. Articles were then only selected from the following journals: Journal of the American Academy of Dermatology, Journal of the European Academy of Dermatology and Venereology, Cutis, Dermatology and Therapy (Heidelb), JAMA Dermatology, Australasian Journal of Dermatology, Journal of Cutaneous Medicine and Surgery, NEJM and The Journal of Clinical and Aesthetic Dermatology. This search returned 55 articles. After assessing titles and abstracts, eight journal articles were chosen as suitable to review for mechanism of action and five were chosen to review for efficacy and safety. A further two articles were chosen to describe the important drug interactions. Other articles for contextual background were obtained through more general searches of the literature.

DISCUSSION

Mechanism of Action

Unique among topical agents utilized for the field therapy of AK, ingenol mebutate possesses a dual mechanism of action that enhances its efficacy [11], expediting the process such that lesion destruction is observed after a period of 2–3 days [6]. Ingenol mebutate exerts its effects by acting as an agonist for intracellular protein kinase C (PKC) [12], which induces rapid cellular necrosis and a neutrophil-mediated form of antibody-dependent cellular cytotoxicity (ADCC).

Rapid Cellular Necrosis

Ingenol mebutate preferentially induces a rapid necrosis of the dysplastic keratinocytes of AK [13] through activation of the pro-apoptotic intracellular PKC, with subsequent mitochondrial swelling and rupture of the plasma membrane [12]. Keratinocytes that have undergone normal differentiation are resistant to the PKC mediated pro-apoptotic effects on the mitochondria for reasons that have yet to be defined [14].

Neutrophil-Mediated ADCC

In addition to having pro-apoptotic effects on dysplastic cells, ingenol mebutate also has immunostimulatory effects [15] which effectively 'mop-up' any dysplastic epidermal cells that might survive the immediate necrotic effects. Activated keratinocytes provide a milieu of cytokines that promote an infiltration of neutrophils into the area of application [16]. The neutrophils then activate reactive oxygen species and other cytotoxic mechanisms to lyse dysplastic cells [6]. This process is further enhanced by the action of ingenol mebutate functioning as an adjuvant [9], stimulating antibody production that stimulates cytotoxic T cells against dysplastic cells.

Efficacy and Safety

A number of clinical trials have indicated ingenol mebutate is effective following a short duration of application, is well tolerated, safe and has minimal local effects [7, 10, 17, 18].

Siller et al. [17]

Siller and colleagues conducted a multicenter, randomized, double-blind, vehicle-controlled phase IIa trial of ingenol mebutate at concentrations of 0.0025%, 0.01% and 0.05%. Two doses were administered: one on day 1 and the second on either day 2 or day 8, and the response assessed at day 85. Patients that had five or more AK of 3–15 mm diameter were selected for the trial. A total of 58 patients and 285 lesions were assessed. Anatomically, the lesions were located predominantly on the upper limbs, scalp and face, in keeping with the usual areas of predilection of AK, and were distributed equitably across the treatment arms. Clinical efficacy was assessed on a per lesion and per patient basis, with complete clearance defined as no clinical evidence of disease and marked clearance being 50–90% lesion reduction. The greatest level of clinical efficacy was seen with the 0.05% concentration of ingenol mebutate gel. On a per lesion basis, 71% were completely cleared, while 67% of patients receiving the 0.05% dosage had clinical clearance of 80% or more of their lesions. Local skin responses (LSR) were seen in 47% of patients receiving the 0.05% concentration, and for the most part were assessed as mild/moderate, however, a total of 14 were recorded as severe. The most commonly seen effects were erythema, flaking/scaling/dryness and scabbing/crusting. Scarring and/or abnormal lesion proliferation did not occur in any of the subjects.

Anderson et al. [10]

A phase IIb study examined the efficacy and safety outcomes of field therapy for non-facial AK lesions using ingenol mebutate at concentrations of 0.025% and 0.05%. Patients were randomized into four study cohorts. Treatment using 0.025% concentration was applied once daily for three consecutive days. Treatment with the 0.05% concentration was given daily to two groups: three consecutive days of treatment or day 1 vehicle treatment

followed by 2 days of treatment. Vehicle treatment was applied for 3 days to the control group. The primary efficacy end point was the partial clearance rate. This was defined as the proportion of patients at the end of the study with at least 75% reduction in AK lesions in the area of field treatment, compared with those that were identified at baseline. This criterion was achieved for all three of the dosing regimens: 56.0% of the group receiving 0.025% for 3 days, 61.8% of the group receiving 0.05% for 2 days and 75.4% of the group receiving 0.05% for 3 days. Compared with the vehicle group, the results were statistically significant and indicated a dose-dependent response. Three secondary efficacy endpoints were included: the complete clearance rate (the number of patients at the end of the study with no clinically evident AK lesions in the field area), the baseline clearance rate (the number of patients with 100% reduction in the amount of AK lesions detected at baseline) and the percentage reduction of the number of AK lesions (the number of lesions at baseline minus the number at the end of the study divided by the number at baseline). These measures were all significantly higher in those patients who received any of the three ingenol mebutate regimes compared to those who received the vehicle treatment. The study also included subjective assessments of patient satisfaction with their treatment, all measures of which came back positive for ingenol mebutate compared with the vehicle treatment. Safety end points included the incidence and grade of LSRs, the incidence of AEs, changes in laboratory tests between screening and day 8, and the 'global severity rating' (GSR)—the examiner's overall clinical impression of any local reactions observed (mild, moderate or severe). LSRs peaked from day 3 to 8, the most commonly observed responses being erythema, flaking/scaling and crusting. LSRs were scored on a scale from 0 to 4 and the individual scores were used to obtain a composite LSR score (sum of the individual scores at each examination in each treatment cohort). The mean composite LSR scores were at their highest at day 8 for the active treatment groups, but had declined substantially by the end of the study. The most common application site AEs were pruritus, pain and irritation, and were observed most frequently in the 0.05% for 3 days cohort, further indicating a dose-dependent response. All application site reactions had resolved spontaneously by 4 weeks, and nil serious AEs were noted during the follow-up period. No patients discontinued participation in the trial due to an AE. The GSR, as a function of observed LSRs, peaked at day 8 and dwindled towards the end of the study.

Lebwohl et al. [18]

This study looked at four double-blinded trials: two trials considered lesions of the face and scalp while the other two focused on lesions of the trunk and extremities. Patients with facial or scalp lesions were given either a placebo or 0.015% ingenol mebutate gel to apply for three consecutive days while those with lesions elsewhere on the trunk and extremities were provided with either a vehicle treatment or 0.05% ingenol mebutate to be applied for 2 days. In both cases, patients were to self-apply the gel to a 25 cm^2 contiguous area once daily. The facial lesion cohort was assessed for safety at day 3 while the trunk and extremities group was assessed on day 4, and both were then assessed at days 8, 15, 29 and 57. In both cohorts, efficacy was assessed at baseline and at day 57. The primary end point assessment of efficacy was complete clearance of all clinically detectable AK lesions in the field area by the end of the study. Complete clearance was

observed in 42.2% of the face and scalp cohort (compared to 3.7% with placebo) and 34.1% of the trunk and extremities cohort (versus 4.7% with placebo). The secondary endpoint was partial clearance: a reduction of >75% of clinically detectable AK lesions by the end of the study. Partial clearance was achieved in 63.9% of the face and scalp group (compared with 7.4% with placebo) and 49.1% among the trunk and extremities group (versus 6.9% with placebo). A further secondary end point was the percentage difference in the amount of AK lesions detected compared to the baseline. The percentage change was zero among all patients receiving placebo in all trials. A median reduction of 83% of lesions was noted in the face and scalp cohort and 75% in the trunk and extremities cohort. Overall, the number needed to treat value for ingenol mebutate to achieve complete and partial clearance among the face and scalp cohort was 2.6 and 1.8, respectively, while for the trunk and extremities cohort the number needed to treat to achieve complete and partial clearance was 3.4 and 2.4, respectively. Safety end points that were considered were similar in method to that of Anderson et al. [10] described above: AEs, composite LSR scores, scarring and pigmentation. However, the GSR was not used in this study design. The most common AEs reported across all four trials were application site-specific pruritus, irritation and pain, which is consistent with the findings of Anderson et al. [10]. None of the four trials highlighted any incidences of scarring or changes in pigmentation. In the face and scalp cohort, day 4 was the peak of the composite LSR score, which then declined as the study progressed. Individual LSR scores for erythema were greater than 3 (on a scale of 0–4) in 69.7% of participants compared with 2.2% in the placebo group, and a small group of the active treatment group had a score greater than 3 for flaking or scaling, crusting, swelling, vesiculation or ulceration. In the trunk and extremities group, the composite LSR had three peaks in a decrescendo pattern at day 3, day 8 and day 15. Individual LSR scores for erythema and flaking or scaling were above 2 for the majority of subjects. Vesiculation occurred in 43.6% of those on active treatment and ulceration in 25.8%. The patients who had complete clearance in the two trials involving lesions of the face, as well as those patients in one of the trials involving body lesions, were monitored for a further 12 months.

Lebwohl et al. [7]

This is the follow-up study of the patients who had achieved complete clearance in the above study. These patients were seen at three monthly intervals up to 12 months, during which time further field therapy was not administered, however, lesion-directed therapy was available if the assessors deemed necessary. Information was also recorded on possible confounders such as concomitant treatments and conditions that could alter immune function. AK lesions in the field area were counted at each three monthly visit: the primary end point in this follow-up study was recurrence of AK lesions in the field area. Sustained clearance was defined as a field area free of AK lesions after a 12-month period. For the face and scalp cohort, the sustained clearance rate was 46.1% and for the trunk and extremities group was 44.0%. A second end point was sustained lesion reduction, defined as the total percentage reduction of AK lesions in the field area at 12 months compared to the baseline. For the face and scalp this was 87.2% and for the trunk and extremities this was 86.8%.

Based on the number of recurrences recorded at each follow-up, the estimated median time for new or recurrent lesions to occur in the field area was calculated: 365 days for the face and scalp and 274 days for the trunk and extremities. AEs in the field area were also assessed. Three patients suffered adverse symptoms in the field area during the follow-up period; however, the investigators did not consider these to be related to the application of ingenol mebutate. All three events resolved completely. This absence of any AEs supports the idea that ingenol mebutate has an excellent safety profile.

Dosik et al. [19]

This study is an evaluation of the results of three phase I trials in which ingenol mebutate was applied to normal skin to determine its sensitization potential, photo irritation potential and photo allergic (photosensitizing) potential, respectively. In the dermal sensitization study, none of the subjects experienced reactions that would indicate an allergic response. In the photo irritation study, very mild erythema was observed in the field area following irradiation that was considered statistically significant compared to non-irradiated areas. However, the erythema was clinically at a level so mild that it did not reflect photo irritation. Moderate erythema was observed in the irradiated field area when assessing for photo allergic potential, however, since mild erythema is an accepted LSR for ingenol mebutate; this was not considered to be an AE. Thus, these three pharmacology trials provide further evidence for the safety profile of ingenol mebutate: ingenol mebutate does not appear to have any potential for skin sensitization, photo irritation or photoallergy.

Important Drug Interactions

Ingenol mebutate gel is available in two doses: 0.015% for the face and 0.05% for the rest of the body [12], administered as a field therapy to a contiguous area roughly 25 cm^2 around the lesion. It is applied once daily in both instances, for 3 days duration when applied to the face and 2 days when applied to the body [6]. Ingenol mebutate has no known drug interactions and its metabolites have no effect on cytochrome P450 enzymes [13], hence there are currently no contraindications to the use of this agent. Blood levels of the drug are undetectable following topical administration, indicating that systemic absorption does not occur [10]. Therefore, ingenol mebutate has not been associated with any systemic AEs [20].

CONCLUSIONS

Ingenol mebutate is proving to be a promising new addition to the available repertoire of field therapies for the treatment of AK. Delivering similar outcomes to the more established field therapies available, in a matter of days, improves patient convenience and, therefore, improves compliance with treatment. Furthermore, at the doses approved for administration the safety profile of ingenol mebutate appears excellent. Local effects are mild and self-resolving within a short space of time (owing to the short duration of administration) while systemic effects appear to be negligible. However, a number of caveats should be considered. First, the therapeutic limit is determined by the amount of product available in the commercial dose. Ingenol mebutate is packaged in doses with sufficient product to cover a field area of 25 cm^2, which

translates to an area roughly the size of the dorsum of the hand. This might be ample for field therapy of facial lesions, however, over more widespread anatomical locations, such as the trunk, multiple doses could potentially be required to cover the total expanse of field cancerization. This would undoubtedly lead to added cost to the patient requiring multiple doses, which could detract from its improved levels of compliance. More importantly, insufficient product could open up the potential for an inadequate spread of field treatment over larger areas of skin. A second limitation lies in an inherent risk with topical therapies such as ingenol mebutate, in that they theoretically only mediate an effect on the superficial extent of a lesion, leaving the more basal layers intact. Deeper SCC lesions could ultimately result from this, requiring further treatment, and this is an important consideration.

On balance, this agent appears to have a place alongside 5-fluorouracil, diclofenac and imiquimod as suitable topical agents for the field therapy of AK.

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Compliance with ethics guidelines. The analysis in this article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by the author.

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