Emerging Research on Ingenol Mebutate Gel for Actinic Keratosis Treatment

BY MARK LEBWOHL, MD AND MARIA D’ALESSANDRO

Of the currently available actinic keratosis (AK) treatments, only field therapy achieves high rates of sustained clearance. Field therapy targets not only clinically visible AKs, but also subclinical AKs within the treatment area.

Revolutionizing AK treatment is ingenol mebutate gel (Picato, Leo Pharma). Ingenol mebutate gel is a botanical-based topical field therapy approved in the United States for AKs on the face, scalp, trunk, and extremities that has shown multiple effects on tumor cells in vivo and in vitro. Ingenol mebutate is derived from the extract of the plant Euphorbia peplus, a traditional herbal remedy used for skin conditions. Ingenol mebutate directly induces cell death in tumor cells within hours via mitochondrial swelling and loss of cell membrane integrity. It also modulates protein kinase C isoforms and promotes apoptotic mechanisms and an inflammatory response, killing remaining tumor cells. Ingenol mebutate reduces the number of mutant p53 patches, which have been associated with the development of AK and non-melanoma skin cancer.

The sustained clearance of AK lesions and long-term safety of this two- to three-day therapy with multiple mechanisms of action have not been documented yet. However, the efficacy and safety of ingenol mebutate gel have been demonstrated in a recent publication. In four multicenter, randomized, double-blind studies of patients with AKs, a significantly higher proportion of those receiving active treatment achieved complete clearance of AKs in the field of treatment versus placebo. The most com-

KEY POINTS

Ingenol mebutate gel is a topical field therapy FDA approved for treatment of actinic keratoses (AKs) on the face, scalp, trunk, and extremities that has shown multiple effects on tumor cells in vivo and in vitro. Ingenol mebutate directly induces cell death in tumor cells within hours by mitochondrial swelling and loss of cell membrane integrity.

In multiple trials, patients received ingenol mebutate gel once a day on consecutive days. For the face and scalp, a 0.015% concentration was used for three days, while a 0.05% concentration was used for two days for the trunk and extremities. Approximately 46 percent of patients with AK achieved sustained clearance after ingenol mebutate gel treatment of a 25 cm² field. After 12 months of follow-up of patients who had achieved complete clearance, the number of new or recurrent actinic keratoses in relation to the number at baseline in the original study was 13 percent. Most patients treated four to six AKs, which were cleared by day 57 of the original studies, so an 87 percent reduction translates to <1 actinic keratosis in the treatment area 12 months after clearance for the majority of patients.

There were no safety issues during the 12-month follow-up period. Ingenol mebutate gel applied as field therapy for only three or two consecutive daily doses was effective and well-tolerated when treating head or body AKs, producing sustained clearance and long-term reductions of lesion numbers in the selected fields.
Most adverse events were local skin reactions, including erythema, flaking/scaling, crusting, and swelling. In the trials, patients received ingenol mebutate gel once a day on consecutive days. For the face and scalp, a 0.015% concentration was used for three days, while on the trunk and extremities a 0.05% concentration was used for two days. Almost all patients (94 percent) had skin categorized as Fitzpatrick type I, II, or III.

LOCAL SKIN RESPONSES

Patient-applied topical field therapies for the treatment of AKs can cause local skin responses (LSRs), which can be unpleasant for patients. LSRs can reduce treatment adherence, particularly when the treatment regimen is lengthy. Historically, LSRs have been subjectively graded as 0 = none, 1 = mild, 2 = moderate, or 3 = severe. However, the US Food and Drug Administration (FDA) required an objective, quantitative LSR scale for the trials of ingenol mebutate. This new LSR scale was developed and validated by 36 board-certified dermatologists. The scale was used in 14 studies of ingenol mebutate gel, including the four discussed here. The treatment area was assessed for six types of individual LSRs, including erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration, and was graded from 0 (not present) to 4 (maximum possible response) through a series of photographs with different degrees of skin. A composite score representing the sum of the scores for the six individual LSR types was calculated at all scheduled time points (total possible score, 0 to 24).

Across multiple trials for the face/scalp and trunk/extremities, ingenol mebutate gel was well-tolerated and demonstrated significant reductions in AKs, as well as high adherence to treatment.

Erythema and flaking/scaling were present to some extent before study medication was applied. These LSRs persisted with vehicle gel application and worsened with ingenol mebutate gel. The distinguishing factor for these LSRs from grade 3 to 4 is that the response extends outside the treatment area, rather than remaining restricted to treatment area.

Higher maximum composite LSR scores were also associated with achieving partial clearance and greater percent reduction in the number of AKs. Erythema in particular was associated with efficacy across all three end points and anatomical locations; however, in patients with face or scalp AKs, the association was higher with swelling.

The LSR scale developed for ingenol mebutate gel trials provides an objective and quantifiable way to consistently assess LSRs. This scale may be a useful tool for assessing the LSRs associated with existing and future AK therapies.

**FDA-APPROVED AK THERAPIES**

- 5-fluorouracil (5-FU) ointment or liquid 0.5% to 5%
- Imiquimod cream 3.75% or 5%
- Diclofenac sodium 1%
- Ingenol mebutate gel 0.015% or 0.05%
- 5-aminolevulinic acid (5-ALA) PDT

_Euphorbia peplus_ is a traditional herbal remedy used for skin conditions from which ingenol mebutate is derived. Ingenol mebutate directly induces cell death in tumor cells via mitochondrial swelling and loss of cell membrane integrity, modulates protein kinase C isoforms, and promotes apoptotic mechanisms and inflammatory response.

PATIENT QUALITY OF LIFE AND TREATMENT ADHERENCE

The Treatment Satisfaction Questionnaire for Medication was administered to patients at day 57.14 Patients treated with active drug reported less satisfaction regarding side effects but greater global satisfaction than patients in the vehicle group.

The Skindex-16 Dermatological Survey was administered to patients at days 8, 29, and 57.15 After an initial worsening of symptoms (all locations) and functioning (face/scalp only) at day 8, patients thereafter reported improvements in symptoms, functioning, and emotions with ingenol mebutate gel compared with vehicle gel. In the ingenol mebutate gel groups, 98.2 percent of patients with face or scalp AKs applied all three doses of study drug, and 98.7 percent of patients with trunk or extremity AKs applied both doses of study drug.

DISCUSSION AND IMPLICATIONS

Approximately 46 percent of patients with AKs achieved sustained clearance (had no new or recurrent AK lesion in the selected treatment area) after ingenol mebutate gel treatment of a 25cm² field.

NOTABLE AK FINDINGS IN THE LITERATURE

The risk (odds ratio [OR]) of developing non-melanoma or melanoma was increased more than six-fold (p ≤ 0.0001) in patients with AK, multivariate analysis showed. An increased risk of skin cancer was found in whites (OR, 4.3; p ≤ 0.01) and increased age by year (OR, 1.04; p ≤ 0.01).


Squamous cell carcinoma (SCC) may arise in AK, based on the finding that an AK was contiguous with an SCC in 72% of cases. Men presented with thicker and more ulcerated SCCs than women (not statistically significant). Ulcerated SCCs were more likely to arise on the head and neck (p = 0.02), on patients who had multiple skin cancers (p = 0.005), and on patients who had a family history of skin cancer (p = 0.03).


An estimated 10% of AKs will develop into an SCC, and the progression will take approximately two years.


The one-year risk of progression of AK to primary SCC (invasive or in situ) was 0.60%; 2.57% at four years. Approximately 65% of all primary SCCs and 36% of all primary BCCs diagnosed in the study cohort arose in lesions that previously were diagnosed clinically as AKs.

—Cancer. 2009; 115(11):2523-30

—Compiled by COT Staff

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intermediate intensity (maximum composite LSR scores were ≤12 out of 24).

The absence of safety issues during the 12-month follow-up period confirms previous observations with ingenol mebutate. Ingenol mebutate gel applied as field therapy for only three or two consecutive daily doses was effective and well tolerated when treating head or body AKs, producing sustained clearance and long-term reductions of lesion numbers in the selected AK fields.6-18

Dr. Lebwohl has consulted for Graceway, Pharmaderm, and LEO Pharma and was an investigator on the ingenol mebutate clinical program.

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