Ingenol Mebutate Gel for Actinic Keratosis

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ABSTRACT

BACKGROUND
Actinic keratosis is a common precursor to sun-related squamous-cell carcinoma. Treating actinic keratoses and the surrounding skin area (i.e., field therapy) can eradicate clinical and subclinical actinic keratoses. Topical field therapy currently requires weeks or months of treatment. We investigated the efficacy and safety of a new topical field therapy for actinic keratosis, ingenol mebutate gel (0.015% for face and scalp and 0.05% for trunk and extremities).

METHODS
In four multicenter, randomized, double-blind studies, we randomly assigned patients with actinic keratoses on the face or scalp or on the trunk or extremities to receive ingenol mebutate or placebo (vehicle), self-applied to a 25-cm² contiguous field once daily for 3 consecutive days for lesions on the face or scalp or for 2 consecutive days for the trunk or extremities. Complete clearance (primary outcome) was assessed at 57 days, and local reactions were quantitatively measured.

RESULTS
In a pooled analysis of the two trials involving the face and scalp, the rate of complete clearance was higher with ingenol mebutate than with placebo (42.2% vs. 3.7%, P<0.001). Local reactions peaked at day 4, with a mean maximum composite score of 9.1 on the local-skin-response scale (which ranges from 0 to 4 for six types of reaction, yielding a composite score of 0 to 24, with higher numbers indicating more severe reactions), rapidly decreased by day 8, and continued to decrease, approaching baseline scores by day 29. In a pooled analysis of the two trials involving the trunk and extremities, the rate of complete clearance was also higher with ingenol mebutate than with placebo (34.1% vs. 4.7%, P<0.001). Local skin reactions peaked between days 3 and 8 and declined rapidly, approaching baseline by day 29, with a mean maximum score of 6.8. Adverse events were generally mild to moderate in intensity and resolved without sequelae.

CONCLUSIONS
Ingenol mebutate gel applied topically for 2 to 3 days is effective for field treatment of actinic keratoses. (Funded by LEO Pharma; ClinicalTrials.gov numbers, NCT00742391, NCT00916006, NCT00915551, and NCT00942604.)
Actinic keratoses are premalignant lesions that are common in light-skinned populations worldwide. In the United States, the most common form of lesion-directed therapy for actinic keratoses is cryosurgery, although other locally ablative therapies are used. In addition to potential scarring, recurrence rates are high with some of these treatment approaches. Other treatments for actinic keratoses are applied to an entire field of sun-damaged skin, and many studies have shown the emergence of clinically visible actinic keratoses after application.

These treatments include imiquimod, fluorouracil, diclofenac, and photodynamic therapy. Drawbacks to the self-applied topical field therapies currently available include a long duration of treatment and consequently prolonged local reactions, which could lead to less-than-ideal adherence to therapy. Specifically, various formulations of imiquimod must be applied for periods of weeks to months, fluorouracil for weeks, and diclofenac for months.

Ingenol mebutate (LEO Pharma), a macrocyclic diterpene ester, is the active agent in the sap of the plant Euphorbia peplus, which has long been used as a traditional remedy for common skin lesions, including cancerous lesions. Preclinical studies have indicated that ingenol mebutate is a pleiotropic effector that induces rapid and direct cell death and immune responses mediated by specific activation of protein kinase C delta, including neutrophil-mediated oxidative burst and clearance of tumors. The current studies were conducted to evaluate the efficacy and safety of ingenol mebutate gel, as compared with vehicle gel, administered once daily for 2 to 3 consecutive days to a 25-cm² contiguous field containing actinic keratoses.

METHODS

STUDY DESIGN

In four multicenter, randomized, parallel-group, double-blind, vehicle-controlled studies, patients with actinic keratoses were randomly assigned to receive ingenol mebutate gel or placebo for self-application. Eligibility criteria included an age of at least 18 years and the presence of four to eight clinically typical, visible, and discrete actinic keratoses within a 25-cm² contiguous field on the face or scalp or on the trunk or extremities. Women with childbearing potential had to be using effective birth control. The trials were performed between September 2008 and February 2009 (PEP005-014), June and September 2009 (PEP005-016 and PEP005-025), and July and October 2009 (PEP005-028).

Patients were excluded from the trial if the target treatment area was within 5 cm of an incompletely healed wound or within 10 cm of a suspected basal-cell or squamous-cell carcinoma, if they had received previous treatment with ingenol mebutate gel, or if the target treatment area contained hypertrophic and hyperkeratotic lesions, cutaneous horns, or lesions that had not responded to repeated cryosurgery. Additional exclusion criteria were recent use of medications or other treatments that could interfere with evaluation of the treatment area (e.g., topical medications, artificial tanners, immunosuppressive medications, immunomodulating agents, cytotoxic drugs, ultraviolet B phototherapy, other therapies for actinic keratoses, or oral retinoids).

Enrolled patients with actinic keratoses on the face or scalp were randomly assigned to receive ingenol mebutate gel 0.015% or vehicle gel to be self-applied to a 25-cm² contiguous area once daily for 3 consecutive days; those with actinic keratoses on the trunk or extremities were randomly assigned to receive ingenol mebutate gel 0.05% or vehicle gel to be self-applied to a 25-cm² contiguous area once daily for 2 consecutive days. Patients were assessed for safety on days 3 (if they had lesions on the trunk or extremities) or 4 (for lesions on the face or scalp), 8, 15, 29, and 57, and they were assessed for efficacy at baseline and on day 57. In the two trials involving lesions on the face and scalp and in one of the two trials involving lesions on the trunk or extremities, patients who had complete clearance were followed for an additional 12 months to assess the durability of the response and adverse events.

STUDY ASSESSMENTS

The primary end point was complete clearance of all clinically visible actinic keratoses in the target treatment area on day 57. Partial clearance on day 57, defined as a reduction of 75% or more in the number of clinically visible actinic keratoses in the target treatment area, was a secondary efficacy end point. An additional secondary end point, which was not prespecified in the protocol, was the percentage change from baseline in the total number of actinic keratoses. These outcomes were assessed by a study investigator who examined the selected treatment area in person at each visit. Investigators, study-site personnel, and patients were unaware of the study-group assignments.
Safety end points included adverse events; local reactions, evaluated according to a prespecified scale; and pigmentation and scarring in the treatment field. As with all topical treatments for actinic keratosis, local reactions were expected and were recorded quantitatively with the use of a clearly defined local-skin-response grading scale with photographic guides to ensure uniform reporting. The scale ranged from 0 to 4 (with higher numbers indicating greater severity) for the following six responses: erythema, flaking or scaling, crusting, swelling, vesiculation or pustulation, and erosion or ulceration. The composite local-skin-response score is the sum of the six individual scores that were reported at each study visit for each patient (maximum composite score, 24).

STUDY OVERSIGHT

The study protocols were approved by the institutional review board at each participating center. Patients provided written informed consent and agreed to allow photographs of the selected treatment area to be taken and used. The study was designed by the investigators with input from the original sponsor (Peplin), and data were gathered by the investigators. Data from the individual studies were analyzed by LEO Pharma, and the pooled data were analyzed by one of the industry authors. The first and second authors vouch for the accuracy of the data and the analysis and the fidelity of the study to the protocols. All the authors wrote sections of the first draft of the manuscript, which were then combined and reviewed by all of them, with editorial assistance provided by ProHealth, whose fees were paid by LEO Pharma. All the authors decided to submit the manuscript for publication. The study protocols are available with the full text of this article at NEJM.org.

STATISTICAL ANALYSIS

Individual patient data from the two studies involving lesions on the face or scalp were pooled, as were the data from the two studies involving lesions on the trunk or extremities, and all analyses were performed with the use of SAS software, version 9.1.3 (SAS Institute). Logistic-regression models were used for between-group comparisons of the primary and secondary efficacy end points in the two pooled data sets, with treatment group, study, and anatomical location as covariates. These main-effect models were used because logistic-regression models that included interaction terms showed no evidence of an interaction between either study and group assignment or anatomical location and group assignment in the two data sets. Data from each of the four trials were also analyzed individually, and the results were consistent with the pooled results, as shown in the Supplementary Appendix, available at NEJM.org.

In all studies, randomization was central and was stratified according to study site and anatomical location, because response rates could differ on the basis of the location of the selected treatment area. A dynamic randomization scheme with a biased-coin approach was used in the first study to obtain a ratio of approximately 1:1 between the study groups.9 For the next three studies, however, a simple stratified randomization scheme was deemed to be sufficient to obtain a ratio of approximately 1:1.

RESULTS

PATIENTS

All patients identified themselves as white, and the majority had Fitzpatrick skin type I (always burns, never tans) or II (burns easily, tans minimally). The mean age of all patients in the randomized population for the four studies was 65.1 years. Approximately half the patients (44.4 to 53.5%) in all study groups had a history of skin cancer. More than 75% of the patients in all study groups had received treatment with cryotherapy, and smaller percentages had received treatment with imiquimod or topical fluorouracil. The active-treatment and placebo groups did not differ significantly with respect to geographic location, age, sex, Fitzpatrick skin...
A  Face or Scalp Studies

828 Patients were screened

547 Underwent randomization

281 Were excluded

277 Were assigned to receive ingenol mebutate, 0.015%

2 Discontinued early
2 Withdrew consent
1 Received incorrect study kit and was included in safety population for placebo group

274 Were included in safety population
269 (98.2%) Received 3 doses
2 (0.7%) Received 2 doses
3 (1.1%) Received 1 dose

821 (98.9%) Completed the study (randomized population)

270 Were assigned to receive placebo

271 Were included in safety population
271 (100%) Received 3 doses

8 Discontinued early
6 Withdrew consent
1 Had adverse events or abnormal laboratory test
1 Had protocol violation

262 (97.0%) Completed the study (randomized population)

B  Trunk or Extremities Studies

595 Patients were screened

458 Underwent randomization

137 Were excluded

226 Were assigned to receive ingenol mebutate, 0.05%

1 Discontinued early
1 Had protocol violation
1 Received incorrect study kit and was included in safety population for placebo group

225 Were included in safety population
222 (98.7%) Received 2 doses
3 (1.3%) Received 1 dose

220 (97.3%) Completed the study (randomized population)

232 Were assigned to receive placebo

232 Were included in safety population
232 (100%) Received 2 doses

5 Discontinued early
1 Withdrew consent
2 Had adverse events or abnormal laboratory test
1 Had protocol violation
1 Relocated or was lost to follow-up

227 (97.8%) Completed the study (randomized population)
type, lesion count at baseline, presence or absence of a history of skin cancer, or use or nonuse of other therapies (see the Supplementary Appendix).

A total of 547 patients were enrolled in the two studies involving lesions on the face or scalp, with 277 randomly assigned to receive ingenol mebutate gel and 270 assigned to receive placebo (Fig. 1). A total of 3 patients (1.1%) in the ingenol mebutate group discontinued the study early: 1 had an adverse event (burning, eye pain, and periorbital edema that was related to the study medication) and 2 withdrew consent. In the placebo group, 8 patients (3.0%) discontinued the study early: 6 withdrew consent, 1 had an adverse event (multiple trauma unrelated to the study treatment), and 1 had a protocol deviation (Fig. 1, and the Supplementary Appendix). In the ingenol mebutate group, 269 of the 274 patients in the safety population (98.2%) adhered to the 3-day dosing regimen; 3 patients (1.1%) applied only the first dose, and 2 (0.7%) applied only the first and second doses. All 271 patients in the safety population for the placebo group (including 1 patient assigned to the ingenol mebutate group who was erroneously given placebo) applied the placebo gel on 3 consecutive days.

In the studies involving lesions on the trunk or extremities, 458 patients were enrolled; 226 were assigned to receive ingenol mebutate and 232 to placebo (Fig. 1). Six patients (2.7%) in the ingenol mebutate group discontinued the study early: 2 had an adverse event (cervical fracture and exacerbation of spondylostenosis, which were both considered to be unrelated to the study treatment), 2 had a protocol violation, 1 was lost to follow-up, and 1 relocated. In the placebo group, 5 patients (2.2%)...
discontinued the study early: 2 had an adverse event (acute myocardial infarction and injury due to a fall on ice, which were both considered to be unrelated to the study treatment), 1 withdrew consent, 1 had a protocol violation, and 1 relocated (Fig. 1, and the Supplementary Appendix). Of the 225 patients in the ingenol mebutate group, 222 (98.7%) applied the study medication on both days, whereas all the patients in the placebo group applied both doses.

**Efficacy**

**Face and Scalp Studies**
In the ingenol mebutate group, 42.2% of patients had complete clearance of actinic keratoses in the treated area at day 57, as compared with 3.7% of patients in the placebo group (P<0.001). Partial clearance was observed in 63.9% of patients in the ingenol mebutate group, as compared with 7.4% of those in the placebo group (P<0.001). There was a median reduction of 83% from baseline in the number of actinic keratoses in patients treated with ingenol mebutate, as compared with 0% in those who received placebo (Fig. 2A). We calculated that the number of patients who needed to be treated with ingenol mebutate to obtain complete clearance in 1 patient was 2.6, whereas for partial clearance, the number needed to treat was 1.8. In an observational follow-up trial involving 108 patients who had received ingenol mebutate and whose lesions had completely cleared at day 57, a mean of 85.1% of the number of lesions in the treatment area at baseline were clear during 12 months of follow-up; one or more lesions developed or recurred in 50% of patients (95% CI, 35.5 to 66.6).10

**Trunk and Extremity Studies**
Complete clearance occurred in 34.1% of the patients treated with ingenol mebutate gel 0.05%, as compared with 4.7% of those who received placebo (P<0.001). Partial clearance occurred in 49.1% of patients in the ingenol mebutate group, as compared with 6.9% in the placebo group (P<0.001). The median percentage reduction from baseline in the number of actinic keratoses was 75% in patients treated with ingenol mebutate, as compared with 0% in those who received placebo (Fig. 2B). We calculated that the number of patients who would need to be treated with ingenol mebutate to obtain complete clearance in 1 patient was 3.4, whereas for partial clearance, the number needed to treat was 2.4. In an observational follow-up trial involving 38 patients who had received ingenol mebutate and whose lesions had completely cleared by day 57, a mean of 85.1% of the number of lesions in the treatment area at baseline were clear during 12 months of follow-up; one or more lesions developed or recurred in 50% of patients (95% CI, 35.5 to 66.6).10

**Individual Studies**
Each of the four studies yielded highly significant results in terms of the primary efficacy end point (P<0.001) (see the Supplementary Appendix). A sensitivity analysis conducted for each study yielded similar results (P<0.001). In the sensitivity analysis, all patients who received treatment with ingenol mebutate who missed the day 57 visit or were not assessed during the window for that visit (i.e., they were assessed before day 51 or after day 84) were classified as not having complete clearance at day 57, and all patients in the placebo group who were not assessed during the window for the day 57 visit were classified as having complete clearance.

**Safety**

**Face and Scalp Studies**
The mean (±SD) maximum composite local-skin-response score for patients treated with ingenol

![Figure 3. Time Course of Mean Composite Local-Skin-Response Scores in the Safety Population.](image-url)

The composite local-skin-response score is the sum of the six individual local-skin-response scores (which range from 0 to 4, with higher numbers indicating more severe reactions), calculated at each study visit for each patient, with a maximum composite score of 24. For the studies involving the trunk or extremities, patients were assessed on days 1, 3, 8, 15, 29, and 57; for the face and scalp studies, patients were assessed on days 1, 3, 8, 15, 29, and 57. I bars indicate standard errors.
mzbekate was 9.1±4.1, as compared with 1.8±1.6 for those who received placebo. A maximum composite local-skin-response score greater than the baseline score was noted in 97.8% of patients treated with ingenol mzbekate and in 35.8% of those who received placebo. For patients in the ingenol mzbekate group, the composite score peaked at day 4 and declined thereafter (Fig. 3). More than two thirds of patients treated with ingenol mzbekate (69.7%) had a local-skin-response score of 3 or higher for erythema, as compared with only 2.2% of those who received placebo; a minority of patients treated with ingenol mzbekate had scores of 3 or higher for flaking or scaling, crustimg, swelling, vesiculation or pustulation, or erosion or ulceration. Figure 4A shows local reactions in a representative patient, in whom the score peaked around day 8 and had begun to resolve by the day 15 visit, with a score lower than baseline at the end of follow-up.

There was minimal change in pigmentation and minimal scarring in both study groups. Of all the adverse events that occurred during treatment in the ingenol mzbekate group, application-site conditions were reported most commonly (in 52 of 274 patients [19.0%], vs. 7 of 271 [2.6%] who received placebo) (Table 1). The most common application-site conditions reported by patients treated with ingenol mzbekate gel were pain (in 13.9%), pruritus (8.0%), and irritation (1.8%). One patient (0.4%) in each study group had one or more adverse events that led to discontinuation of the study. No serious adverse events related to the study treatment occurred.

Trunk and Extremity Studies
The mean maximum composite local-skin-response score for patients who received ingenol mzbekate was 6.8±3.5, as compared with 1.6±1.5 for those who received placebo. The maximum composite local-skin-response score was higher than the baseline score in 96.4% of patients treated with ingenol mzbekate and 31.0% of those who received placebo. The maximum composite score in the ingenol mzbekate group occurred on day 3 for 55.1% of the patients, on day 8 for 32.4%, and on day 15 for 8.4%. The majority of patients treated with ingenol mzbekate had a score of 2 or higher for erythema, 2 or higher for
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flaking or scaling, 1 or higher for crusting, and 1 or higher for swelling. Vesiculation or pustulation of any degree occurred in 43.6% of patients in the ingenol mebutate group, and erosion or ulceration occurred in 25.8%. Figure 3 shows the mean composite local-skin-response scores over time.

There was minimal change in pigmentation and minimal scarring in both study groups. Figure 4B shows the treatment area in one patient before the administration of ingenol mebutate gel and at the end of the study. Of all adverse events that occurred during treatment in the ingenol mebutate group, application-site

| Table 1. Adverse Events in the Safety Population.* |
|---------------------------------------------|---------------------------------------------|
| Event                                      | Studies Involving Face or Scalp | Studies Involving Trunk or Extremities |
|                                            | Ingenol Mebutate | Placebo | Ingenol Mebutate | Placebo |
|                                            | 0.015% (N = 274) | (N = 271) | 0.05% (N = 225) | (N = 232) |
| Any serious adverse event                  | 6 (2.2) | 5 (1.8) | 8 (3.6) | 12 (5.2) |
| Any adverse event                         | 102 (37.2) | 60 (22.1) | 75 (33.3) | 63 (27.2) |
| General disorder or administration-site condition | 52 (19.0) | 7 (2.6) | 27 (12.0) | 6 (2.6) |
| Pruritus at administration site          | 22 (8.0) | 3.1 (1.1) | 19 (8.4) | 0 |
| Pain at administration site              | 38 (13.9) | 1 (0.4) | 5 (2.2) | 0 |
| Irritation at administration site        | 5 (1.8) | 0 | 8 (3.6) | 1 (0.4) |
| Other                                    | 8 (2.9) | 3 (1.1) | 7 (3.1) | 5 (2.2) |
| Infection or infestation                 | 20 (7.3) | 12 (4.4) | 15 (6.7) | 14 (6.0) |
| Infection at application site            | 7 (2.6) | 0 | 0 | 1 (0.4) |
| Other                                    | 14 (5.1) | 12 (4.4) | 15 (6.7) | 13 (5.6) |
| Skin or subcutaneous-tissue disorder      | 11 (4.0) | 3 (1.1) | 10 (4.4) | 7 (3.0) |
| Periorbital edema                         | 7 (2.6) | 0 | 0 | 0 |
| Other                                    | 4 (1.5) | 3 (1.1) | 10 (4.4) | 7 (3.0) |
| Injury, poisoning, or procedural complication | 10 (3.6) | 16 (5.9) | 8 (3.6) | 3 (1.3) |
| Neoplasms — benign, malignant, or unspecified, including cysts and polyps | 4 (1.5) | 3 (1.1) | 7 (3.1) | 10 (4.3) |
| Nervous system disorder                   | 11 (4.0) | 6 (2.2) | 2 (0.9) | 2 (0.9) |
| Headache                                 | 6 (2.2) | 3 (1.1) | 1 (0.4) | 2 (0.9) |
| Other                                    | 5 (1.8) | 3 (1.1) | 1 (0.4) | 0 |
| Musculoskeletal or connective-tissue disorder | 4 (1.5) | 7 (2.6) | 6 (2.7) | 3 (1.3) |
| Respiratory, thoracic, or mediastinal disorder | 4 (1.5) | 3 (1.1) | 5 (2.2) | 6 (2.6) |
| Cardiac disorder                         | 2 (0.7) | 7 (2.6) | 9 (4.0) | 8 (3.4) |
| Eye disorder — eyelid edema and other    | 8 (2.9) | 2 (0.7) | 1 (0.4) | 0 |
| Abnormalities on routine investigation†  | 5 (1.8) | 8 (3.0) | 10 (4.4) | 9 (3.9) |

* The safety population included all patients who received at least one dose of the study drug and underwent at least one safety evaluation after the baseline visit. Serious adverse events and all adverse events with an incidence of 2% or higher in any study group are reported here. Some patients had more than one event. All serious adverse events and all adverse events with an incidence of 1% or higher in any study group are listed in the Supplementary Appendix.

† This category includes abnormalities in vital-sign readings, electrocardiographic (ECG) studies, or laboratory (cellular and biochemical) tests, which were performed as part of routine safety monitoring. In the studies involving the face and scalp, there were three ECG events and two laboratory events in the ingenol mebutate group and four ECG events and four laboratory events in the placebo group. No abnormalities of vital signs were found in either group. In the studies involving the trunk and extremities, there were five ECG events, four laboratory events, and two vital-sign events in the ingenol mebutate group and seven ECG events, five laboratory events, and one vital-sign event in the placebo group.
conditions were reported most commonly (in 27 of 225 patients [12.0%], vs. 6 of 232 [2.6%] who received placebo) (Table 1). The most common application-site conditions reported by patients treated with ingenol mebutate gel were pruritus (8.4%), irritation (3.6%), and pain (2.2%). No serious adverse events related to the study treatment occurred.

**DISCUSSION**

To be successful in the clinical setting, a topical treatment for actinic keratoses that the patient applies must be effective, safe, and convenient to use. In our studies, ingenol mebutate gel was effective in treating actinic keratoses as a 0.015% concentration applied once daily on 3 consecutive days to the face or scalp and as a 0.05% concentration applied once daily on 2 consecutive days to the trunk or extremities.

Several other therapies are approved for the treatment of actinic keratoses. In one study, 3.0% diclofenac gel applied twice daily for 60 days resulted in complete clearance of target treatment areas in 33% of patients, as compared with 10% of those who received placebo. When the agent was applied twice daily for 90 days, complete clearance of target sites occurred in 50% of sites, as compared with 20% with placebo. Imiquimod 5% cream applied two times per week for 16 weeks resulted in complete clearance in 45.1% of target areas, as compared with 3.2% with placebo. Imiquimod 2.5% and 3.75% were compared with placebo in a regimen in which they were applied daily for 2-week cycles, with 2 weeks off between two treatment cycles. Rates of complete clearance in target sites were 30.6%, 35.6%, and 6.3% with imiquimod 2.5%, imiquimod 3.75%, and placebo, respectively. In one study, fluorouracil 0.5% cream applied daily for 1, 2, or 4 weeks resulted in complete clearance in 26.3% of patients treated for 1 week, 19.5% of those treated for 2 weeks, and 47.5% of those treated for 4 weeks, as compared with clearance in 3.4% of patients who received placebo for up to 4 weeks. In addition, fluorouracil 5% cream, cryotherapy, and other ablative methods of treatment have been available for years and are also highly effective. The main advantage of therapy with ingenol mebutate is that similar degrees of efficacy can be achieved with only two or three daily applications of the medication.

Two clear benefits are derived from the short exposure to ingenol mebutate. The first benefit is the relatively rapid resolution of local reactions. On the face or scalp, where irritation is most noticeable, the peak local-skin-response score was recorded at the day 4 visit; the score declined rapidly thereafter, and local reactions were almost resolved by the day 15 visit. Second, the short duration of treatment may result in very high (>98%) adherence to the therapy, contributing to the effectiveness of ingenol mebutate. Many patients find it difficult to adhere to the currently available regimens of topical treatment that last for periods of 1 to 4 months, which may result in “real-world” effectiveness lower than that achieved in supervised and patient-compensated clinical trials. The lack of response to treatments with imiquimod and fluorouracil may be due to failure to complete the regimens.

There are limitations of this study. First, the local reactions limit the blinding of the study. Second, treatments were limited to target areas of 25 cm². Treatment of target areas of this size has been the basis for approval of a number of recently introduced therapies for actinic keratosis. Third, these studies also restricted the repetition of treatment and the use of adjunctive therapies; future studies are needed to assess the risks and benefits of treating larger areas of skin, using multiple treatments in the same area, and using combination therapies. The data from these four controlled studies provide evidence that ingenol mebutate gel is an effective treatment for actinic keratoses on the head and body, with local reactions of generally low-to-intermediate intensity and short duration.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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**REFERENCES**


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