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Ingenol Mebutate and the Treatment of Actinic Keratosis

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INTRODUCTION

Actinic keratoses (AKs) are common skin lesions association with increased exposure to ultraviolet radiation; these lesions have the potential to transform into squamous cell carcinomas (SCCs).[1] Therapeutic options for AKs vary depending on the number of lesions and overall skin involvement. Destructive lesion-directed therapies, such as cryosurgery, are appropriate for patients with few AKs; patients with a higher number of lesions often require field-directed therapies, which are capable of treating not only a larger number of visible lesions over a greater area of skin, but subclinical disease as well.[1] Options for field therapies include patient-administered therapies such as imiquimod, fluorouracil, and ingenol mebutate, and physician-administered therapies such as photodynamic therapy (PDT), among others.[2] Each treatment option has distinct advantages and disadvantages with regards to overall efficacy, safety, cost, and feasibility (Table 1).[1-3] Patient preferences with regards to tolerance of side effects, therapy convenience, and cost of treatment are important considerations when choosing a therapy.

TABLE 1.

Field-Directed Therapeutic Options for AKs

	Efficacy from direct comparison study† (% of patients free from treatment failure at 12-months post-treatment)	Efficacy from drug labels§ (% of patients achieving 75% skin clearance)	Safety	Cost¶	Feasibility
Patient-administered					
Fluorouracil (5% cream)	74.7%	Approximately 60% to 80% at four weeks	Erythema, burning, pruritus, scaling	$267.32 for 40g of 5% cream*	Twice daily application for four weeks
Imiquimod (5% cream)	53.9%	58% to 60% at eight weeks post 16-week treatment	Erythema, pruritus, crusting, induration Rarely results in systemic flu-like symptoms	$143.02 for 12 packets of 5% cream*	Once daily application, three days a week for four weeks
Ingenol mebutate (0.015% gel)	28.9%	60% to 68% at day 57	Erythema, swelling, crusting, scaling, vesiculation, pruritus	$1,299.22 for three tubes of 0.015% gel*	Once daily application for three consecutive days
Physician-administered					
Photodynamic therapy	37.7% treated with MAL-PDT	79% to 81% at three months post second treatment session	Erythema, pain, stinging, crusting Strict avoidance of sun exposure 24–48 hours after treatment	$550.00 average per treatment session††	One treatment session lasting one to three hours every four to six weeks

†Jansen MHE, Kessels J, Nelemans PJ, et al. Randomized Trial of Four Treatment Approaches for Actinic Keratosis. *N Engl J Med.* 2019;380(10):935-946.
§Efficacy info for drug labels retrieved from dailymed.nlm.nih.gov/dailymed (accessed 5/19/20)
¶Drug costs are subject to change and prices listed may not represent contract prices paid by payers and price after rebates
*Pricing retrieved from GoodRx.com (accessed 5/04/20)
††Uhlenhake EE. Optimal treatment of actinic keratoses. *Clin Interv Aging.* 2013;8:29-35.

AK- actinic keratosis; G- grams; MAL-PDT- methyl aminolevulinate photodynamic therapy

Although not the most efficacious treatment when compared to fluorouracil, imiquimod, and methyl aminolevulinate photodynamic therapy (MAL-PDT) in clinical trials, ingenol mebutate may be a good option for patients who prefer a treatment regimen with a relatively short duration, as initial therapy with 0.015% ingenol mebutate requires only three consecutive days of topical application over a four week span compared to twice daily or thrice weekly topical application over four weeks for 5% fluorouracil and 5% imiquimod, respectively.[3] Because all AK treatments have increased efficacy with retreatment, patients may be more willing to accept retreatment from an agent with an easier treatment regimen compared to regimens requiring longer treatment courses. However, in January 2020, ingenol mebutate (Picato) was withdrawn from the market by the manufacturer and precautionarily suspended in the European Union following concerns about increased rates of skin malignancy (particularly SCCs) associated with ingenol mebutate use.[4,5] In April 2020, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) concluded in its safety review of ingenol mebutate that the drug may carry an increased risk of skin malignancy, which outweighs possible benefits of the agent.[4,6]

The EMA reached this conclusion following results of a three-year two-arm safety study comparing ingenol mebutate with imiquimod, which demonstrated a higher incidence of malignancy in patients treated with ingenol mebutate than with the comparator.[5,7] According to the initial EMA press release recommending suspension of ingenol mebutate, 3.3% of patients receiving ingenol mebutate developed skin malignancy, compared to 0.4% of patients receiving imiquimod per both the preliminary and final results of the study.[5,7] The same press release cited an additional eight week vehicle-controlled trial including 1,262 patients with a higher incidence of skin tumors in the ingenol mebutate treatment arm (1% versus 0.1%).[5] Lastly, the EMA referenced four clinical trials involving a total 1,234 patients with higher incidences of skin tumors in patients treated with ingenol disoxate, an ester related to ingenol mebutate, compared to patients treated with a vehicle control (7.7% versus 2.9%).[5] The EMA determined the similarity between ingenol mebutate and ingenol disoxate warranted consideration of those results in the safety review of ingenol mebutate.[5]

Although the results of these studies demonstrate a higher incidence of skin malignancy in patients receiving ingenol mebutate or the closely related compound ingenol disoxate versus the respective comparative agents, patients with multiple AKs warranting treatment with field-directed therapies such as ingenol mebutate and imiquimod have an inherently higher likelihood of developing SCC secondary to disease extent,[8] independently of any possible increased risk conferred by a chosen treatment. Thus, it is possible ingenol mebutate doesn't decrease the risk of SCC as much as imiquimod does, rather than overtly causing SCC; this notion may account for the differences in incidence of skin malignancy between the agents in the safety study. Additionally, the overall incidence of malignancy in both groups was small, with 96.7% and 99.6% of patients without SCC at the time of study completion in the ingenol mebutate and imiquimod groups, respectively, in populations at high risk for developing SCC. In an alternate pooled study of two randomized controlled trials comparing imiquimod and diclofenac, another field-therapy utilized for the treatment of AKs, diclofenac-treated patients had a higher incidence of grade III AK and invasive SCC compared to imiquimod-treatment patients (11.0% versus 5.4%).[9] This result may further suggest an imbalance in overall incidence of malignancy in clinical trials comparing imiquimod with other field therapies. In the vehicle-controlled studies, lesion clearance by ingenol mebutate and ingenol disoxate may have created an environment in which residual SCCs were more easily detectable, resulting in a higher documented incidence of skin tumors in those treatment groups versus the vehicle groups.

The reproducibility of these findings in multiple clinical trials warrants consideration when comparing adverse effect profiles associated with different field-directed therapies. At this time, ingenol mebutate remains available for treatment of AKs in the United States, although the Food and Drug Administration is currently collecting data to further investigate safety and risks associated with its use.[4] However, instead of removing the drug from the market, it may be more reasonable for physicians and their patients to weigh the risks and benefits when deciding whether to treat AKs with ingenol mebutate. Although not the most effective field-therapy compared to other available agents, ingenol mebutate has a short course of treatment and an overall mild side-effect profile, potentially increasing patients' willingness to treat with the therapy. Thus, the decision to treat AKs with ingenol mebutate may be best decided on a case-by-case basis after a conversation between patients and providers outlining efficacy, ease of use, speed of response, cost, and potential adverse effects.

DISCLOSURES

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