Evaluation of Different Approaches in Managing Local Skin Reactions With the Use of Ingenol Mebutate 0.015% and 0.05% During the Treatment of Actinic Keratosis

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Introduction

- Actinic keratoses (AKs) are epidermal lesions on the skin caused by damage from chronic exposure to UV rays from the sun and/or indoor tanning[1]
- AKs have a risk of progressing to invasive squamous cell carcinoma (SCC) if untreated; the majority of clinically diagnosed SCCs originate from concomitant AKs[1]
- Ingenol mebutate (IMB) (0.015% or 0.05%) gel is a topical AK treatment used to treat AK on the trunk and extremities, but it can elicit local skin reactions (LSRs) at the application site[2-4]
  - LSRs are associated with erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration
  - Managing LSRs during treatment of AK may be important for treatment adherence and setting patient expectations
- Previous clinical data have demonstrated that the treatment burden of LSRs associated with IMB gel is minimal, manageable, and short lasting[5]

Objective

- To perform a systematic review of approaches used for managing or decreasing LSRs during treatment of AK with IMB

Materials and Methods

- We systematically searched the electronic databases PubMed and Medline to identify all relevant records through August 2019
- Search terms included "ingenol mebutate," "ambulatory care facilities,""actinic keratosis," "therapy," and "LSR"
  - All relevant clinical studies in humans examining the clinical utility of IMB were included
  - Scientific review articles, as well as studies not published in English, were excluded
  - There were no limitations for date of publication
- The literature search returned 49 results
  - Titles, abstracts, and full text articles of the search results were screened for relevance
  - 6 studies were identified for in-depth analysis

Results

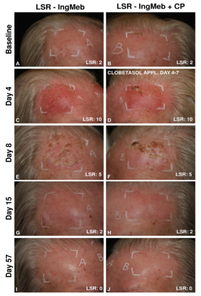
- The 6 studies selected for the analysis represented a range of study designs (**Table 1**)
  - Retrospective chart reviews[1,6,7] n=3
  - Randomized controlled trial[8] n=1
  - Investigator-initiated single-blinded study[9] n=1
  - Observational longitudinal cohort study[10] n=1
- The 6 studies examined a total of 1437 patients; 1424 patients were evaluated for LSRs associated with IMB
- 3 of the studies only examined the resolution of LSRs over time in the absence of any intervention[6,7,10]
- The other studies evaluated different approaches in managing or minimizing LSRs during the treatment of AK
  - Use of various topical moisturizers[1,2,10]
  - Implementing a low-dose regimen of IMB[6]
  - Application of dimethicone[9]
  - Application of clobetasol propionate[8]

In-Depth Analysis of Individual Studies

Erlendsson AM et al, 2016

- In a blinded, randomized controlled trial, Erlendsson AM et al, treated patients with multiple AKs on the face and scalp with IMB daily for 3 days[8]
- For each patient, 1 of 2 areas was randomized to receive topical clobetasol propionate (0.05%) twice daily for 4 days to treat LSRs, while the other area was left untreated
- LSR rates in patients treated with IMB were:
  - Erythema (100%)
  - Flaking (100%)
  - Crusting (91%)
  - Swelling (91%)
  - Vesiculation (69%)
  - Erosion (29%)
- Areas randomized to receive clobetasol propionate had no benefit over untreated areas in reducing LSRs and their associated pain and pruritis (**Figure 1**)
  - By 2 weeks after treatment initiation, LSRs had returned to baseline both in areas treated with IMB (0.67) and in areas treated with IMB + clobetasol propionate (0.38; *P*=.250)

Figure 1. Development of LSRs in a patient treated with IMB with or without clobetasol propionate



CP=clobetasol propionate; IngMeb=ingenol mebutate. Figure 1 was republished with permission of Journal of American Academy of Dermatology from Topical corticosteroid has no influence on inflammation or efficacy after ingenol mebutate treatment of grade I to III actinic keratoses (AK): A randomized clinical trial, Erlendsson AM, et al. *J Am Acad Dermatol* 2016 Apr;74(4):709-15.

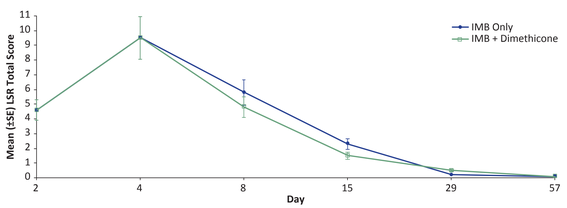
Table 1. Profile of Studies Evaluating Management of LSRs With the Use of IMB in Treating AK

	Reference	Study Design	Number of Patients in Study	Number of Patients Evaluated for LSRs	Treatment for LSRs Used	Conclusions
1	Erlendsson AM et al. *J Am Acad Dermatol.* 2016;74(4):709-715.	Randomized controlled trial	21	21	Clobetasol propionate, twice daily for 4 days, to one of 2 areas on the face or scalp	Patients randomized to receive clobetasol propionate had no benefit over untreated patients in reducing LSRs and their associated pain and pruritus
2	Jim On SC. *J Drugs Dermatol.* 2017;16(5):432-436.	Investigator-initiated single-blinded study	20	20	1% dimethicone lotion, applied once daily to one of 2 areas on the face containing 3-8 AKs	Dimethicone lotion with IMB had no significant effect on LSR severity over treatment with IMB alone
3	Neri L et al. *J Eur Acad Dermatol Venereol.* 2019;33(1):93-107.	Observational longitudinal cohort study	1136	420 during first 8 days; 149 during follow-up	Follow-up 1 • Emollient creams: 47% • Topical antibiotics: 53% Follow-up 2 • Emollient creams: 70% • Antibiotics: 29%	There was a steep decrease in average LSR score (0-4) from the first follow-up visit (2.7±1.4) to the second follow-up visit (0.8±0.8), which was seen in both LSR-treated and untreated groups
4	Bettencourt MS. *J Clin Aesthet Dermatol.* 2016;9(3):20-24.	Retrospective chart review	78	65	34 of 78 treated their LSRs with: Moisturizers (n=16) Neosalus hydrating cream (n=9) Skin barrier emollient cream (n=3) Antipruritic hydrogel (n=3) Petrolatum-based cream (n=2) Dimethicone-based cream (n=2) Anti-itch hydrogel (n=1)	LSRs were resolved by 10-14 days in 98% of patients evaluated regardless of their use of moisturizers or emollients • In 1 patient, LSRs resolved by day 20
5	Bettencourt MS. *J Drugs Dermatol.* 2014;13(3):269-273.	Retrospective chart review	135 total Face (n=77) Scalp (n=45) Trunk (n=32)	Face (n=72) Scalp (n=41) Trunk (n=24)	No treatment: 26% Moisturizers & creams: 4% Oral prednisone & tacrolimus 0.1%: 1 patient	LSRs were cleared 1 week after peak inflammation in most patients, independent of treatment with moisturizers, creams, or oral prednisone and tacrolimus
6	Joe HJ, Oh BH. *Clin Cosmet Investig Dermatol.* 2017;10:93-98.	Retrospective chart review	47	47	None	Below-recommended dosing of IMB (10 mg/cm^2) significantly reduced LSR score and pain score but was associated with a significantly lower AK clearance rate vs recommended dose IMB (18.8 mg/cm^2)

Jim On SC et al, 2017

- Jim On SC, et al, studied 20 patients with multiple facial AKs being treated with IMB gel, 0.015%[9]
- 1% dimethicone lotion was applied once daily to 1 of 2 areas on the face containing 3-8 AKs in an investigator-blinded manner
- LSRs included the following and were graded on a scale from 0 (no reaction) to 4 (severe reaction)
  - Erythema
  - Flaking/Scaling
  - Swelling
  - Vesiculation/Pustulation
  - Erosion/Ulceration
- Dimethicone lotion with IMB had no significant effect on LSR severity over treatment with IMB alone (**Figure 2**)

Figure 2. Mean LSR scores in patients treated with IMB vs IMB + 1% dimethicone[9]



SE=standard error.
Figure 2 republished with permission of Journal of Drugs in Dermatology from Assessment of Efficacy and Irritation of Ingenol Mebutate Gel 0.015% Used With or Without Dimethicone Lotion for Treatment of Actinic Keratosis on the Face, Jim On SC, et al. *J Drugs Dermatol.* 2017; 16(5):432-436.

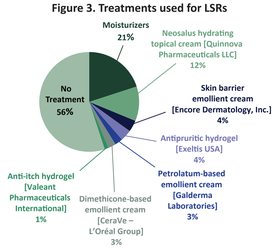
Neri L et al, 2017

- Neri L et al, conducted an observational, multicenter, longitudinal cohort study in 1136 adult patients with multiple grade I/II AKs[10]
- LSRs were assessed at 2 follow-up visits:
  - T1: 8 days after initiation of AK treatment
  - T2: 25-30 days after initiation of AK treatment
- Approximately 37% of patients received treatment for LSRs at T1
  - 53% received topical antibiotics
  - 47% received emollient creams
- Roughly 14% received treatment at T2
  - 70% received emollient creams
  - 29% received antibiotics
- There was a steep decrease in average LSR score (scale=0-4) from the first follow-up visit (2.6±1.5) to the second follow-up visit (0.9+1.0), which was seen in both LSR-treated and untreated groups

Bettencourt MS, 2016

- Bettencourt MS conducted a study at a community dermatology practice in 78 male patients with recurring and relapsed scalp AK[2]
- All patients exhibited LSRs on the first day of treatment
  - Erythema (100%)
  - Flaking/Scaling (97%)
  - Crusting (66%)
  - Swelling (6%)
  - Vesiculation/Pustulation (32%)
  - Erosion/Ulceration (13%)
- 44% of the patients treated their LSRs with a topical product (**Figure 3**)
- LSRs were resolved in 10-14 days regardless of the use of a topical product
  - In 1 patient, LSRs were resolved at day 20

Figure 3. Treatments used for LSRs



Bettencourt MS, 2014

- Bettencourt MS conducted a retrospective chart review of 135 patients who had a prolonged history of AKs treated with IMB[7]
- Regardless of body area or use of LSR treatment, most patients had developed LSRs by day 2 of treatment (**Table 2**)
- Most patients used no additional treatment for their LSRs
  - Face: 83% used no treatment vs 17% used additional treatment
  - Scalp: 85% used no treatment vs 15% used additional treatment
  - Trunk/Extremities: 92% used no treatment vs 8% used additional treatment

Bettencourt MS, 2014 (cont'd)

Table 2. LSR Incidence and Resolution by Severity[7]

	Erythema		Flaking/Scaling		Crusting			Resolution of LSRs Without Treatment
	Mild	Moderate	Mild	Moderate	Mild	Moderate	Severe	Mild, Moderate, & Severe
Face (n=72)	72%	28%	75%	25%	19%	7%	1%	**60/72 (83.3%)**
Scalp (n=72)	73%	33%	34%	66%	7%	5%	0%	**35/41 (85.4%)**
Trunk/ Extremities (n=24)	75%	4%	0%	8%	13%	4%	0%	**22/24 (91.7%)**

- LSRs improved by 1 week after peak inflammation, despite being untreated in most patients[7]
- LSRs may resolve over time without the need for additional treatment

Joe HJ et al, 2017

- Joe HJ et al, retrospectively evaluated patients with AK treated with normal (recommended-amount) or low-dose (low-amount) IMB[6]
- Recommended-amount group (RAG) 18.8 mg/cm^2 (n=20)
- Low-amount group (LAG)[a] 10 mg/cm^2 (n=27)
- Although the low-dose IMB produced a significantly lower LSR score, the mean AK clearance rate in the RAG was significantly greater than that of the LAG
  - Maximum composite LSR score, mean ± SD: 15.45 ± 2.70 in the RAG vs 12.18 ± 3.29 in the LAG, *P*<.001
  - Maximum pain score (VAS), mean ± SD: 7.95 ± 0.99 in the RAG vs 6.55 ± 1.42 in the LAG, *P*<.001
  - AK clearance rate, mean ± SD: 88.16 ± 12.30 in the RAG vs 75.56 ± 9.44 in the LAG, *P*<.001
  - AK clearance rate (%), range: 66.67-100 in the RAG vs 63.64-100 in the LAG, *P*<.001

Clearance rate = (the number of AKs decreased after treatment/the number of AKs before treatment) x 100 (%); *P* value, independent samples test.
VAS=visual analog scale; SD=standard deviation.
[a]Dose used in the LAG is lower than the approved labelling for IMB.

Conclusions

- Topical application of IMB gel in patients with AK elicits LSRs at the application site
- Based on available literature, LSRs in most patients treated with IMB resolve spontaneously over time without the need for additional treatment
  - Evidence is lacking to support a singular strategy for reducing or preventing IMB-induced LSRs
  - Studies evaluating the role of topical lotions, antibiotics, or moisturizers to treat LSRs found that these treatments provided no significant benefit in improving LSR severity over treatment with IMB alone
- After treatment with IMB gel, 0.015% or 0.05%, LSRs only peak in intensity up to 1 week following treatment completion, and resolve spontaneously in 2-4 weeks without treatment[3]
  - Therefore, LSRs are unlikely to influence patients' adherence behavior to IMB
  - An understanding that LSRs typically resolve spontaneously over time may help manage patient expectations and improve patient satisfaction

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Disclosures

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