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

Andrés Már Erlendsson, MD, PhD,[a] Katrine Elisabeth Karmisholt, MD,[a] Christina Skovbølling Haak, MD, PhD,[a] Ida-Marie Stender, MD, PhD,[b] and Merete Haedersdal, MD, PhD, DMSc[a]
Copenhagen, Denmark

Background: Ingenol mebutate (IngMeb) is approved for treatment of actinic keratoses (AK) and may cause unpredictable local skin responses (LSR).

Objectives: We sought to investigate whether IngMeb-induced LSR, pain, and pruritus could be alleviated with a topical glucocorticoid and, further, to assess efficacy, cosmetic outcome, and patient satisfaction in patients with severe photodamage.

Methods: In this blinded, randomized controlled clinical trial, patients with multiple AK and field cancerization of the face or scalp were treated in 2 areas with IngMeb (0.015%) daily for 3 days. After finalized IngMeb treatment, 1 area was randomized to receive topical clobetasol propionate (0.05%) twice daily for 4 days. Assessments included LSR (0-24; days 1, 4, 8, 15, 57), pain (0-10) and pruritus (0-3; days 1-15), AK clearance (days 15, 57), and cosmetic outcome (0-3; day 57).

Results: Clobetasol propionate application had no influence on LSR (P = .939), pain (P = .500), pruritus (P = .312), or AK cure rate (P = .991). Overall, IngMeb cleared 86% of all AK lesions, exerting a therapeutic effect on all AK severity grades; cure rates were 88%, 70%, and 60% for grade I, II, and III AK, respectively. Skin texture improved significantly in remedied areas (2.0 vs 1.0; $P < .001$); no hypopigmentation, hyperpigmentation, or scarring were observed.

Limitations: These results do not provide safety and efficacy beyond 2 months of follow-up.

Conclusion: Application of clobetasol propionate does not alleviate IngMeb-induced LSR after 3 days of IngMeb treatment. (J Am Acad Dermatol 2016;74:709-15.)

Key words: actinic keratoses; actinic keratosis; blinded; clearance; clobetasol; corticosteroid; cosmesis; cosmetic outcome; cure rate; glucocorticoid; hyperkeratotic; inflammation; ingenol mebutate; local skin responses; pain; patient satisfaction; photodamage; pruritus; rejuvenation; skin texture.

Actinic keratoses (AK) represent focal areas of abnormally proliferating and differentiating keratinocytes.[1] Subclinical lesions are commonly present in surrounding field-cancerized

Abbreviations used:

AK:	actinic keratoses
IngMeb:	ingenol mebutate
LSR:	local skin responses

From the Department of Dermatology, Bispebjerg University Hospital, University of Copenhagen,[a] and Hudklinikken på Jaegersborg Alle.[b]

This is an investigator-initiated study. Research grant and ingenol mebutate gel provided by Leo Pharma A/S, which had no role in the design, study conduction, or preparation of the manuscript.

Disclosure: Drs Erlendsson and Haedersdal received research grants from Leo Pharma A/S. Drs Karmisholt, Skovbølling Haak, and Stender have no conflicts of interest to declare.

Presented at the 73rd Annual Meeting of the American Academy of Dermatology in San Francisco, CA, March 20-24, 2015.

Accepted for publication November 2, 2015.

Reprint requests: Andrés Már Erlendsson, MD, PhD, Department of Dermatology, Bispebjerg University Hospital, Bispebjerg Bakke 23, 2400, Copenhagen, Denmark. E-mail: andres.erlendsson@gmail.com.

Published online January 22, 2016.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2015.11.034

skin, and contemporary treatments are thus advancing toward field-directed therapies.[2,3]

Ingenol mebutate (IngMeb) gel was introduced as a field treatment for AK in 2012 and is available in 2 concentrations.[4] AK on the face and scalp are treated with IngMeb 0.015% once daily for 3 days, whereas AK on the trunk and extremities are treated with 0.05% once daily for 2 days.[5,6] With a dual mechanism of action, IngMeb initially induces cell death by necrosis and apoptosis, followed by a strong inflammatory response generated by stimulation of immune regulatory pathways.[7-10] The inflammation clinically manifests as local skin responses (LSR) with initial erythema and edema, followed by pustules, epidermal flaking, and crusting.[6,11] The LSR appear within hours of application and subside in less than 2 weeks, during which the most frequently reported side effects are pain and pruritus.[6]

CAPSULE SUMMARY

- Ingenol mebutate is approved for the treatment of actinic keratosis and may cause unpredictable local skin responses.
- This study investigates the influence of a topical glucocorticoid on local skin responses, pain, and pruritus.
- Application of a topical glucocorticoid after 3 days of ingenol mebutate treatments does not alleviate local skin responses, pain, or pruritus.

To date, clinical studies have been conducted only in patients with nonhyperkeratotic AK, and safety and efficacy remains to be established in patients with severe photodamage.[6,12] The severity of the LSR varies between patients and some individuals may develop insufferable inflammation with swelling and pain where alleviating therapy is desired. Clobetasol propionate is a potent glucocorticoid with immunosuppressive, anti-inflammatory, and vasoconstrictive properties. It is believed to counteract the immune response induced by IngMeb.[13] However, whether the inflammatory response is essential for achieving optimal treatment response or simply an adverse reaction is not fully understood; accordingly, it is unknown whether glucocorticoids attenuate the therapeutic effect of IngMeb.[14,15]

In this blinded, intraindividual, randomized, controlled clinical trial, the primary objective was to evaluate clobetasol propionate's influence on IngMeb-induced LSR, pain, and pruritus in patients with severe photodamage. The secondary objectives were to assess clobetasol propionate's influence on treatment efficacy, along with overall cosmetic outcome and patient satisfaction.

METHODS

Study conduction

The study was conducted at the Department of Dermatology, Bispebjerg University Hospital, Copenhagen, Denmark, during September 2013 through January 2014. Approvals were obtained from the Danish Health and Medicines Authority (EudraCT: 2013-0022583-80) and the Regional Committee on Health Research Ethics (H-4-2013-073). The trial was monitored by Copenhagen University Hospital's Good Clinical Practice Unit (2013-584).

Patients

Patients aged 18 years or older with multiple grade I to -III AK[16] and field cancerization on the face or scalp were recruited for participation. Inclusion required 2 similar treatment areas of 25 cm^2 containing a minimum of 7 AK on field-cancerized skin. Exclusion criteria included: (1) clinical suspicion of nonmelanoma skin cancer in the treatment area; (2) previous treatment with IngMeb; (3) active dermatologic condition in the treatment area; (4) intake of systemic immunosuppressive, cytotoxic, immune-modulating, or retinoid agents within 3 months of study start; (5) pregnancy or lactation; and (6) patients considered unable to comply with the trial protocol. Verbal and written consent were obtained from all study patients before inclusion.

Randomization, treatment procedures, and outcome assessments

Randomization was done using consecutively numbered, closed, nontransparent envelopes containing a computer-generated allocation indicating the area assigned to clobetasol propionate treatment.

Three applications of IngMeb (Picato 0.015%, Leo Pharma A/S, Ballerup, Denmark) were applied to the face or scalp. The first application was administered by the treating physician and the second and third application were patient administered.

On day 4, after finalized IngMeb treatment, clobetasol propionate was applied on 1 of the 2 IngMeb-treated areas. The first clobetasol propionate application (Dermovate 0.05%, GlaxoSmithKline, Brentford, United Kingdom) was administered by the treating physician after which patients were instructed to apply a thin layer of clobetasol propionate twice daily for 4 days (days 4-7).

Two physicians (A. M. E. and C. S. H.) conducted on-site assessments of LSR[11] (days 1, 4, 8, 15, and 57) and reflectance measurements[17] (days 1, 4, 15, and 57). A blinded dermatologist (K. E. K.) evaluated AK presence[17] (days 1, 15, and 57) and cosmetic

Table I. Lesion count, lesion reduction, and complete clearance per treatment area

	Baseline	2 wk Follow-up			2 mo Follow-up		
	No. of AK (IQR)	No. of AK (IQR)	Clearance	Complete clearance	No. of AK (IQR)	Clearance	Complete clearance
IngMeb	16 (14-20)	3 (1-4)	84% (76%-91%)	10%	2 (0-4)	86% (76%-100%)	29%
IngMeb + CP	16 (14-20)	3 (2-4)	85% (78%-86%)	5%	3 (1-3)	86% (78%-95%)	19%
P value	-	-	.766	1.000	-	.991	.625

Medians with corresponding (IQR). *P* values compare areas treated with IngMeb vs IngMeb + CP.
AK, Actinic keratoses; *CP*, clobetasol propionate; *IngMeb*, ingenol mebutate; *IQR*, interquartile range.

outcome (day 57). Patients completed a diary on days 1 to 15 evaluating pain (0-10: 0 = none, 10 = worst imaginable) and pruritus (0-3: 0 = none, 1 = light, 2 = moderate, 3 = severe). Cosmetic outcome included evaluations of hyperpigmentation, hypopigmentation, and scarring (0-3: 0 = not present, 1 = isolated, 2 = scattered, 3 = generalized) and skin texture (0-3: 0 = rough/rugged, 1 = even without ruggedness, 2 = smooth, 3 = silk smooth). At study completion, patients were asked to rate their overall satisfaction with the IngMeb treatment (0-10: 0 = could not be more unsatisfied, 10 = could not be more satisfied), and state their preferred choice of treatment, IngMeb or IngMeb + clobetasol propionate.

Statistics

With a minimal relevant reduction in LSR score of 3.5, SD of 4.0,[6] alpha set to 0.05, and power to 80%, the sample size for paired difference was 20 patients. A 5% dropout rate was taken into account and 21 patients were included. Kolmogorov-Smirnov test indicated normal distribution for LSR, pain, and pruritus and was compared using paired *t* test. Wilcoxon signed rank test compared clearance rates and cosmetic outcome, while McNemar test compared paired ratios of complete clearance. Clearance of grade I to III AK was pooled for all patients and presented as clearance rates in the population. *P* values were 2-sided and considered statistically significant when less than .05. Statistical analyses were performed using software (SPSS, Version 20, IBM Corp, Armonk, NY).

RESULTS

Demographics

Twenty-one patients with severe photodamage and a mean age of 71 years (range 55-88) completed the study. A majority of patients had a history of skin cancer (71% basal cell carcinoma, 33% squamous cell carcinoma). Patients presented with multiple grade I to III AK (699 AK total) and field cancerization with a median lesion count of 16 (range 8-27) AK per treatment area (Table I).

Local skin responses

LSR included erythema (100%), flaking (100%), crusting (91%), swelling (91%), vesiculation (69%), and erosion (29%) (Fig 1). Application of clobetasol propionate was initiated on day 4 when LSR were most severe (IngMeb 9.95, IngMeb + clobetasol propionate 9.52, *P* = .285). No reduction in LSR was observed in areas receiving clobetasol propionate (day 8: IngMeb 6.81 and IngMeb + clobetasol propionate 6.81; *P* = .939) (Fig 1). Two weeks after treatment initiation, LSR returned to baseline in areas treated with both IngMeb (0.67) and IngMeb + clobetasol propionate (0.38; *P* = .250) (Fig 1). Reflectance measurements supported clinical findings; no difference in erythema was found between areas treated with IngMeb and IngMeb + clobetasol propionate (Fig 1).

Patient-reported pain and pruritus

A majority of patients experienced pain (71%) and pruritus (67%) during and after IngMeb treatment. Pain scores were of mild to moderate intensities and started on the day of first IngMeb application. Pain intensity peaked on day 3 (IngMeb 2.6 vs IngMeb + clobetasol propionate 2.9; *P* = .500) and declined gradually thereafter. Pruritus had a delayed onset starting on day 3 and reached peak intensity on day 7 (IngMeb 1.0 vs IngMeb + clobetasol propionate 1.2; *P* = .312). Clobetasol propionate application had no impact on pain, but pruritus was marginally increased in clobetasol propionate–treated areas on days 9 to 10 (day 9: IngMeb 0.8 vs IngMeb + clobetasol propionate 1.1; *P* = .042).

Clearance of AK

Lesion clearance was similar in areas treated with IngMeb and IngMeb + clobetasol propionate (Table I). At 2 weeks' follow-up, overall, 84% (IngMeb) and 85% (IngMeb + clobetasol propionate) of AK were cleared (*P* = .585) and clearance

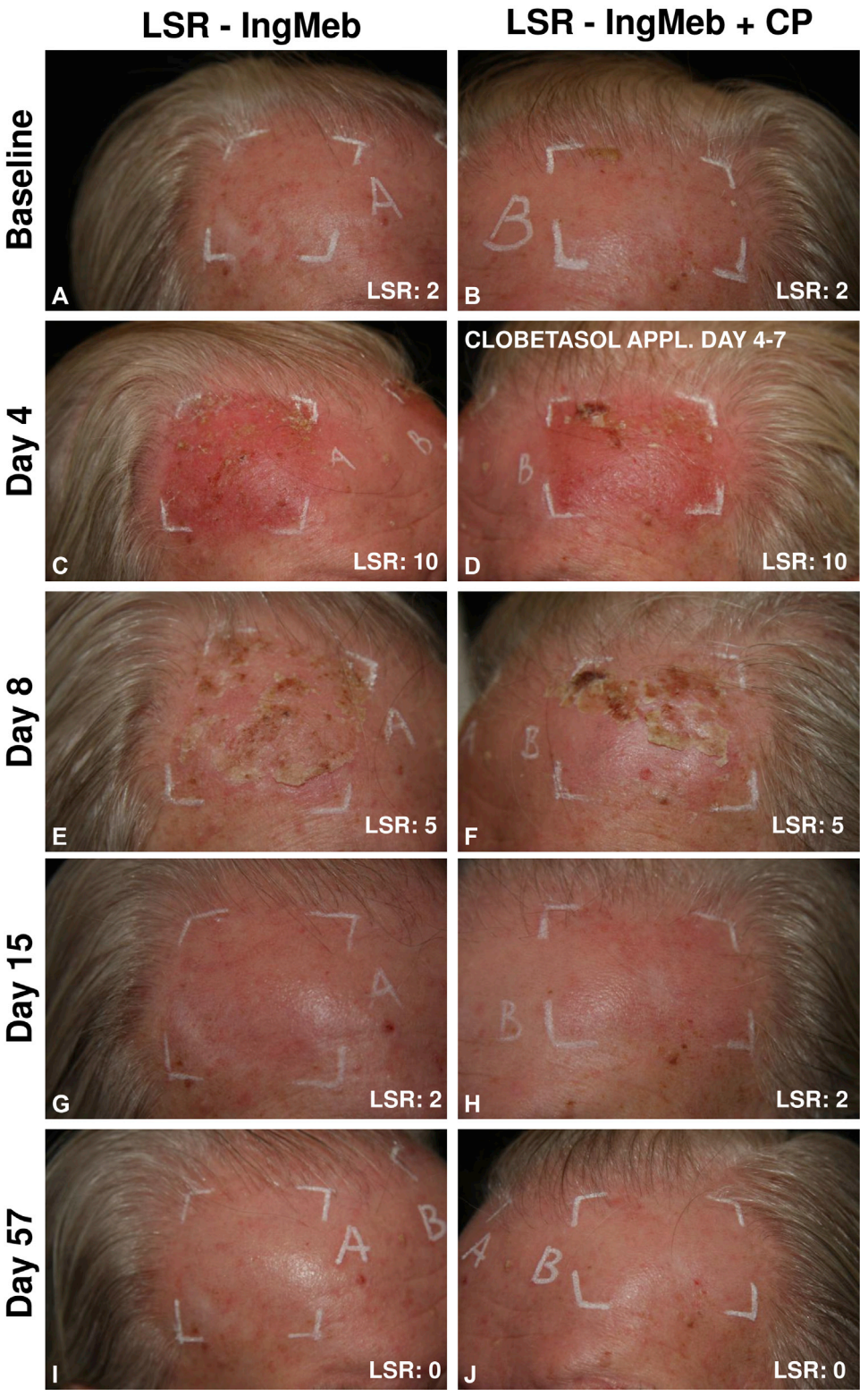

Fig 1. Development of local skin responses (*LSR*) in a patient treated with ingenol mebutate (*IngMeb*) (**A**, **C**, **E**, **G**, and **I**) and IngMeb followed by clobetasol propionate (*CP*) (**B**, **D**, **F**, **H**, and **J**). IngMeb induced erythema, flaking, crusting, swelling, vesiculation, and erosion. Application of clobetasol propionate started on day 4 when LSR peaked (**D**), but no alleviating effect on LSR was observed. Similar LSR were found on day 8 (**E** and **F**), and on day 15 responses were back to baseline in both treatment areas (**G** and **H**). Two months after treatment (day 57) no LSR were observed (**I** and **J**). Reflectance measurements confirmed clinical findings. Peak values were observed on day 4 (IngMeb 57%, IngMeb + CP 57%; $P = .976$). On day 15, minimal subclinical redness was present (IngMeb 50%, IngMeb + CP 54%; $P = .543$), returning to baseline at 2 months' follow-up (IngMeb 45%, IngMeb + clobetasol propionate 48%; $P = .076$).

rates persisted until 2 months' follow-up (IngMeb 86% vs IngMeb + clobetasol propionate 86%; $P = .991$) (Table I).

IngMeb had a therapeutic effect on all AK severity grades, including hyperkeratotic AK. Cure rates of 88%, 70%, and 60% were observed for grade I, II, and III AK, respectively (Fig 2). When not cleared by initial treatment, 86% of grade II AK (18/21) and 100% of grade III AK (6/6) were reduced in severity grade. In addition, only 3 new AK lesions were observed during the study (2 months: IngMeb n = 2, IngMeb + clobetasol propionate n = 1).

Cosmetic outcome

Skin texture significantly improved in areas treated with both IngMeb and IngMeb + clobetasol propionate with a median skin texture score of 2.0 compared with 1.0 in nontreated skin ($P < .001$). Improvement was more prevalent in patients treated on the face (80%) compared with the scalp (36%). No clinical hypopigmentation, hyperpigmentation, or scarring were found after IngMeb or IngMeb + clobetasol propionate treatment (Fig 2).

Patient satisfaction

Patient satisfaction was high with an average score of 9.52 (range 8-10). Moreover, 62% of patients (13 of 21) reported the highest level of treatment satisfaction (10) and when asked about treatment preference (IngMeb vs IngMeb + clobetasol propionate); 81% preferred treatment with IngMeb alone.

DISCUSSION

To our knowledge, this randomized controlled clinical trial is the first to study alleviation of IngMeb-induced LSR and to investigate efficacy and cosmetic outcome in patients with severe photodamage and hyperkeratotic AK. We found that application of a potent glucocorticoid after completed IngMeb treatment does not alleviate LSR, pain, or pruritus. However, IngMeb exerts a therapeutic effect on all AK severity grades, including hyperkeratotic AK, and provides a good cosmetic outcome with a significant improvement in skin texture.

Topical glucocorticoids are widely used in dermatology and provide effective treatments for many inflammatory skin diseases. Despite a theoretically conceivable effect, we found that clobetasol propionate did not reduce IngMeb-induced LSR, pain, or pruritus. The lack of effect may have several explanations. IngMeb induces a complex inflammatory process, initially causing cell

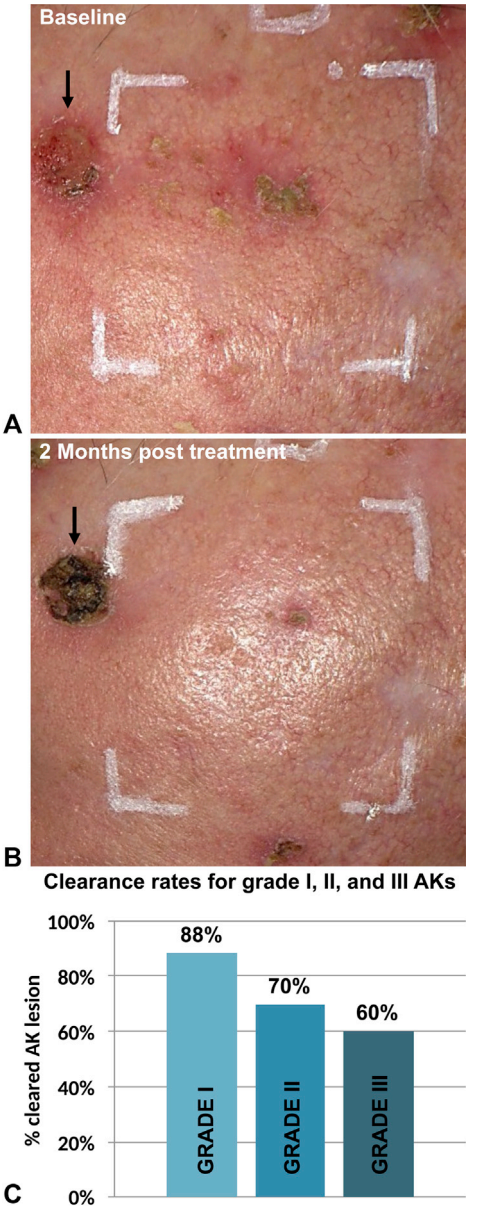

Fig 2. **A** and **B**, Clearance of actinic keratoses (*AK*) after ingenol mebutate (IngMeb) treatment. **A**, Patient with severe photodamage presented with multiple grade I to III AK, field cancerization, and a basal cell carcinoma undergoing radiotherapy (*arrow*). *White corners* mark intended treatment area, in which 16 AK (10 grade I, 4 grade II, 2 grade III) were identified at baseline. **B**, After IngMeb treatment, 81% (13/16) of the AK were cleared (9/10 grade I, 3/4 grade II, and 1/2 grade III). No clinical hypopigmentation, hyperpigmentation, or scarring were observed and skin texture was smoother in the remedied area compared with adjacent untreated skin (2.0 vs 1.0). **C**, Overall, IngMeb exerted a therapeutic effect on all AK severity grades, clearing 88% (542/615) of grade I, 70% (48/69) of grade II, and 60% (9/16) of grade III AK.

death followed by protein kinase C-δ activation and rapid neutrophil recruitment to treated skin.[13,14,18-20] Histologic analyses have revealed that during IngMeb treatments, a majority of keratinocytes undergo apoptosis or necrosis, which may leave them unresponsive to glucocorticoid stimuli.[21] In addition, neutrophil invasion, which is prevented by clobetasol propionate, is most pronounced in the early phase of IngMeb-induced inflammation; accordingly, initiating clobetasol propionate on day 4 may be too late to impact LSR.[14] Previous studies attempting to alleviate externally induced inflammation, such as acute sunburn, have failed to do so using subsequent topical glucocorticoids.[22,23] In contrast, when applied prior to the inflammatory stress, both acute sunburn and photodynamic therapy-induced inflammation have been successfully reduced.[22,24] Future studies investigating earlier application of glucocorticoids or the exploration of other remedies, such as nonsteroidal anti-inflammatory drugs, for alleviation of IngMeb-induced LSR are thus needed.

IngMeb is derived from the sap of Euphorbia peplus and is approved for topical treatment of nonhyperkeratotic AK. Previous studies have demonstrated AK cure rates of around 83% to 92% in patients with moderate photodamage (4-8 grade I-II AK/25 cm^2), while the evidence in patients with severe photodamage and hyperkeratotic AK is limited.[6,12] To our knowledge, the current study presents the first data on IngMeb efficacy in patients with severe photodamage, demonstrating that IngMeb exerts a therapeutic effect on all AK severity grades, including hyperkeratotic AK (grade II 70%, grade III 60%). Despite the high AK density (16 AK/25 cm^2), treatments were well tolerated and patient satisfaction was excellent (9.52/10). No hypopigmentation, hyperpigmentation, or scarring were observed, and skin texture improved significantly in remedied areas.

IngMeb has a brief application time of only 2 to 3 days and, as shown in the current and previous studies, LSR peak around day 4 and subside within 2 weeks of application.[6,25] This study adds to the literature by demonstrating that treated AK are cleared just 2 weeks after treatment initiation and cure rates persist until 2 months' posttreatment. In contrast, application of other patient-administered topical treatments, ie, imiquimod, diclofenac, and 5-fluorouracil, extends beyond 3 weeks, rendering IngMeb the most fast-acting drug currently available for AK.[26-28] In addition, very few new AK (n = 3) were observed in this study, supporting the notion of IngMeb as a field treatment, targeting not only visible AK, but also subclinical changes present in the surrounding skin.[24,29]

In conclusion, application of a glucocorticoid after finalized IngMeb treatment does not alleviate IngMeb-induced LSR, pain, or pruritus. However, IngMeb exerts a therapeutic effect on all AK severity grades while significantly improving skin texture in remedied areas.

REFERENCES

1. Callen JP, Bickers DR, Moy RL. Actinic keratoses. *J Am Acad Dermatol*. 1997;36:650-653.
2. Gupta A, Paquet M, Villanueva E, Brintnell W. Interventions for actinic keratoses (Review). *Cochrane Database Syst Rev*. 2012;12:CD004415.
3. Stockfleth E. The paradigm shift in treating actinic keratosis: a comprehensive strategy. *J Drugs Dermatology*. 2012;11(12):1462-1467.
4. Picato gel [product information]. Leo Pharma A/S, Ballerup, Denmark; 2012.
5. European Medicines Agency. Ingenol mebutate. Available from: URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002275/human_med_001600.jsp&mid=WC0b01ac058001d124. Accessed July 11, 2015.
6. Lebwohl M, Swanson N, Anderson LL, Melgaard A, Xu Z, Berman B. Ingenol mebutate gel for actinic keratosis. *N Engl J Med*. 2012;366(11):1010-1019.
7. Berman B. New developments in the treatment of actinic keratosis: focus on ingenol mebutate gel. *Clin Cosmet Investig Dermatol*. 2012;5:111-122.
8. Ogbourne SM, Suhrbier A, Jones B, et al. Antitumor activity of 3-ingenyl angelate: plasma membrane and mitochondrial disruption and necrotic cell death. *Cancer Res*. 2004;64:2833-2839.
9. Stahlhut M, Bertelsen M, Høyer-Hansen M, et al. Ingenol mebutate-induced cell death patterns in normal and cancer epithelial cells. *J Drugs Dermatology*. 2012;11(10):1181-1192.
10. Kedei N, Lundberg DJ, Toth A, Welburn P, Garfield SH, Blumberg PM. Characterization of the interaction of ingenol 3-angelate with protein kinase C. *Cancer Res*. 2004;64(9):3243-3255.
11. Rosen R, Marmur E, Anderson L, Welburn P, Katsamas J. A new, objective, quantitative scale for measuring local skin responses following topical actinic keratosis therapy with ingenol mebutate. *Dermatol Ther (Heidelb)*. 2014;4(2):207-219.
12. Berman B, Nestor MS, Newburger J, Park H, Swenson N. Treatment of facial actinic keratoses with aminolevulinic acid photodynamic therapy (ALA-PDT) or ingenol mebutate 0.015% gel with and without prior treatment with ALA-PDT. *J Drugs Dermatol*. 2014;13(11):1353-1356.
13. Cronstein BN, Kimmel SC, Levin RI, Martiniuk F, Weissmann G. A mechanism for the antiinflammatory effects of corticosteroids: the glucocorticoid receptor regulates leukocyte adhesion to endothelial cells and expression of endothelial-leukocyte adhesion molecule 1 and intercellular adhesion molecule 1. *Proc Natl Acad Sci*. 1992;89(21):9991-9995.
14. Challacombe JM, Suhrbier A, Parsons PG, et al. Neutrophils are a key component of the antitumor efficacy of topical chemotherapy with ingenol-3-angelate. *J Immunol*. 2006;177:8123-8132.
15. Li L, Shukla S, Lee A, et al. The skin cancer chemotherapeutic agent ingenol-3-angelate (PEP005) is a substrate for the

epidermal multidrug transporter (ABCB1) and targets tumor vasculature. *Cancer Res*. 2010;70(11):4509-4519.
16. Olsen EA, Abernethy L, Kulp-Shorten C, et al. A double-blind, vehicle-controlled study evaluating masoprocol cream in the treatment of actinic keratoses on the head and neck. *J Am Acad Dermatol*. 1991;24(5):738-743.
17. Togsverd-Bo K, Lei U, Erlendsson AM, et al. Combination of ablative fractional laser and daylight-mediated photodynamic therapy for actinic keratosis in organ transplant recipients - a randomized controlled trial. *Br J Dermatol*. 2015;172(2):467-474.
18. Parrillo JE, Fauci AS. Mechanisms of glucocorticoid action on immune processes. *Annu Rev Pharmacol Toxicol*. 1979;19:179-201.
19. Hughes J, Rustin M. Corticosteroids. *Clin Dermatol*. 1997;15(5):715-721.
20. Serova M, Ghoul A, Benhadji K, et al. Effects of protein kinase C modulation by PEP005, a novel ingenol angelate, on mitogen-activated protein kinase and phosphatidylinositol 3-kinase signaling in cancer cells. *Mol Cancer Ther*. 2008;7(4):915-922.
21. Cozzi S-J, Ogbourne SM, James C, et al. Ingenol mebutate field-directed treatment of UVB-damaged skin reduces lesion formation and removes mutant p53 patches. *J Invest Dermatol*. 2012;132(4):1263-1271.
22. Faurschou A, Wulf HC. Topical corticosteroids in the treatment of acute sunburn: a randomized, double-blind clinical trial. *Arch Dermatol*. 2008;144(5):620-624.
23. Russo PM, Schneiderman LJ. Effect of topical corticosteroids on symptoms of clinical sunburn. *J Fam Pract*. 1978;7(6):1129-1132.
24. Wiegell SR, Petersen B, Wulf HC. Topical corticosteroid reduces inflammation without compromising the efficacy of photodynamic therapy for actinic keratoses: a randomized clinical trial. *Br J Dermatol*. 2014;171(6):1487-1492.
25. Samorano LP, Torezan LA, Sanches JA. Evaluation of the tolerability and safety of a 0.015% ingenol mebutate gel compared to 5% 5-fluorouracil cream for the treatment of facial actinic keratosis: a prospective randomized trial. *J Eur Acad Dermatol Venereol*. 2015;29(9):1822-1827.
26. Weiss J, Menter A, Hevia O, et al. Effective treatment of actinic keratosis with 0,5% fluorouracil cream for 1,2 or 4 weeks. *Cutis*. 2002;70(2 Suppl):22-29.
27. Rivers JK, Arlette J, Shear N, Guenther L, Carey W, Poulin Y. Topical treatment of actinic keratoses with 3.0% diclofenac in 2.5% hyaluronan gel. *Br J Dermatol*. 2002;146:94-100.
28. Stockfleth E, Ulrich C, Lange-Asschenfeldt B, et al. Treatment of multiple, multiform actinic keratoses on the head with imiquimod 5% cream. *Eur J Dermatol*. 2009;19(4):355-359.
29. Togsverd-Bo K, Haak CS, Thaysen-Petersen D, Wulf HC, Anderson RR, Hædersdal M. Intensified photodynamic therapy of actinic keratoses with fractional CO2 laser: a randomized clinical trial. *Br J Dermatol*. 2012;166(6):1262-1269.